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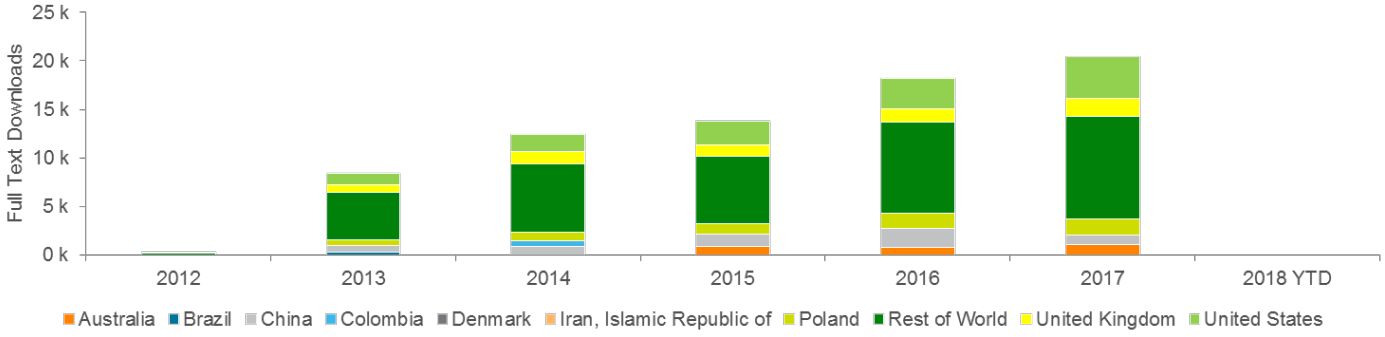

Countries	2012	2013	2014	2015	2016	2017	2018 YTD
Australia	0	0	0	895	806	1,050	0
Brazil	0	324	0	0	0	0	0
China	0	629	909	1,276	1,981	1,003	0
Colombia	0	0	545	0	0	0	0
Denmark	16	0	0	0	0	0	0
Iran, Islamic Republic of	12	0	0	0	0	0	0
Poland	38	638	895	1,033	1,501	1,725	0
Rest of World	102	4,853	7,007	7,020	9,378	10,549	0
United Kingdom	14	846	1,324	1,132	1,427	1,850	0
United States	28	1,161	1,745	2,475	3,098	4,244	0
Unknown	161	440	805	568	556	3,806	0
Total	**371**	**8,891**	**13,230**	**14,399**	**18,747**	**24,227**	**0**

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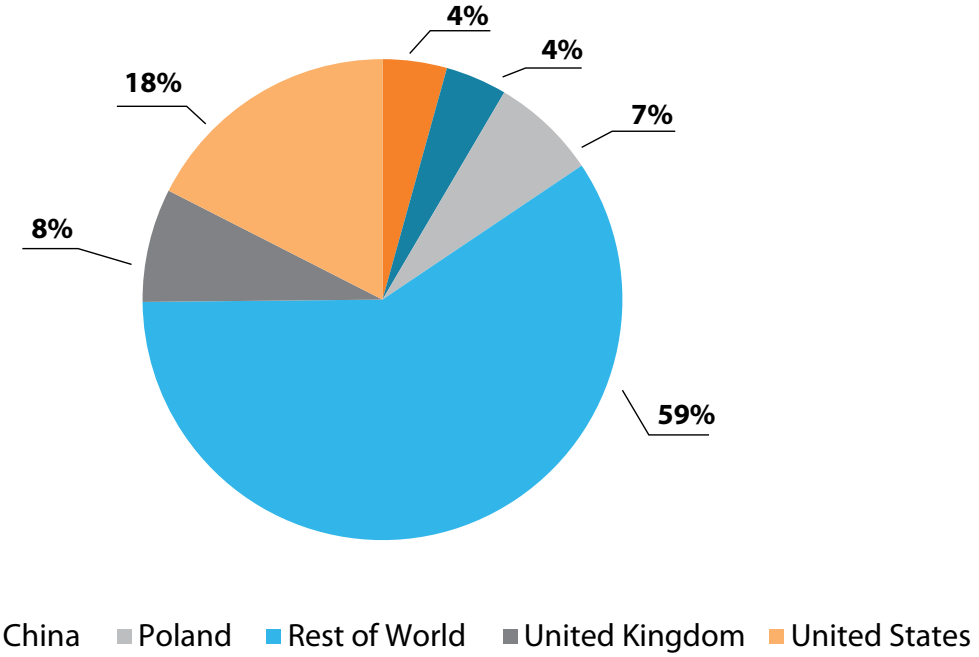

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Original article

Clinical and sociodemographic characteristics of cardiovascular disease in Sudan

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ABSTRACT

Introduction: The burden of cardiovascular disease states is stabilizing in high-income countries, and it continues to rise in low-to-middle-income countries.

Aim: The aim of the study was to explore the clinical and sociodemographic characteristics of cardiovascular disease risk factors in Sudan.

Material and methods: This is a prospective cross-sectional study consisted of 123 patients with cardiovascular disease admitted to Sudan Heart Center, Khartoum, Sudan.

Results and discussion: In total, 60.97% were females, most were 61–70-year-old, 65.85% were living in urban area and 60.66% were from northern Sudan. Physical inactivity was common for 92.68% of patients, tobacco and alcohol were used by 12.19% and 1.63% of patients, respectively. The prevalence of ischemic heart disease, cardiomyopathy, endomyocardial fibrosis, rheumatic heart disease, congenital heart disease and angina were 57.72%, 32.52%, 4.88%, 17.89%, 9.76% and 16.26%, respectively. The prevalence of risk factors for developing heart diseases stroke, diabetes mellitus, hypertension and kidney disease were 3.25%, 27.64%, 44.72% and 8.13%, respectively. Most patients have family history of heart attack 12.19%, angina 13.01%, stroke 3.25%, diabetes mellitus 37.39% and hypertension 43.90%. The anthropometric measures body weight (kg), BMI and waist-to-hip ratio were 72.32 ± 1.42, 43.87 ± 0.79 and 1.05 ± 0.06, respectively.

Conclusions: The results conclude that there is a high prevalence of cardiovascular disease in Sudan, and the risk factors were strongly influenced by clinical and sociodemographic characteristics of the population.

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1. INTRODUCTION

The World Health Organization (WHO) estimates that a total of 57 million deaths occurred worldwide in 2008, 36 million of which were due to noncommunicable diseases.[1] The burden of cardiovascular disease states is stabilizing in high-income countries, while in low-to-middle-income countries it continues to rise.[2] Over the past 55 years in West Africa, there has been a 20% decrease in communicable diseases, which has been offset by a proportionate increase in noncommunicable diseases, particularly cardiovascular disease.[3] Sub-Saharan African countries are currently experiencing one of the most rapid epidemiological transitions characterized by increasing urbanization and changing lifestyle factors. This has resulted in an increase in the incidence of noncommunicable diseases, especially cardiovascular disease.[4]

Steyn et al.[5] noted that globally, including sub-Saharan African countries, 90% of cardiovascular risk factors include smoking, alcohol consumption, obesity, diet, low physical activity, psychosocial factors, diabetes mellitus, hypertension and high lipid levels.

Cardiovascular disease is strongly influenced by socioeconomic status in all societies, whether one considers accepted risk factors, heart disease, hypertension or stroke.[6] As a population, blacks have one of the highest rates of coronary artery disease in the world.[7] Hypertension is widely recognized as a major cause of cardiovascular morbidity and mortality in indigenous people of Africa.[8] Furthermore, several studies have shown that male urban dwellers in Africa have a higher incidence of hypertension compared to males living in rural areas.[9,10]

Hyperhomocysteinaemia is associated with an increased risk of cardiovascular disease that can lead to stroke or heart attack, both of which are causes of mortality in African populations, especially males.[11]

Previous individual and case-control studies from Sudan have reported importance of smoking, hypertension, diabetes mellitus, abnormal lipids, insulin resistance, and dietary factors in cardiovascular disease.[12–15] Large studies for identification of risk factors for cardiovascular disease among Sudanese subjects are not available and most of them are limited to 50–100 subjects.

2. AIM

The purpose of this study is to explore the clinical and sociodemographic characteristics of cardiovascular disease risk factors in Sudan.

3. MATERIAL AND METHODS

3.1. Study design and data collection

This is a cross sectional study consisted of 123 patients with cardiovascular disease admitted to Sudan Heart Center, Khartoum, Sudan, recruited prospectively in 2014. The study was approved by the ethical committee of the University of Khartoum, and the informed consent was obtained from all participants. Detailed demographic and medical histories were collected using a structured questionnaire. The data include sociodemographic characteristics such as age, sex, ethnicity/race, residence, education, occupation, income and housing status for classification of socioeconomic status. The prevalence of cardiovascular disease phenotype and risk factors included ischemic heart disease, cardiomyopathy, endomyocardial fibrosis, rheumatic heart disease, congenital heart disease, angina, stroke, diabetes mellitus, hypertension and kidney disease were recorded. The family history including heart attack, angina, stroke, diabetes mellitus and hypertension were determined.

3.2. Anthropometric measures

Participants were assessed for anthropometric measures height and weight to assess body mass index (BMI) and waist and hip circumferences to assess the waist-to-hip ratio (WHR).

With participants in bare feet, height was measured in centimeters to the top of the head using a non-stretching measuring tape secured to the wall. Weight was measured in kilograms using a professional body-weight scale; participants wore only light clothing, empty of all belongings, and no shoes. BMI was calculated using the formula: body mass divided by the square of the body height (kg/m^2). Waist circumferences were measured in centimeters by placing a nonstretching measuring tape in a horizontal plane around a participant's bare abdomen at the top of the iliac crest. Hip measurement was taken at the point of maximum circumference over the buttocks, with the measuring tape held in a horizontal plane touching the skin but not indenting soft tissue. WHR was calculated by dividing waist measurement by hip measurement.

3.3. Statistical analysis

Results are expressed as mean and standard error or in percentages. A two-sample *t*-test was used for determining the statistical significance of a parameter between the different groups. A P value of less than 0.05 was considered as statistically significant. Statistical analyses were performed using SPSS v. 18 (SPSS, Chicago, Illinois, USA).

4. RESULTS

4.1. Sociodemographic characteristics

In 123 cardiovascular disease patients studied 60.97% are females and 39.03% are males, and the most effected age groups are 61–70-year-old. In total, 65.85% of patients live in urban area, and the most presented ethnic group is from northern Sudan followed by western and central Sudan. A 71.54% of patient's father and mother are first degree relatives, 80.49% of patients are married with average number of 5 children, and 61.40% of subject's spouse is his/her first degree relative. Most patients have one job and 50.82% are house wife, 22.13% practice nonprofessional job, 15.57%

Table 1. Sociodemographic characteristics of the patients.

Characteristics	Frequency	Percentage (%)
Age		
<40	17	13.82
41–50	13	10.57
51–60	30	24.39
61–70	42	34.15
>70	21	17.07
Sex		
Male	48	39.03
Female	75	60.97
Residence		
Urban	81	65.85
Rural	42	34.15
Ethnic		
Northern Sudan	74	60.66
Western Sudan	23	18.85
Eastern Sudan	2	1.64
Southern Sudan	0	0
Central Sudan	23	18.85
Were Subject's father and mother first degree relatives?		
Yes	88	71.54
No	35	28.46
Marital Status		
Single	8	6.50
Married	99	80.49
Divorced	2	1.63
Widow	14	11.38
Is subject's spouse his/her first degree relative?		
Yes	70	61.40
No	44	38.60
Type of job		
House wife	62	50.82
Professional	19	15.57
Non Professional	27	22.13
Business	14	11.48
Subject		
Uneducated	56	45.53
School	53	43.09
University	14	11.38
Mother		
Uneducated	117	95.12
School	6	4.88
University	0	0
Father		
Uneducated	114	92.68
School	8	6.50
University	1	8.81

practice professional job and 11.48% have their own business. Therefore, 45.53% of patients are uneducated, 95.12% of their mothers are uneducated and 92.68% of their fathers are uneducated (Table 1).

4.2. Physical activity

Approximately 92.68% of patients do not practice any physical activities. About 8.13% of patients experience marital separation or divorce in the past years, 26.02% loss their job or retirement, 63.41% had major personal injury or illness, 79.67% have death or major illness of a close, and 18.69% dead their spouse. A 11.38% of patients faced high level of stress at work, 24.39% at home and 2.44% face high financial stress (Table 2).

Table 2. Physical activity of patients.

Characteristics	Frequency	Percentage (%)
Physical activity		
Yes	9	7.32
No	114	92.68
Subject experience in the past years		
Marital separation / Divorce		
Yes	10	8.13
No	113	91.87
Loss of job / Retirement		
Yes	32	26.02
No	91	73.98
Major personal injury or illness		
Yes	78	63.41
No	45	36.59
Death / Major illness of a close		
Yes	98	79.67
No	25	20.33
Death of a spouse		
Yes	23	18.69
No	100	81.31
Subject stress level		
Stress at work		
High	14	11.38
Mild	9	7.32
None	100	81.30
Stress at home		
High	30	24.39
Mild	34	27.64
None	59	47.97
Financial stress		
High	3	2.44
Mild	45	36.59
None	77	62.60

4.3. Clinical characteristics and modifiable risk factors

The risk for the cardiovascular disease in Sudanese patients could be multiple, ranging from social, economic, lifestyle (smoking, sedentary lifestyle, improper diet) and biological (abnormal lipids, hypertension, diabetes, obesity). In the present study 12.19% of patients are past user of tobacco and 1.63% are alcohol drunker. The prevalence of cardiovascular disease phenotype and risk factors included ischemic heart disease (57.72%), cardiomyopathy (32.52%), endomyocardial fibrosis (4.88%), rheumatic heart disease (17.89%), congenital heart disease (9.76%), angina (16.26%), stroke (3.25%), diabetes mellitus (27.64%), hypertension (44.72%) and kidney disease (8.13%) (Table 3). The family history of heart attack, angina, stroke, diabetes, hypertension for patients were 12.19%, 13.01%, 3.25%, 37.39% and 43.90%, respectively (Table 3).

4.4. Anthropometrics measures

As shown in Table 4, the overall body weight were 72.32 ± 1.42 kg, height 168.97 ± 4.39 cm, BMI 43.87 ± 0.79, waist circumference 100.55 ± 3.02 cm, hip circumference 98.85 ± 2.55 cm, WHR 1.05 ± 0.06, systolic blood pressure 123.57 ± 1.96 mm Hg and diastolic blood pressures 72.41 ± 1.00 mm Hg and 77.27 ± 1.32 mm Hg, respectively. However, there were no significant different ($P < 0.05$) between males and females in anthropometrics measures.

5. DISCUSSION

Cardiovascular disorders are the second most common causes of adult deaths in sub-Saharan Africa, in addition to a major cause of chronic illness and disability. Both cardiovascular disease mortality and associated major risk factors vary widely between countries, with a major burden of cardiovascular diseases predicted in developing countries in the near future.[16] Observational studies have revealed large differences in the clinical management of patients with cardiovascular diseases when comparing different regions within a country, different countries in specific regions, or different regions across the globe.[17]

In the present study 60.97% of patients are females and most are from northern Sudan followed by western and central Sudan. Their age are 61–70 year, and 65.85% are residing in urban area. In the previous study we found that 53.1% of coronary heart disease patients were male, 45% were from northern Sudan and 72.7% were residing in urban areas, while the most infected age group 26.8% was less than 40 years.[15] Baingana and Bos[18] noted that half of cardiovascular disease deaths occur among people aged of 30–69, which are 10 or more years younger than in more developed regions.

Yach et al.[19] indicated that mortality by cardiovascular disease is expected to increase by 120% for women and 137%

Table 3. Clinical and modifiable risk factors for patients.

Characteristics	Frequency	Percentage (%)
Tobacco use		
Never used	103	83.74
Current user	5	4.07
Past user	15	12.19
Alcohol drink		
Never drunk	119	96.75
Current drunk	2	1.63
Past drunk	2	1.63
Cardiovascular history		
Ischemic heart disease	71	57.72
Cardiomyopathy	40	32.52
Endomyocardial fibrosis	6	4.88
Rheumatic heart disease	22	17.89
Congenital heart disease	12	9.76
Angina	20	16.26
Stroke	4	3.25
Diabetes	34	27.64
Hypertension	55	44.72
Kidney disease	10	8.13
Family history		
Heart Attack	15	12.19
Angina	16	13.01
Stroke	4	3.25
Diabetes	46	37.39
Hypertension	54	43.90

Table 4. Anthropometrics measures.

Characteristics	Male $n = 45$	Females $n = 68$	All $n = 113$	P value
Body weight, kg	74.18 ± 2.37	71.09 ± 1.76	72.32 ± 1.42	0.290
Height, cm	176.73 ± 10.91	163.83 ± 0.87	168.97 ± 4.39	0.151
BMI, kg-m^2	44.59 ± 1.24	43.30 ± 1.05	43.87 ± 0.79	0.463
Waist circumference, cm	99.42 ± 4.44	101.19 ± 4.08	100.55 ± 3.02	0.782
Hip circumference, cm	97.00 ± 5.76	99.90 ± 2.41	98.85 ± 2.55	0.592
Waist-to-hip ratio	1.10 ± 0.15	1.01 ± 0.03	1.05 ± 0.06	0.455
Systolic blood pressure, mmHg	123.37 ± 3.55	123.69 ± 2.29	123.57 ± 1.96	0.936
Diastolic blood pressure, mmHg	73.41 ± 1.58	71.76 ± 1.29	72.41 ± 1.00	0.424
Heart rate, bpm	77.85 ± 1.50	76.89 ± 1.95	77.27 ± 1.32	0.723

for men by 2020. Disentangling the effects of socioeconomic status and ethnic background is therefore difficult, and it is a major potential confounding factor in most studies that have been undertaken. Some, although not all, of the apparent differences between ethnic groups may be explained by socioeconomic factors.[6] Popkin[20] indicated that urbanization and economic development have led to the emergence of a nutritional transition characterized by a shift to a higher caloric content diet and/or reduction of physical activity. Together, these transitions create enormous public health challenges, and failure to address the problem may impose significant burden for the health sector and the economy of sub-Saharan African countries.[21] In consistent to Dallongevillle et al.[22] females were generally older and had a lower educational level compared to male.

Approximately 92.68% of patients do not practice any physical activities, but they faced high level of stress at home compared to work and financial stress, this may be due to the large number of family member as the average numbers of children are five. Similarly, the prevalence rate of low physical activity was 86.8% in the STEPS survey.[14]

Cigarette smoking increases the impact of other risk factors (such as obesity, high cholesterol, diabetes, or older age) on the risk of coronary events.[23] The percentage of patients used tobacco and alcohol are less than those reported in the previous study.[15] However, the percentage is very low when compared with other population. Pinto et al.[24] indicated smoking cessation is considered a 'gold standard' of chronic disease interventions in terms of cost effectiveness for disease treatment and prevention.

The prevalence of ischemic heart disease was 57.72%, cardiomyopathy 32.52%, endomyocardial fibrosis 4.88%, rheumatic heart disease 17.89%, congenital heart disease 9.76%, and angina 16.26. In the previous studies endomyocardial fibrosis represented 18% of all the cases of cardiomyopathy seen at the level of tertiary cardiac center in Sudan.[25]

The prevalence rates of rheumatic heart disease for all ages were 10 : 1000 for boys and 14 : 1000 for girls.[13] The prevalence rate was significantly increased among the inner town inhabitants (15 : 1000) compared to the outer town inhabitants 4 : 1000 ($P < 0.001$).[13] In the Sudan, rheumatic heart disease in still the most frequent cause of heart disease in the 5–30 year age group, and it accounts for 36% of the total hospital admissions for cardiovascular disease.[12] It is seen in children as young as 4 years, and is frequently complicated by congestive heart failure and pulmonary hypertension, making surgical treatment imperative at an early age.[13]

The prevalence of risk factors were: for stroke 3.25%, diabetes mellitus 27.64%, hypertension 44.72%, and kidney disease 8.13%. Family history such as heart attack, angina, stroke, diabetes mellitus, hypertension for patients were 12.19%, 13.01%, 3.25%, 37.39% and 43.90%, respectively. Similarly, we reported that the Sudanese coronary heart disease patients had strong family history of cardiovascular disease.[15] STEPS survey of chronic risk factors for ischemic heart disease in Khartoum state, Sudan showed high prevalence rates for hypertension 23.6%, diabetes mellitus 19.2%, overweight and obesity 53.9%, hypercholesterolaemia 19.8%, smoking 12% and physical inactivity 86.8%.[14] Steyn et al.[5] indicated that hypertension is a strong contributor to the hazards of cardiovascular disease in black Africans, with an odds ratio of 7.0 v. 2.3–3.9 in other ethnic groups ($P = 0.0002$). In sub-Saharan Africa, prevalence and burden of type 2 diabetes are rising quickly, rapid uncontrolled urbanization and major changes in lifestyle could be driving this epidemic.[26] The development of cardiovascular disease in diabetes mellitus is often predicted by several factors which include central obesity, hypertriglyceridemia, elevated low high density lipoprotein (HDL-C) levels, and hypertension.[27]

In Ghana subjects with cardiovascular disease were older and had a higher incidence of hypertension 66% and nearly a quarter had diabetes.[28] Whereas, in Cameroon obesity 80%, hypertension 60%, hyperlipidaemia 43%, smoking 36%, and diabetes 26% were the major risk factors.[29]

To identify which of the three simple anthropometric indices, BMI, WHR and waist circumference, best predicts cardiovascular risk factors, and to determine if the association between the anthropometric indices and cardiovascular risk factors varies with gender. We observed nonsignificant gender differences in the association between central or general obesity with cardiovascular risk factors. Ho et al.[30] indicated that BMI had an independent and significant association with metabolic risks in men, but not in women, whereas WHR was more strongly correlated with metabolic risks for women than for men.[30] Whereas, Borne et al.[31] noted that raised BMI, WC and WHR increase the risk of heart failure hospitalization. In addition, Choi and Tan[32] indicated that anthropometric measures such as BMI, waist circumference, and WHR have been associated with physiological indicators of CHD risk e.g., blood pressure, glucose, and plasma lipids.

6. CONCLUSIONS

The results conclude that there is a high prevalence of cardiovascular disease in Sudan, and the risk factors were strongly influenced by clinical and sociodemographic (such as age, sex, ethnicity, residence and income) characteristics of the population. Physical inactivity was common in 92.68% of patients, tobacco and alcohol were used by 12.19% and 1.63% of patients, respectively. The prevalence of ischemic heart disease, cardiomyopathy, endomyocardial fibrosis, rheumatic heart disease, congenital heart disease and angina were 57.72%, 32.52%, 4.88%, 17.89%, 9.76% and 16.26%, respectively. The prevalence of risk factors for developing heart diseases stroke, diabetes mellitus, hypertension and kidney disease were 3.25%, 27.64%, 44.72% and 8.13%, respectively. Most patients have family history of heart attack 12.19%, angina 13.01%, stroke 3.25%, diabetes mellitus 37.39% and hypertension 43.90%. The anthropometric measures body weight, BMI and WHR were 72.32 ± 1.42 kg, 43.87 ± 0.79 and 1.05 ± 0.06, respectively.

Conflict of interest

The authors declare that they have no conflict of interests.

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Original article

Assessing the effects of newly designed pressure vest on children with autism spectrum disorders

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ABSTRACT

Introduction: Pressure vest is usually used as a training intervention for the treatment of autistic children by medical experts. This article assessed the effect of pressure vest on attention and involuntary behaviors of children with autism.

Aim
The aim of this study is to expand the pressure vest therapy as a new non-invasive method to treat the autism spectrum disorder.

Material and methods: Pressure vest have cells dilated to apply pressure to the body and an air compressor manually adjustable for proper functioning. It is needed to apply pressure in a different way to enter some dynamic pressure that has a characteristic rhythmic massage. In this study, we used an alternative treatment plan for five children with autism within seven days of seven weeks. At first, the vest was worn to the baby and then a series of tasks and common games were performed. The Micro had three different programs to control valves of pressure vest.

Results and discussion: Children in most cases did the exercises and assignments with interest and had more patience. Assessing four main parameters including the focus, anger, learning and speaking in children indicates that at the end of the seven-weak course, the behavior of children has improved in the form of a reduction in the anger level and the improvement of speaking, learning and focus. The device had an acceptable performance in the prevention of sudden behaviors. The major advantage of these vests were increasing focus and concentration, enhancing comprehension and learning and reducing hyperactivity.

Conclusions: Further work with a larger database of subjects and different psychological evaluation methods is required to confirm our findings. The Micro three different programs to control valves of pressure vest had no significant effects.

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1. INTRODUCTION

Autism spectrum disorder as a psychological disorder emerges as the poor communication and social interaction in children, anger, anxiety, lack of focus and etc. It also makes them experience unwanted actions such as hand or finger flapping, body rocking and indiscoverable vocals. There is a need to expand global examinations to diagnose and treat the autism in children.[1,2]

The main reason for the autism is still unknown but the early diagnosis and intervention can be highly effective in reducing the long-term consequences of the disease such as verbal damages.[3] Many treatments have already been tried to find ways to improve the behavior of children with autism such as using embryonic stem cells and adult sensory intervention, behavior therapy, massage therapy and drug treatments.[4]

Another method of treatment is the use of therapeutic behavior with low and high intensity.[5] In the study performed by Lovaas et al.,[6] the intensive therapeutic behavior was tested on 19 four-year-old children for a period of 40 hours during a week. The results showed that after 6 years, 47% of the children had reached a normal behavior, in comparison with a control group of 19 children, who had undergone non-severe therapeutic behavior. Beyond the practices, some principles can be applied in areas such as child health, stress management, and behavioral therapies to treat the autism spectrum disorders as behavior therapies.[7–11]

Also, sensory treatments as the effective methods in treating autism are widely being used in autistic children for reducing stress and increasing the health level. Sensory interventions are applied in different types of intervention, sensory methods and practices, with the goal of self-regulation.[12]

Sensory based interventions are widely being used to help children with autism. They aims to alter the underlying neurological processing of sensory information in order to improve functional outcomes.[9,13] Interventions have been developed that apply specific sensory input to modulate behavioral responses to sensory stimuli. Examples of sensory-based interventions include: brushing or deep pressure applied to the body, manual compression of the joints, weighted vests, and hammocks.[14]

The design of therapeutic pressure vest in the previous research is based on the vest that makes constant pressure (static) to the body or there are a number of weights hanging from the body in the vest to enforce the pressure to the trunk. Weighted options used for more than 10% of the child's body weight are evenly distributed throughout the vest, providing joint compression in the shoulders and spine. Therapists use weighted vets to increase trunk stability and reduce activity levels (thereby increasing calm behavior). Using dynamic pressure instead of static pressure has potential benefits.[15,16] The overall goals of pressure therapy are relaxation, muscle tension relief, pain reduction, mobility of soft tissues and blood circulation improvement. There is considerable scientific evidence regarding the positive effects of massage therapy in the treatment of anxiety and stress, pain in joints and tendons and even sleep.[17]

In this study, a pressure vest adjustable cell with dynamic pressure pattern was presented to massage the body according to the programmable logic method. Filling and emptying of different cells inside the vest caused the rhythmic massage loss, thereby helping the patient to feel better. In this study, the effects of dynamic pressure vest were tested on children with autism on series of tasks and common games within seven weeks. Also the effect of inflated pressure vest, on autistic children psychological manner has been evaluated and the advantage of this system was evaluated in comparison to the former methods of pressure therapy.

2. AIM

The aim of this study is to expand the pressure vest therapy as a new non-invasive method to treat the autism spectrum disorder.

3. MATERIAL AND METHODS

In this study a device including a controller was used to fill specific arrays, empty cells and therefore exerting a dynamic pressure to the trunk. The design and manufacturing methods include: design and construction of wearable vest, air compressor mechanism, electroneumatic valve, pressure regulator design, controller design and electrical circuits.

3.1. Design and construction of the wearable vest

The vest had six separated cells (calf) opening in the front and back. These cells were embedded in the vest. Cuffs were placed symmetrically on the front and back of the vest and a faced pair was filled and emptied simultaneously. This phenomenon created more pressure. Pocket was built inside the jacket where the cuffs were placed and there was some access for the pocket outside the vest. Inside the jacket, the cuffs using hose connectors were connected two by two, providing the possibility of inflating two cuffs at the same time. The vest was completely open and free from both sides and anyone could easily wear it (free size). Then we put together the back and forth of our jackets by some tags sewn on the dress (Figure 1).

3.2. Mechanism of air compressor and electroneumatic pressure regulator valve design

The electromagnetic air pump was used for feeding air and suitable air pressure inside the vest. The compressor could create pressure up to 260 mmHg and discharge up to 60 L/min, making it very suitable for our work. The body of the pump was made of an aluminum alloy reducing the air flow resistance and the heat loss from the body was handled more effectively. Other characteristics important in the study were the low noise pump, high efficiency, low pressure and lack of pollution on the environment. Low noise working of the pump was very important. It prevented the stress

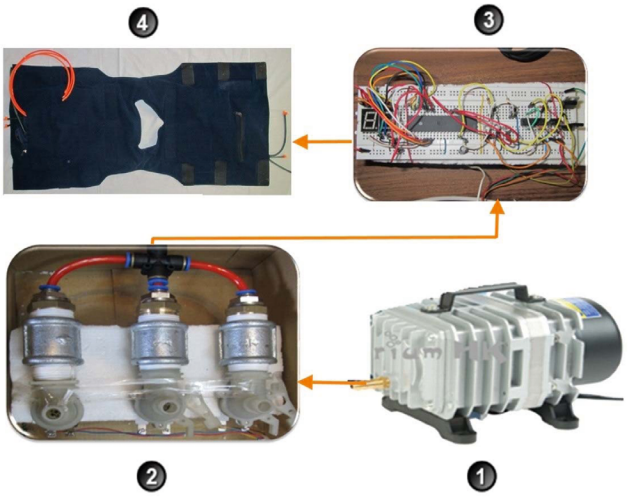

Figure 1. The overview of the therapeutic pressure vest: (1) compressor, (2) electromechanical valve, (3) control circuit, (4) pressure vest.

on the patient and helped the patient to feel comfortable. To control the entry and exit of air in cells, an electroneumatic valve was required for each pair of cells with a high response rate since these valves were controlled by the inner core and a coil. In this system, three valves were placed in parallel, open or close, by the command control circuit. Pressure regulator was placed immediately after the compressor and before the electroneumatic valve. By rotating that, the input air pressure to any cell could be adjusted. So the unique feature of this device was applied for rhythmic massage (not static), which was done by the pressure regulator. Some of the features of the pressure regulator are as follows: manufacturer – Jacob Aerodynamic, type – NAR-200-RNKG, structure – diaphragm, material – zinc and techno polymer, ports – 4/1 and 8/1, working temperature – from –20°C to 50°C, maximum inlet pressure – PSI 250, and discharge pressure – up to 135 PSI 5.0.

This valve could set output pressure from 0.5 PSI to 135 PSI. By connecting a pressure gauge to the pressure regulator, pressure applied to the patient's body was measured in every moment.

3.3. Design and construction of the electrical circuit controller

To use different methods of applying pressure, valves in various forms had to be opened or closed. In the proposed system, AVR was used to control the valve. The circuit was simulated using the Proteus software and then implemented on board. The Micro had three different programs to control valves. These programs are described below.

3.4. The first program

In the first program (P1), valves did not act together and each valve was opened separately for a specified period of time by a micro-relay command. For example, if the duration were determined by the micro in 5 s, by running the program, the first valve would be opened for 5 s, and the other two valves would be closed. In the second 5 s, the second valve was opened and the other two valves were closed and the cycle was continued until the machine power was cut off.

3.5. The second program

In this program (P2), the valve was opened and closed at the same time and then the third valve was opened when the other valve was closed. It was as if there were only two valves in the machine.

3.6. The third program

In the third program (P3), each phallus was opened and closed simultaneously. So, in this case, only one valve was in orbit. Due to these different programs, different massage techniques could be used. For example, in the state number two, two cells could be wound in the upper trunk simultaneously and then under cell as another cell. The importance of this is the ability of massaging the upper and lower body separately, one after another. We could set the number and duration of each valve (s) as an input control circuit.

4. RESULTS AND DISCUSSION

To test the system, a seven-day course of treatment was considered. Five boys and girls, who were willing to attend the tests, participated in the test, according to teachers and the parents present in this period. Children wore a vest in the Child Support Autism and the device started the first program on schedule. Also, the instructor asked them to do some work such as writing, reading, playing and painting. This program was performed almost every day for 20 minutes. The lecturer took note at the same time to get information regarding children's reactions at the end of a detailed report. We classify the level of speaking ability, learning ability, focus and anger and score them from 1 to 5. Score 5 and 1 respectively means good and poor learning/speaking/focus ability. Score 5 and 1 respectively means very angry and not angry manner. The results of test subjects have been shown in Figure 2.

Among the deficiencies observed, the device was importable, so the children had to sit in their place. Another disadvantage of the device was the sound produced by air compressor, causing children's distraction. To overcome this drawback, it is possible to replace the compressor with compressed air lines used in hospitals and clinics. A suggested by teachers, the use of the device for a few months is required to view more details. By a dynamic vest, the amount, location, and timing of the pressure can be varied, potentially stimulating the mechanoreceptors more frequently, and the vest could be effective for a longer period of time. Second, since the amount, location, and timing of the pressure can be varied, a dynamic vest can be more child-specific than a static vest, as the

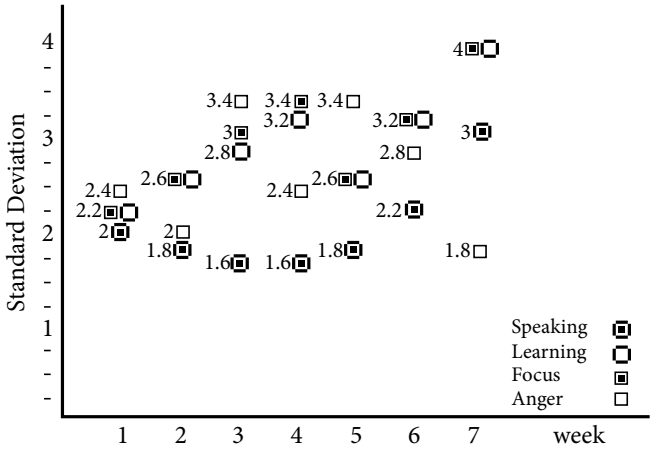

Figure 2. Standard deviation of test subjects in the 7th week follow-up.

parameters of the vest are adapted to each child's sensory needs. In this research the effect of pressure vest, on autistic children has been evaluated based on coaches and experts experience it could be replaced by psychological test like questioner or analyzing the EEG signals.

5. CONCLUSIONS

According to the experts of the Autism Center, the devices had a positive effect on children's behavior, such that they liked to do things and showed less angry behavior. The device had an acceptable performance in the prevention of sudden behaviors because, except a special case, children followed the tasks and demands of the instructor very well. The benefits of these vests were: increasing body awareness, improving balance and coordination, increasing focus and concentration, enhancing comprehension and learning, dramatically reducing hyperactivity, maximizing the benefits of therapy sessions, and increasing therapy carry over.

Conflict of interest

None declared

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Original article

An assessment of computed tomography laser mammography in breast cancer diagnosis

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ABSTRACT

Introduction: Computed tomography laser mammography (CTLM) is a type of opticaltomography imaging. The main advantage of optical methods is the absence of ionizing radiation. Therefore, it can be used regardless of the age or pregnancy condition of the patient. Moreover, CTLM does not require breast compression.

Aim: The aim of the study is to evaluate the accuracy of CTLM for detecting breast cancer and therefore to asses the suitability to place this new technique in the diagnostic chain of procedures.

Material and methods: A group of 175 white European women were enrolled in the study (age 25–79, average 55 years old). All of the subjects had a CTLM performed in 2006 at the Department of Radiodiagnostics in the Maria Sklodowska-Curie Memorial Cancer Centre.

Results and discussion: Based on the histopathology, breast cancer was found in 70 (40%) cases; in 105 (60%) cases malignancy was not found. When comparing CTLM results to the golden standard of histopathology, a differentiation between benign and malignant foci was found, obtaining the following values for the sensitivity of 71%, specificity of 72%, PPV 63,2% and NPV 79,1%).

Conclusions: The obtained levels of sensitivity and specificity in this study exclude CTLM as a stand-alone diagnostic method and it is assessed as unable to compete with current state-of-the-art approaches.

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1. INTRODUCTION

Breast cancer is the most common malignant tumor found in women. Efficient disease prevention is very difficult, almost impossible. However, breast cancer detection in its early and clinically limited stage gives women a chance for full recovery. The basic method for breast cancer detection is X-ray mammography. However, this examination has two major limitations. The first is ionizing radiation and the second is an insufficient level of sensitivity in breast cancer detection, especially in dense breasts. These limitations provide the motivation for searching new methods that would be more efficient in early cancer stage detection. One of these methods is computed tomography laser mammography (CTLM), which is a type of optical tomography imaging.

The first attempts of breast imaging with optical methods using 600–1000 nm wavelength date back to the 1930's. However, technical issues concerning low sensitivity and specificity for many years precluded this method from clinical practice.[1] The return of optical imaging was in the last decade of the 20th century.[2] The main advantage of optical methods is the absence of ionizing radiation. Therefore, it can be used regardless of the age or pregnancy condition of the patient. Moreover, laser mammography does not require breast compression and a dense breast is not as problematic as in radio-mammography.[3] The laser light used in a CTLM scanner has a wavelength of 808 nm and it is strongly absorbed by the haemoglobin, but it penetrates other tissues of the breast with ease.[4,5]

2. AIM

The aim of this study is to evaluate the accuracy of laser mammography in breast cancer detection and also to create reference images of breast cancer with CTLM and therefore to asses the suitability to placing this new technique in the diagnostic chain of procedures.

3. MATERIAL AND METHODS

The study included a group of 175 white European women, age range 25–79 (average 55 years old). This patient sample was selected by requiring a positive result with RTG mammography (MMG) and/or with an ultrasound (US) examination.

Afterwards, in each case a CTLM acquisition and histopathological (HP) verification was performed. All examinations were performed in 2006, at the Department of Radiology, Maria Curie-Skłodowska Memorial Cancer Centre and at the Institute of Oncology, Gliwice Branch. None of the patients included in the study had multiple lesions in the breasts. Therefore, the analysis was conducted on 175 pathological lesions.

The study was performed using CTLM scanner Model 1020 (Imaging Diagnostics Systems, FL, USA). The system's wavelength was 808 nm. The result of a CTLM examination was determined positive, if there were regions of a pathological increment of light absorption found. This result was considered to be cancer positive. The negative CTLM result was determined, if there were no pathological light absorption regions found. This result excluded the presence of cancer. It was established that the region of high light absorption corresponds to foci visible in the MMG/USG, if it was found in the same quadrant. Regions of high light absorption (CTLM+) were analyzed in the second step using Matlab (Mathworks, MA, USA) software.

Two factors were calculated using MATLAB:

1. Anisotropy factor (AF). An ellipsoid was fitted to each region. A ratio between the standard deviation and the root mean square of ellipsoid's radiuses was calculated. This way the anisotropy factor was independent from spatial orientation and it ranged from 0 in the case of a sphere to 1 for an ellipsoid.
2. Signal-to-noise (SNR). It was calculated as a ratio between the median of values in the region of interest and the median value of the surrounding area.

The findings of CTLM were compared with the HP results to examine sensitivity and specificity of the method in breast cancer. Images of breast cancer described as CTLM+ or CTLM– were compared with:

– morphology in mammography (size less and more than 2 cm),
– HP type (preinvasive, infiltrating cancer), malignancy level (G).

The null hypothesis of no correlation between CTLM and other breast cancer properties was tested with 2 Pearson's test with Yate's correction for a small group. The correlation between CTLM and the malignancy level was verified with a Mann-Whitney's test.

Prior to analysis used patients' records were anonymized and de-identified for this study in accordance to Polish law. The approval of Local Bioethics Commission, Data Protection Agency and participants was not required.

4. RESULTS

The analysis consisted of 175 findings. In 70 cases it was cancer and in 105 cases it was benign. This classification was confirmed by microscopic examinations and 12 months of follow-up. The most commonly found was infiltrating ductal cancer (65%). In a subgroup of benign lesions, the most occurring was dysplasia (78%). In 79 cases out of a total of 175 (45%), a strong light absorption was found and in the remaining 96 cases the CTLM result was negative. The CTLM+ result was true positive in 63% of the cases and CTLM– was a true negative in 79%.

Increased light absorption CTLM+ was found significantly more often in cases of a malignant cancer (50/70 = 71%) than in the benign (29/105 = 28%) ones ($P < 0.001$).

In evaluating if the CTLM is beneficial as a predictive factor distinguishing malignant and benign types of lesions, a sensitivity of 71% and specificity of 72% were found. The positive predictive value was 63.2% and the negative predictive value was 79.1%.[6]

SNR was calculated for each of 79 CTLM+ cases. The obtained values ranged from 1.08 up to 1.8. The SNR for most of the lesions was lower than 1.3; therefore, to enhance detectability, a 3D data representation and contrast enhancing colour scales were used (Figure 1). Only with these tools, the delineation of low contrast changes was possible.

Unfortunately like AF, the SNR was not useful to discriminate between benign and malignant cases. The statistically significant differences were not found. A positive result of CTLM was found in 32 of 45 (71%) total cases of cancer with a size smaller than 2 cm. Similarly, in cases of cancer with a size greater than 2 cm, a positive CTLM was found in 18 of total of 25 (72%) (Table 1).

The HP result was not clear in 8 cases (Table 2). Therefore, only 62 cases could be included in this part of the analysis. According to the HP results, the material was divided into the subgroups: infiltrating cancers (54 cases) and pre-invasive cancers (8 cases). In the first group of cancers 40 cases of CTLM+ were found and in the latter only 5 cases.

Although the statistical tests showed no relation between the CTLM result and the cancer growth type, it may be blurred by the low and unbalanced number of cases in the second subgroup.

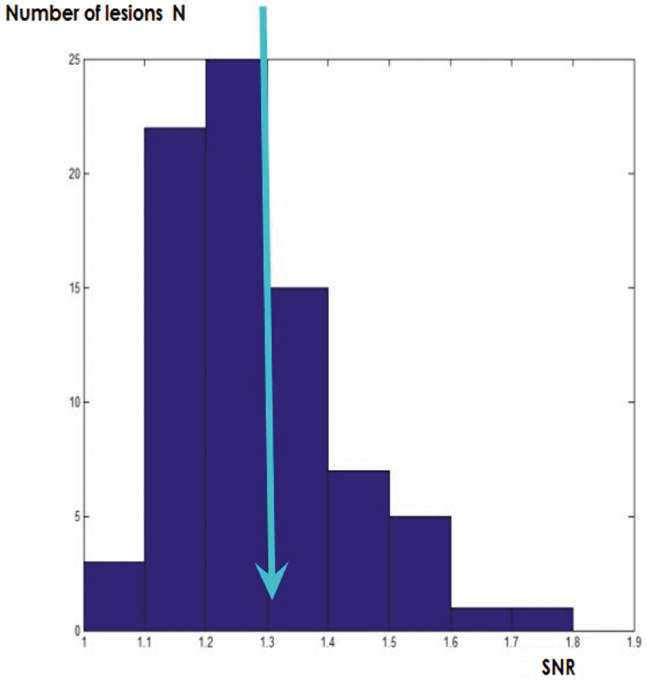

Figure 1. SNR value in CTLM+ lesions.

Table 1. Dependence of CTLM results and line diameter of a tumor (cancer), correlation between CTLM results and HP properties.

	Line diameter of a tumour less than 2 cm	Line diameter of a tumour more than 2 cm
CTML+ CTML–	32 13	18 7
	X	P
Pearson's test with Yate's correction	0.01 0.04	0.937 0.843

The connection between CTLM results and malignancy level (G) was analysed in a subgroup of 56 cases (Table 3). However, no statistically significant difference was found.

A comparison between results of CTLM and HP of breast lesions was shown in Table 4. The low number of

Table 2. Correlation of histologic type of breast cancer with CTLM image.

	Invasive cancers	Preinvasive cancers
CTML+ CTML–	40 14	5 3
	X	P
Pearson's test with Yate's correction	0.469015 0.067726	0.4934408 0.7946774

Table 3. Correlation of grade of malignancy with CTLM image.

Grade of malignancy	Number of lesions	CTLM+	CTLM–
G1	12	10/12; 83%	2/12; 17%
G2	32	23/32; 72%	9/32; 28%
G3	12	8/12; 66%	4/12; 34%

Table 4. Comparison of CTLM and HP results in breast lesions.

HP result	No. of lesions	CTML+ n(%)	CTLM– n(%)	False negative	False positive
Ductal carcinoma in situ (DCIS) percent from the line	8	5 (65%)	3 (37%)	3/8; 37%	
Invasive ductal cancer percent from the line	45	34 (76%)	11 (24%)	11/45; 24%	
Infiltrating lobular cancer percent from the line	7	6 (86%)	1 (14%)	1/7; 14%	
Undefined cancers, mucoid, papillary percent from the line	10	5 (50%)	5 (50%)	5/10; 50%	
Fibroadenoma percent from the line	9	5 (55%)	4 (45%)		5/9; 55%
Benign dysplasia percent from the line	83	17 (20%)	66 (80%)		17/83; 20%
Atypical ductal hyperplasia percent from the line	8	6 (75%)	2 (25%)		6/8; 75%
Papilloma percent from the line	3	1 (33%)	2 (67%)		1/3; 33%
Tubular adenoma percent from the line	1	_	1 (100%)		0/1; 0%
Radial scar percent from the line	1	_	1 (100%)		0/1; 0%
Sum	175	79	96	20/70; 29%	29/105; 28%

cases in subgroups made the interpretation of results very difficult. The regions of high light absorption were significantly more often found in cases of atypical ductal hyperplasia, than in benign dysplasia ($P < 0.01$). No connections between CTLM results and the linear size or cancer growth type or malignancy level were found.

5. DISCUSSION

In the group of 175 cases included in the study, in 70 cases, a cancer was found and in 105 cases, the foci were benign. A positive CTLM result was significantly found more often in malignant cases (71%) than in benign cases (28%) with $P < 0.001$. Such a significantly more frequent positive CTLM result in a group of cancers can be explained by the presence of a dense vascular network and a higher concentration of haemoglobin than found in normal breast tissue.[4,5]

Obtained results are in an agreement with those presented by Floery.[7] He used a similar CTLM scanner with 808-nm wavelength and found a positive CTLM result in 70% of invasive cancer cases. Assuming the positive CTLM result as diagnostic criteria, the sensitivity was found at the level of 71% and specificity at the level of 72%. The false-positive (29%) and false-negative (28%) number of cases found in this material is at a similar level found in the literature (Floery 30%, Athanasiou 27%).[1,7]

The sensitivity and specificity of CTLM was lower than conventional X-ray mammography. Intriguing questions arose from the data analysis: Why some of the cancers do not attenuate laser light and why do benign lesions in some cases show increased haemoglobin deposition?

In a group of 70 cancers (62 invasive and 8 DCIS) 20 lesions did not show increased light attenuation. Preinvasive cancers appeared more often CTLM– than the invasive ones. However, these differences were not statistically significant and a low number of DCIS cases could influence the result.

The opinions regarding neoangiogenesis in ductal cancer in situ are not coherent.[8] DCIS is limited by the basement membrane. It does not infiltrate the stroma and it does not present the ability of angiogenesis.[9] However, there are reports[10–12] that state the ductal cancer (DCIS) may present hypervascularization. In spite of changes, the DCIS does not grow beyond the basement membrane, but the vessel's density (MVD) in stroma between ducts affected by DCIS may be higher than that of a normal tissue.[10,11] This fact may explain positive CTLM results in 5/8 cancers in the subgroup.

The situation in atypical ductal hyperplasia cases is similar. This may justify the concept that the angiogenesis is not necessarily a typical feature of invasive cancers, but it may occur in preneoplastic lesions.[11–13] In the analysed group, a positive CTLM result was found in 29/105 (28%) benign lesions. Most of the ADH tumours (6/8) presented elevated laser light absorption (CTLM+), but even 1 in 5 cases of benign dysplasia was CTLM+.

Similarly, Floery[7] found in group of 53 benign lesions 34% of CTLM+ results. The features of hypervascularization in benign lesions were found by Bobek-Billewicz as well.[5] The level of vascularization in fibroadenomas varies and depends on the proportion of cellular and fibrous elements[14] – the more cellular components, the higher the level of vascularization.[15] The HP image of atypical ductal hyperplasia is close to the one of DCIS. DCIS is an atypical epithelial hyperplasia affecting at least two ducts or covering an area of 2–3 mm. If such hyperplasia is not accompanied by high grade atypical and necrotic foci, a smaller lesion is considered to be an atypical ductal hyperplasia.[16]

For the facts mentioned above, in 2003 the WHO proposed a common name for atypical ductal hyperplasia and DCIS – intraductal neoplasia.[1] In both the lesions there is an increased vascularization in stroma between affected ducts.[10] If within the performed examinations 8 cases of the atypical ductal hyperplasia were in the same group as DCIS, the specificity would rise from 72% to 76%.

The Anisotropy factor was analysed in order to find differences between malignant and benign lesions with high laser light absorption. The spherical lesions were found with similar frequency in both subgroups (41% vs. 52%). This concurs in agreement with Floery,[7] stating that the shape of the lesion is not a diagnostic parameter. No correlation between light attenuation and malignancy level G was found. The highest number of false negative results was found in group G3. It can be explained by a more frequent presence of necrosis, which does not absorb laser light.

Different results were presented by Floery,[7] who was the only one analysing the correlation between CTLM and the malignancy level. Floery found that the false-negative results are found more frequently in G1 group. These findings may seem contradictory with those here presented. The cancers with the highest malignancy level have a different vascularisation density, but also necrosis regions are found more often. Therefore, the obtained sensitivity in G3 groups can depend on the ratio between the number of cancers with and without necrotic regions. Moreover, the ratio between the volume of necrosis and tumour tissue can influence the results.

A very important restriction of this optical method is the low spatial resolution and low SNR.[17] In this study, more than half of the lesions had SNR lower than 1.3.

The detectability of this level is limited for the human eye. Therefore, an additional 3D image augmentation and colour scales had to be used to enhance contrast of the cancer lesions.

Laser light penetrates tissues of the breast easy but 5% light is totally absorbed by every centimetre of tissue. If breast is big the laser light may be totally absorbed before it reaches the detector. This fact may explain difference our results and presented for Chinese women were sensitivity of mammography CTLM+ even was 95.34% in heterogeneously dense breast.[18]

6. CONCLUSIONS

CTLM cannot be considered as an independent diagnostic tool for breast cancer. CTLM NPV should be compared with MMG and ultrasound; therefore, this excludes CTLM as a method for screening a group of young women with a high risk of breast cancer.

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Original article

Trends in the utilization of advanced diagnostic imaging and lumbar disc disorders diagnosis in the Warmia and Mazury Province, Poland

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) is one the most important diagnostic techniques, and the use of MRI scanners is becoming progressively more extensive and increase annually worldwide and in Poland. MRI scans are used by neurosurgeons, orthopedists and neurologists indicating that the diseases most frequently diagnosed using MRI are related to musculoskeletal and central nervous system dysfunction.

Aim: The main aim of this study was to determine the extent of MRI scanner utilization in the University Clinical Hospital (UCH) in Olsztyn, in the years 2011–2015 and to examine data sets concerning spinal and back injuries, the age and sex of patients within the most frequently examined sub-populations.

Material and methods: Analyses were performed using the patients' digital database including 13 298 MRI reports in UCH, in years 2011–2015.

Results and discussion: The results show that the use of MRI scanner in the UCH increased over the study period. The diseases most frequently diagnosed using MRI were musculoskeletal diseases, among which the spinal diseases were most common. More women than men were enrolled in the diagnostic tests and majority of patients were in the age range of 50–61 years.

Conclusions: The number of MRI tests indicates high demand for MRI scanners in the Warmia and Mazury Province. As the intervertebral disc disorders are most common in people of working age (51–60 years), early checkups and prevention of vertebral column diseases should be implemented at younger age, by introducing examinations followed by recommendations of corrective gymnastics and/or physiotherapy when indications of pathological changes are noticed.

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1. INTRODUCTION

The magnetic resonance imaging (MRI) is currently one of the most advanced diagnostic imaging techniques. The use of MRI scanners has been increasing since the 1980s.[1] Although patients and radiologists-technicians are exposed to the low energy static magnetic fields during examinations, MRI scanners are safe and each year the number of MRI-diagnosed patients is increasing due to the unique features of this technology.[2] These include advanced image enhancement, and a more complete diagnosis compared to X-rays, particularly in case of changes in joints' structures or soft tissues and organs.[1,3] Since MRI provides an accurate, noninvasive evaluation, MRI tests are very often either replacing or being used in addition to traditional tests such as X-rays. The diagnostic potentials of MRI are further increased by the use of improved contrast resolution, and introduction of the high-magnetic field equipment of 1.5 T, 3 T and higher. On the other hand, the availability of MRI in hospitals worldwide is still relatively low, and there are some disadvantages of this technique, such as much longer testing time compared to computer tomography, difficulties in examining some patients, i.e. unconscious or with contraindications to MRI such as cardiac pacemakers, metallic implants in soft tissues, foreign objects in the eye or claustrophobia.[3,4]

Although MRI is already the most expensive among the new imaging techniques, the further technical developments are still ongoing because of the unique imaging abilities described above.

The use of MRI scanners has been increasing each year in many European countries, the Middle East and Asia.[4,5] In the United States, the number of MRI examinations has been increasing by about 26% per year and nearly tripled in one decade (1997–2006).[6–8]

The first MRI scanner in Poland was launched in 1991, and according to The Statistical Bulletins of The Polish Ministry of Health, the number of MRI scanners increased from 47 in 2003 to 246 in 2014, mostly in public hospitals, and in the same time period, a number of MRI laboratories increased from 46 to 143. In the reporting period, the availability rate of MRI scanners in Polish hospitals has increased from 0.12 to 0.40 for 100 000 people. In hospitals of the Warmia and Mazury Province this indicator has changed from 0.07 to 0.10.[9]

According to the Polish Central Statistical Office, in 2011 the number of MRI scanners for 1 000 000 people in Poland was one of the lowest in the world (4.8) whereas the highest was in Japan (46.9). MRI scans rate per 1000 people was the highest in the USA (102.7), whereas in Poland it was much lower (17.7).[10]

MRI is reportedly the best method of imaging of the spinal cord and its disorders, as the examination enables visualization of intervertebral discs, roots of spinal nerves, spinal cord vascularization and spinal column ligaments.[1,3] In the Middle East, neurosurgeons, orthopedists and neurologists contributed to more than 88% of MRI utilization and the spinal column was among body parts most commonly scanned by MRI machines.[4] Although traditionally low back pain occurs in about 80% of the adult human population, some reasons for the spinal column disorders are work- and sports-related, are due to the motor vehicle accidents, falls from heights, violence, diving into shallow water, genetic factors and others.[11–22]

2. AIM

To determine: (1) the extent of MRI scanner utilization in the University Clinical Hospital in Olsztyn in the years 2011–2015, (2) the percentage of tests concerning spinal and back injuries and (3) correlation of the spinal injuries with age and sex of patients.

3. MATERIAL AND METHODS

The changes in the utilization of MRI scanner Magnetom Trio A Tim System 3T in the University Clinical Hospital in Olsztyn, in the years 2011–2015 were evaluated. The digital database included 13 298 MRI reports and an information about the patients' age, sex, the time of tests, and the disease codes assigned by physicians using *International Statistical Classification of Diseases and Related Health Problems*, tenth Revision (ICD-10).[23]

The first MRI scans in the University Clinical Hospital in Olsztyn were performed at the end of 2010, but in this study scans from January 1st 2011 to December 31th 2015 were examined.

Following the analyses of the MRI scanner utilization each year, categories of diseases were examined and the most frequently diagnosed disorders were chosen for the more detailed evaluations.

This study has focused on the diseases of the musculoskeletal system and connective tissue (codes M00–M99; ICD-10), and only the diseases described with the general term 'spinal test' and including the dorsopathies such as damage of vertebral column, roots of spinal nerves and paravertebral tissue (codes M40–M51) were selected, while back diseases described by other codes were excluded. Subjected to analysis were the patients' age and sex, and proportions of the female and the male patients in each examined year. Moreover, to determine the most numerous age group, patients were subdivided into the 10 age groups in each study year.

4. RESULTS

4.1. Characteristic of the analyzed population

In this study 13 298 MRI examinations from a 5-year period have been evaluated. The average number of scans was 2659.6 per year and the number of tests gradually increased. The highest number of tests was observed in 2013 and was nearly 2.5 times higher than at the beginning of the use of MRI scanner in 2011 (Figure 1). The most frequent referrals were for musculoskeletal tests among which the most-

Table 1. Musculoskeletal, back, and spine MRI scans in years 2011–2015.

Years	2011	2012	2013	2014	2015	2011–2015
Total number of MRI scans	1443 (44.01%)[2]	2340 (53.46%)[2]	3527 (43.78%)[2]	3139 (51.86%)[2]	2849 (49.95%)[2]	13298 (48.74%)[2]
Total of MRI scans in all musculoskeletal (M) diseases[1]	724 (46.08%)[3]	1414 (57.52%)[3]	1810 (48.09%)[3]	2001 (57.25%)[3]	1755 (54.26%)[3]	7711 (57.98%)[3]
Back and spine MRI scans	665	1346	1696	1797	1546	7050
Spine MRI scans	635	1251	1544	1628	1423	6481
Percentage of spine and back MRI tests among all M tests	91.85	95.19	93.70	89.81	88.09	91.51
Percentage of spine MRI tests among spine and back tests	95.49	92.94	91.04	90.60	92.04	91.93

Comments: [1] *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10)[23]; [2] Percentage of musculoskeletal scans among total MRI scans; [3] Percentage of spinal MRI scans among total MRI scans. Source: University Clinical Hospital in Olsztyn.

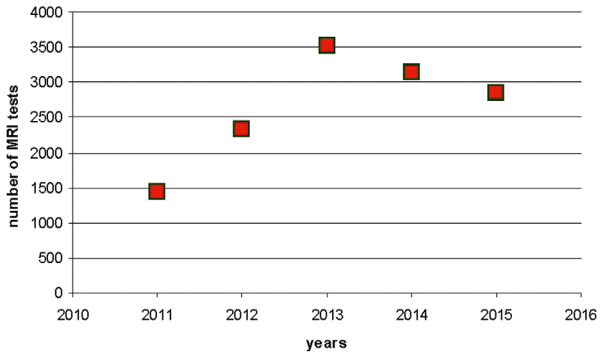

Figure 1. The changes of utilization of MRI scanner in University Clinical Hospital in Olsztyn in 2011–2015.

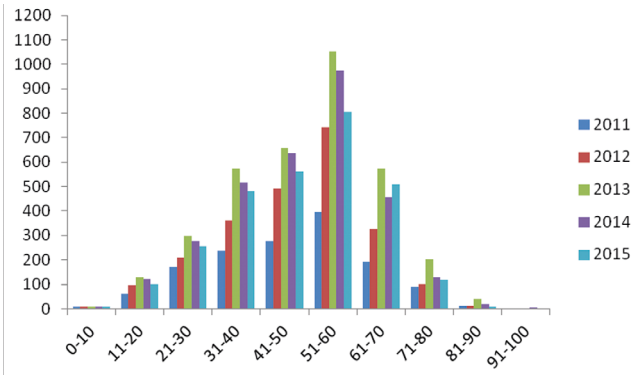

Figure 2. The number of total MRI tested patients in 10 age ranges from 2011 to 2015. Source: University Clinical Hospital in Olsztyn.

common were back and spine tests. They constituted about 50% of all cases per year and only small fluctuations were observed over the years. The results show that among all back and spine tests, most were related only to spine diseases (about 90%) and their number was similar during the entire period examined (Table 1).

During the whole investigated period, the average age of the male and the female patients with various diseases was similar: 47 ± 15 and 49 ± 14 years, respectively. In the spinal tests the average age of patients was higher the male 49 ± 12 and the female 51 ± 12, respectively (Table 2).

Table 2. Mean age of patients by sex enrolled in MRI tests in 2011–2015.

Gender	Female	Male
Age: all MRI scans	49±14	47±15
Age: spine MRI scans	51±11	49±12

The results show that in all MRI tests the most numerous age group was 51–60 years and the least numerous group was 90–100 years. The range of 50–61 years of age was the most numerous in each year of using MRI scanner and had slightly increased by 2013 (Figure 2). In

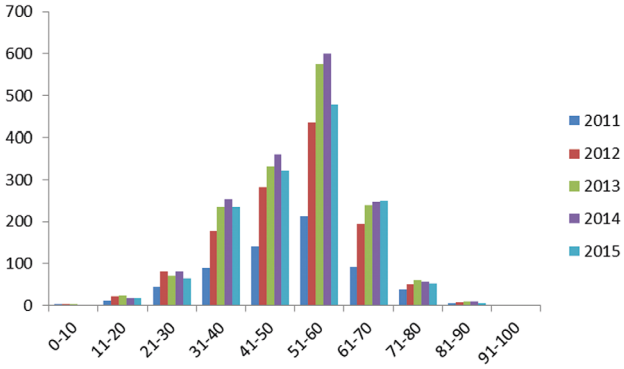

Figure 3. The number of spinal MRI tested patients in 10 age ranges from 2011 to 2015. Source: University Clinical Hospital in Olsztyn.

spinal MRI tests the least numerous group was 0–10 years old (patients 90–100 years old were absent), whereas the most numerous age range was 50–61 years for the whole 5-years as well as for each single year. In this group the number of patients has increased by 2014 (Figure 3). The results show that more women than men were enrolled in all MRI examinations during the 5 years. Women represented over 60% of the population both in the all MRI

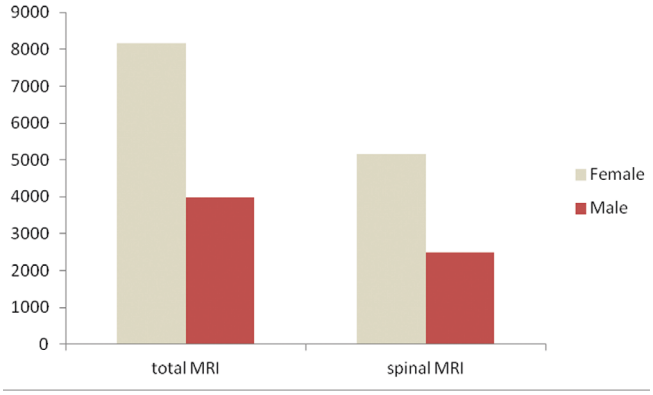

Figure 4. Female and male patients in total MRI scans and spinal MRI scans. Source: University Clinical Hospital in Olsztyn.

Table 3. Percentage of female and male patients scanned in all MRI tests and spine MRI tests from 2011 to 2015.

	All MRI tests		Spine MRI tests	
Year of tests	Female	Male	Female	Male
2011	60.78	39.22	61.57	38.43
2012	61.54	38.46	62.51	37.49
2013	61.20	38.80	61.72	38.28
2014	61.77	38.23	61.43	38.57
2015	60.93	39.07	60.51	39.49
2011–2015	61.29	38.71	61.52	38.48

and in selected spinal tests. The same proportion was observed in the most numerous age range group of 51–60 (Figure 4; Table 3).

4.2. Details of analyzed diseases

The analyzed digital database provided information about presumed diseases ascribed to the patients according to ICD-10 codes. In the investigated period of time most of the diseases included in ICD-10 have been distinguished. Diseases of the musculoskeletal system and connective tissue (M category; M00-M99) were the most frequent in each year and in the whole period of time.

In the whole M category only dorsopathies (M40–M51) were selected for detailed analysis. The database provides two types of ICD-10 codes, i.e. general diseases codes such as M51 and more detailed codes e.g. M51.1. or M51.2.

Results have shown that the most frequently occurring diseases in each year and in the entire 5-year studied period were M47 (spondylosis), M50 (cervical disc disorders) and M51 (other intervertebral disc disorders). Among all spinal diseases they represented over 4%, 12% and 30%, respectively (Table 4). The subject of main interest in the presented study was the most numerous M51 group. In this group all subtypes of diseases classified in ICD-10 such as e.g. M51.0–M51.4 and M51.8–M51.9 were found. The most numerous of them were chosen for detailed analysis in the present study (Table 5).

Intervertebral disc disorders were described in 4095 cases in the entire examined time period and the vast majority was defined by a general code M51 (3262 cases). Very few of the cases had more specific codes and among those the most numerous were M51.1 (lumbar and other intervertebral disc disorders with radiculopathy) represented by 232 cases, M51.2 (other specified intervertebral disc displace-

Table 5. Percentage of M51 category diseases among all spinal diseases 2011–2015.

code	number of cases	percent
M51	3262	79.66
M51.0	16	0.39
M51.1	232	5.66
M51.2	337	8.23
M51.3	212	5.18
M51.4	2	0.05
M51.8	31	0.76
M51.9	2	0.05
total	4095	100.0

Table 4. Percentage of specific M-category diseases in M category of ICD-10.

Percentage of disease codes [%]	2011	2012	2013	2014	2015	2011–2015
M40	0	0.00	0.00	0.13	0.07	0.05
M41	0.14	0.04	0.17	0.16	0.18	0.14
M42	0.16	0.04	0.03	0.03	0.00	0.03
M43	0.07	0.09	0.03	0.03	0.04	0.05
M45	0.00	0.00	0.00	0.06	0.11	0.04
M46	0.00	0.04	0.03	0.00	0.00	0.02
M47	3.81	3.29	3.74	5.38	6.14	4.57
M48	0.00	0.00	0.48	1.34	0.77	0.61
M49	0.14	0.00	0.00	0.00	0.00	0.02
M50	10.88	11.11	13.58	14.40	10.92	12.48
M51	28.90	38.85	25.72	30.33	31.73	30.75

Table 6. Number of M51 categories diseases, 2011–2015.

Types of category M diseases	2011	2012	2013	2014	2015	2011–2015
M51	417	909	839	668	430	3263
M51.1	0	0	44	110	78	232
M51.2	0	0	3	91	236	330
M51.3	0	0	3	64	145	212
Others	0	0	18	19	15	52
All M51 diseases	417	909	907	952	904	4089

ment) represented by 337 cases and M51.3 (other specified intervertebral disc degeneration) represented by 212 cases (table 6). The number of M51 cases showed an increase until 2012 and small fluctuations in the following years. The M51.1, M51.2 and M51.3 cases were observed for the first time in 2013. The number of lumbar and other intervertebral disc disorders with radiculopathy (M51.1) was increasing until 2014 and subsequently decreased in 2015, whereas the number of M51.2 and M51.3 cases was increasing between 2013 and 2015. Others diseases were detected for the first time in 2013 and their number remained similar till 2015.

5. DISCUSSION

5.1. Utility of MRI scanners

Our study shows that utilization of the MRI scanner Magnetom Trio A Tim System 3T in the University Clinical Hospital in Olsztyn gradually increased between 2011 and 2015 and that increasingly more patients have been examined. Reports from the United States have shown that from 1997 to 2005 the importance of the MRI method has increased compared to other techniques such as ultrasound or computer tomography.[6,8] Moreover, MRI utilization rate per 1000 persons has increased in 2000–2009.[8] The results also show that the most numerous age group using MRI tests was 51–60 years old, i.e. similarly to the USA where the most numerous group using MRI was over 45 years old.[6–8] Overall, more women than men were enrolled in all MRI tests in the University Clinical Hospital in Olsztyn and the same pattern was observed in the USA.[6]

The study shows that most of MRI scans were related to musculoskeletal diseases and this finding is consistent with previous data showing that the spinal column is one of the most frequently MRI-scanned parts of the body.[5]

Inspection of the literature also shows that musculoskeletal disorders (MSD) represent one of the most common and most expensive occupational health problems both in developed and developing countries. The database employed in the present study did not provide information about patient's occupations however, other studies have shown that MSD occurs in many professions and is primarily related to physical work. The work-related MSD (WRMD) has been defined as a musculoskeletal injury that results from a work-related event. Some reports have shown that the most frequent among WRMD complaints was the low back pain (26%–70%) and neck pain (12%–34%). In both, healthcare workers like physiotherapists, nurses or dentist, and hand-workers like construction workers, farmers and shipyard workers, the percentage of complaints about any of musculoskeletal disorders was similar (47%–91%).[14–22] Moreover in healthcare workers, the age, sex, years of work and workload had a huge influence on the appearance of the diseases[16–19] and musculoskeletal pain was a risk factor for long-term sickness absence in some of these professions.[16,21]

5.2. Intervertebral disc disorders (M51)

In the present study the intervertebral disc disorders (M51) were the most common diseases found during MRI tests. According to ICD-10 codes, this category includes thoracic, thoracolumbar and lumbosacral disc disorders. M51 was found most frequently at the age of 51–60 years with more cases in women than men. Moreover, three specify codes such as M51.1 – lumbar and other intervertebral disc disorders with radiculopathy, M51.2 – other specified intervertebral disc displacement, and M51.3 – other specified intervertebral disc degeneration were distinguished. The present data does not provide any details about location of damage or level of back pain. The code M51.1 indicates only that changes were on the lumbar level. Most cases reported in the literature describe low back pain related to lumbar and lumbosacral disc disorders[24–26] so all M51 diseases were treated as degeneration at lumbar and lumbosacral levels.

Spinal diseases are a serious social problem. The back pain can be due to various factors and in 90% of patients it is mainly caused by damage or degenerative changes in the intervertebral discs or spondyloarthrosis.[24] The lumbar disc degeneration (LDD) has a broad meaning that encompasses apparent desiccation, fibrosis, narrowing of the disc space, diffuse bulging of the annulus beyond the disc space, defects and sclerosis of the endplates, and osteophytes at the vertebral apophyses.[27,28] Moreover, LDD can be caused by many factors such age, environmental and behavioral influences or genetics.[11–13] Early degenerative changes may be undetectable in MRI image and they could be related to impaired disc metabolism, biochemical changes and many types of disc structural failures.[11]

Symptoms of back problems have been very often described by patients as low-back pain (LBP) and/or sciatica,

such as pain going down the lower limb from the back usually only on one side of the body. In the Unites States, 2% of patients complain about LBP and in 2005 the total health care expenditures related to LBP were estimated at $89 000 000.[24] The relationship between changes detected with MRI of the vertebral column and clinically-manifested changes are of general interest and it is thought that the pain at lumbar or sacral levels strongly correlates with the extent of changes observed in MRI scans.[25]

It is believed that the lumbar part of the vertebral column is less likely to be damaged during an accident than the cervical part. Some studies have shown that only 16%–14% of car accidents cause it[29,30] and that almost all changes in the lumbar part are related to disc degeneration. In Denmark, 36% of changes in the lumbar part of the vertebral column were non-traumatic.[31] In China, the occurrence of non-traumatic lumbar disc damage has doubled in 20 years.[26]

Moreover, each level of lumbar inter-vertebral discs shows a different vulnerability to injuries and diseases. Specifically, changes consequent to injuries and/or diseases are very often observed at the cartilage endplate at the L1–L3 level but are less common at the upper level of lumbar vertebrae (L1–L3).[32] Notably, very often more than one of lumbar inter-vertebral disc is affected by morphological changes.[33]

In previous studies, the most numerous changes were typically observed in the L4–L5 and L5–S1 inter-vertebral discs and the most frequently found changes were due to herniation, dehydration and decreased disc height.[25,26,33–36] All changes at lower lumbar levels appear to correlate with the age and body mass index, which are well-recognized risk factors for LDD.[32]

In Poland, lumbar changes were observed at each stage of the development.

6. CONCLUSIONS

The increase in the number of MRI tests indicates a high demand for MRI scanners in the Warmia and Mazury Province. The most commonly affected is the working-age population indicating the importance of early checkups and prevention of the vertebral column diseases during younger age. The intervertebral disc disorders are also likely associated with the type of profession and work.

It would therefore be valuable to add to the public health policies, a model of spinal health education and vertebral column disease prevention starting from the school age and run through the retiring age, finding problems before they start. The prevention model would include vertebral column examinations followed by recommendations of a corrective gymnastics and/or physiotherapy when early indications of existing or potential pathological changes are noticed, and it could be implemented as a routine component of a regular health exams and tests.

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Original article

Application of MRI for diagnosis of selected diseases and disorders in patients admitted to the teaching hospital in Olsztyn

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ABSTRACT

Introduction: Early and accurate identification of diseases and disorders is critical for patients and medical staff. Magnetic resonance imaging (MRI) offers a wide range of diagnostic applications to fulfill these expectations.

Aim: This study aimed to determine the incidence of selected diagnoses and evaluate the population of patients examined with an MRI during the years 2011–2015 at the University Clinical Hospital in Olsztyn (UCH).

Material and methods: The retrospective analysis of 5587 MRI scans and 5454 patients diagnosed in the MRI Laboratory at UCH was performed. Disease categories were assigned according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10). SPSS software was used to determine the incidence of specific diagnoses and descriptive variables of the studied population.

Results and discussion: More women (61%) than men (39%) were enrolled, and the diseases of the nervous system (G-letter-coded category) were predominant with one-third of patients presenting with nerve root and plexus disorders. Benign neoplasms of the nervous system were also diagnosed, but those results are beyond the scope of this article. Among symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified mostly dizziness and giddiness were found, and injuries and consequences of external causes included mostly dislocations, sprain and strain of joints and ligaments of knee.

Conclusions: The total number of MRI-diagnosed females was higher in all disease categories and age-groups, with the exception of young- and middle-aged adults 31–60 years of age in the category of injuries and consequence of external causes.

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1. INTRODUCTION

Magnetic resonance imaging (MRI) is a noninvasive and safe medical technique, generating a large volume of data over a short period of time.[1] During the last decade, the most popular examination areas included the spine and head. Those scans make up more than 50% of all studies.[2] The most commonly applied MRI technique was concerned with the central nervous system (CNS), backbone and spine disorders, disorders of the extremities and cardiovascular system diseases.[3,4] At emergency departments, often nearly half of all the scan numbers are performed for a head diagnostic.[5] The MRI application is most beneficial in brain and spinal examinations for both adult and pediatric patients. The benefits of MRI scanning are mostly confirmed in the head, neck, abdomen, pelvis, chest and breast areas, the musculoskeletal system and prenatal diagnostics.[6]

When compared to computed tomography (CT), MRI shows more anatomic details of the nervous system, which makes it a great tool for the examination of abnormalities and disorders of the CNS. In traumatic joint injuries, the traditional methods of diagnostics such as physical examination and X-ray may be insufficient, whereas MRI provides excellent spatial and contrast resolution of the intra- and extra-articular anatomical structures.[7] MRI is also a method of choice in examinations of knee injuries and it is mostly preferable in diagnostics of meniscal and cruciate ligaments of the knee.[8] Traumatic injuries of the knee joint are very common. In many sport disciplines, injures of the lower limb occur in more than 50% of all cases, with the most common injury sites being the knee, ankle and thigh.[9]

It has been suggested that the aging of society significantly increases the use and costs of high-technology diagnostic tools such as CT and MRI; not all authors, however, agree with that statement.[10] The general trend shows the increasing use of advanced imaging technologies in patients 55–64 years of age,[11] and it has also been noticed that female patients participated in advanced imaging diagnostics more than males.[10]

2. AIM

The aim of the present study was to determine the incidence of the most common MRI applications in selected diagnostic categories and evaluate the population of patients examined with a Siemens Magnetom Trio A Tim System at the University Clinical Hospital in Olsztyn (UCH) between 2011 and 2015.

3. MATERIAL AND METHODS

The study population included patients examined by the Siemens Magnetom Trio A Tim System MRI scanner at the UCH during the years 2011–2015. The age of the studied population ranged from 2 to 92 years of age, and included 61% women and 39% men. The data was collected at the MRI Laboratory of the UCH. Specific diagnoses, number of scans, number of patients, and patient characteristics were analyzed in three categories of diseases: diseases of the nervous system (G), symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (R), as well as injures and consequences of external causes (S).

Methodology of the diagnosis and patients coding procedure as well as the data processing were described in the previous paper.[12] The χ^2 test was used to determine the level of significance in chosen areas if the number of observations was more or equal to 5 in each group.

4. RESULTS

Overall, 13 298 MRI scans were conducted between the years 2011–2015. In total, 58% of all visits were diseases of the musculoskeletal system and connective tissue in the M-letter-coded category according to ICD-10. The other most frequently represented disease categories were G – diseases of the nervous system; C and D – neoplasms; R – symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified and S – injuries and consequences of external causes. The representation of subgroups in the total number of visits is shown in Table 1. The M category data has been excluded, and the number of 5587 visits and 5454 patients has been extensively analyzed. Disease categories C and D were not closely analyzed in this particular study.

In the analyses presented below, the frequency of the chosen diagnoses excluding M, and with the cumulative number of patients with rare diagnostic codes as 'other' are shown. Table 2 shows the number of patients with a G, R, or S diagnosis in the context of gender and age. The S diagnosis was connected with males in the age range of 31–60 who had injuries. In the remaining subgroups, the number of female patients were larger than number of male patients. The total number of male patients was higher than the total number of female patients in the S subgroup.

The R-subgroup is a very heterogenic category including symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99), and the S-subgroup includes injury, poisoning and certain other consequences of external causes (S00–S99). The category 'other' summarizes rare diagnoses A, B, E, F, H, I, J, K, L, N, Q, T and Z. The χ^2 test showed statistically significant differences in diagnostic distribution in females and males aged 31–60 in comparison to the left over subgroups.

The annual distribution of patients with an MRI-diagnosed disease in the study period is shown in Table 3. The number of patients diagnosed with the G code showed the same trend as the observed numbers of examinations, which means that an increase in the number of examinations was paralleled by an increase in the number of patients with G-diagnoses. The number of patients with R and S diagnostic codes showed fluctuations not connected with an increase or decrease in performed MRI scans.

Table 1. Number of MRI examinations during the 5-year period 2011–2015.

Group of diagnoses	M	C	D	G	R	S	Other	Total
Number of visits	7711	118	722	2903	487	340	1017	13298
[%]	58.0	0.9	5.4	21.8	3.7	2.6	7.6	100

Source: MRI Laboratory, University Clinical Hospital in Olsztyn 2011–2015.

Table 2. Number of patients with G, R, S ICD-10 diagnosis codes during the 5-year MRI utilization of 2011–2015.

Age range	Gender	G	R	S	Total
≤30	Females	85	13	26	177
	Males	74	6	16	162
31–60[a]	Females	1401	236	107	2394
	Males	749	123	146	1477
≥61	Females	350	69	25	783
	Males	197	35	18	461
Total	Females	1836	318	158	3354
	Males	1020	164	180	2100
Total		2856	482	338	5454

Source: MRI Laboratory, University Clinical Hospital in Olsztyn 2011–2015. Comments: [a] $P < 0.05$.

Table 3. Annual number of MRI examined patients between 2011–2015.

Year	G	R	S	Total	Average	Median	SD
2011	359	125	79	707	141	103	112
2012	569	77	32	897	179	77	199
2013	732	109	92	1665	333	170	263
2014	647	69	78	1120	224	158	215
2015	549	102	57	1065	213	164	175
Total	2856	482	338	5454	1091	792	911

Source: MRI Laboratory, University Clinical Hospital in Olsztyn 2011–2015.

Specific diseases and health disorders diagnosed with MRI in the years 2011–2015 are described below.

4.1. MRI in the diagnosis of the nervous system (G00–G99)

Within the diseases of the nervous system, 126 individual diagnostic codes belonging to 11 categories were recorded in a group of 2856 patients (Table 2), and 2903 MRI scans were collected (Table 1) which constituted 21.8% of the total number of examinations. In the G-letter-coded category, the most frequently diagnosed were episodic and paroxysmal disorders, nerve, nerve root and plexus disorders, other disorders of the nervous system, and there were significant differences in the numbers of female and male patients. The most frequently diagnosed specific disease types were nerve root and plexus disorders (G54–G54.9), with the total number of patients being $n = 869$ (Table 4), which represented 30.4% of all patients in the G-letter-coded category (Figure 1). Figure 2 shows the cumulative number of patients in the context of age and gender.

4.2. MRI in the diagnosis of the symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)

In the symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified category, 26 individual codes belonging to 8 categories were recorded in a group of 482 patients (Table 2), and 487 MRI scans were collected (Table 1). Figure 3 shows the cumulative number of patients in the context of age and gender.

In the R-letter-coded category, the most frequent diagnosis in both females and males were two subgroups including symptoms and signs involving cognition, perception, emotional state and behaviour (R40–R46) and general symptoms and signs (R50–R69). The most common specific diagnosis in the category of symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified were dizziness and giddiness (R42); which was found in 205 patients (42.5% of all patients in the R category) as shown in Table 4, Figure 1.

Table 4. G, R, S ICD-10 diagnosis codes in the context of demographic characteristics of the MRI diagnosed population between 2011–2015.

	Females				Males				Total
	≤30	31-60	≥61	Total	≤30	31-60	≥61	Total	
Diseases of nervous system (G)									
G54–G54.9	5	417	101	523	5	263	78	346	869
G44–G44.8	33	362	79	474	13	119	30	162	636
G40–G40.9	18	155	14	187	25	102	7	134	321
G93–G93.9	6	92	31	129	5	34	14	53	182
G94–G94.8	7	74	20	101	8	56	12	76	177
G55–G55.3	1	44	17	62	1	45	11	57	119
G98	0	36	12	48	5	30	8	43	91
G35	0	33	4	37	1	11	1	13	50
G45–G45.9	2	23	10	35	1	9	3	13	48
G96–G96.9	1	23	5	29	2	14	2	18	47
G99–G99.8	3	14	8	25	1	7	1	9	34
Other	9	128	49	186	7	59	30	96	282
Total	85	1401	350	1836	74	749	197	1020	2856
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R)									
R42	3	95	35	133	1	56	15	72	205
R51	5	59	11	75	3	31	7	41	116
R29–R29.8	1	48	8	57	1	16	6	23	80
R10–R10.1	0	19	9	28	0	11	6	17	45
Other	4	15	5	24	1	9	1	11	35
Total	13	236	68	317	6	123	35	164	481
Injuries and consequences of external causes (S)									
S83–S83.7	15	40	7	62	7	63	3	73	135
S06–S06.5	0	4	1	5	2	15	3	20	25
S23	2	9	2	13	1	9	1	11	24
S43–S43.4	1	4	2	7	2	11	3	16	23
S13–S13.4	0	13	2	15	2	2	2	6	21
S46–S46.0	0	4	1	5	0	7	2	9	14
Other	8	33	10	51	2	39	4	45	96
Total	26	107	25	158	16	146	18	180	338

Source: MRI Laboratory, University Clinical Hospital in Olsztyn 2011–2015.

4.3. MRI in the diagnosis of injuries and consequences of external causes (S00–S99)

In the injuries and consequences of external causes category, 58 individual codes belonging to 10 categories were recorded in a group of 338 patients (Table 3), and 340 MRI scans were collected (Table 1). Figure 4 shows the cumulative number of patients in the context of age and gender. In this disease group, male patients were more frequently diagnosed with limbs and head injuries. Patients under 40 years of age were predominantly diagnosed with injuries of the head and with injuries of the knee and lower leg, whereas in the category of injuries of the shoulder, upper arm and thorax, a larger number of patients 51–60 years old were recorded. Injuries of the elbow and forearm were typical for male patients and injuries of the hip, thigh, wrist and hand were typical for female patients.

The most frequent specific diagnose types were dislocation, sprain and strain of joints and ligaments of the knee (S83–S83.7), with the total number of patients being $n = 135$ (Table 4), which represented 39.9% of all patients in the S-letter-coded category (Figure 1).

5. DISCUSSION

There is evidence that early and easy access to diagnostic equipment and physicians' experience have an important impact on the type, frequency and adequateness of diagnostic imaging applications. It has also been shown that the appropriateness of using imaging techniques varies with age,

Figure 1. Percentage of patients with specific diagnose G-, R-, S-letter-coded category during 5-year MRI use. Comments: G54 Nerve root and plexus disorders, G44 Other headache syndromes, G40 Epilepsy, G93 Other disorders of brain, G94 Other disorders of brain in diseases classified elsewhere, G55 Nerve root and plexus compressions in diseases classified elsewhere, G98 Other disorders of nervous system, not elsewhere classified, G35 Multiple sclerosis, G45 Transient cerebral ischaemic attacks and related syndromes, G96 Other disorders of central nervous system, G99 Other disorders of nervous system in diseases classified elsewhere, R42 Dizziness and giddiness, R51 Headache, R29 Other symptoms and signs involving the nervous and musculoskeletal systems, R10 Abdominal and pelvic pain, S83 Dislocation, sprain and strain of joints and ligaments of knee, S06 Intracranial injury, S23 Dislocation, sprain and strain of joints and ligaments of thorax, S43 Dislocation, sprain and strain of joints and ligaments of shoulder girdle, S13 Dislocation, sprain and strain of joints and ligaments at neck level, S46 Injury of muscle and tendon at shoulder and upper arm level.

gender, size, patient's physical limitations, as well as the symptoms and conditions investigated.[6]

Although cardiovascular disorders are commonly diagnosed using MRI and the worldwide literature shows an increased trend of MRI angiography utilization,[13] they were not as frequently diagnosed in our study group as would be expected. The significance of this health problem in the general population was therefore not mirrored in the analysed MRI examinations of our study population. The MRI is considered to be a very useful technique in the diagnosis of cardiac, vessel and visceral organs anomalies,[14] and the development of such MRI applications at the UCH could further benefit its patients.

In the examined population, the number of patients sent for MRI diagnostics due to headache symptoms were appreciable (G44, R51) (Table 4, Figure 1). Some authors suggest that neuroimaging methods should not be routinely ordered in the case of initial reports of headache. This is in contrast to patients with a neoplasm suspicion, vascular malformations, posttraumatic or focal brain lesions; who must be diagnosed with a neuroimaging technique since this could be a life-saving diagnostic application.[15]

The MRI technique provides much more precise data in brain examinations and diagnostics than CT.[16] Furthermore, it shows advantages in acute ischemia and chronic haemorrhage detection. For these reasons, it should be preferred for the diagnosis of suspected acute stroke.[17] MRI has had a major impact on the diagnosis and understanding of multiple sclerosis and it is routinely used in multiple sclerosis diagnostics[18–20] and in epilepsy.[21] Both multiple sclerosis and epilepsy were diagnosed in the studied population.

The analysis of ICD-10 general diagnoses of the S-letter-coded category showed that the most common injures were: the knee and lower limb, shoulder and upper limb and head injuries. The most commonly affected group was males aged 31–60 years. In females, injuries of the ankle and foot, hip and thigh, neck and wrist and hand injuries occurred more commonly than in males (Figure 1, Table 4). According to the National Collegiate Athletic Association, the most common injury sites were the ankle, knee, and lower leg, the most common injury types were muscle strains, ligament sprains, and contusions. Intrinsic risk factors of injury include (among others) age and gender. Their significance may vary depending on the sport discipline and type of injury. The literature also discusses gender differences in the frequency of some specific types of injury by hormonal, anatomical and neuromuscular factors.[9] In the present study, causes of injury were not available in the data source – so the linkage between physical activity or sport disciplines and demographics or injury types and locations could not be identified.

It should be stressed that the present study is based on the data obtained in only one academic teaching hospital, and over a 5-year time period. This did not generate a sufficient volume of data for detailed statistical analyses. It is recommended to continue the analyses for an additional period of 10 to 15 years in order to follow the trends in MRI-diagnosed diseases. However, despite this disadvantage, our analyses provided descriptive statistics which gives important information about the MRI-diagnosed population at the UCH.

6. CONCLUSIONS

Considering the wide range of MRI use in the diagnosis of different diseases and disorders, the analysis presented here of MRI-generated data identifies the most frequent areas of applications of this technique and describes the distribution

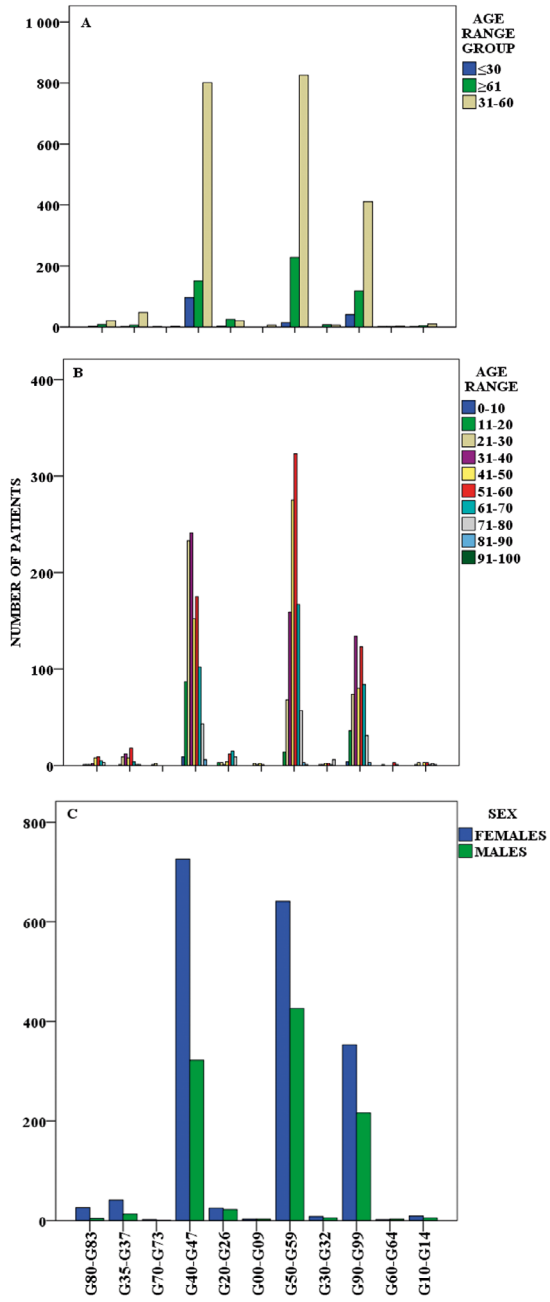

Figure 2. Number of patients age range – A; 10-years intervals – B; gender – C breakdown in relation to the categories of diseases of the nervous system (G) in 5-year period of MRI utilization. Comments: G80-G83 Cerebral palsy and other paralytic syndromes, G35-G37 Demyelinating diseases of the central nervous system, G70-G73 Diseases of myoneural junction and muscle, G40-G47 Episodic and paroxysmal disorders, G20-G26 Extrapyramidal and movement disorders, G00-G09 Inflammatory diseases of the central nervous system, G50-G59 Nerve, nerve root and plexus disorders, G30-G32 Other degenerative diseases of the nervous system, G90-G99 Other disorders of the nervous system, G60-G64 Polyneuropathies and other disorders of the peripheral nervous system, G10-G14 Systemic atrophies primarily affecting the central nervous system.

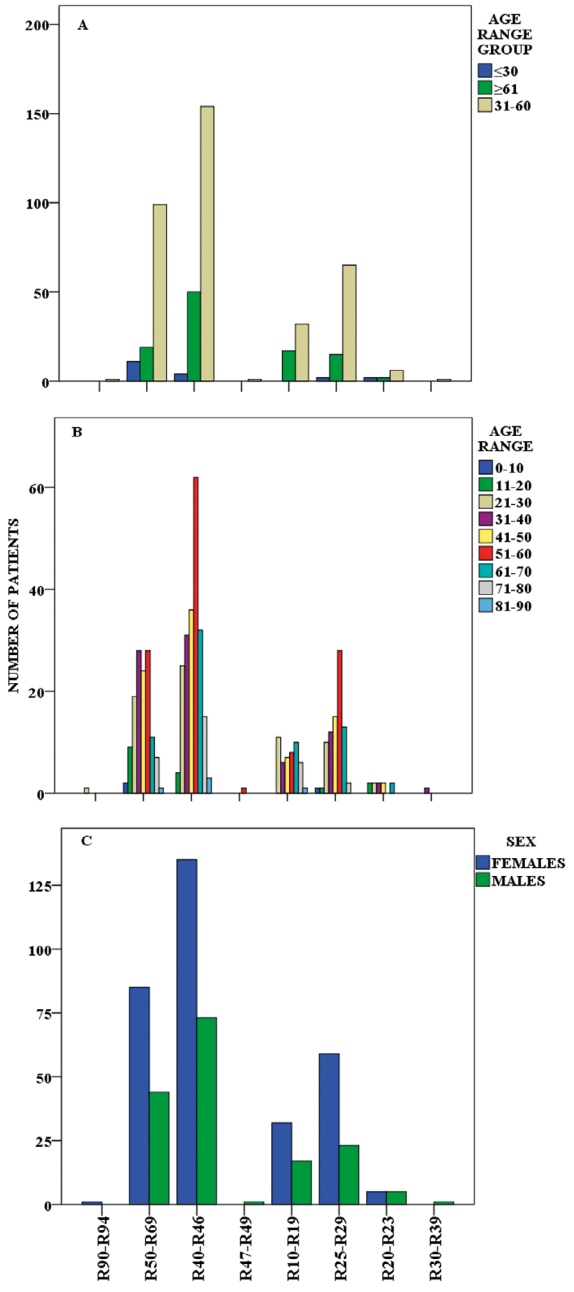

Figure 3. Number of patients with age range – A; 10-years intervals – B; gender – C breakdown in relation to the categories of symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R) in 5-year period of MRI utilization. Comments: R90-R94 Abnormal findings on diagnostic imaging and in function studies, without diagnosis, R50-R69 General symptoms and signs, R40-R46 Symptoms and signs involving cognition, perception, emotional state and behaviour, R47-R49 Symptoms and signs involving speech and voice, R10-R19 Symptoms and signs involving the digestive system and abdomen, R25-R29 Symptoms and signs involving the nervous and musculoskeletal systems, R20-R23 Symptoms and signs involving the skin and subcutaneous tissue R30--R39 Symptoms and signs involving the urinary system.

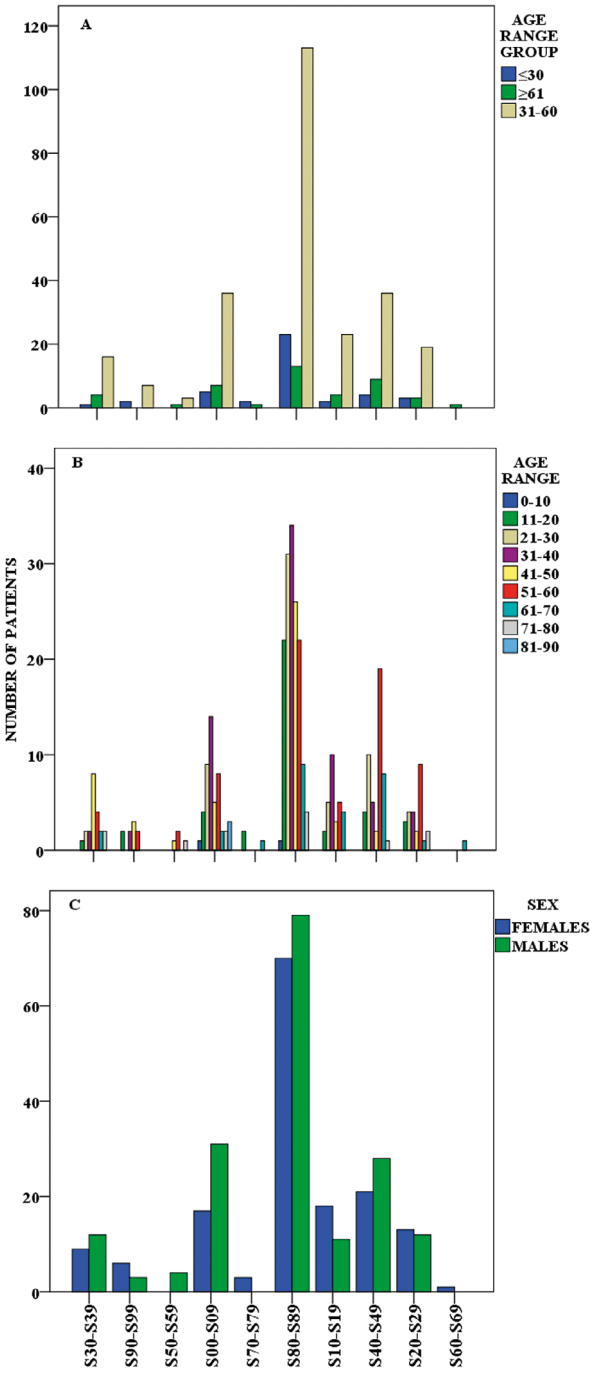

Figure 4. Number of patients with age range (A); 10-years intervals (B); gender (C) breakdown in relation to the categories of injuries and consequences of external causes (S00–S99) in 5-year period of MRI utilization. Comments: S30–S39 Injuries to the abdomen, lower back, lumbar spine and pelvis, S90–S99 Injuries to the ankle and foot, S50–S59 Injuries to the elbow and forearm, S00–S09 Injuries to the head, S70–S79 Injuries to the hip and thigh, S80–S89 Injuries to the knee and lower leg, S10–S19 Injuries to the neck, S40–S49 Injuries to the shoulder and upper arm, S20–S29 Injuries to the thorax, S60–S69 Injuries to the wrist and hand.

of patients within the specific disease subgroups. The total number of MRI-diagnosed females was higher in all disease categories and age-groups with the exception of young- and middle-aged adults 31–60 years of age with externally caused injuries.

Conflict of interest

The authors declare no conflict of interest.

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Original article

SCN1A gene variations in epilepsy and migraine patients in Aceh, Indonesia

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ABSTRACT

Introduction: Mutation of the sodium voltage-gated channel alpha subunit 1 (*SCN1A*) gene is an important cause of genetic epilepsy and familial hemiplegic migraine. However, data related to genetic variations of *SCN1A* in Indonesia are limited.

Aim: To identify *SCN1A* gene variation in idiopathic epilepsy and common migraine patients in Aceh province, Indonesia.

Material and methods: A case-control study was conducted at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia from 1 March to 30 August 2015. Gene variation analysis of exon 26 of the *SCN1A* gene was conducted in 33 patients with idiopathic epilepsy, 33 patients with common migraine and 30 controls using polymerase chain reaction and direct sequencing.

Results and discussion: *SCN1A* gene variations were identified in two partial secondary generalized epilepsy patients. In 1 patient, four silent mutations at nucleotide positions A4440T (Leu1480Leu), T4443C (Leu1481Leu), A5046G (Leu1682Leu) and C5121T (Asn1707Asn) were identified. One silent mutation at position G5505A (Glu1835Glu) was found in another patient. No gene variation was identified among controls and common migraine patients.

Discussion: This study is the first report on genetic variations of the *SCN1A* gene in adult patients with idiopathic epilepsy and common migraine in Indonesia. However, the association between these genetic variants and epilepsy needs to be clarified.

Conclusions: Five genetic variations in exon 26 of *SCN1A* were identified in 2 patients with partial secondary generalized epilepsy in Aceh, Indonesia.

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1. INTRODUCTION

Voltage gated sodium channels (NaV) are essential for the generation of neuron excitability. These channels are the target of antiepileptic drugs, and mutations of their genes are responsible for genetic epilepsy.[1] Sodium voltage-gated channel alpha subunit 1 gene (*SCN1A*), which encodes the alpha subunit of the sodium channel termed NaV1.1, is one of the most clinically relevant epilepsy genes with hundreds of identified mutations. Genetic variations in *SCN1A* have been reported to be associated with epilepsy syndromes characterized by various phenotypes including generalized epilepsy with febrile seizure plus (GEFS+),[2] Dravet syndrome,[3–5] severe myoclonic epilepsy in infancy (SMEI),[6,7] intractable childhood epilepsy with generalized tonic-clonic seizures (a variant of Dravet syndrome without myoclonus)[8] and cryptogenic epilepsy.[9]

Mutations of the *SCN1A* gene are also associated with familial hemiplegic migraine (FHM).[10–12] FHM is a rare severe autosomal dominant inherited subtype of migraine with aura characterized by hemiparesis during the attacks. Several missense substitution mutations have been identified to be associated with FHM subtypes, these include pure FHM, migraine with or without aura, and mixed phenotypes with seizures and migraine.[13] At least five mutations in the *SCN1A* gene have been identified in individuals with FHM-type III.[13] Each of these mutations changes a single protein building block (amino acid) in the NaV1.1 channel, which alters the structure of the channel.[13] This increases the flow of sodium ions into neurons and triggers the cell to release more neurotransmitters.[13]

Although several studies have been conducted to identify variations of the *SCN1A* gene among epilepsy and migraine patients from different countries, no research has been conducted in Aceh province, Indonesia. Therefore, this study sought to provide data from Indonesia regarding *SCN1A* gene variations in epilepsy and migraine patients.

2. AIM

This study was conducted to identify variations of the *SCN1A* gene among patients with idiopathic epilepsy and common migraine in Aceh, Indonesia.

3. MATERIALS AND METHODS

3.1. Ethical approval

The protocol used in this study was approved by the Ethics Committee of the Faculty of Medicine, Sumatera Utara University, Medan, Indonesia in compliance with the national legislation and the code of ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki, No. 131/KOMET/FK USU/2015). Written informed consent was obtained from each subject prior to enrolment. Participation in this study was voluntary, and no incentives were provided.

3.2. Study setting and subjects

A case-control study was conducted at the Neurology Polyclinic of the Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia from 1 March to 30 August 2015. The cases were adult patients with confirmed idiopathic epilepsy (generalized or partial) and common migraine patients, while controls were healthy individuals or patients with mild traffic accident injuries. Diagnosis and classification of epilepsy and migraine were conducted based on criteria of the International League Against Epilepsy (ILAE)[14,15] and International Classification of Headache Disorders (ICHD),[16] respectively. Epilepsy patients who were unable to communicate appropriately due to other underlying clinical problems, such as mental retardation, aphasia or dementia, were excluded. Upon admission, demographic data, clinical signs and symptoms and neurologic status were assessed and venous blood samples were collected under hospital Standard Operation Procedures. The blood samples were kept at –20°C until analyzed.

3.3. DNA extraction and SCN1A genotyping

DNA extraction was carried out at the School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia as described previously.[17] Amplification of exon 26 of the *SCN1A* gene was conducted at the Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia. The sequencing of amplified gene was conducted in 1st BASE Pte. Ltd. Laboratory, Singapore, with the same platform as described previously.[18] Briefly, DNA from peripheral blood leukocytes was extracted using a Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA). Exon 26 of *SCN1A* was amplified by polymerase chain reaction (PCR) using three pairs of primer (Table 1). The length of amplicon of fragments A, B and C were 587, 470 and 593 base pairs, respectively. Amplification was performed for 35 cycles (denaturation at 95°C for 1 minute, annealing at 60°C for 2 minutes and extension at 72°C for 1 minute) in a total 30 μL PCR mixture containing 2 μL DNA template, 15 μL PCR Master MixGo Taq Green Promega (1X buffer PCR, 150 nM dNTP, and 0.5 U Taq DNA polymerase) (Promega, Madison, WI, USA), 11 μL nuclease free water, and 2 μL primer mix (1 μL forward primer and 1 μL reverse primer). PCR products

Table 1. The primers used to amplify exon 26 of the *SCN1A* gene.

Fragment	Forward (5' to 3')	Reverse (5' to 3')
A	AGGACTCTGAACCTTACCTTG	TACATGTTCACCACAACCAGG
B	TAACCCTGGAAGCTCAGTTAA G	TGATTGGCTGATAGGAGACCTT
C	TTGCTTTTACAAAGCGGGTTCT	GTTTGCTGACAAGGGGTCAC

Table 2. Subject characteristics of patient and control groups.

Characteristics		Epilepsy $n = 33$		Migraine $n = 33$		Control $n = 30$		P value*
		n	%	n	%	n	(%)	
Age group	< 20 years	7	21.21	4	12.12	2	6.67	0.001*
	21–30 years	13	39.39	3	9.09	4	13.33	
	31–40 years	8	24.24	12	36.36	11	36.67	
	41–50 years	5	15.15	10	30.30	9	30.00	
	> 50 years	0	0.00	4	12.12	4	13.33	
Gender	Male	17	51.52	6	18.18	18	60.00	0.002**
	Female	16	48.48	27	81.82	12	40.00	
Education	Primary or junior high school	5	15.15	7	21.21	4	13.13	0.292**
	Senior high school	21	63.64	10	30.30	14	46.67	
	University diploma degree	2	6.06	6	18.18	3	10.00	
	University graduate or higher	5	15.15	10	30.30	9	30.00	
Occupation	Civil servant	3	9.09	9	27.27	13	43.33	0.001***
	Entrepreneur	7	21.21	8	24.24	10	33.33	
	University student	12	36.36	5	15.15	3	10.00	
	Housewife	5	15.15	11	33.33	4	13.33	
	Unemployment	6	18.18	0	0.00	0	0.00	
Ethnic	Acehnese	29	87.88	29	87.88	30	100.00	0.294***
	Non-Acehnese	4	12.12	4	12.12	0	0.00	

Comments: * Calculated using Mann-Whitney test, * Calculated using χ^2 test, * Calculated using Likelihood ratio.

were electrophoresed through ethidium bromide-stained 2% agarose gels. The PCR products were then sequenced using a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) on an ABI PRISM 3730xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions.

3.4. Statistical analysis

Differences in distributions of the data between case and control groups were analyzed using the Mann-Whitney test, χ^2 test, or likelihood ratio as appropriate for the type of data. Two-sided testing was employed and $P \leq 0.05$ was designated statistically significant. The data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows v. 15, Chicago, IL).

4. RESULTS

In this study, the exon 26 of the *SCN1A* gene of 33 idiopathic epilepsy patients (4 generalized epilepsy and 29 partial secondary generalized epilepsy), 33 common migraine patients (16 migraine without aura and 17 migraine with aura) and 30 control individuals was analyzed. The characteristics of each of the patient groups and the control group are presented in Table 2. Clinical characteristics of the epilepsy and migraine groups are presented in Table 3.

Five gene variations in exon 26 of the *SCN1A* gene were identified in 2 epilepsy patients. Four gene variations were identified in a 32-year-old male with partial secondary gener-

Table 3. Characteristics of migraine and epilepsy groups.

Case	Characteristics	n	%
Migraine			
	Aura		
	With aura	17	51.52
	Without aura	16	48.48
	Headache attacks		
	Less than 12 days per year	3	9.09
	12-180 days per year	30	90.91
Epilepsy			
	Type of seizure		
	Partial seizures evolving to secondarily generalized seizure	29	87.88
	Generalized seizure	4	12.12
	Frequency of seizure		
	1-11 seizures per year	23	69.70
	Frequent seizure	10	30.30
	Aura		
	With aura	20	60.61
	Without aura	13	39.39
	Interictal EEG		
	Abnormal	21	63.64
	Normal	10	30.30
	Not available	2	6.06
	Level of stigma		
	Mild	4	12.12
	Moderate	29	87.88

alized epilepsy, and a single gene variation was identified in a 19-year-old female with partial secondary generalized epilepsy. The 4 variations in the first patient were mutations at nucleotide positions 4440, 4443, 5046 and 5121 causing silent mutations at codons 1480 CTA→CTT (Leu1480Leu), 1481 CTT→CTC (Leu1481Leu), 1682 CTA→CTG (Leu1682Leu) and 1707 AAC→AAT (Asn1707Asn), respectively (Figure 1A–C). In the second patient, a silent mutation at position 5505 causing a silent mutation at codon 1835 GAG→GAA (Glu1835Glu) was identified (Figure 1D). No gene variations were identified among the common migraine patients or controls.

5. DISCUSSION

This study is the first report on genetic variations of the *SCN1A* gene in adult patients with idiopathic epilepsy and common migraine in Indonesia. We found 5 silent mutations that were spread throughout exon 26 of the *SCN1A* gene in 2 epilepsy patients. Several studies have been conducted to show that *SCN1A* mutations are associated with epilepsy[3–9] and migraine.[10–12] More than 100 epilepsy-associated mutations spread throughout the *SCN1A* gene have been reported.[19] A study found that 14.66% of 150 Italian pediatric probands with epilepsy carried *SCN1A* gene mutations.[2] Another study identified *SCN1A* mutations in 24 out of 29 patients with SMEI.[20] In this study, we found that 6.60% (2/33) of idiopathic epilepsy patients carried *SCN1A* gene variations, and none of the common migraine patients had gene variations.

Previously, a study in Indonesia identified 2 novel *SCN1A* mutations in Indonesian children with SMEI and borderline SMEI (SMEB).[7] These mutations were located at nucleotide 4834 (c.4834G>A) in exon 25 leading to substitution of valine with isoleucine at amino acid position 1612 (p.V1612I), and at nucleotide 5266 (c.5266T>G) in exon 26 leading to substitution of cysteine with glycine at amino acid 1756 (p.C1756G).[7] In our study, *SCN1A* gene variations were identified at exon 26 in 2 patients with partial secondary generalized epilepsy. The variations were 4 silent mutations at nucleotide positions A4440T (Leu1480Leu),

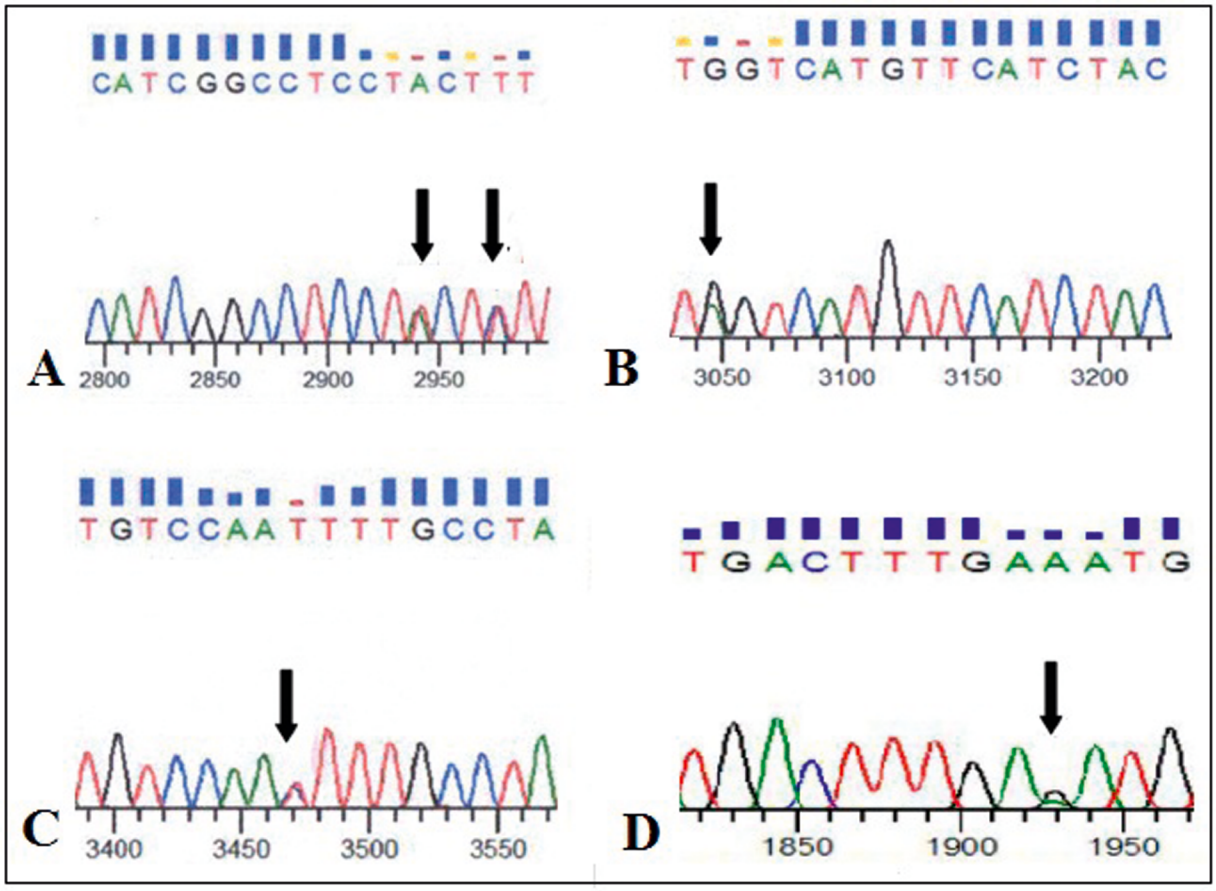

Figure 1. Sequencing electropherogram of *SCN1A* genetic variations in two patients: (A) The arrows show the genetic variations in the first patient at nucleotide positions 4440 and 4443 causing silent mutations at codons 1480 CTA→CTT (Leu1480Leu) and 1481 CTT→CTC (Leu1481Leu), respectively. (B–C) The arrows show the genetic variations in the first patient at nucleotide positions 5046 and 5121 causing silent mutations at codons 1682 CTA→CTG (Leu1682Leu) and 1707 AAC→AAT (Asn1707Asn), respectively. (D) The arrow shows genetic variations at nucleotide position 5505 causing a silent mutation at codon 1835 GAG→GAA (Glu1835Glu) in the second patient.

T4443C (Leu1481Leu), A5046G (Leu1682Leu) and C5121T (Asn1707Asn) in patient 1 and a silent mutation at position G5505A (Glu1835Glu) in patient 2. To the best of our knowledge, these variations have never been reported in Indonesia.

Interpretation of genetic results is challenging, especially in multifactorial diseases, such as epilepsies and the common migraine. Our study was unable to determine the association between these genetic variations and epilepsy for several reasons. First, the sample size in this study was relatively small. Second, the identified genetic variations were silent mutations that produced the same amino acid and therefore might not effect NaV1.1 channel configuration and function. Lastly, unlike some disorders where mutations are largely concentrated in 'hot spots' within the gene, mutations within *SCN1A* are widely distributed throughout the gene.[19,21] In this study, we did not investigate the genetic variations that might have existed within other exons. Therefore, the association of genetic variations in other exons with epilepsy needs to be further clarified.

6. CONCLUSIONS

For the first time, this study has identified five genetic variations of SCN1A in 2 patients with partial secondary generalized epilepsy in Aceh, Indonesia. No genetic variation of the SCN1A gene was identified in common migraine patients.

Conflict of interest

None declared.

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Original research article

Influence of myofascial taping application on postural stability in adolescents with pain in the anterior joint of the knee

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ABSTRACT

Introduction: Regardless of the cause of pain in the anterior joint of the knee, therapeutic possibilities aside from kinesitherapy also include myofascial applications using Flexotape tape.

Aim: The aim of the research is to analyze the postural stability of the lower limbs after the application of myofascial taping (Flexotape) for pain in the knee joints.

Material and methods: Seventeen patients with pain in the anterior compartment of the knee at age 13–17 were enrolled in the study. A two-plate posturograph CQW2P-vUSB consisting of two platforms with embedded sensors was used for the measurements. The first test was performed without the application of taping. The second examination was performed directly after applying the application and the third test was half an hour after applying the taping. The Flexotape application was placed in the area of the strainer fascia of the broad, painful lower limb.

Results: The total length of the statokinesiogram (SP_EO) path counted in both axes does not change during the tests. The attached taping application does not affect the change of the statokinezjogram (SA_EO) surface area and the mean deflection of the foot pressure center in the direction of the AP axis. However, it has a statistically significant effect at the level of $\alpha = 0.01$ for the deflection of the foot pressure center in the direction of the ML axis.

Discussion: The present study shows that stretching and the selective work of muscle strengthening is not sufficient to improve the function of the lower limb with pain symptoms. The use of myofascial taping as a support in the process of rehabilitation seems to be the most justified, because its impact on the fascial system can affect the reduction of pain and improve the stability of the lower limb.

Conclusions: The Flexotype application improves the average deflection of foot pressure only in the frontal plane. The other parameters of postural stability remain unchanged. The application used in this study does not reduce the pain.

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1. INTRODUCTION

Ailments of anterior knee joint pain in adolescents relate to a significant group of patients who apply to orthopedic and rehabilitation clinics. The etiology of pain is often not conclusive. Many studies indicate a complex problem resulting from patellar patency, patellar instability, abnormalities in the lower limbs, asymmetry of the pelvis, low motor activity or excessive loads resulting from practicing sports.[1–5] Patients who have been qualified for conservative treatment after the diagnosis are being subjected to physiotherapy. The use of modern physiotherapeutic methods based on detailed diagnostics allows patients to quickly return to functioning in daily life without any ailments.[6–8] One of the methods used in this case is myofascial taping with the use of Flexotape tapes, where the goal is to regulate myofascial tone to obtain better stability within the application and to reduce pain.[9,10] In recent years, methods of supporting rehabilitation have been widely disseminated. These methods include Kinesiology Taping. The methodology is based on the use of Kinesiotape tapes, which are made of cotton and have an extensibility approximating the flexibility of the muscles. The methodology of the application depends on the patient's needs. Through appropriate applications, it can affect the skin, muscles, joints and lymphatic system.[11–13] Variations of the taping are spreading relatively quickly. Myofascial taping (flexotaping) is becoming more and more popular, the assumptions of which are derived mainly from the theory of Tensegrity, or the use of anatomical tapes. The method of gluing is based on the anatomical patterns of the muscle chains. The applications are glued on stretched myofascial structures.[9,10] The composition of the cotton adhesive tape is different and it has greater extensibility than the tapes used for kinesiotaping. So far, there are no studies that provide specific information about the effects of myofascial taping (flexotaping). Therefore, an attempt was made to analyze postural stability after applying flexotaping.

2. AIM

The aim of the study is to analyze postural stability after application of the myofascial taping (Flexotape) for knee joint ailments.

3. MATERIAL AND METHODS

Seventeen patients (aged 13–17) with pain in the anterior compartment of the knee were enrolled in the study. The methodology used a two-plate posturograph CQW2P-vUSB, which consists of two platforms with embedded sensors. The platforms were connected via a USB connection to a computer that records all data in real time. The apparatus used during the study has a specification and appropriate standards for the use of this type of equipment.[14–16] The patients were examined without shoes, in a free-standing position with the head set in a straight line and with the eyes focused at one point, and then with eyes closed. Upper limbs were laid freely along the torso. The apparatus was reset before each test (Figure 1).

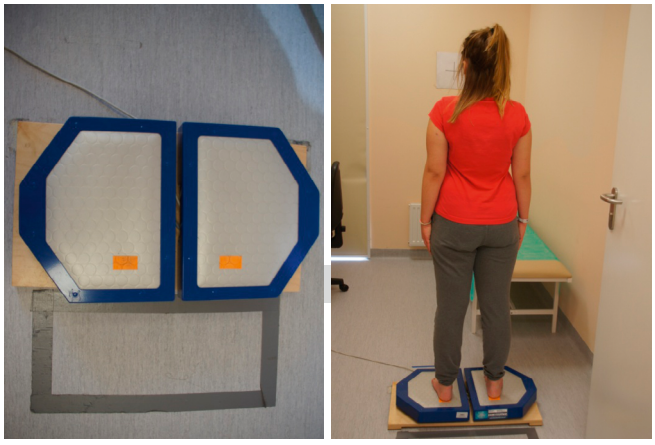

Figure 1. 2-plate posturograph and examination of the patient in a standing position.

Three parts of the study were planned for the analysis of postural stability: (1) without the flexotape application, (2) directly after the application of the Flexotapping, and (3) 30 minutes after the application of the taping. Three parts of the study were carried out with eyes opened and closed. Each part of the study was carried out using identical procedures. First entry into a 2-plate posturograph: eyes opened, 15 s of adaptation to the tested position, 30 s of proper examination, descent from 2-plate posturograph to a designated rectangle. Second entry: eyes closed from the moment of setting the feet on the platforms and repeating all activities from the first part of the test. The Flexotape application was placed in the area of the wide fascia stretcher of the painful lower limb, according to the myofascial taping methodology. To attach the tape, the patient was placed on a healthy side, positioning the painful lower limb in the abduction, bent at the hip and knee joint at a 90°. The tape was glued at a height of 5 cm from the popliteal perimeter along the ilium-tibial band towards the greater trochanter. The length of the first application was 15–20 cm with a tension of about 70%. The second tape was glued from the end of the first application laterally towards the anterior hip spine on the iliac crest with an average length of 15 cm and a stretch of 70% (Figure 2).

Figure 2. Application of taping to the area of the limb wide fascia stretcher affected by pain in the area of the front compartment of the knee.

In addition, the subjective pain perception of the patient was analyzed using a numerical rating scale (NRS) before application and 30 minutes after applying the taping.

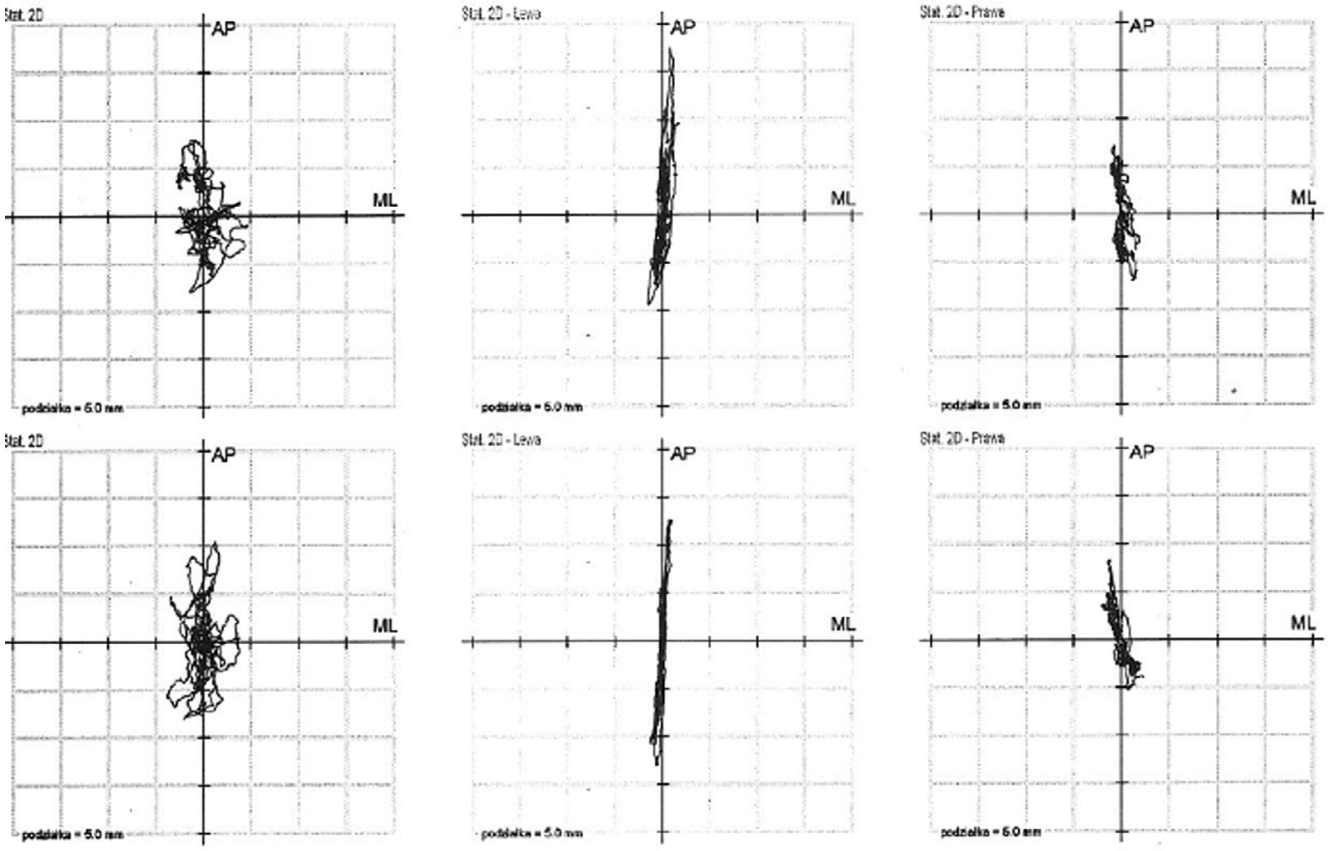

Figure 3. An exemplary graph of the 2-plate posturograph test result.

4. RESULTS

In the statistical analysis, the student's t-test was used to analyze the mean values of the total statokinesiogram path, center of pressure (CoP) surface area, mean values of the foot pressure from the point O towards the anterio-posterio axis (AP) and the medio-laterale (ML) axis (Figure 3).

In the Student's t-test, hypotheses were put forward: the average value of the analyzed feature does not change depending on the tested foot (Ho), the average value of the analyzed feature changes depending on the tested foot (H1).

The results of the tests are presented in Tables 1–5.

Table 1. The Student's *t*-test results for the total statokinesiogram track counted in both 2D axes (SP-EO).

Feature	SP-EO	Comparison between feet		
Examination number	1	2	3	Total
Degrees of freedom *df*	16	16	16	2
Empirical *t*	3.45	3.12	2.97	1.39
Tabular *t* $\alpha = 0.05$	2.12	2.12	2.12	4.30
Tabular *t* $\alpha = 0.01$	2.92	2.92	2.92	9.92
Conclusion based on $\alpha = 0.05$	reject Ho	reject Ho	reject Ho	accept Ho
Conclusion based on $\alpha = 0.01$	reject Ho	reject Ho	reject Ho	accept Ho

Table 2. The Student's *t*-test results for the size of the surface area of the statokinesiogram defined by the center of gravity (SA_EO).

Feature	SA_EO	Comparison between feet		
Examination number	1	2	3	Total
Degrees of freedom *df*	16	16	16	2
Empirical *t*	1.87	1.68	2.63	1.63
Tabular *t* $\alpha = 0.05$	2.12	2.12	2.12	4.30
Tabular *t* $\alpha = 0.01$	2.92	2.92	2.92	9.92
Conclusion based on $\alpha = 0.05$	reject Ho	reject Ho	reject Ho	accept Ho
Conclusion based on $\alpha = 0.01$	reject Ho	reject Ho	reject Ho	accept Ho

Table 3. The Student's t-test results for mean values of the foot pressure center (MAAP_EC) from point O in the direction of the AP axis.

Feature	MAAP_	Comparison between feet		
Examination number	1	2	3	Total
Degrees of freedom *df*	16	16	16	2
Empirical *t*	3.38	2.95	3.43	1.45
Tabular *t* $\alpha = 0.05$	2.12	2.12	2.12	4.30
Tabular *t* $\alpha = 0.01$	2.92	2.92	2.92	9.92
Conclusion based on $\alpha = 0.05$	reject Ho	reject Ho	reject Ho	accept Ho
Conclusion based on $\alpha = 0.01$	reject Ho	reject Ho	reject Ho	accept Ho

Table 4. The student's t-test results for the mean values of the foot pressure center (MAML_EC) from the point O in the direction of the ML axis.

Feature	MAML_EC	Comparison between feet		
Examination number	1	2	3	Total
Degrees of freedom *df*	16	16	16	2
Empirical *t*	3.00	2.51	2.62	1.18
Tabular *t* $\alpha = 0.05$	2.12	2.12	2.12	4.30
Tabular *t* $\alpha = 0.01$	2.92	2.92	2.92	9.92
Conclusion based on $\alpha = 0.05$	reject Ho	reject Ho	reject Ho	accept Ho
Conclusion based on $\alpha = 0.01$	reject Ho	accept Ho	accept Ho	accept Ho

The analysis of partial variance was used to calculate the subjective pain assessment.

Table 5. Subjective pain assessment according to the NRS scale.

Groups	Number of subjects	Sum	Mean	Variance
Examination 1	17	76	4.47	5.89
Examination 2	17	52	3.06	4.18
Examination 3	17	48	2.82	3.40

Source of variance	SS	*df*	MS	*F*	*P* value	*F* test for $\alpha = 0.05$	*F* test for $\alpha = 0.01$
Between groups	26.98	2	13.49	3.00	0.06	3.19	5.07
Within groups		215.64	48			4.49	
Total			242.63	50			

5. DISCUSSION

The diagnostics and proper selection of therapeutic methods are very important factors to effectively cure patients conservatively. The dynamic development of physiotherapeutic methods allows a wide impact on the musculoskeletal system through selective strengthening exercises, stretching, functional training, and proprioceptive exercises. The modern rehabilitation program in the ailments of the frontal knee includes stretching exercises of the sciatic-tibial muscles, quadriceps, activating the broad fascia muscle, building the axiality of the lower limbs, taking into account the correct patellar track, and also strengthening the medial torso, which facilitates proper visuo-motor coordination and a more economical function of the body in space. Research shows that stretching, selective work to strengthen muscles, is not sufficient to improve the function of the lower extremity with pain symptoms.[3,17] It is important to choose the right functional training in the most common dysfunctions of the knee. Also, an important thing is to prevent injuries in adolescents practicing the most popular sport disciplines.[6,19,20] However, an incorrectly selected exercise program may adversely affect the knee joint, pelvis or lower limb functioning in the kinematic chain.[4,21] Many authors emphasize that it is important to introduce proprioceptive exercises into the rehabilitation program.[6–10] Exercises should be selected along with the adaptation of appropriate nerve fibers useful for a specific movement in space. Studies show that surface layers, not deep ones, have a denser network of mechanoreceptors and process information from the myofascial system. It is particularly important to pay attention to the areas affected by pain.[22,23] Posture control and its stability depend on many factors, including the proprioception and feedback neuromuscular reactions.[8,22] The use of myofascial taping as a support in the process of rehabilitation seems to be the most justified, because its impact on the fascial system can affect the reduction of pain and improve the stability of the lower limb.[24,25] Our research shows that the total length of the statokinesiogram (SP-EO) path counted in both axes does not change during the tests (Table 1). Attached along the wide fascia strainer application of taping has no effect on the change of the tested parameters. The results of the surface area statokinesiogram (SA-EO) measurements delineated by the COP do not change during all tests (Table 2). This means that the taped application does not affect the surface of the loaded feet. Sticky taping applications in the second and third study do not affect the mean deflection of the center of the foot pressure in the direction of the AP axis, i.e. the sagittal plane (Table 3). The application of taping in the wide fascia strainer area has a statistically significant effect at the level $\alpha = 0.01$ on the deflection of the foot pressure center in the direction of the ML axis (Table 4). This is important information about the local effects of the taping application and its impact on the frontal plane. The tested parameters do not change depending on the time of applying the application, i.e. the taping works immediately after sticking and it persists for some time after sticking. The subjective evaluation of the pain showed no statistically significant differences during the tests. This means that the intensity of the pain did not change after applying the application in the wide fascia stretcher area (Table 5). The results suggest that flexotaping should be applied to each patient individually, with consideration of the functional tests and the location of the pain reported by patients, to reduce the pain.[24–31]

6. CONCLUSIONS

1. The Flexotape application improves the average deflection of foot pressure only in the frontal plane.
2. The other parameters of postural stability remain unchanged.
3. The application used in the study does not affect pain reduction.

Conflict of interest

None declared.

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Original article

Anatomical variations of nose causing rhinogenic contact point headache – a study at a tertiary care hospital of eastern India

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ABSTRACT

Introduction: Headache is a common complaint presented by the patients in daily clinical practice. Anatomical variation of the nose may lead to headache due to contact of nasal mucosa.

Aim: The aim of this study is to find out the role of different types of anatomical variations of the nose causing contact point headache in a tertiary care hospital.

Material and methods: 108 patients of headache with anatomical variations of nose were studied within period of three years. Careful evaluations of anatomical variations of the nose were done with the help of diagnostic nasal endoscopy and CT scan in chronic headache. These anatomical variations were treated surgically. Data from this group were analyzed.

Results and discussion: Among 108 patient of rhinogenic contact point headache, nine distinct types of anatomical variations were seen. Different anatomical variations like septal deviation (35.18%), septal spur (26.85%), middle turbinate concha bullosa (23.14%), hypertrophied inferior turbinate (10.85%), medialized middle turbinate (0.92%), large bulla ethmoidalis (1.85%) and septal bullosa (0.92%) were found in patients with contact point headache. All were treated surgically. Treatment of each anatomical contact point was personalized for every patient.

Conclusions: Headache is a common clinical entity and is nearly universal in the course of everyone's life. Pressure of two opposing mucosa in the nasal cavity without evidence of inflammation can be a cause of headache or facial pain. There are different anatomical situations leading to rhinogenic contact point headache where each contact point has its own characteristic.

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1. INTRODUCTION

Headache is a common complaint by the patients in day to day clinical practice and creates a distressing situation for both patient and the physician. There are myriads of causes for headache varying from simple tension headache, migraine, refractory errors in eye, brain tumours, temperomandibular joint arthralgia, myofacial spasm. It needs a multidisplinary approach to diagnose the causative factors for headache.

Often the rhinogenic cause of headache is undiagnosed, even this cause is not suspected on preliminary evaluation. Even without presence of sinusitis, the referred headache often due to pressure on the nasal mucosa because of the anatomical variations in the nose.[1]

Contact point headache is a new type of headache in the international classification of headache disorders (ICHD), supported by limited evidence. Rhinogenic contact point headache (RCPH) is defined as intermittent pain localized in the periorbital and medial canthal or temporozygomatic regions; evidence of mucosal contact points with postural movements; cessation of headache within 5 minutes following topical use of local anesthesia at contact area and significantly resolution of headache in less than 7 days following removal of contact points.[2]

Intranasal contact points denotes to a contact between two opposing intranasal mucosal surfaces. Intranasal contact points are present in about 4% of noses.[3] Stammberger and Wolf documented the role of substance P in RCPH. They also described that this kind of headache is not only due to abnormal middle turbinate but by abnormal mucosal contact causing referral pain.[4]

This study demonstrates the role of anatomical variations in nose leading to headache, which is a prudent evaluation with inclusion and exclusion criteria before accurate diagnosis of rhinogenic cause of headache.

2. AIM

The aim of this study is to assess the role of different types of anatomical variations of the nose causing contact point headache in a tertiary care teaching hospital.

3. MATERIAL AND METHODS

A prospective cross sectional study was carried out in the department of otorhinolaryngology in a tertiary care hospital of eastern India from January 2013 to February 2016. During this period, 108 patients with headache were evaluated clinically and radiologically having anatomical variations in the nose. Detailed history taking, clinical and systemic examinations were done to rule out migraine, tension headache, neurologic causes, hypertension, temporomandibular joint disorders, inflammatory causes like sinusitis, ophthalmic causes like refractory errors, glaucoma and gynecological causes like premenstrual syndrome causes of headache.

All patients were undergone diagnostic nasal endoscopy using 0° and 30° rigid nasal endoscopes. Diagnostic nasal endoscopy was performed using the standard three pass technique for obtaining information for anatomical variations of the nose. All patients with headache were evaluated with CT scan of nose and sinus and by diagnostic nasal endoscopy. Patients with previous sinonasal surgery, acute sinusitis or nasal allergy or malignant lesions of the nose and sinuses were also excluded from this study by clinical examination and CT scan.

The severity of headache was assessed by using a visual analogue score (VAS) where 0 indicates no pain and 10 for worst imaginable headache. We operated all cases of 108 patients who diagnosed with RCPH.

4. RESULTS

In total, 108 patients of RCPH were studied. All of them had facial pain or headache. The duration of headache was ranging from 6 months to 5 years. A total of 108 patients of headache with anatomical variations in the nose were examined. Presence of various anatomical variations was documented.

Out of 108 patients 62 patients were male and 46 were female with male female ratio being 1.34 : 1.00. By conventional criteria, in T test, it was found $P = 0.58$ and this difference is considered to be not statistically significant (Table 1).

Table 1. Anatomical variations of nose seen in diagnostic nasal endoscopy and CT scan of patients with headache

Anatomical variations	Male *n*(%)	Female *n*(%)	Total
Nasal septal deviation	21(22.68)	17(18.36)	38
Septal spur	15(16.2)	14(15.12)	29
Bilateral concha bullosa of middle turbinate	9(9.72)	6(6.48)	15
Unilateral concha bullosa of middle turbinate	7(7.56)	3(3.24)	10
Hypertrophied inferior turbinate	6(6.48)	5(5.4)	11
Large ethmoidal bulla	2(2.16)	0(0)	2
Hypertrophied superior turbinate	1(1.08)	0(0)	1
Medialized middle turbinate	0(0)	1(1.08)	1
Nasal septal bullosa	1(1.08)	0(0)	1
	62(66.96)	46(49.68)	108

Among all patients 38 (35.18%) patients had deviated nasal septum, 29 (26.85%) had septal spur (Figure 1), 15 (13.88%) had bilateral concha bullosa of middle turbinate (Figure 2), 10 (9.25%) unilateral concha bullosa of middle turbinate (Figures 3a and 3b), 11 (10.85) had hypertrophied inferior turbinates, 2 (1.85%) had large ethmoidal bulla, 1 (0.92%) had hypertrophied superior turbinate, 1 (0.92%) medialized middle turbinate and 1 (0.92%) nasal septal bullosa (Figure 4, Table 1).

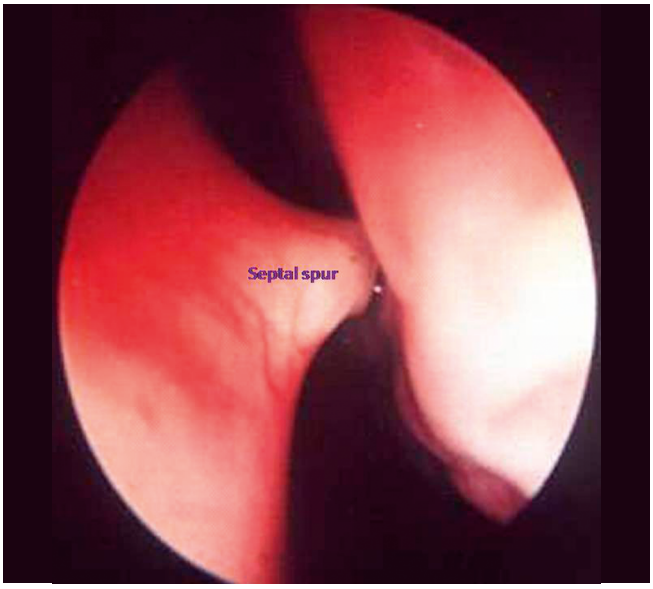


Figure 1. Endoscopic picture showing sharp septal spur touching with the inferior turbinate.

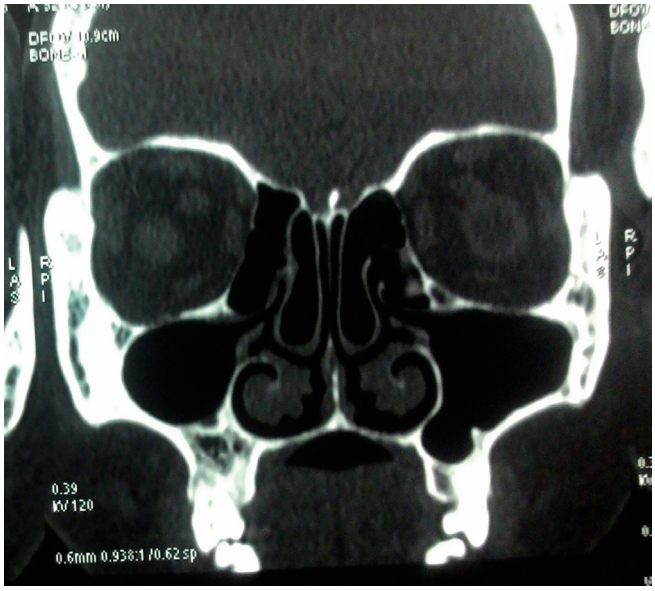
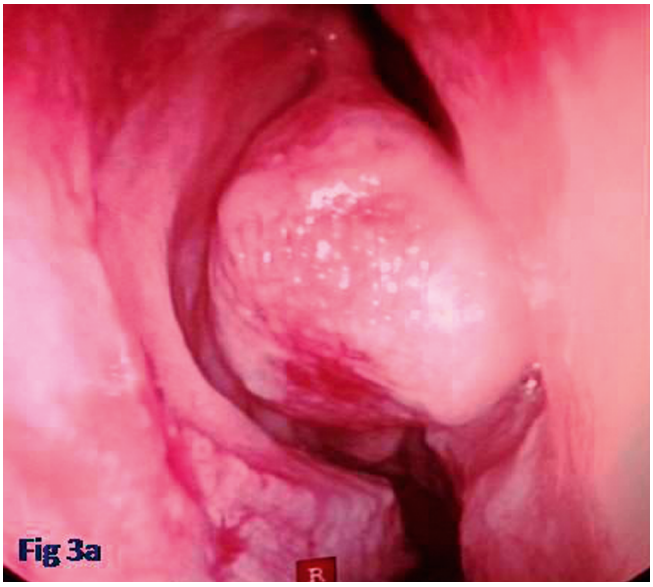


Figure 2. CT scan showing bilateral concha bullosa of middle turbinate.



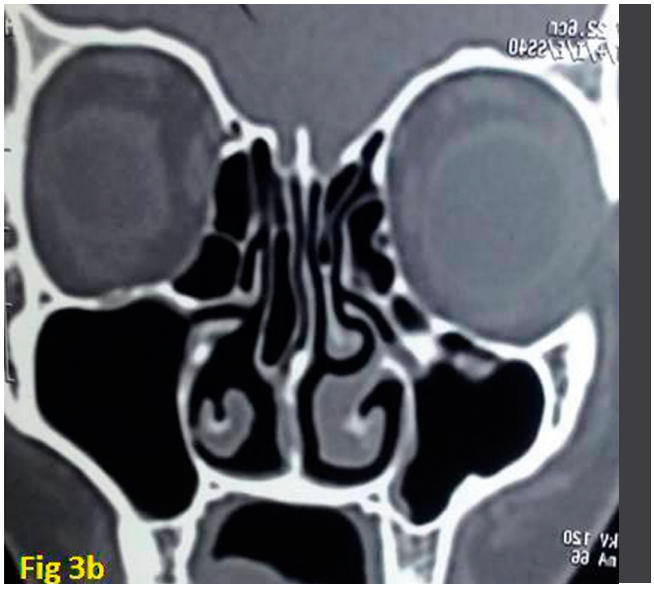


Figure 3A, B. Unilateral concha bullosa of middle turbinate (endoscopic and CT picture).

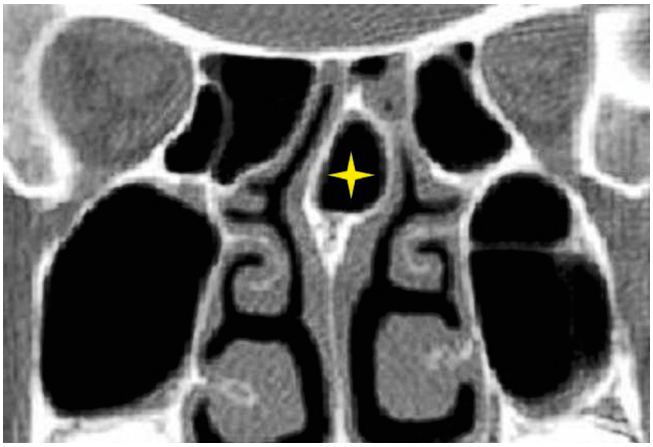


Figure 4. CT scan showing nasal septal bullosa (star).

Out of 108 patients of anatomical contact points, 44 had right side contact, 36 had left side contact points whereas 28 had bilateral mucosal contact points. Out of 108 patients, 41 had right side contact points were from concha bullosa of middle turbinate (4), nasal septal deviation (22) and septal spurs (15) where as rest 3 contact points were from large ethmoidal bulla (2) and medialized middle turbinate (1). Out of 36 left side contact points, all are from concha bullosa (6; Table 2), septal deviations (16) and septal spurs (14; Table 3). Out of total 28 bilateral contact points, 15 are from bilateral concha bullosa of middle turbinates, 11 are from inferior turbinate hypertrophy, 1 from nasal septal bullosa and 1 from superior turbinate hypertrophy. Concha bullosa of middle turbinate could be very large or small, unilateral or bilateral and multichambered or unichambered.

Table 2. Distributions of contact points of concha bullosa of middle turbinate

Concha Bullosa	Contact point	Total
Right concha bullosa	Nasal septum-3 Lateral nasal wall-1	4
Left concha bullosa	Nasal septum-4 Lateral nasal wall-2	6
Bilateral concha bullosa	Nasal septum-11 Lateral nasal wall-4	15

Table 3. Distribution of contact points by septal deviation/Spur

Contact points	Total
Septal deviation touching to right inferior turbinate	22
Septal deviation touching to left inferior turbinate	16
Septal spur touching to right inferior turbinate	15
Septal spur touching to left inferior turbinate	14

The headache due to concha bullosa of middle turbinate is usually felt in medial canthus and forehead area.

The anatomical variations of nose with headache are divided into different age groups. Maximum number patients are seen in the age group of 18–32 followed by age group of 8–17 years, and least in age group above 50 years.

Deviated nasal septum was most common anatomical variations causing headache (35.18%). Second most common variation causing headache was septal spur followed by concha bullosa, hypertrophied inferior turbinates, large ethmoidal bulla, hypertrophied superior turbinate, medialized middle turbinate and nasal septal bullosa.

The commonest site of referred headache was the frontal area (81%) followed by nose/glabellar (29%) area. None was seen over occipital area. Contact point headache due to septal spur has the highest severity in comparison to other variety.

The average headache severity in our patients was 5.9.

The endoscopic nasal surgeries were done for all cases in our study which significantly reduced the headache. Out of 108 patients in our study, 11 (10.18%) patients showed partial improvement of the headache. Out of the patients who had improvement, they all had concomitant clinical improvement of nasal obstruction, whereas 8 out of 11 patients who did not experience headache improvement did not have relief of nasal obstruction.

5. DISCUSSION

Headache is a very commonly encountered clinical symptom seen in everyone's life. Headache may be classified into primary and secondary where primary headache does not have specific etiology and include migraine, tension headache and cluster headache. Secondary headache are due to infections, trauma, tumour, vascular lesions and metabolic diseases.[5] Most relevant etiology concerned for otolaryngologists are anatomical variations of nose causing secondary headache which include septal deviation, septal spur and concha bullosa.[6]

There are different types of septal deviations including cartilaginous deviation, bony deviation, bony spur and high septal deviation. The significant RCPH is seen in septal spur. Concha bullosa is hypertrophied pneumatized middle turbinate and rarely seen in superior and inferior turbinate. The cause of RCPH is multifactorial. RCPH may result from nociceptors in the nasal mucosa, which ends up in the sensory neucleus of the trigeminal nerve.

Pressure effect on the nasal mucosa is associated with changes in microvascular supply, followed by release of biologic substances, induces pain or decreasing the pain threshold. The contact between mucosal lining of concha bullosa and nasal septum or the lateral wall of nose result in release of substance P, calcitonin gene related peptide (CGRP)[7] and neurokinin A.[8] These chemicals are found in nociceptive fibers in the central nervous system and trigeminovascular system. So the contact point between intranasal mucosa may be a cause of secondary headache or triggering factor to primary headache.[9] This phenomenon is also called as middle turbinate syndrome.[10] Substance P has a known role in pathophysiology of contact point headache.[4] Substance P is a neuropeptide that can be identified in the mucosa of the nasal cavity. When it is released around vascular area, vasodilatation, plasma extravasations and perivascular inflammation, causing headache similar to clinical manifestations of migraine without aura.[11] Normal nasal mucosa has a higher concentration of substance P than chronic hyperplastic mucosa or polypoidal tissue. This explains why contact point headache are almost always seen in patients without rhinosinusitis. RCPH is frequently seen in septal deviations/spur followed by concha bullosa of middle turbinates in our study. Hypertrophied superior turbinate is rarely seen and often mistaken with a posterior ethmoidal cell. The contact point between upper septum and medial lamella of hypertrophied superior turbinate leads to headache. The contact point headache due to superior turbinate concha bullosa usually causes pain over forehead, medial and lateral canthus. One case of superior turbinate concha bullosa causing contact point headache was seen in our study. Sometimes medialized middle turbinate cause mucosal contact with nasal septum. Creating a space between middle turbinate and septum is needed for reversing this situation. This is done by trimming the parts of middle turbinate. One case of medialized middle turbinate was seen in our study. Bulla ethmoidalis is the large anterior ethmoidal air cells and when it is larger than normal; its medial surface may push the middle turbinate and cause a contact with nasal septum. To reverse this situation, anterior ethmoidectomy and lateralization of middle turbinate is needed. In our study we had two cases of hypertrophied bulla ethmoidalis pushing the middle turbinate leading to contact between nasal septum and middle turbinate causing contact point headache. One case of nasal septal bullosa was found in our study. Nasal septum bullosa is an abnormal aeration of bony septum which involves perpendicular plate of ethmoid bone. In this case, dissecting

the mucoperichondrium of both sides of septum and removal of septal bullosa was done with its central chamber and mucus linings. RCPH is a referred pain which arises from contact point between the mucosa of nasal septum and lateral nasal wall. Exact mechanism for different characteristic pain in various anatomical variations is not known. It is thought that large contact point as in lamella bullosa and tight contact as in sharp spur may cause severe contact point headache. Diagnostic nasal endoscopy in conjunction with CT scan has proven to be ideal combination for diagnosis of sinonasal pathology. Anatomical variations like septal deviation, spurs, concha bullosa, hypertrophied inferior turbinate, medialized middle turbinate, uncinate bulla, medially or laterally bent uncinate process, paradoxically middle turbinate, large ethmoidal bulla are often cause for headache. However, there is limitations exists in diagnosis as characteristic headache should be relieved after application of local anesthetics which was not done in all cases of our study. In one study of 30 patients with applications of local anesthetic agents, 43% showed complete recovery, 47% showed slight improvement and 10% showed no improvement.[1]

This is why contact point with headache are properly diagnosed by endoscopic examination and CT scan to rule out differential diagnosis. Few authors described treatment of contact point headaches using transaction of fifth cranial nerve or injection of Gasserian ganglion by alcohol or novocaine.[2] Before era of endoscopic sinus surgery, complete removal of middle turbinate was done to manage concha bullosa. After evolution of endoscopic sinus surgery, techniques like partial turbinectomy and turbinoplasty are practiced aiming to relieve the contact point headaches.[12] Wolf and Tosum et al. documented that nasal septal deviation/spur are causing referred headache in the absence of inflammation.[1]

Our study significantly supported these correlation. Different types of septal deviations like cartilaginous deviation, bony deviation, high septal deviation and septal spurs were found in around 62% cases of contact point headache patients in this study. Septal spur had a significant relation with headache in this group. Hypertrophied inferior turbinate (10%) was another cause of RCPH in our study. Other than septal spur and hypertrophied middle turbinate, contact point headache may also caused by the contact between the septum and superior turbinate or medial wall of the ethmoidal sinus.[13] After identification of contact points, RCPH can be treated with surgical management.[14] Nose has a diverse anatomical variation. Relation between these anatomical variations and contact point headache was confirmed in septal spur, septal deviations, concha bullosa and large ethmoidal bulla. So above lesions should not be ignored from mind during evaluation of headache and their respective treatment helps to relief the symptoms.

6. CONCLUSIONS

Headache due to contact of nasal mucosa is often considered as an exclusion of diagnosis. The outcome of this study highlights that diagnostic nasal endoscopy and CT scan are important tools in the diagnosis RCPH. DNS or septal spur are common anatomical variations of the nose in our study for causing contact point headache followed by concha bullosa and enlarged bulla ethmoidalis. Relation of anatomical variations with headache should not be ignored during decision making for headache management.

Conflicts of interest

None of the authors has any conflict of interest, financial or otherwise.

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Original article

Decade-long trends in prostate cancer incidence and mortality in Poland, 1999–2012

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ABSTRACT

Introduction: In Poland, prostate cancer is the second most common cancer and third leading cause of cancer death among men. Understanding trends in prostate cancer incidence and mortality can inform efforts for prostate cancer prevention and control, yet information on national trends is lacking.

Aim: This study examined temporal trends in prostate cancer incidence and mortality in Poland for the years 1999–2012.

Material and methods: Data on prostate cancer cases and deaths in Poland were provided by the Polish National Cancer Registry (PNCR). For each year, age-standardized incidence and mortality rates were calculated overall, as well as for each vovoideship, urban and rural regions, and age category.

Results and discussion: The overall standardized incidence rate in Poland was found to double during this time period, from 17.39 cases per 100,000 person-years in 1999, to 36.12 in 2012. In contrast, standardized mortality rates remained stable, with 11.89 deaths per 100,000 person-years in 1999 and 12.41 deaths per 100,000 person-years in 2012. Standardized incidence and mortality varied by vovoideship. Standardized incidence but not mortality was higher in urban regions.

Conclusions: This study demonstrates the utility of using PNCR data for cancer epidemiologic research and identifies trends in prostate cancer incidence and mortality that require further inquiry.

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1. INTRODUCTION

There is substantial worldwide variation in prostate cancer incidence and mortality.[1] In Poland, prostate cancer is the second most common cancer and the third leading cause of cancer death among men.[2] Despite the large burden of the disease, however, few studies have examined the epidemiology of prostate cancer in Poland. Of the studies that have compared prostate cancer incidence, prevalence, mortality, and survival across European countries, most have utilized only regional registry data for Poland, and none have taken a detailed look at Polish prostate cancer trends in incidence and mortality across region and time.[3–9] Understanding such trends can help to promote further research and target resources for prostate cancer prevention and control, as well as clarify the public health burden of this prevalent cancer among men worldwide.

2. AIM

The purpose of the current study was to examine temporal and regional trends in prostate cancer incidence and mortality in years 1999–2012 using population-based data from the Polish National Cancer Registry (PNCR).

3. MATERIAL AND METHODS

This study utilized data provided by the PNCR. The PNCR collects data from a network of 16 regional registries located throughout Poland. There is one regional registry within each of Poland's 16 voivodeships (administrative units). Each regional registry captures data from the entire population of its voivodeship; as a result, 100% of Poland is covered by cancer registration.

Regional registries receive data in the form of Cancer Registration Forms that are filled out by physicians upon cancer diagnosis and treatment of cancer patients. Prior to 2013, each regional registry maintained its own database. In 2013, the registry data were combined into a single, centralized database managed by the PNCR. The PNCR works to ensure the quality and completeness of the data and is responsible for publishing annual reports of cancer burden in Poland (published at http://onkologia.org.pl).

For the current project, the PNCR provided data on the number of incident cases of prostate cancer, the number of deaths attributed to prostate cancer (International Classification of Diseases for Oncology, 10th Edition, code C61), and the total number of men in the Polish population, per five-year age category and per year. These counts were also given for each of Poland's 16 voivodeships and for urban and rural regions, separately. The data were provided for the years 1999–2012.

Using these data, yearly incidence and mortality rates were calculated for all of Poland, for each voivodeship, for urban and rural regions, and for five age groups (>50, 50–59, 60–69, 70–79, ≤80). Incidence and mortality rates were age-adjusted using the method of direct standardization and the World Standard Population.[10,11] Annual percent change (APC) was used to quantify time trends in incidence and mortality and was computed using generalized linear models;12 trends with a $P < 0.05$ were considered statistically significant. Calculations were run using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Table 1. Standardized incidence rates and annual percent change (APC) by voivodeship, 1999–2012.*

Voivodeship	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	APC	*P* value
Dolnoslaskie	23.15	24.27	25.63	22.60	21.65	25.58	27.79	28.54	28.54	30.73	30.84	27.66	32.10	31.68	2.70	<0.0001
Kujawsko-Pomorskie	23.97	19.05	22.48	16.59	23.00	27.20	28.70	36.41	36.49	37.57	40.51	36.03	35.73	36.55	5.35	<0.0001
Lubelskie	13.16	15.92	22.25	22.41	19.02	23.38	35.17	30.20	32.04	27.56	27.46	33.02	36.19	37.90	5.99	<0.0001
Lubuskie	14.97	14.79	13.80	10.23	19.10	21.52	29.19	22.77	25.34	26.03	33.38	42.61	36.59	44.29	10.20	<0.0001
Lodzkie	11.43	16.58	16.97	15.30	15.94	19.07	24.15	21.59	20.04	23.42	21.75	24.13	45.99	22.21	6.55	0.0004
Malopolskie	20.11	22.27	25.20	27.68	26.75	26.35	30.05	36.11	30.99	29.29	33.56	31.53	33.47	42.68	4.10	<0.0001
Mazowieckie	16.42	21.06	24.08	24.37	28.36	32.98	30.80	30.00	30.46	34.57	33.70	35.14	31.11	29.90	3.38	<0.0001
Opolskie	22.64	20.63	21.52	23.86	22.07	23.30	24.29	22.84	26.92	32.34	26.39	26.73	25.05	34.03	2.89	<0.0001
Podkarpackie	13.60	28.57	26.86	23.45	35.26	30.18	31.80	29.93	27.14	28.55	35.90	34.50	36.02	41.35	4.06	<0.0001
Podlaskie	17.60	21.13	22.81	18.94	19.97	19.72	32.01	30.19	24.06	27.77	28.79	34.21	40.96	33.55	5.59	<0.0001
Pomorskie	19.97	26.65	28.99	27.46	24.45	24.86	29.39	34.47	36.86	40.94	55.06	47.70	51.12	54.45	7.93	<0.0001
Slaskie	16.84	19.16	24.25	28.94	29.62	29.38	31.60	32.83	34.95	33.77	36.61	33.80	33.47	38.53	4.30	<0.0001
Swietokrzyskie	25.88	30.39	29.52	39.37	35.94	29.60	34.39	30.69	30.84	29.12	30.17	26.77	26.30	39.27	0.04	0.9642
Warminsko-Mazurskie	12.08	14.22	18.83	21.86	23.72	28.49	32.24	25.98	29.07	26.72	27.49	23.85	26.52	31.21	3.98	0.0003
Wielkopolskie	16.03	18.95	24.43	27.52	26.13	29.13	35.93	35.16	40.20	44.68	42.95	36.33	38.69	37.40	5.27	<0.0001
Zachodniopomorskie	15.57	19.60	20.85	17.17	20.05	20.06	23.44	23.31	28.76	27.03	29.44	28.51	27.18	31.25	4.71	<0.0001
All	17.39	20.86	23.57	23.96	25.22	26.74	30.38	30.43	31.04	32.18	34.11	32.94	35.07	36.12	4.58	<0.0001

* Rates are expressed per 100 000 person-years, age-standardized to the World Standard Population.[10,11]

Table 2. Standardized mortality rates and annual percent change (APC) by voivodeship, 1999–2012.*

Voivodeship	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	APC	*P* value
Dolnoslaskie	10.20	10.72	12.45	13.33	12.59	11.66	12.83	13.24	11.98	13.66	12.01	11.81	12.10	11.79	0.48	0.3184
Kujawsko-Pomorskie	12.04	14.82	15.23	14.35	12.24	13.86	11.95	12.94	13.47	12.43	14.83	14.09	15.39	13.29	0.27	0.632
Lubelskie	11.11	11.68	10.69	12.35	11.88	11.89	11.63	13.01	11.17	12.90	12.88	11.92	12.27	11.27	0.5	0.161
Lubuskie	10.10	10.98	14.12	14.22	16.02	11.86	14.49	11.99	16.17	12.91	11.81	11.13	13.91	12.65	0.26	0.766
Lodzkie	10.95	12.94	13.40	14.27	13.49	14.74	12.44	12.48	12.60	12.77	11.30	13.33	11.07	12.24	-0.59	0.2667
Malopolskie	10.74	10.83	12.54	12.17	12.08	13.86	12.36	12.54	12.21	11.93	12.23	12.22	11.91	11.92	0.34	0.3678
Mazowieckie	11.69	12.56	12.23	12.47	12.55	12.73	12.22	13.25	13.68	13.40	12.48	10.86	12.23	11.64	-0.14	0.7053
Opolskie	11.19	8.45	9.87	13.08	11.72	12.11	11.51	9.77	12.03	10.02	13.74	12.29	11.71	10.67	0.85	0.2618
Podkarpackie	12.55	12.87	13.88	13.18	12.72	14.76	13.10	13.37	13.10	12.35	12.80	11.65	12.57	11.21	-0.83	0.0217
Podlaskie	11.21	12.30	13.89	12.75	12.13	12.28	15.03	13.42	12.85	14.50	17.35	15.56	13.80	16.31	2.29	<0.0001
Pomorskie	15.82	16.57	15.23	14.93	14.01	13.33	13.66	14.41	13.55	13.91	14.20	12.94	12.47	14.48	-1.37	<0.0001
Slaskie	11.43	11.67	13.43	13.33	11.88	12.45	12.91	11.92	13.69	12.13	12.51	12.32	11.65	12.75	0.09	0.8043
Swietokrzyskie	11.65	13.05	12.46	15.41	14.17	14.03	14.08	13.44	15.16	9.39	13.11	12.48	11.51	11.72	-0.86	0.2458
Warminsko-Mazurskie	12.33	12.82	13.90	13.07	13.67	12.76	14.14	13.98	14.89	13.36	15.92	11.39	12.59	11.97	-0.08	0.8826
Wielkopolskie	14.47	14.87	16.09	15.51	14.10	14.93	14.65	13.56	15.87	15.04	15.23	13.87	14.62	12.78	-0.59	0.0963
Zachodniopomorskie	13.05	12.47	12.65	14.18	13.32	16.32	10.91	12.11	12.85	12.81	11.20	12.34	12.49	14.03	-0.38	0.5562
All	11.89	12.54	13.20	13.50	12.85	13.33	12.88	12.93	13.35	12.87	13.07	12.36	12.51	12.41	-0.07	0.7612

* Per 100 000 person-years, age-standardized to the World Standard Population.[10,11]

4. RESULTS

The standardized incidence rate (SIR) of prostate cancer in Poland increased over the period of 1999–2012 (Table 1). In 1999, the SIR of prostate cancer was 17.39 cases per 100,000 person-years. This rate more than doubled by 2012, reaching 36.12 cases per 100 000 person-years. The APC was 4.58% ($P < 0.0001$). Though incidence rates varied approximately two-fold across the 16 voivodeships, the trend of increasing incidence was nearly universal and was statistically significant in all but one voivodeship (i.e., Swietokrzyskie). Incidence rates also varied substantially across Poland's 380 poviats (Figure 1).

In contrast, the mortality rate for prostate cancer remained largely unchanged over this time period (Table 2). In 1999, the standardized mortality rate (SMR) was 11.89 deaths per 100 000 person-years, while in 2012, the SMR was 12.41 deaths per 100 000 person-years. The APC did not differ significantly from zero. At the level of the voivodeships, mortality rates increased slightly in 1 voivodeship (Podlaskie), decreased slightly in 2 (Podkarpackie, Pomorskie), and remained stable in the other 13. Mortality varied slightly, but was more consistent than SIRs across the 380 poviats (Figure 2).

When the regions of Poland were dichotomized into urban and rural regions, the time trends remained the same.

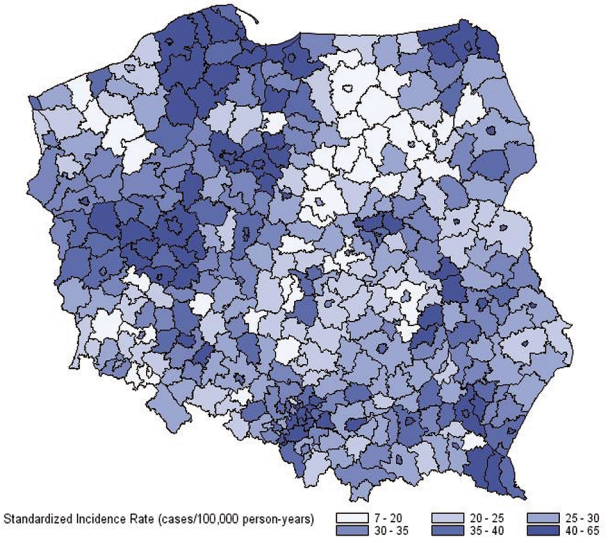

Figure 1. Standardized incidence rates by poviat, 2008–2012.

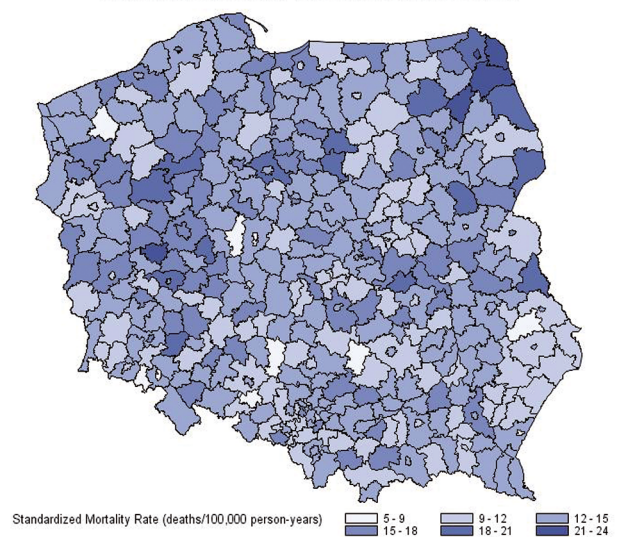

Figure 2. Standardized mortality rates by poviat, 2008–2012.

In both urban and rural regions, SIRs for prostate cancer increased steadily from 1999–2012 while SMRs did not change (Figure 3). However, incidence of prostate cancer in urban regions was consistently higher than incidence in rural regions by 30%–50%. By 2012, the end of the study period, the SIR was 39.27 in urban regions and 30.67 in rural regions. No concurrent gap in SMRs was observed.

Across all time points, incidence and mortality were highest for the older age groups (Figures 4 and 5). In 2012, SIRs were 402.17, 412.51, 223.67, 41.79, and 0.38 for the ≥80, 70–79, 60–69, 50–59, and ≤50 age groups, respectively. All age groups experienced an increase in incidence of prostate cancer across the study period, but for the group of men aged 80 years and older, the incidence rate peaked at 405.96 in 2005. By 2009, there was no difference in incidence rates for the 70–79 and ≥80 age groups. Mortality rates were highest for the ≥80 age group and decreased for each subsequent age group (in 2012: 429.26, 143.48, 44.15, 7.34, and 0.08 for the ≥80, 70–79, 60–69, 50–59, and ≤50 age groups, respectively).

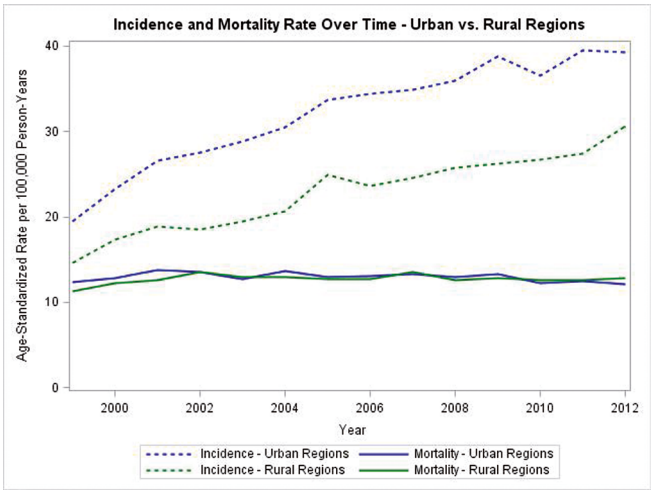

Figure 3. Standardized incidence and mortality rates over time for urban and rural regions. Prostate cancer incidence increased over time in both urban and rural regions, but was consistently higher in urban regions. Mortality rates were similar across region and time.

5. DISCUSSION

The PNCR data indicate a sharp increase in prostate cancer incidence during the calendar period of 1999–2012. This observed increase may be attributed to several factors. The most well documented risk factor for prostate cancer development is increasing age.[13] With a growing proportion of Polish men over the age of 50, a concomitant increase in prostate cancer incidence is not unexpected. At the same time, the average life expectancy of a Polish man has been steadily increasing, which could contribute to increased detection of new prostate cancers within the Polish male population. Environmental and behavioral factors might also be driving the observed changes in prostate cancer incidence reported in this study. Specifically, changes in dietary intake, physical activity, and presence of inflammatory conditions might also play a role in increasing prostate cancer incidence.[14] Variation in the timing and duration of these factors would need to be examined to better understand their impact on these observed increases in prostate cancer incidence.

Increased detection of prostate cancer, resulting from improvements in cancer diagnosis and the expanding use of the prostate specific antigen (PSA) serum test to screen or test for prostate cancer might also underlie the observed changes in incidence. Most Polish urologists follow the European Association of Urology guidelines, which promote the use of technological modalities, such as transrectal ultrasound, for prostate cancer diagnosis, prostate core biopsy, depending on a patient's risk factor profile, and use of risk calculators or nomograms in the treatment decision making process.

PSA testing at the beginning of study period was not widespread in Poland, but has had increasing popularity over the years. Although information from IMS Health on the sale of PSA tests indicates that such testing is slow growing, these data represent over the counter sales which are a marginal phenomenon in Poland (Table 3). While there

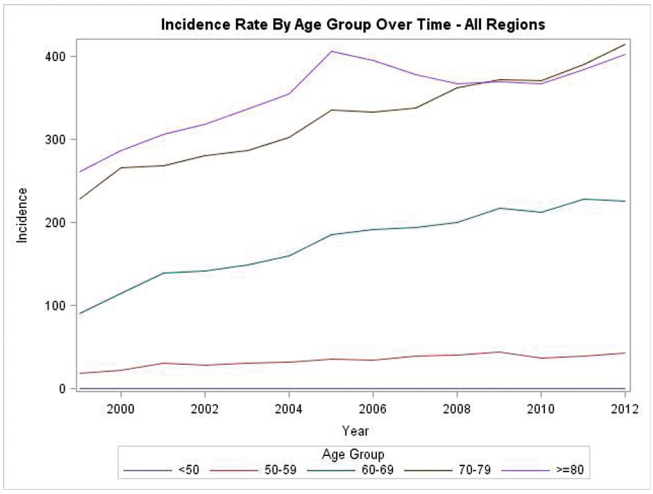

Figure 4. Incidence rates over time by age group.

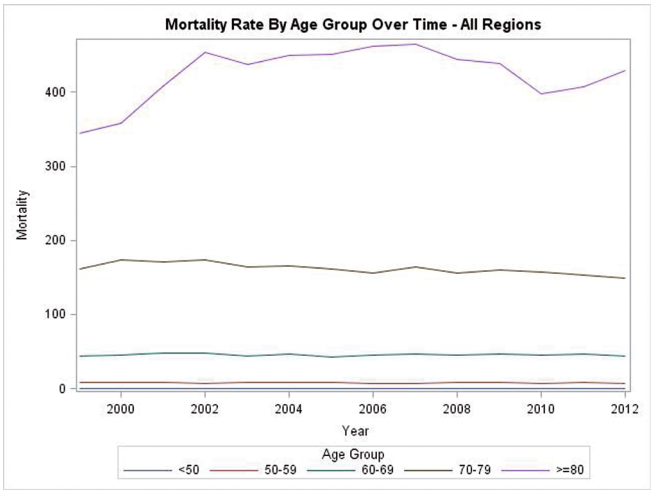

Figure 5. Mortality rates over time by age group.

Table 3. Number of PSA tests sold in Poland by a single reporting pharmaceutical company.

	2007	2008	2009	2010	2011	2012	2013
No of PSA tests	15 100	66 700	93 600	133 900	193 300	189 900	229 300

is still no widespread prostate cancer screening program for Poland nationally or for any specific region within the country, there have been several local educational and early detection efforts in recent years. Most notably, a series of one-day educational sessions, organized by local, nonscientific organizations were conducted but without long-lasting follow up of screened patients. Such short-term efforts were limited to selected cities, poviats or municipalities. There have also been national and local health awareness campaigns with special attention on early prostate cancer detection, proper diagnosis and treatment but those campaigns were initiated toward end of our study period and could not have meaningfully impacted the study findings.[15]

Finally, significant cancer patient under-registration was believed to have occurred at the end of the 1980's, and continual improvements in the quality and completeness of cancer registration may have contributed in part to the rise in cancer incidence over the study period.

Though prostate cancer incidence in Poland increased from 1999 to 2012, the mortality rate remained stable. In fact, a recent population-based study of cancer survival across Europe found that in Poland, the five-year age-standardized survival from prostate cancer improved from 54.3% in 1995–1999, to 68.5% in 2000–2004, and 74.1% in 2005–2009.[6] Increased survival rates may have resulted from improvements in the treatment and management of prostate cancer over this time period. In the recent years the number of radical prostatectomies, especially minimal invasive ones, increased, which improves oncological results as well as quality of life. Those results, as well higher level of health awareness due to educational programs, may have encouraged patients to seek procedures with curative intent instead of palliative treatment. Possible advances include increased availability of prostate cancer drugs, as changes to Poland's political system in 1989 facilitated the expansion of international pharmaceutical companies, and the intensive exchange of radiotherapy equipment that began in Poland in the mid-2000's. Conversely, an increased detection of indolent, low-grade cancers unlikely to cause metastases and cancer-specific death may explain stable mortality despite increasing incidence over time. Stage data from the PNCR, though incomplete, provide support for this explanation (Table 4). The percentage of tumors that were localized at diagnosis increased substantially in recent years, while the percentage of patients presenting with distant metastasis decreased. These trends are consistent with a stage shift to more localized disease, likely a result of expanded opportunistic screening and increased levels of awareness of the importance of early detection. Since uptake of PSA screening has been slow in Poland, and since it takes approximately ten years to be able to assess the impact of early diagnosis on prostate cancer mortality, it may be several years before this stage shift translates into a mortality decline across Poland, if mortality is to decline at all.

Table 4. Stage distribution of prostate cancer cases.

Year	Unknown	Local	Regional	Distant metastasis
1999	42%	27%	10%	21%
2000	44%	28%	10%	18%
2001	42%	31%	10%	17%
2002	44%	31%	9%	16%
2003	37%	35%	12%	15%
2004	40%	35%	11%	15%
2005	39%	36%	11%	14%
2006	35%	40%	11%	14%
2007	33%	42%	11%	15%
2008	28%	46%	11%	15%
2009	29%	46%	11%	14%
2010	28%	46%	11%	14%
2011	31%	46%	10%	14%
2012	24%	52%	9%	16%

A novel finding in this study was the variation in population-based incidence rates for urban versus rural regions. Age-related variation has been well documented and was anticipated.[13] Differences in prevalence of behaviors such as smoking, alcohol use, obesity, physical inactivity, and environmental exposures, plus the impact of health policy within these regions, could all contribute to this disparity.[16,17] There could also be similar underlying rates, but increased detection of prostate cancer in the urban regions, possibly due to greater access to healthcare. This observed gap was observed for the entire study period; however, mortality rates were comparable over time, similar to previous reports in the literature.[18]

The primary strength of the current study was the use of the PNCR data. The PNCR covers 100% of Poland and has been collecting data continuously for 60 years. The data are collected according to the same protocol and standards nationwide, leading to good data quality and completeness. Recently all most all of the PNCR work has been made available on-line, which creates ease of access for researchers and the population. More than 85% of all cancers reported to the PNCR are histopathologically verified. Under-registration is believed to be approximately 10%–15%, depending on the cancer type.

Limitations of this data source include the low quality of stage data, which is only reported as broad categorizations of local, regional, or distant metastasis and is missing for 25%–40% of registered cases. Stage based on the TNM classification system is only available for 20% of registered cases. Furthermore, data on Gleason grade at diagnosis was only collected beginning in 2013. Treatment data is available, but its completeness is unknown. Improved collection of stage, grade, and treatment data as well as follow-up data by the PNCR would be beneficial for future epidemiologic investigations.

Other future studies should explore the diffusion of PSA screening throughout Poland and the effect of local screening programs on regional incidence and mortality. Urban–rural disparities in prostate cancer incidence should also be investigated with more attention and focus on healthcare facilities and utilization of diagnostic and treatment services for the Polish rural population.

Our results should be read with special emphasis by institutions responsible for the Polish health system. The anticipated trends in the short term, based on a recent study, mimic our findings – that the incidence rate will continue to increase.[19] The growing number of prostate cancer patients could have a strong influence on health care utilization and demands. The trend in stage migration could lead to greater interests in less invasive treatment including active surveillances or focal treatment, which is currently not often offered to Polish patients.

6. CONCLUSIONS

The overall standardized incidence rate of prostate cancer in Poland was found to double from 1999 to 2012, based on data from the PNCR. The standardized mortality rate was stable throughout this time period. Differences in standardized incidence and mortality were observed across vovoideship, and incidence was higher in urban regions. This study demonstrates the utility of using PNCR data to identify trends in prostate cancer incidence and mortality that may aid in informing efforts for prostate cancer prevention and control.

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Conflicts of interest

None.

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Original article

Patients clinically diagnosed with asthma search the Internet less often for information about the reputation of health care institutions: the results of a Polish survey study

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ABSTRACT

Introduction: Physicians and representatives of health care institutions are only the second source of information on health, after the Internet, which is disturbing.

Aim: The aim of the study was to demonstrate the relation between the occurrence of allergic diseases and searching for information about health and disease on the Internet.

Material and methods: The study group was composed of inhabitants of Poland aged 20–44 years (n = 1728). The research tool was a questionnaire developed by the researchers, completed individually by each respondent.

Results and discussion: Statistically relevant relations have been noticed between the frequency of searching for information about health and disease on the Internet, and the occurrence of the symptoms of allergic diseases at any time ($P < 0.001$), as well as the occurrence of declaring any allergic diseases of the upper respiratory track ($P < 0.01$). Those clinically diagnosed with asthma less often search the Internet for information about the reputation of health care institutions ($P < 0.05$). A statistically relevant relation has been observed between searching for information on the Internet related to the health of the respondent or the health of a family member during the last month, and declaring asthma ($P < 0.05$).

Conclusions: The occurrence of allergy symptoms influences the frequency of searching the Internet for information about health and disease of a respondent or a family member, about health protection or medical services.

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1. INTRODUCTION

Owing to universal almost unlimited access to the Internet, it seems justified to evaluate the scale of the phenomenon of searching for information on the Internet for health purposes. Until now only a few studies have been conducted in the world on the issue of e-health and social/marketing media, and each of them differs in objective and methodology. In the case of e-health, studies analysing the following aspects have been carried out:

- the level of trust in the general population of Internet-based information about health;[1]
- factors influencing the practical use of information about health available on the Internet by the general population;[2]
- the use of information about health available on the Internet by patients treated psychiatrically;[3]
- the efficiency of using an online e-health application in pharmacological treatment of patients with generalised anxiety disorders;[4]
- online health interventions in the group of persons abusing alcohol;[5]
- the use of information about health available on the Internet by the elderly.[6]

Liang et al. have been working on the Internet platform Multiple Profile Manager (MPM), to enable users to create and manage an integrated profile, which can be shared on many of the social networking services.[7] The platform will make it easier to collect data related to the health of users, which will then facilitate online contact between the patients and physicians. Currently works have also been carried out on implementation of e-health in health care system.[8,9] Scientists have been working on research results related to factors influencing the implementation of e-health in health care institutions in four countries: Finland, Norway, Scotland and Sweden.[8,9]

Research studies on social/marketing media in connection with allergies that are available in world literature, analyse issues related to:

a) social networking services, such as Facebook or Twitter;[10]
b) the contact between a patient and a physician with the help of instant messenger and electronic mail;[10–13]
c) media campaigns (posters, billboards, TV).[14,15]

Those studies refer mainly to the use of social networking services or e-mail by patients suffering from allergies in contacting a physician. None of the studies published to date have analysed the correlation between the information published on websites dedicated to health, and the quality of life of patients suffering from asthma and/or allergies.

As a result of the progress of civilization and the development of information and communication technologies, 63% of adult Poles use the Internet regularly, i.e. at least once a week. According to data from the Centre for Public Opinion Research, the number of Internet users has increased three fold since 2002. Those youngest 18–24 years and those with tertiary education are among the largest groups – over 94%.[16] With such a numerous group of Internet users as many as 88% use services dedicated to health when trying to acquire information on health, diseases or methods of treatment. The physicians and representatives of health care institutions are only a second source of information on health after the Internet, which is disturbing.[17]

2. AIM

The main objective of the study was to evaluate the relation between the occurrence of allergic diseases and searching for information about health and disease on the Internet. The influence of gender and economic status was also evaluated.

3. MATERIAL AND METHODS

The study was carried out in the Masovian voivodeship of Poland as a form of fully anonymous questionnaire. The respondents were identified based on an ID number allocated for the purpose of the study.

The research tool questionnaire contained 45 questions developed by the researchers to be completed individually by each respondent. Most of the questions had a multiple choice format. The questionnaire included questions on: the frequency and purposefulness of using the Internet, the types of information on health or disease searched on the Internet, the attitude towards the possibilities of Internet use, the use of medical services or solutions related to disease prevention, the use of medicines, health status of the respondent. Some fragments of the questionnaire of International Study of Asthma and Allergies in Childhood as well as European Community Respiratory Health Survey II (ISAAC and ECRHS II) have been used to develop the research tool.

The target group comprised inhabitants of the Masovian voivodeship of Poland aged between 20–44 years. The sampling was based on the availability of respondents. As many as 1728 questionnaires were collected and 1720 were accepted for analysis (average age 28.14 years, median 26 years). Women accounted for 60% of the study group. Also people with higher education accounted for more than 60% of the study group. Over 80% of respondents use the Internet every day. The characteristics of the study group are presented in Table 1.

Statistical analysis was carried out with the following tests: odds ratio (OR), Pearson's 2 test. A difference $P < 0.05$ was considered statistically relevant.

4. RESULTS

4.1. Allergic diseases

In the group of nearly 5% of the respondents declared that they currently have asthma. Nearly 7% of people reported that they have ever suffered from asthma. In this group, 84% had asthma confirmed by a physician (Table 2).

Table 1. Characteristics of the study group.

	n	Percentage
Sex		
Men	683	39.7
Women	1037	60.3
Age groups		
20–24	661	38.3
25–29	495	28.6
39–34	246	14.2
35–39	178	10.3
40–44	148	8.6
Education		
Primary	9	0.5
Lower secondary	8	0.5
Basic vocational	56	3.2
Secondary	602	34.9
Tertiary	1049	60.8
Self-assessment of financial status		
Affluent, no need to save up, even for higher expenditures	59	3.5
Enough money for all expenditures, some can be saved	746	43.8
Enough money for everyday expenditures, but cannot afford higher expenditures	767	45.1
Must deny many things to have enough money for everyday expenditures	110	6.5
Not enough money even for immediate needs	20	1.2
The frequency of using the Internet (websites, electronic mail, instant messenger, etc.)		
Everyday	1419	82.1
Several times a week	163	9.4
Several times a month	62	3.6
Once a month	13	0.8
Less than once a month	39	2.3
Not at all	30	1.7

Table 2. The frequency of allergic diseases occurrence in the study group (n = 1720).

Positive responses to the question:	Percentage	*n*
Do you suffer from any chronic condition? Asthma.	4.5	1710
Have you taken any medicine for shortness of breath or respiratory problems?	13.4	1699
Have you experienced wheezes or whistles in the chest at any time during last 12 months?	12.5	1704
Have you ever suffered from asthma?	6.7	1699
Has the asthma been confirmed by a physician?	84*	112*
Have you experienced at any time problems with sneezing, running or congested nose while not having a cold, fever or flu?	44	1682
Have you suffered from any nasal allergic diseases, including nasal congestion caused by an allergy to the pollen of plants (allergic rhinitis)?	26.6	1685

* From those declaring they have suffered from asthma.

Table 3. The relation between searching the Internet for information about the health of a respondent or a family member, health protection or medical services, and the occurrence of allergy symptoms (in percentages)

The frequency of using the Internet to search for information about the health of a respondent or a family member, health protection or medical services	Respondent experienced at any time problems with sneezing, running or congested nose while not having a cold, fever or flu n = 1682		Respondent suffered from any nasal allergic disease, including nasal congestion caused by an allergy to the pollen of plants (allergic rhinitis) n = 1685	
	YES	NO	YES	NO
Everyday	2.9	1.6	3.8	1.6
Several times a week	5.3	8.8	5.6	8.0
Several times a month	29.3	25.4	30.6	25.5
Once a month	17.9	15.3	16.3	16.5
Less than once a month	39.6	40.8	38.8	40.8
Not at all	4.9	8.1	4.9	7.6

A statistically significant relation was observed between the frequency of searching the Internet for information about the health of a respondent or a family member, health protection or medical services, and the occurrence of allergy symptoms (P = 0.001), and the occurrence of declaring having suffered from any nasal allergic disease (P = 0.005) (Table 3).

Persons clinically diagnosed with asthma statistically significantly less often searched the Internet for an opinion about healthcare institutions than those declaring asthma that had not been confirmed by a physician (respectively: 25% and 52.9%; P = 0.02).

A statistically significant relation between searching the Internet during the last month for information related to the health of a respondent or a family member, and those declaring asthma was found (68.4% vs. 56.1%; P = 0.031). No such relationship was found in the case of those clinically diagnosed with asthma ($P > 0.05$).

No statistically significant relation was found between the frequency of using the internet to search for information about the health of a respondent or a family member, health protection or medical services, and: declaring asthma (P = 0.072), taking medicines for shortness of breath or respiratory problems (P = 0.072), experiencing wheezes or whistles in the chest at any time during the last 12 months (P = 0.059), or asthma diagnosed by a physician (P = 0.515). No statistically significant relation was found between declaring asthma and searching the Internet for information about health or diseases ($P > 0.05$).

4.2. Gender

Women used the Internet significantly more often than men to search for the information about their health or the health of a family member, about health protection or medical services ($P < 0.001$) (Figure 1).

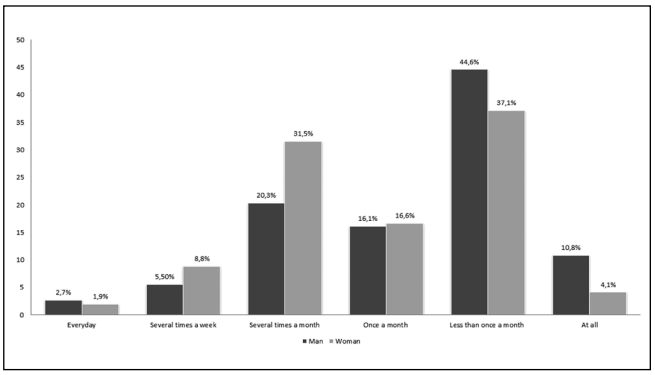

Figure 1. The frequency of using the Internet to search for information about the health of a respondent or family member, about health protection or medical services, depending upon gender (in percentage), $n = 1702$

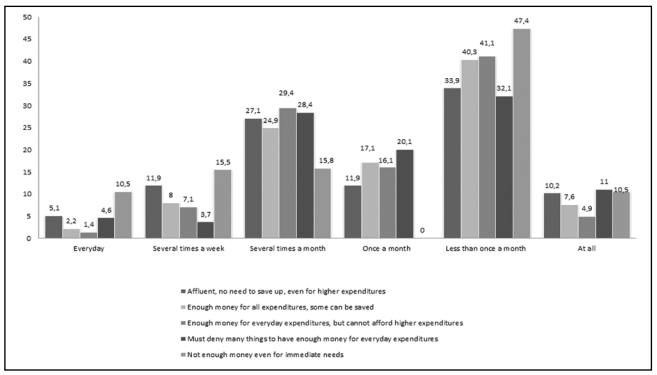

Figure 2. Searching in the Internet for information about the health of a respondent or a family member, health protection or medical services depending on economic status of the family (in percentage), $n = 1685$

Women searched the Internet significantly more often than men for information on: physicians' opinion (46.3% vs. 30.9%, $P < 0.001$), reputation of health care institutions (27.4% vs. 21.9%, $P = 0.011$), interpretation of test results (38.5% vs. 23.1%, $P < 0.001$), specific diagnostic test (26.7% vs. 20.6%, $P = 0.004$), specific medicines, effects, uses and side effects (50.6% vs. 39.3%, $P < 0.001$), different methods of treatment of the same disease (41.5% vs. 36.4%, $P = 0.036$), specific diseases (70.4% vs. 58.8%, $P < 0.001$), methods that other persons use to cope with the same health problems (31.8% vs. 20.7%, $P < 0.001$), making a doctor's appointment (35.1% vs. 29.4%, $P = 0.017$).

Women also significantly more often than men verified diagnoses made by a physician and recommendations on websites dedicated to health (77.7% vs. 66.4%, $P < 0.001$), as well as Internet forums (59% vs. 48.9%, $P < 0.001$). A statistically significant relation was found between searching the Internet for information about the health of a respondent or a family member and gender (women – 62.9%, men – 47.1%; $P < 0.001$). Women significantly more often than men agreed with the statement that they frequently: search the Internet for information about health when they are not feeling well or suffer from a disease ($P < 0.001$), compare doctor's recommendations with opinions presented on the Internet ($P = 0.004$), search for opinions on physicians they plan to visit ($P < 0.001$), search for information on health or disorders when they do not want to or cannot see the doctor ($P < 0.001$), find most of the information published on the Internet credible ($P = 0.025$).

4.3. Economic status

Persons that are in difficult material circumstances search for information about the health of a respondent or a family member, health protection or medical services more often during the week, whereas persons that are more wealthy do it more often per month ($P = 0.006$) (Figure 2).

5. DISCUSSION

The narrow range of age of the study groups and questionnaire nature both constitute a fundamental limitation in this study. The declarations of the respondents are the source of the obtained data and not the observation of their behaviour. In the case of questions on using the Internet to search for health-related information, there is a slight risk that the respondents could have hidden their true opinions. At present, searching for health-related information online and even self-diagnosis and self-treatment are not socially criticized. It could then be assumed that the data obtained within the study are not significantly affected.

This is the first study in Poland carried out on such a large study group to analyze the issue of the search for health information on the Web. The wide range of questions on the use of the Internet for health purposes should be considered a strength of the study, as they make it possible to analyse different aspects of this phenomenon.

The information provided by persons involved health care (e.g. physicians, nurses) is treated by the patients very seriously.[18] There is the pressing need to build an e-health infrastructure and make it an integral part of health care system. Therefore, there is a need of educating and training of nursing personnel to enable their involvement in the e-health implementation efforts.[19] People suffering from chronic diseases, and their guardians, are particularly active in searching the Internet for information about health. They are considered to be pioneers looking for new ways towards a healthy lifestyle.[18] The results of the present study show that persons showing allergy symptoms (in comparison to healthy individuals) more often search the Internet for the information about their health or the health of a family member. What's more, in our study, the results indicate that persons clinically diagnosed with asthma search the Internet half as often for opinions about healthcare institutions than those declaring asthma that had not been confirmed by a physician. This result suggests that those suffering from chronic asthma and not under constant medical care, need more a professional medical opinion than those

who are under medical supervision. It is worth underlining that Fox presents examples in which searching the Internet for information about health proved very helpful in difficult circumstances, when physicians did not try to find a method in a therapeutic process that would bring relief to suffering patients.[18] The use of social forums, where other patients share their experiences in similar situations, proved very useful. Access to medical advice on the Internet is regarded as a new model of contact between a patient and a physician, and which can be promising for improvements in health care.[18] However, Pías-Peleteiro et al. underline that the so-called information about health published on the Internet does not provide users with credible and reliable medical advice.[20] They analysed information published on the Internet about vaccinations against HPV and concluded that the information was incomplete, outdated, unreliable and unreasonable from a scientific point of view.[20] The results of the present study demonstrated that women declare confidence in the information about health issues available on the Internet, and that those suffering from asthma and/or allergic diseases search the Internet for health information, which was also confirmed by Duplaga (2013),[21] Heaivilin et al. (2011),[22] Moretti et al. (2012),[23] Bujnowska-Fedak (2015)[24] and Kisilowska and Jasiewicz (2013).[25] The results obtained in our study and by the cited authors are very important, bearing in mind that in 2009 MacNeily and his team analysed the credibility of information about health published on the Internet.[26] As many as 124 websites were analysed: only 35% of these websites dedicated to health issued were accredited by non-profit organisations, 77% did not provide any references to the information and 48% did not provide the names of the authors of the published texts.[26] These results are fundamental due to the scale of the phenomenon. Considering the results of MacNeily and the results of this study, which indicate that disease affects the frequency of use of the Internet, it appears advisable to create professional websites with medical information. Portals should reference the medical encyclopaedia and provide Internet users with reliable and accurate information about the interest of their health problem. The portals should be reviewed by independent experts in the field of medicine. Contemporary society has free unlimited access to the Internet, thus to information that can influence a diagnostic process.[27] Avery gives an example of a patient who, because of a self-diagnosis made with 'Dr Google,' had damaged his health by influencing the diagnostic process of the physician.[27] In our study, we obtained results that women seek information on the Internet about health or discomfort when they do not want or cannot go to the physician. Furthermore, people with a lower economic status are more likely to seek health information on the Internet. The results obtained in our study are different from the results of a systematic review conducted by Zschorlich et al., which showed that searching for health-related information on the internet – either on their own behalf or on behalf of others – consists of middle-aged women with a higher level of education and income.[28] The results are very disturbing, as a diagnosis made by a patient as well as a therapeutic process undertaken on their own are often dangerous for health and even the life of the patient.[3,27] Patients could verify the credibility of the information published online with their physician and, in any case, should not undertake a therapeutic process just based on data available on the Internet.[3] Therefore, women are in a risk group in this area.[28–30]

According to the results published by Hesse, 'Dr Google' is the most frequently used source of information about health in the USA.[31] While Hesse describes this trend as positive, he stresses that health care should aim at improving and making information published online credible, so that it does not mislead the patient.[31] The author underlines that health education of patients from websites can have a measurable impact on the health care system. However, these systems should endeavour to create a global collection of reliable and scientifically confirmed data on health that would be available online. Hesse thinks that the online involvement of patients in therapeutic and diagnostic processes can bring optimized economic benefits for the health care sector.[31] Considering the results of a systematic review carried out by a team of Morrison et al., this issue is promising. Morrison et al. showed that in patients with asthma digital interventions may be effective at improving knowledge, reducing activity limitation, improving markers of self-management, improving quality of life, and optimizing medication use in those less than 65 years of age.[32]

Owing to the growing number of persons searching the Internet for information on health and disease, it is crucial to verify the following issues:

(1) Does society indeed base its knowledge on health solely on the information found online?
(2) Are these data verified by a primary care physician or a specialist?
(3) Can this information positively influence the quality of life of a chronically ill person?

It should be emphasized that until now no studies have been carried out that would indicate how information on health obtained from the Internet can influence the quality of life of those suffering from asthma and/or allergies. This issue is of vital importance as it will indicate new environmental risks for public health that would influence epidemiology and the development of allergic diseases (e.g. medical advice published on the Internet by unqualified persons through social media, for instance). Therefore, this issue requires further studies from the perspective of public health.

6. CONCLUSIONS

The results of this study showed that persons clinically diagnosed with asthma search the Internet less often for information about the reputation of health care institutions. This suggests that those suffering from chronic diseases and not under constant medical care, particularly need more professional medical information. Persons who declare asthma search the Internet more often for infor-

mation about health and disease during the month. In addition, results of the survey showed that searching for information about health and disease on the Internet depends on gender, with more women searching than men. People with a lower economic status are more likely to seek health information on the Internet. These results suggest that issues discussed and searched via the Internet should be provided to physicians for appropriate commentary. Due to the high availability of incorrect medical content on the Internet, physicians should be subject to training, in the field of: how to talk to an Internet user, which questions or comments to expect, what content requires a strong reaction by the physician, etc.

Conflict of interest

We declare that there is no relevant conflict of interest.

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Case study

The use of EEG biofeedback in rehabilitation of a patient with amyotrophic lateral sclerosis with cognitive, mood and motivation disorders

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ABSTRACT

Introduction: Amyotrophic lateral sclerosis (ALS) is primarily a degenerative disease of the nervous system, progressive, and of unknown aetiology. It leads to the limitation of movement (muscular dystrophy), impaired communication with others (speech disorders, dysarthria), dietary problems (dysphagia) and mental dysfunctions.

Aim: Our purpose was to assess the neurorehabilitation effectiveness of patient with ALS.

Case study: A 71-year-old male patient was diagnosed with ALS. The study of cognitive, mood and motivation disorders was performed using neuropsychological and neurophysiological methods. The authors assessed the impact of the neurofeedback method on EEG neurophysiological parameters: beta, beta2, sensorimotor (SMR) and theta waves. We used 4-channel headbox EEG DigiTrack BF.

Results: Neuropsychological diagnosis showed the presence of executive deficits: the ability to plan and perform complex tasks, and distraction in response to an external stimulus. Test for depression showed moderate mood decline and impulsiveness. Fear of the disease was manifested by excessive concentration on health, depersonalization, diurnal mood swings and intense obsessions. Reinforcement of behaviours responsible for an increase in SMR waves (the so-called high alpha 12–15 Hz) was aimed at reducing impulsive behaviour. Our goal was to diminish the amplitude and percentage share of: theta (4–8 Hz) and beta2 (frequency above 18 Hz) waves whose excess was manifested by emotional states, such as anxiety and psychomotor agitation. After a series of 10 sessions, the amplitude of SMR waves in the right hemisphere was increased. In addition, the desired reduction of beta2 waves was achieved.

Conclusions: The study suggests that neurofeedback can be used as a neurorehabilitation component of the personalized complex rehabilitation protocol for the ALS patients. The improvement of mental health is largely associated with better patient collaboration in the management of somatic disease by: enhancing motivation for rehabilitation, increasing tolerance of the disease and reducing anxiety.

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1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is primarily a degenerative disease of the nervous system, progressive, and of unknown aetiology. It leads to the limitation of movement (muscular dystrophy), impaired communication with others (speech disorders, dysarthria), dietary problems (dysphagia) and mental dysfunctions. In Poland, the incidence of ALS is 4–6 cases per 100,000 people. The mean age of incidence falls in the 6th to the 7th decade of life; it is more common in men than in women (about 1.5 : 1.0).

Neurofeedback (NFB) is one of the mechanisms known as electroencephalographic (EEG) feedback and involves monitoring of the brain activity by analysing EEG signals.[1] Changes in the bioelectricity of the brain are reflected in human cognitive processes. This assumption allows for the use of NFB in the process of diagnosing and treating neuropsychological defects, and mood and motivation disorders. NFB can also be used as a supportive psychotherapy procedure. It allows the establishment of the harmony of brain wave activity on the principle of bioregulation and self-learning of the brain through video training games.[2]

Studies show that while working with NFB, the human brain learns via conditioning: instrumental and classic.[3] Instrumental conditioning means rewarding the patient for obtaining a psychophysical state of the body which is consistent with thresholds determined for individual brain waves. By working with the therapist, the patient learns to react in the desired manner. In instrumental conditioning of brain waves, the patient acquires the ability to influence the information observed on the screen by changing his/her mental state (e.g., relaxation, concentration) until he/she gets a reward, i.e. a certain number of points (sound and visual feedback). Because the exercise is repeated many times, training activities are fixed and then automatically restored. Classic conditioning in NFB therapy is when the patient learns to transpose into a specific psychophysical state of the body, e.g., the state of concentration is connected with reduced free-wave activity and increased high-speed activity. Then, after the end of the training, the patient associates this condition with the performance of certain intellectual tasks.

Table 1. Bioelectric activity of the brain and mental states.[3]

Frequency bands	Cerebral waves	Feature
0.5-3.0 Hz	delta	1. Learning disorders. 2. Brain damage. 3. Motion artefacts.
3-5 Hz	low theta	Drowsiness.
6-7 Hz	high theta	1. Lack of concentration on external stimuli. 2. Internal orientation. 3. Memory extraction and visualization (7.5-8.5 Hz).
8-10 Hz	low alpha	Internal orientation.
11-13 Hz	high alpha	State of alertness, wide awareness.
13-15 Hz		1. State of alertness, high concentration. 2. State of calmness, reduced anxiety in which action is preceded by thought.
16-20 Hz	beta	Cognitive activity, status of mobilization for problem solving.
19-23 Hz	beta2	Anxiety, emotional intensity of mental experiences.
24-36 Hz		Rumination.
38-42 Hz	gamma	Cognitive activity (high attention).

Table 1 summarizes brain waves and their correlation with mental states.

Instrumental learning with the use of NFB is possible based on the following assumptions:

- mental states can be described by the record of bioelectrical activity of the brain;
- normal brain wave patterns correlate with disorders and psychiatric syndromes;
- a person can learn to influence the pattern of their own brain waves;
- changing brain pattern changes behaviour;
- brain mapping can help diagnose psychiatric syndromes and show patterns of communication between areas of the brain.

2. AIM

The aim of the study is to present the use of NFB in rehabilitation of a patient with ALS with cognitive, mood and motivation disorders.

3. MATERIAL AND METHODS

A 71-year-old male patient was diagnosed in 2012 with ALS. The study of cognitive, mood and motivation disorders was performed using neuropsychological and neurophysiological methods. The authors assessed the impact of the NFB method on EEG neurophysiological parameters: beta, beta2, sensorimotor (SMR) and theta waves. We used 4-channel headbox EEG DigiTrack BF. The purpose of the therapy was to reduce the number of theta and beta2 waves and strengthen SMR waves.

Quantitative EEG (QEEG) diagnosis was introduced before and after training, and both records were analyzed. The degree of NFB training difficulty was chosen taking into account the individual capabilities of the patient. Workouts were conducted in a series of 10 sessions, 3 times a week. Each session lasted 30 minutes. The study used standard training with mounting electrodes in the central band C3 : C4 (beta/theta : SMR/theta), with classic setting of the frequency bands. The speed of delivering audio feedback was 150-200 ms.[3]

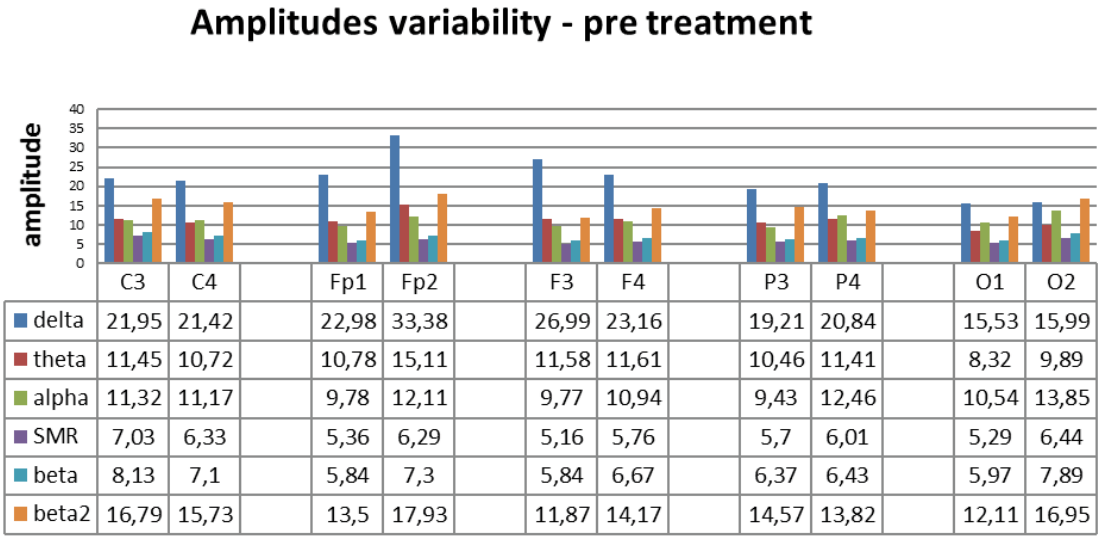
Psychological diagnosis was made using the STAI-Spielberger State-Trait Anxiety Inventory, the Eysenck Personality Questionnaire (EPQ-R), the Beck Depression Inventory (BDI), the Points Matching Test - Common Task Test, and Raven's Progressive Matrices.

4. RESULTS

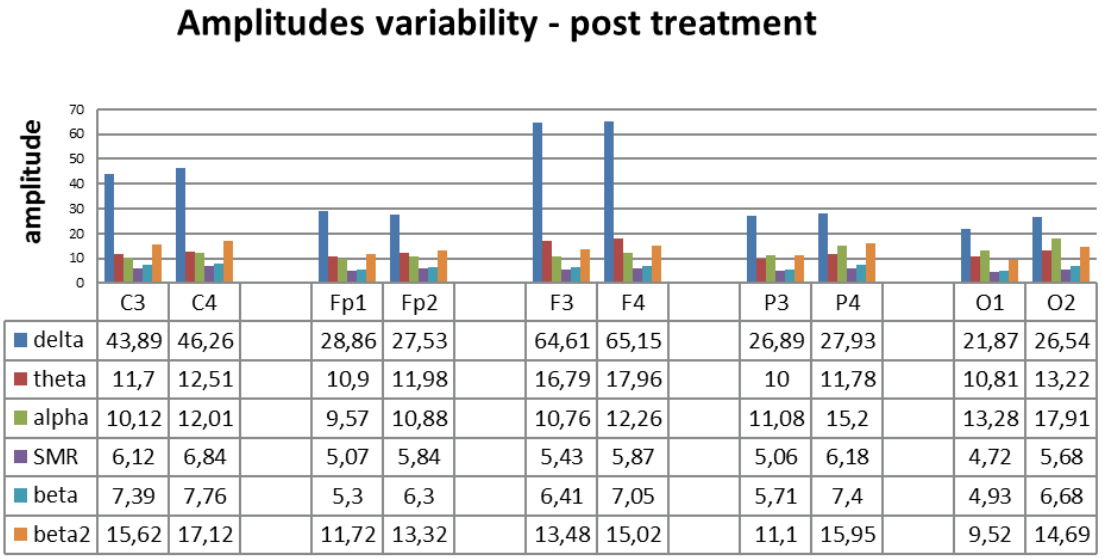
Neuropsychological diagnosis showed the presence of executive deficits. Disruptions in the executive functions

concerned the ability to plan and perform complex tasks, and distraction in response to an external stimulus (CTT1 – ten 43, centile 24; CTT2 – ten 31, centile 3). The following abilities were reduced: visual searching, maintaining and divisibility of attention and sequential processing of information. The assessment of intellectual capacity revealed the functioning of the patient as above average. The ability to concentrate and maintain attention in terms of auditory and visual modality was weakened. Test for depression (BDI-18 points) showed moderate mood decline. Fear of the disease was manifested by excessive concentration on health, depersonalization, diurnal mood swings and intense obsessions. The patient lost interest and willingness to act, work and devote time to hobbies. Slight slowdown in thinking and speech, weakening of concentration, tension and irritability were also reported. The patient felt guilty for disappointing other people, and was discouraged in life. The STAI study (L-feature sten 7, L-state sten 4) identified the elevated level of anxiety manifesting itself as a subjective, consciously experienced feeling of anxiety and tension, accompanied by arousal of the autonomic nervous system. No sleep disorders or suicidal thoughts were observed in the study.

The patient had a limited insight into his own functioning. He was oriented as to the place, time and schema of his own body. Orientation in space was slightly disturbed. Procedural learning and the ability to acquire motor skills and master specific tasks were preserved. In the sphere of



	C3	C4	Fp1	Fp2	F3	F4	P3	P4	O1	O2
delta	21,95	21,42	22,98	33,38	26,99	23,16	19,21	20,84	15,53	15,99
theta	11,45	10,72	10,78	15,11	11,58	11,61	10,46	11,41	8,32	9,89
alpha	11,32	11,17	9,78	12,11	9,77	10,94	9,43	12,46	10,54	13,85
SMR	7,03	6,33	5,36	6,29	5,16	5,76	5,7	6,01	5,29	6,44
beta	8,13	7,1	5,84	7,3	5,84	6,67	6,37	6,43	5,97	7,89
beta2	16,79	15,73	13,5	17,93	11,87	14,17	14,57	13,82	12,11	16,95



	C3	C4	Fp1	Fp2	F3	F4	P3	P4	O1	O2
delta	43,89	46,26	28,86	27,53	64,61	65,15	26,89	27,93	21,87	26,54
theta	11,7	12,51	10,9	11,98	16,79	17,96	10	11,78	10,81	13,22
alpha	10,12	12,01	9,57	10,88	10,76	12,26	11,08	15,2	13,28	17,91
SMR	6,12	6,84	5,07	5,84	5,43	5,87	5,06	6,18	4,72	5,68
beta	7,39	7,76	5,3	6,3	6,41	7,05	5,71	7,4	4,93	6,68
beta2	15,62	17,12	11,72	13,32	13,48	15,02	11,1	15,95	9,52	14,69

Figure 1. Pre- vs. post-treatment changes in the amplitudes of the given waves for the respective leads in the quantitative EEG analyses.

personality, the EPQ-R questionnaire was used to evaluate mean scores for the following features: psychotism, extravagance, neuroticism, positive self-presentation, and tendency to addiction and criminality.

At admission to the clinical department of neurological rehabilitation the physical examination revealed: flaccid tetraparesis, more pronounced in the left limbs, extensive muscle atrophy within the shoulder girdle and muscles of the limbs, limited fine hand movements, weakening of muscle strength, numerous fasciculations especially in the upper torso, limited mobility of the cervical and lumbar spine, right-sided first degree scoliosis of the thoracic and lumbar spine, and decreased exercise and breathing capacity. In the march test, the patient stepped 192 m with the help of a walker. He complained of pain in the spine and joints (up to 10 points on the VAS scale).

The QEEG performed prior to the initiation of therapy showed the dominance of SMR (12–15 Hz) and beta (15–20 Hz) waves in the left hemisphere (beta band – normal, SMR – abnormal). Delta (1–3 Hz) and theta (4–8 Hz) waves in the central band slightly exceeded the norm. The beta2 frequency (20–34 Hz) in leads C3 and C4 was rated above the norm. The bilateral elevation of beta2 values suggested increased emotional tension, anxiety and mood disturbance. The aim of NFB therapy was to achieve a state of relaxation, reinforce attention and motivate the patient to exercise.

Reinforcement of behaviours responsible for an increase in SMR waves (the so-called high alpha, 12–15 Hz) was aimed at reducing impulsive behaviour. Our goal was to diminish the amplitude and percentage share of: theta (4–8 Hz) and beta2 (frequency above 18 Hz) waves whose excess was manifested by emotional states, such as anxiety and psychomotor agitation. After a series of 10 sessions, the amplitude of SMR waves in the right hemisphere was increased. In addition, the desired reduction of beta2 waves was achieved.

Figure 1 shows pre- and posttreatment changes in the amplitudes of the given waves for the respective leads in the quantitative EEG analyses.

Kinesiotherapy included: respiratory exercises, gait improvement exercises, manipulation exercises, shoulder joint relief exercises, classic shoulder and upper limb shoulder massage, relaxation exercises, PNF exercises, equivalent exercises, occupational therapy, lower limbs relief exercises, lasers for painful areas, lower extremity drooping exercises, pain trigger points mobilization, warm gel packs for painful areas, and TENS currents for the lumbar spine.

Initially, kinesiotherapy was hindered by the depressed mood of the patient and his weak motivation for exercising, and after a few minutes he gave up the rehabilitation. NFB therapy was introduced. NFB training, adjusted to the patient's deficits, improved his mental state: his mood stabilized, motivation for physical rehabilitation increased, and concentration improved.

Complex rehabilitation improved the following parameters: muscle strength in the upper and lower limbs as well as postural muscles, movement coordination, balance and fine hand movements, respiratory and exercise capacity. In addition pain reduced (up to 3 points on the VAS scale) and gait quality improved. In the march test, the patient stepped 224 m with a walker.

5. DISCUSSION

ALS is an incurable disease. In its initial stage, the patient denies the existence of the disease. He cannot accept the diagnosis and starts to become isolated from other people. In the second phase, when he realizes that he can no longer deny the disease, he becomes angry at his inability to control the situation. Before the patient starts to accept the disease and the inevitability of death, he tries to 'bargain.' The awareness of the ineffectiveness of therapeutic actions causes mental disorganization: mood disorders, aggression, passivity, apathy, suicidal thoughts, or addiction. The loss of self-mobility is the end of an important stage in life. Realizing dependence on others often means limiting the socio-occupational functioning.[4] People with fatal illness often suffer from depression, high levels of anxiety, and a lack of motivation to participate in rehabilitation. Patients complain of severe pain. Pain has a huge negative effect on the human psyche, and this directly affects how the patient copes with illness and disability.[5] Pain can be intensified by anxiety or environmental factors. It enhances the feeling of loneliness and rejection, lowers mood, and increases the risk of depression.

Psychotherapy plays an important auxiliary role in the treatment of patients with somatic disease and anxiety disorders. The treatment not only leads to a symptomatic improvement resulting from the cessation of functional disturbances, but also causes a betterment of the somatic status. As the general condition gets better, the patient more eagerly collaborates in the management of the somatic disease by:

(1) abolition of anxiety that prevents participation in diagnostic tests and necessary consultation;[6]
(2) increased ability to tolerate illness and discomfort, and acceptance of limitations;
(3) dealing with internal and external conflicts, and regulating negative emotions that may affect the course of the somatic disease;
(4) successful resolution of problems resulting from somatic disease-related limitations, mainly through redevelopment of the value system;
(5) strengthening of motivation for rehabilitation.[7]

The limbic system plays an important role in recognizing and evaluating stressful situations.[8]

The hippocampus and entorhinal cortex are involved in the creation of memory traces and cognitive schematics. Chronic stress can lead to degeneration of dendrites in hippocampal neurons, which explains the cognitive decline.[9] The amygdala holds emotional response programmes throughout life. Despite the lack of real danger, the conditioning of fear generates anxiety in certain situations. Fear attacks may be due to pathological discharges in the

amygdala neurons, as confirmed by functional tests in PET, SPECT.[10] The poor development of connections between the neocortex and limbic system is responsible for alexithymia (difficulty with reading emotions). Inhibitory neurons run from the frontal lobes to the amygdala, but projections in the opposite direction are much more numerous. Perhaps that is why emotions more easily dominate thoughts, and it becomes more difficult for thoughts to control emotions.[8] The presence of coupling between the frontal cortex and the limbic system provides justification for psychotherapeutic activities restoring balance, which create a chance of controlling the disease.[11]

There is evidence for the negative impact of stressors on immune responses.[12] It has been shown that those who experience stress related to the loss of a family member have decreased activity of B and T cells and weakening of NK (Natural Killer) cells.[13]

Since 1997, research into neuroimmunology of depression has been closely linked to studies on stress neuroimmunology. Depression is associated with the inhibition of some elements of the immune response and the concomitant stimulation of, for example, acute phase proteins and proinflammatory cytokines.[14]

On the other hand, the immune system may have an impact on the mental state, mainly by increasing the secretion of cytokines that alter the metabolism of monoamines: serotonin, noradrenaline, dopamine, which are important in the pathogenesis of depression. Cytokines involved in fighting infections, such as interleukin-6 and interleukin-1, can cause depressive symptoms. They reach the hypothalamus by triggering a response to stress (h-h-a axis stimulation) with all its physiological consequences.[15]

NFB is a therapeutic-assistive approach aimed at achieving a psychophysical state characterized by emotional silence, increased motivation, and improved memory and concentration. Thanks to the performed actions, the patient learns to inhibit the excess and amplify the deficiency of specific brain waves and thus change behaviour in a desired manner. In therapy, it is important to strengthen frequencies that are typical but distorted in a given area.[2] The studies have shown that the therapeutic effects of NFB persist for many years, particularly in the cognitive rehabilitation of non-psychiatric individuals.[16,17]

In patients with severe neurological deficits and uncertain prognosis, standard psychological therapy and rehabilitation often do not produce expected results. Incorporating an original element in the form of NFB therapy creates new therapeutic possibilities. In our patient, the therapy brought a significant reduction of pain, improved motivation for rehabilitation, along with improved physical performance and mood. However, doubts about the introduction of new therapeutic methods to standard treatment could ultimately be resolved only in randomized, long-term, double blind studies, with a control group not receiving treatment.[18] Unfortunately, longterm placebo-based research in rehabilitation is often not feasible, because it generates high costs and may be unethical.[19]

In our work, we have highlighted the possibility of organizing clinical trials using biological feedback as a complementary therapy to existing treatments. Choosing exercises (training protocols) and duration of therapy requires further studies.

6. CONCLUSIONS

1. NFB can be used to treat psychological disorders and as supportive therapy in rehabilitation.
2. The improvement of mental health is largely associated with better patient collaboration in the management of somatic disease by: enhancing motivation for rehabilitation, increasing tolerance of the disease and reducing anxiety.

Conflict of interest

None declared.

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Original article

Poor lumbar movement control in males exercising at the gym: Assessment and training using pressure biofeedback unit

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ABSTRACT

Introduction: Mechanical overloading is one of the causes of low back pain (LBP). Dysfunction of movement control and impaired movement patterns can constitute a potential risk factor for LBP development.

Aim: The aim of the study was to assess lumbar extension control in young physically active males with the use of the pressure biofeedback unit (PBU) in the context of the most relevant literature.

Material and methods: Randomly 30 young men regularly training at the gym (mean age 19.7 years) were selected to participate in the study. The survey contained basic data (such as: age, profession, height and weight). The dynamic assessment included abdominal muscle endurance test and three tests for movement extension control (the single straight leg test, the double straight leg test in the supine position and the bench press test).

Results and discussion: During the single straight leg test, 63% of the participants did not control lumbar extension for the right leg, and 37% for the left leg. In the double straight leg test, 77% of the participants did not control lumbar extension. During the bench press tests, 22% did not control lumbar extension during barbell lowering and 30% during lifting. Repeated excessive extension, which is frequently inadequately controlled by the neuromuscular system, may cause damage to the spinous processes and the soft tissue.

Conclusions: Individuals training at the gym may have a tendency towards uncontrolled lumbar extension. PBU can be useful tool in view of the prevalence of LBP.

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1. INTRODUCTION

It is estimated that approximately 80% of the population experience at least one episode of low back pain (LBP) in their lifetimes.[1,2] LBP is a major cause of functional disability and pain to the patient, as well as a financial burden to the healthcare system, employers and also for the society.[2–6] LBP is classified into: primary or secondary, mechanical or non-mechanical, with or without neurological complications, or associated with inflammatory, infectious, neoplastic, psychosomatic or other diseases.[4]

The main causes of LBP, or more specifically, mechanical LBP (MLBP), are connected with the musculoskeletal system (incorrect, forced body posture) and wrong dynamics (incorrect biomechanics, impaired movement patterns, and incorrect lumbopelvic-hip rhythm.[4,7–10] Van Dillen et al. emphasize the need for a standardized classification system of homogenous MLBP subtypes.[7] Both the movement system impairment (MSI) and the Kinetic Control standardize the classification of MLBP focusing mainly on the diagnosis of uncontrolled movement in dynamics.[7,11–16]

Identifying and classifying movement faults are becoming an essential tool in contemporary rehabilitative neuromusculoskeletal practice.[11,16–18] Many arguments support the existence of a relationship between LBP, impaired movement patterns, muscle activation and coordination of synergistic muscles.[7,9,11,12,15,19–22]

2. AIM

The aim of the study was to assess lumbar extension control in young physically active males with the use of the pressure biofeedback unit (PBU) in the context of the most relevant literature.

3. MATERIAL AND METHODS

3.1. Participants

The participants consisted of 30 men regularly exercising in the gym. The mean age of participants was 19.7 (SD 4.06). The inclusion criterion was training for a minimum of 3 months at the gym. Exclusion criteria were training for fewer periods of time then 3 months. Participants were selected randomly.

3.2. Questionnaire

The participants were additionally asked to complete a purpose-designed survey containing basic data, such as: age, profession, height and weight. The survey also contained exercise-related questions and questions concerning the participants' awareness of correct execution of the bench press.

3.3. Dynamic assessment

The dynamic assessment included selected motor tests (MSI, Kinetic Control) facilitating the assessment of lumbar extension control. During the test, the participants were in a supine position, with the stabilizer PBU (Figure 1) placed under the lumbar section, with its centre at L3. When the lumbar section was in a neutral position, the PBU was pumped to 40 mm Hg. Next, from the starting position

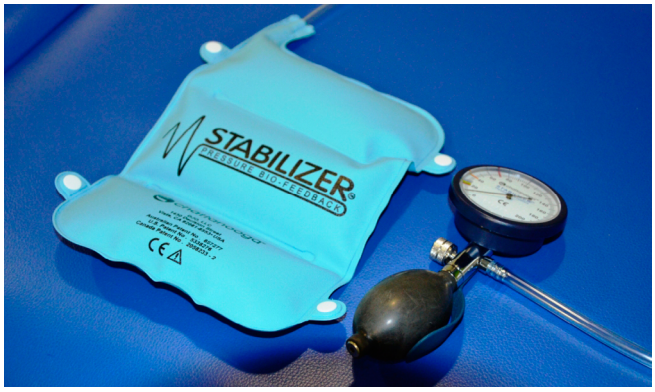

Figure 1. Pressure biofeedback unit.

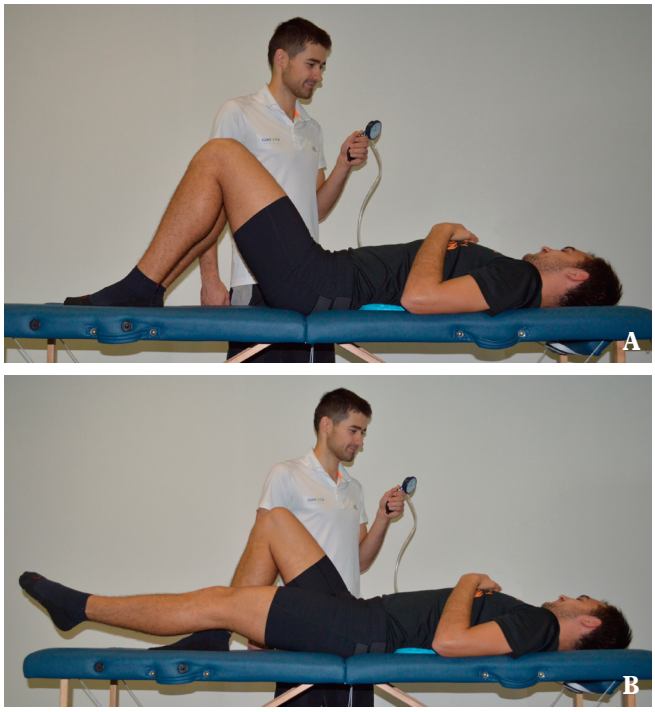

Figure 2. Single straight leg lower test: starting position (A), leg extension (B).

Figure 3. Double straight leg lower test.

Table 1. Tests used for dynamic assessment of participants.

Test	Assessed feature	Norm
Hip extension asymmetrically to the PBU	Extension control short/unilateral lever	±5 mm Hg[23] ±10 mm Hg[13] – due to the short/unilateral lever, the norm applied in this test was ±5 mm Hg
Hip extension symmetrically to the PBU	Extension control long lever	±5 mm Hg[23] ±10 mm Hg[13] – due to the long lever, the norm applied in this test had a higher margin: ±10 mm Hg (to the participants' benefit)
Bench press	Extension control (high load)	±5 mm Hg in all movement tests in supine position[23] ±10 mm Hg in all motor tests in supine position[13] – the norm applied in this test had a higher margin: ±10 mm Hg (to the participants' benefit) – the lifted weight 60% × 1RM

(Figure 2A), the participant was asked to perform a single leg movement to 0° hip extension (Figure 2B) and return to the starting position, maintaining 40 mm Hg on the PBU. The test was performed for each leg, with an acceptable margin of error of ±5 mm Hg. The exercise progressed to double leg extension and return to the starting position (Figure 3). The acceptable margin of error was ±10 mm Hg. In both exercises, the arms were crossed over the chest or positioned alongside the body, with the inner sides leaning against the table.[13] The maximum deviation from the norm (norm 40 mm Hg on the PBU) was recorded for both tests in three positions: during initiation of movement (lifting the leg off the ground), during single/double leg extension, and during return to the starting position.

Each participant had the possibility to perform three trials with visual monitoring of the PBU value. The actual test was then carried out without visual feedback and the obtained result was recorded on a patient's chart.

The stability of the lumbar section during the bench press was assessed with the PBU. The lifted weight was 60% of the maximum load (60% 1RM). The participants performed two trials repeats with visual feedback. The third repeat constituted the actual test; the lowest values at barbell lowering and lifting were recorded. The tests are presented in Table 1.

3.4. Statistical analyses

The obtained results were analysed statistically in order to identify the relationships between variables. Assessment was based on Spearman's rank correlation coefficient. A correlation was considered significant if the value of P was less than 0.05 ($P < 0.05$). The analysis also included scientific data concerning the use of PBU both in assessment and in training in individuals with lumbar extension dysfunction.

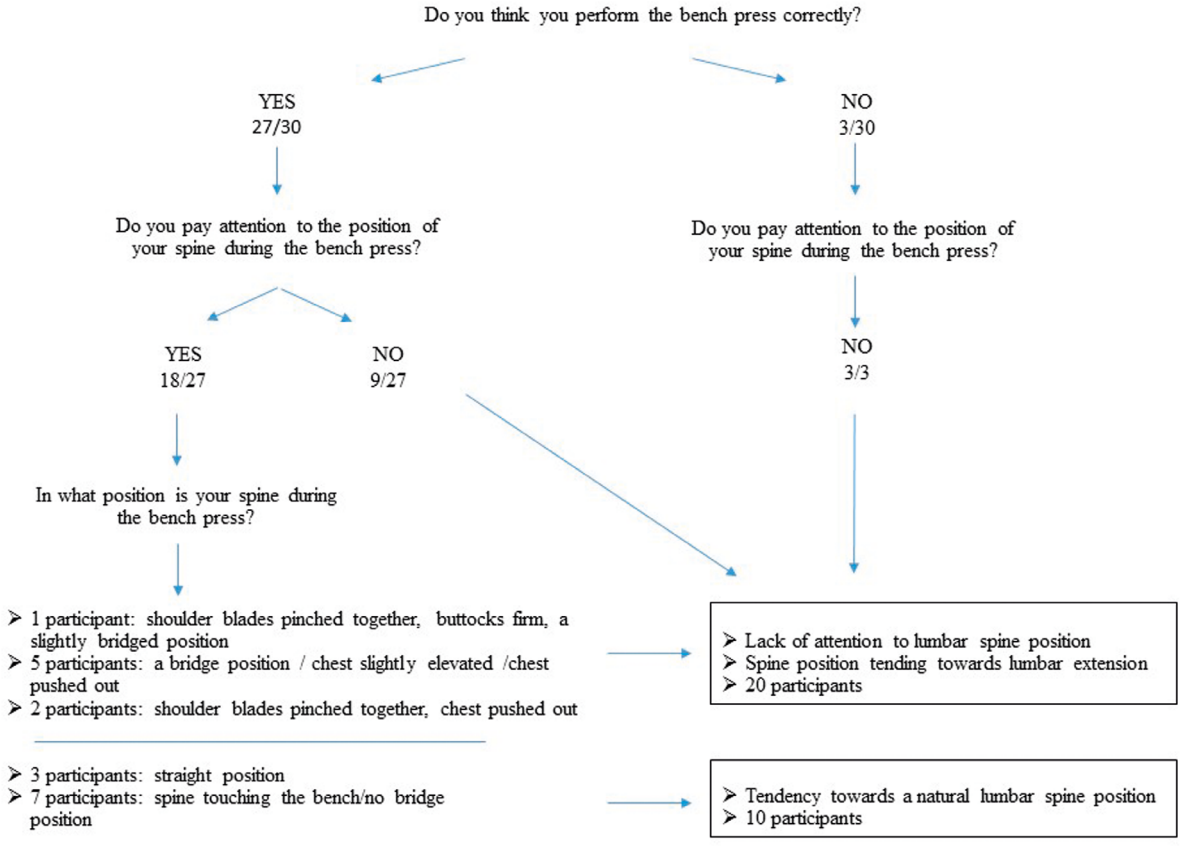

Figure 4. Questions associated with awareness of low back alignment during bench press

4. RESULTS

4.1. Survey

The survey also contained exercise-related questions and questions concerning the participants' awareness of correct execution of the bench press. The obtained data is presented in Figure 4.

4.2. Dynamic tests

In movement tests assessing extension control in asymmetrical extension of one leg (short/unilateral lever) (Figure 2), 63% of the participants did not control right leg extension (<35 mm Hg) and 7% generated compensation, both towards extension and flexion (>45 mm Hg). During left leg extension, 37% of the participants did not control the extension of the lumbar section. In the symmetrical extension of both legs (long lever) (Figure 3), 77% of the participants did not control extension (PBU < 30 mm Hg) especially when they were lowering their legs, whilst 6% showed lack of control of both extension and flexion (PBU > 50 mm Hg) of the lumbar spine.

During the bench press exercise with PBU assessment, 7 participants (23%) did not control the position of the lumbar section when lowering (<30 mm Hg) and 9 (30%) when lifting the barbell (<30 mm Hg).

The statistical analysis of correlations of the different tests is presented in Table 2, where *R* refers to the strength and direction of the relationship. For the bench press test, a significant correlation was observed for the ASIS-PSIS difference (–0.44*) and for the two stages of the bench press: barbell lowering and lifting (0.37*). The individual stages of tests (asymmetrical hip extension, symmetrical hip extension) performed with the PBU also correlated with one another (Table 2). Uncontrolled rotation was not assessed. Table 2 shows statistically significant correlations.

Table 2. Selected statistically significant correlations.

Correlated variables	*R*
Test with the PBU: right leg extension vs. left leg extension	0.38*
Test with the PBU: return from right leg extension vs. return from left leg extension	0.68*
Test with the PBU: initiation of double leg extension vs. right leg extension	0.39*
Test with the PBU: initiation of double leg extension vs initiation of left leg extension	0.45*
Test with the PBU: barbell lowering vs. ASIS to PSIS height difference	–0.44*
Test with the PBU: barbell lowering vs. lifting	0.37*

* Statistically significant

5. DISCUSSION

The spinous processes, intervertebral discs and joints, all passively limit lumbar hyperextension. Repeated excessive extension, which is frequently inadequately controlled by the neuromuscular system, may cause damage to the spinous processes and the soft tissue between them. If the spinous processes are widely spaced, the apophyseal joints are likely to become damaged first.[24] Additionally, excessive extension may cause damage to the interspinous ligament, connected with the mechanism of intervertebral disc damage.[11]

According to Chimenti et al., one of the activity-related factors for LBP may be an impaired lumbopelvic pattern, repeated during sports and every-day activities.[9] Uncontrolled lumbar extension was observed during motor control tests in the young male group. At low load, 37% of the participants experienced problems with the test regarding left leg movement and 70% regarding right leg movement. At high load, 83% of the participants experienced problems with the exercise (double leg movement). During bench-press test 23% (lowering phase) and 30% (lifting phase) of participants experienced uncontrolled lumbar extension.

The movement dysfunction is identified by a series of clinical tests.[13,14,19,25] The lower limb test in a supine position is commonly used to diagnose MLBP and to assess patients' motor ability in order to determine the direction of pain.[9,11,13,14,26] Roussel et al. studied the correlation between musculoskeletal system injuries and lumbar movement control in dancers.[14] The tests included the so-called 'knee lift abdominal test' (KLAT), whereby the individual is in a supine position, with one leg bent at 90°, maintaining lumbar stability (the PBU was also used). The test is used to assess lumbar flexion and extension control.[11,13] The KLAT, together with the 'standing bow' test had a 78% correlation for increased risk of lower limb or lumbar injury. By contrast, a history of LBP or articular hypermobility (typical in dancers) did not indicate an increased risk of injury in the studied group. According to Hodges and Moseley, pain may lead to movement control disorders and vice versa: impaired coordination or timing delay may lead to a higher risk of musculoskeletal injury.[22] Although the interpretation of movement tests does not fully explain the causes of lumbar pain, it shows the validity of extension control tests. A positive movement test result obtained by a healthy patient (without pain), may be a sign of weak neuromusculoskeletal coordination.[11,13,20]

The patient's objective during tests/exercises with the PBU is to maintain the lumbar section in the most neutral position possible.[27,28] According to Panjabi's core stability theory, training the neuromuscular system minimizes passive structure overload.[29-31] The main advantage of the PBU during testing or training is feedback, which facilitates the elimination of lumbar compensation.[27,28]

Awareness and cognitive work is an important key element not only in back pain therapy but also in prevention and sport training. Tests with the use of the PBU facilitate the assessment and awareness of quality of lumbar extension control training. Lack of eccentric control of this movement during basic everyday activities very often generates an excessive amount of lumbar extension movement, thus contributing to MLBP.[11,13,32,33]

6. CONCLUSIONS

1. Excessive changes in the PBU pressure in lumbar movement control tests during lower limb exercise in young male reflect the inability to sustain isometric abdominal muscle contraction. These results can be classified as uncontrolled extension movement.
2. There is no unequivocal evidence confirming that asymptomatic individuals with incorrect movement patterns are bound to suffer from lumbar pain in the future. However, in order to limit the growing problem of LBP, prevention and therapy with the PBU in individuals with poor neuromuscular control of the lumbar spine should be helpful.

Conflict of interest
None declared.

Ethical approval
The research was approved by Bioethical Commision (KB31/2013).

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Original article

Evaluation of hyponatremia among cirrhotic patients in Shariati Hospital, Isfahan, Iran

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ABSTRACT

Introduction: Patients with advanced cirrhosis are susceptible to hyponatremia due to impaired kidney function. Recent studies have shown that hyponatremia can be an independent predictor of hepatic encephalopathy (HE) in these patients.

Aim: The present study performed to evaluate the relationship between serum sodium concentration and HE in patients with cirrhosis.

Material and methods: This cross-sectional study was conducted on 65 cirrhotic patients admitted to the internal ward of Shariati Hospital in Esfahan, Iran. Patients were divided into two groups based on serum sodium concentration: (1) hyponatremic patients with serum sodium less than 135 meq/L and (2) those with serum sodium not less than 135 meq/L. Groups were compared regarding demographic characteristics, causes of cirrhosis, diuretics consumption, prevalence of HE, and severity of cirrhosis assessed using MELD and Child–Pugh scores, as well as biochemical measurements.

Results: Based on serum sodium levels, 21 patients (32.3%) had hyponatremia. Thirty (46.2%) individuals had HE. Comparing hyponatremic patients with those without low serum sodium, there were no statistically significant differences in gender, causes of cirrhosis, and MELD score between groups ($P > 0.05$); however, hyponatremic patients had more prevalence of HE ($P < 0.001$), diuretic intake ($P < 0.001$), lower levels of albumin ($P = 0.003$), and were older ($P = 0.017$). Severity of cirrhosis in patients with hyponatremia was mostly in groups B and C of Child–Pugh ($P = 0.002$).

Discussion: In summary, HE is frequent in cirrhotic patients with hyponatremia.

Conclusions: It is suggested to monitor serum sodium level in patients with cirrhosis to prevent HE and other complications, especially among those who are taking diuretics.

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1. INTRODUCTION

Advanced cirrhosis results in hyponatremia that is reported in nearly 57% of cirrhotic patients.[1] In cirrhosis, hyponatremia may occur due to either hypovolemia or hypervolemia;[2] however, the former, dilutional hyponatremia is more common. The development of dilutional hyponatremia in patients with cirrhosis is multi-factorial. Systemic vasodilation because of nitric oxide (NO) synthesis, release of antidiuretic hormone (ADH), and activation of renin-angiotensin-aldosterone and sympathetic nervous system are involved.[3] Hyponatremia may enhance the risk of early mortality and complications like infection, renal failure, and encephalopathy.[4]

Severity of cirrhosis is assessed by the Model for End-stage Liver Disease (MELD) scores. Some researchers have suggested incorporating serum sodium into the MELD score to make a more accurate survival prediction following liver transplantation.[5,6] Hazard ratio (HR) of risk adjusted mortality at 90 days in hyponatremic patients undergoing transplant have been found to be higher compared with controls with normal sodium levels.[7]

Hepatic encephalopathy (HE) is a complication of liver cirrhosis can occur in about 70%–50% of patients with cirrhosis and is significantly associated with morbidity and mortality rates, as well as poor health-related quality of life (HRQOL).[8] Several factors other than hyperammonemia have been suggested to play a role in the development of HE such as manganese, hyponatremia, and inflammation.[9] Some studies have shown hyponatremia as a predictive factor for the development of HE.[10,11] Additionally, in patients with minimal HE, hyponatremia can be indicative of resistant to treatment with lactulose.[12] However, there are few studies that have been conducted to explore possible association between hyponatremia and development of HE in cirrhotic patients.

2. AIM

The aim of this study was to assess the relationship between serum sodium levels and the prevalence of HE in cirrhotic patients.

3. MATERIAL AND METHODS

To determine the sample size, we assumed a confidence level of 95%, with a power of 80%. Based on previous data, we considered a prevalence of 20% for hyponatremia in our cirrhotic patients and a total of 62 participants were obtained. The study was involved 65 patients diagnosed with cirrhosis based on clinical, biochemical, and morphological criteria. The study was performed in the Internal Clinic of the Shariati Hospital of Isfahan, Iran, from September 2015 and November 2016. The protocol of study was approved by the Ethics Committee of the Najafabad Islamic Azad University. Written informed consent was provided by all patients before study entry. Subjects with neurological disorders, stroke, concussion, history of transjugular intrahepatic portosystemic shunt, neoplasms, cardiovascular diseases, inflammatory or infectious diseases, use of sedative drugs, supplements or medications containing sodium, fever, and shock were excluded.

Demographic, clinical, and biochemical data were obtained from patients. Causes of cirrhosis – cryptogenic, hepatitis C virus (HCV), hepatitis B virus (HBV), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH) – were defined. The patients on diuretic treatment were asked to describe duration of therapy.

Serum sodium was measured and hyponatremia was defined as serum sodium concentration les than 135 mEq/L. Disease severity scores model for end stage liver disease (MELD) was calculated from serum creatinine (mg/dL), serum bilirubin (mg/dL) and prothrombin time (INR) according to the UNOS guidelines.[13] Child–Pugh score was also calculated to evaluate the stage of liver cirrhosis. Accordingly, patients were assigned to one of three groups: stage A, stage B, and stage C .

Results were analyzed using SPSS (2013 IBM SPSS Statistics for Windows, v. 22.0). Categorical variables were analyzed using χ^2 and quantitative continuous data were compared using Student's t test. Whenever data were not normally distributed, we used logarithmic transformation. Otherwise, nonparametric statistics were used. A P value of less than 0.05 was considered to be statistically significant.

4. RESULTS

Mean age of patients was 58.4 ± 14.8 years. Thirty-six (55.4%) participants were males and 29 (44.6%) were females. Most common etiological factors order of frequency were cryptogenic, HCV, HBV, PSC and AIH. Mean MELD score was 13.4

Table 1. Demographic characteristics (n = 65).

Characteristics	*N*
Age (y,) mean ± SD	58.4 ± 14.8
Sex, *n*(%)	
Male	36(55.4)
Female	29(44.6)
Cirrhosis causes, *n*(%)	
Cryptogenic	40(61.5)
HBV	7(10.8)
HCV	11(16.9)
PSC	2(3.1)
AIH	2(3.1)
Others	3(4.6)
MELD score, mean ± SD	13.4 ± 8.7
Serum sodium (mEq/L), mean ± SD	136.3 ± 5.0
Child Pugh, *n*(%)	
A	26(40.0)
B	23(35.4)
C	16(24.6)
Diuretic intake, *n*(%)	
Spironolakton	20(30.8)
Furosemide	6(9.2)
Diuretic intake duration (m), mean ± SD	12.8 ± 7.8
HE, *n*(%)	30(46.2)
Ascites, *n*(%)	65(100)
Hyponatremia, *n*(%)	21(32.3)

Table 2. Biochemical variables in the groups.

Variable	Serum sodium <135 mEq/L (n = 21)	Serum sodium ≥135 mEq/L (n = 44)	P value
Age (y), mean ± SD	64.7 ± 12.1	55.4 ± 15.2	**0.017**
MELD score, mean ± SD	15.8 ± 8.0	12.3 ± 8.8	0.133
Sex, *n*(%)			
Male	12(57.1)	24(54.5)	0.844
Female	9(42.9)	20(45.5)	
HE, *n*(%)	19(90.5)	11(25.0)	**<0.001**
Diuretic intake, *n*(%)	15(71.4)	11(25.0)	**<0.001**
Cryptogenic, *n*(%)	12(57.1)	28(63.6)	0.615
HBV, *n*(%)	1(4.8)	6(13.6)	0.280
HCV, *n*(%)	6(28.6)	5(11.4)	0.084
PSC, *n*(%)	0(0)	2(4.5)	0.321
AIH, *n*(%)	0(0)	2(4.5)	0.321
Others, *n*(%)	1(4.8)	2(4.5)	0.969
Child pugh, *n*(%)			
A	2(9.5)	24(54.5)	**0.002**
B	11(52.4)	12(27.3)	
C	8(38.1)	8(18.2)	
ALT (U/L), median(IQR)	52.5(26.0–117.0)	44.5(23.5–64.0)	0.303
*AST (U/L), mean ± SD	72.3 ± 2.2	49.0 ± 2.6	0.123
*ALP (U/L), mean ± SD	285.2 ± 1.5	291.5 ± 1.7	0.875
Total bilirubin (mg/dL), median(IQR)	1.6(1.2–3.5)	1.4(0.9–2.2)	0.078
Albumin (g/dL), median(IQR)	2.7(2.2–3.3)	3.6(2.7–4.1)	**0.003**
Creatinine (mg/dL), mean ± SD	1.47 ± 0.04	1.02 ± 0.32	0.283
INR, median(IQR)	1.4(1.1–1.8)	1.1(1.0–1.5)	0.057

Comments: * Data are transformed to logarithm.

± 8.7 and most patients (40%) were in class A of Child–Pugh. Based on serum sodium levels, 21 patients (32.3%) had hyponatremia. Thirty (46.2%) individuals had HE (Table 1).

Comparing hyponatremic patients with those without low serum sodium, there were no statistically significant differences in gender, causes of cirrhosis, MELD score, and some biochemical measurements (ALT, AST, ALP, total bilirubin, creatinine, INR) between groups ($P > 0.05$); however, hyponatremic patients had more prevalence of HE ($P < 0.001$), diuretic intake ($P < 0.001$), lower levels of albumin ($P = 0.003$), and were older ($P = 0.017$). Severity of cirrhosis in patients with hyponatremia was mostly in groups B and C of Child–Pugh ($P = 0.002$) (Table 2).

5. DISCUSSION

Low serum sodium is related to poor prognosis, increased risk of mortality, infection, renal failure, and encephalopathy in patients with advanced liver diseases.[4] In total of cirrhotic patients participating in the present study 32.3% had hyponatremia that represents the high prevalence of this electrolytic disorder among patients with cirrhosis. Barakat et al. estimated the prevalence of hyponatremia at 59.46% in cirrhotic patients,[14] while the estimated prevalence rate of hyponatremia were 24.3% and 50.54% in other studies.[15,16] The difference in the prevalence of hyponatremia in cirrhotic patients could be explained by differences in sample size, cut-point used for defining hyponatremia, and severity of cirrhosis in patients.

Hyponatremia has been related to increased severity of liver disease based on the MELD score.[17] We could not find this relationship; maybe because both groups of patients had similar values of bilirubin, INR, and creatinine.

Complications such as severe ascites, impaired kidney function, spontaneous bacterial peritonitis, HE, and hepatorenal syndrome have been reported to be more common in cirrhotic-hyponatremic patients in a large cross-sectional study.[1] The prevalence of HE in our patients was 46.2%. This syndrome impairs quality of life and reduces life expectancy in cirrhotic patients, so it seems necessary to investigate factors associated with HE. Our study showed that 90.5% of cirrhotic patients with hyponatremia had HE which demonstrates high susceptibility of cirrhotic patients with hyponatremia to HE. Our results support findings of other studies. Shaikh and his colleagues reported higher frequency of HE in patients with serum sodium less than 130 meq/L compared to those with normal serum sodium concentration (25.8% vs. 9.7%, respectively).[18] A negative relationship between serum sodium levels and frequency of HE has been shown in previous studies, especially in those with serum sodium less than or equal to 130 mmol/L.[1] Change of cell hydration due to decreased extracellular sodium results in osmotic stress and astrocyte swelling; cells that are involved in the maintenance of central nervous system (CNS) function.[19] Serum sodium less than or equal to 131 mmol/L has been demonstrated to be the best predictor of grade I of HE.[20] In another study of patients with cirrhosis, serum sodium level was reported to be an independent predictor

of electroencephalographic abnormalities.[21] It has shown an association between serum sodium and HRQOL, cognition, and brain MR spectroscopy metabolites in patients with cirrhosis. Furthermore, presence of HE made their abnormalities worse.[22] The underlying reason has been attributed to impaired functioning of CNS.[23] These findings propose a possible potential negative role for low serum sodium concentration in cirrhosis-related complications. As patients with serum sodium levels above 120 meq/L are asymptomatic, regular serum sodium evaluating should be recommended in cirrhotic patients.

High rates of consumption of diuretics among our cirrhotic patients with hyponatremia show possible effects of diuretics on the risk of hyponatremia in HE. This finding is in line with Shaikh et al.[18] Therefore, due to the probable negative impact of hyponatremia on complications such as encephalopathy, diuretics should be prescribed cautiously in cirrhotic patients.

Our findings indicate that mean age of cirrhotic patients with hyponatremia was more than cirrhotic patients without hyponatremia. This finding proposes this hypothesis that older cirrhotic patients are at greater risk of developing hyponatremia and should be screened periodically for hyponatremia (especially if they are on diuretics treatment). In other words, diuretics should be prescribed warily in older cirrhotic patients.

The cirrhosis grade of majority of patients in the present study (40%) was Child–Pugh A. This was Child-Pugh B in Iwasa's study.[24] However, most of our cirrhotic patients with hyponatremia (90.5%) had Child–Pugh B and C. This confirms a significant association between severity of cirrhosis and decreased serum sodium that has been reported in previous studies.

6. CONCLUSIONS

In conclusion, the findings of the current study reveal presence of HE in cirrhotic patients with hyponatremia. So, monitoring serum sodium level in patients with cirrhosis is prudent to prevent HE and other complications, especially among those who are taking diuretics.

Conflict of interest

None declared

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Original article

Propolis alcohol extract attenuates prostate specific antigen disorders and prostate necrosis induced by the cadmium toxicity in rats

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ABSTRACT

Introduction: Cadmium, heavy metal, is causing toxicity. Propolis is a natural product derived from plant resins collected by honeybees. Studies reported this substance is an antioxidant and antitumor.

Aim: The aim of this study is to assess the effects of the propolis alcohol extract (PAE) against the prostate specific antigen (PSA) disorders and prostate necrosis induced by the cadmium (Cd) toxicity in rats.

Material and methods: Parameters as body weight gain, blood PSA, blood Cd^{2+} and prostate tissue examination were performed in four groups of rats as follow: GR1 (controls), GR2 (administered orally with $CdSO_4$ at the dose 28 mg/kg BW), GR3 (exposed to $CdSO_4$ then treated orally with PAE at the dose 250 mg/kg BW) and GR4 (PAE/$CdSO_4$ in the same conditions). Experimental period was 35 days.

Results and discussion: Cadmium toxicity induced a decrease in body weight gain and an increase in prostate gland weight, blood PSA and Cd^{2+} levels. Cd also induced prostate necrosis in which it was noted a marked irregular acini and solid parenchyma. Whereas the treatment of animals with PAE revealed that body weight gain and blood PSA are low. Propolis increased preventive effects in rat's prostate in GR4 better than GR3. Propolis has beneficial effects and could antagonize Cd-induced prostate toxicity.

Conclusions: The results showed that propolis antagonized the harmful effects of $CdSO_4$. These findings showed that propolis could protect the human health through preventing the prostatic diseases.

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1. INTRODUCTION

Since a long time, the toxicity of heavy metals generated an interesting debate. Metals are toxic at low dose and accumulate in living organisms. The urinary excretion of metals is less rapid than their absorption.[1] Cadmium (Cd) exposes human to toxicity risks through various means such as the ingestion of contaminated food and industrial use.[2] International Agency for Research on Cancer (IARC) classified Cd as a category I human carcinogen.[3] However, studies suggested that the prostate is sensitive to Cd toxicity.[2,4] Cd toxicity induces the oxidative stress and the synthesis of the reactive oxygen species (ROS).[3] Prostate cancer is the second most diagnosed cancer of men.[5,6] However, 90% of prostate cancer patients received androgen ablation therapy and chemotherapy that may decrease blood prostate specific antigen (PSA) and improve urinary symptoms. These therapies lead to adverse effects such as toxic death and strokes.[7,8] Various plants and trees covering large areas in the Southwestern Algeria and are the main residence sites of honeybees (*Apis mellifera* L.). Majesty bees collect a natural resinous substance from buds and exudates of plants and to produce the propolis after mixed it with pollen and enzymes secreted by bees.[9] Honeybees used propolis to smooth out the internal walls of the hive and as a protective barrier against their enemies.[10] The local population of Southwestern Algeria used propolis as remedy against diseases. Studies revealed the anti-inflammatory, anti-oxidant and antimicrobial activities of propolis.[10,11] Other works suggested the changes of chemical composition of propolis.[12,13] Propolis is consisted of bioactive molecules such as: polyphenols, flavonoids and terpenoids. Its chemical composition is influenced by climatic, botanical and geographical factors.[13,14] The Southwestern Algeria flora has a high biodiversity with many endemic plants. This could differentiate the composition of Algerian propolis compared to African and European propolis.[13,15]

2. AIM

This study aimed to assess the preventive effects of propolis alcohol extract (PAE) against Cd toxicity induced at prostate gland in rats.

3. MATERIAL AND METHODS

3.1. Chemicals

Dimethyl sulfoxide (DMSO), ethanol (80%), cadmium sulfate ($CdSO_4$), formalin (10%), acetone, xylene, paraffin, toluene, distilled water, hymatoxylene, chloridric acid (HCl), lithium carbonate [$Li_2(CO_3)_2$], eosine were obtained from the Biology Department, Faculty of Sciences, Dr Tahar-Moulay University, Saida, Algeria.

EDTA, murine monoclonal antibodies anti-PSA, conservatives, serum calf (5%), sodium azide (0.9 g/L), wash buffer (Tris 0.05 mol/L and Tween 0.05%), sodium chlorid (NaCl, 0.1 mol/L), 4-methyl-ombelliferyl phosphate (0.06 mmol/L), diethanolamine (DEA, 0.62 mol/L) were purchased from the Laboratory Bio Merieux, France. The dose of $CdSO_4$ was 28 mg/kg BW (i.e. 1/10 of LD50, LD50 = 280 mg/kg BW).[16]

3.2. Preparation of PAE

Fifty grams of the resinous material of the Southwestern Algeria propolis (obtained from Rebahia area, province of Saida, located in Southwestern Algeria) was powdered and extracted with 600 mL of 80% (v/v) ethanol at 70°C for 35 minutes. After extraction, the mixture was centrifuged and the supernatant was evaporated to complete dryness at 40°C.[17] The dried residue was kept at 4°C for the further use. Aqueous suspension of propolis was prepared in gum arabic suspension (1%), and orally administered to the animals for 35 days in a dose of 250 mg/kg.[17]

3.3. Animals

Male Wistar albino rats weighting 180–200 g were provided by the breeding unit of Pasteur Institute, Algiers. They housed under controlled conditions (25°C temperature and 12-hours lighting cycle) and received standard diet and water ad libitum during the study period. The study complies with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996) and approved by the Ethics Committee for Animal Experimentation at Faculty of Sciences, Saida University, Algeria.

3.4. Experimental design

Forty adult male rats were divided into four groups (10 rats in each group):

(1) GR1 – animals received distilled water and standard diet, served as normal control (NC),
(2) GR2 – animals received daily and orally $CdSO_4$ at a dose of 28 mg / kg BW,
(3) GR3 – animals received $CdSO_4$ at 28 mg/kg and propolis alcohol extract (PAE) at a dose of 250 mg / kg BW,
(4) GR4 – animals received PAE and $CdSO_4$ in the same experimental conditions.

3.5. Body and prostate tissue weight

We recorded initial and final body weights of male rats to measure weight body gains. After the sacrifice of animals, prostates were dissected out, trimmed off the attached tissues and weighed individually. Then, the organ/body weight ratio was measured. Specimens of the prostates were fixed immediately in formalin for histological study.

3.6. Blood PSA assay

After 35 days, animals were anesthetized (sodium pentobarbital 40 mg/kg BW), blood samples were obtained from hearts and allowed to clot for 20 minutes in laboratory temperature and then centrifuged at 3000 r/min for 10 minutes for serum separation. Serum-PSA levels were measured by mini VIDAS automate analyzer (Bio-Merieux, France). The method was the technique of enzyme-linked fluorescent assay (ELFA): it is an enzyme immunoassay ELISA 'sand-

wich' in heterogeneous phase. Reading of the PSA values passes through two steps to a final detection by fluorimetry. Validation of results need a quality control performed for each kit VIDAS-PSA used.

3.7. Blood Cd^{2+} assay

The spectrophotometric analysis allowed carrying out the blood Cd^{2+} assay. We collected blood samples in EDTA tubes destined for analysis by the automate instrument (Abacus 4 Hematology Analyzer, Hungary).

3.8. Histological study

The rats were dissected to isolate prostate tissues. After draining the blood, prostate samples were excised, washed with normal saline and processed separately for histological observations. Initially, the materials were fixed in 10% buffered neutral formalin for 48 h and then with bovine solution for 6 h. Paraffin sections were taken at 5 mm thickness, processed in alcohol-xylene series. For light microscopy, semithin sections of prostate tissue were stained with alum haematoxylin-eosin and examined with an Olympus BH-2 light microscope and photographed with Sony DSC-W610 digital camera (Sony Corporation Konan, Minato-ku, Tokyo, Japan).

3.9. Statistical analysis

Results were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed with Sigmaplot version 11.0 softaware. ANOVA test was performed to evaluate if there were any statistically significant differences between treated and control groups.

4. RESULTS

Table 1 shows body and tissue weights and weight ratio of animals. Statistically significant body weight gain (%) was observed in animals treated with PAE according to curative and preventive methods (GR3 and GR4) which showed respectively the values of 8.49% and 9.13% compared to control and experimental groups which respectively had 31.34% and 15.36%. However, no significant difference in prostate tissue weight was recorded in the groups treated with PAE compared to control and experimental animals.

An increased prostate weight, in rats treated with $CdSO_4$, explained the higher Cd levels in the prostatic cells (9.3 ± 0.89 μg/L) compared to the controls (0.02 ± 0.01 μg/L). Whereas, in animals treated with PAE (GR3 and GR4), prostate gland weight slightly decreased which blood Cd^{2+} levels were 1.36 ± 0.29 μg/L and 0.75 ± 0.02 μg/L, respectively (Table 1). These results elucidated curative and preventive effects of PAE, which inhibited the Cd accumulation and protected the prostate tissue from this toxic heavy metal.

Blood-PSA levels were significantly higher in rats treated with $CdSO_4$, which they showed 9.15 ± 1.62 ng/mL as compared to controls (2.27 ± 0.28 ng/mL). Whereas, we noted a significant decrease of blood-PSA in rats administrated orally with PAE (GR3 and GR4). The blood PSA concentrations were 4.69 ± 0.48 ng/mL and 3.9 ± 0.24 ng/mL, respectively.

In general, the prostate of the control rats consists of fibroblasts, connective tissue fibers and layers of smooth muscle cells surrounding acini lined by columnar epithelial cells (Figure 1A). Figure 1B shows the effect of oral $CdSO_4$ exposure on the incidence of proliferative lesions in the prostate. These proliferative lesions were exclusively intraepithelial hyperplasia without stromal invasion. Oval and irregular neoplastic glands associated with confluent solid zones accentuated the prostatic structures. Whereas in animals, exposed to $CdSO_4$ and then treated orally with PAE (Figure 1C), it was revealed slight dysplastic modifications in the ventral prostate acinar epithelium. The control acini showed a columnar monostratified epithelium, whereas the dysplastic acini manifested an irregularly enlarged epithelial lining with occasional polyploidy formations. Prostate glands, in rats treated with PAE and then administered with $CdSO_4$, had apparently normal cells with differentiated glandular structures and relatively little mitosis (Figure 1D).

Table 1. Effects of oral administration of cadmium sulfate and propolis for 35 days on the body and prostate weight, blood PSA and Cd^{2+} in male rats.

	GR 1 (Controls)	GR 2 ($CdSO_4$)	GR 3 ($CdSO_4$ / PAE)	GR 4 (PAE / $CdSO_4$)
Body weight (g)				
Mean (± SEM)	223.16 ± 9.87	167.26 ± 4.49	190.33 ± 2.83	176.65 ± 2.79
Initial BW (± SEM)	192.30 ± 8.60	158.32 ± 4.73	180.42 ± 1.39	168.60 ± 2.79
Final BW (± SEM)	252.58 ± 9.87	182.65 ± 4.49	195.74 ± 2.83	184.00 ± 4.19
Body weight gain (%)	31.34[a]	15.36[a]	8.49[a]	9.13
Prostate weight (g)				
Mean (± SEM)	0.24 ± 0.02	0.84 ± 0.04	0.66 ± 0.12	0.60 ± 0.43
Prostate/body weight ratio				
Mean ($\times 10^{-3}$)	1.07	5.02	3.46	3.39
Blood-PSA (ng/mL)				
Mean (± SEM)	2.27 ± 0.28	9.15 ± 1.62[a]	4.69 ± 0.48	3.9 ± 0.24[a]
Blood-Cd^{2+} (μg/L)				
Mean (± SEM)	0.02 ± 0.01	9.3 ± 0.89[a]	1.36 ± 0.29	0.75 ± 0.02[a]

Comments: a – statistically significant difference as compared with experimental controls ($CdSO_4$) ($P < 0.05$).

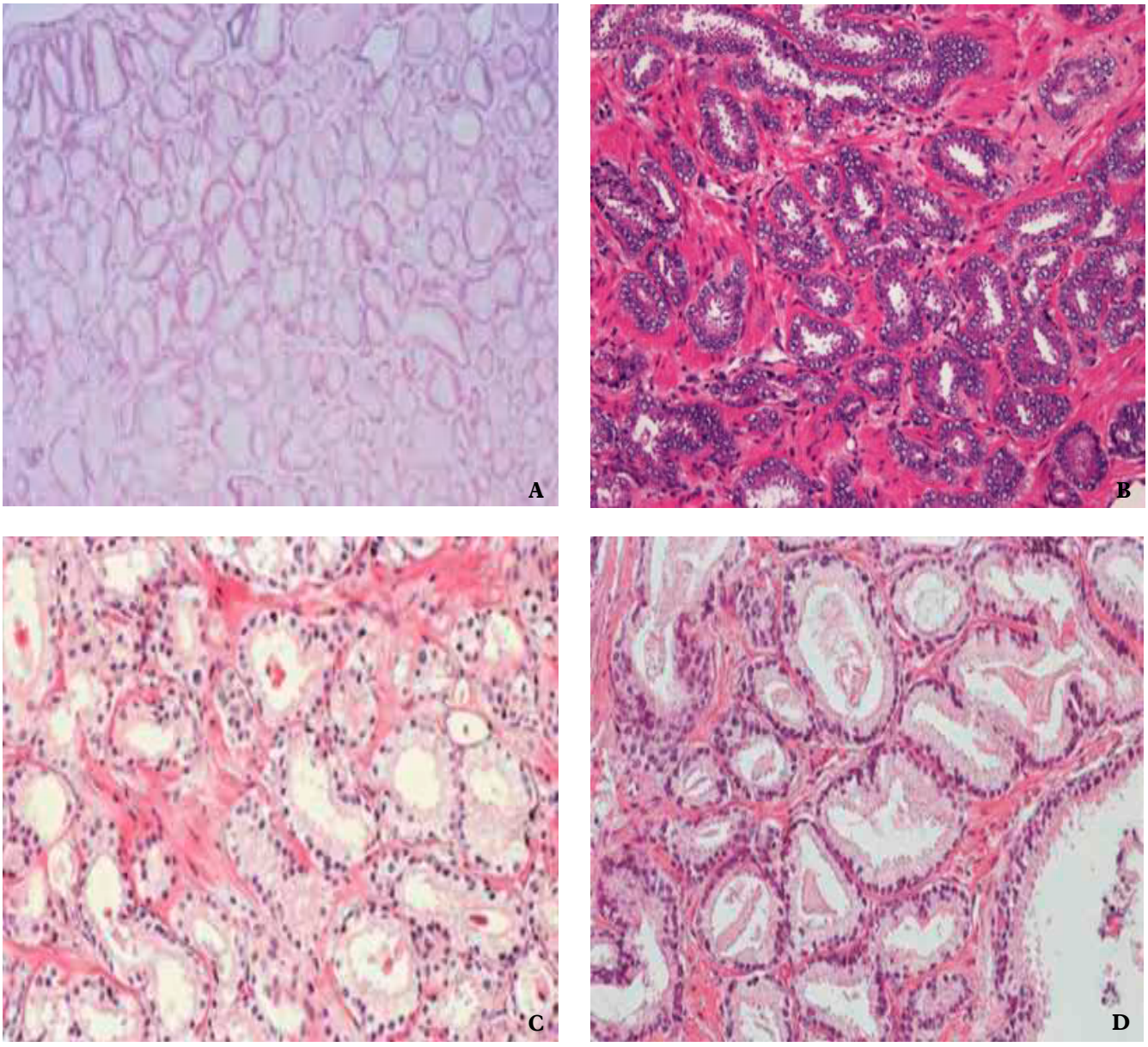

Figure 1. Effects of PAE on prostate tissue in rats exposed to $CdSO_4$ (H-E, magnification 10 × 40): A. Normal prostate gland in control rat. Differenciated acini and regular cell forms. B. Prostate tissue in rats exposed to $CdSO_4$. Irregular acini forms and necrosis tissues associated with solid parenchyma araes. C. Prostate tissue in rats treated in order with $CdSO_4$/Propolis. More or less irregular and angular acini and differenciated prostatic cells were observed. D. Prostate tissue in rats treated in order with the Propolis/$CdSO_4$. Regular acini forms with a less or more an accentuated areas, without necrosis of prostate tissue were observed.

5. DISCUSSION

Studies provide evidence that propolis protects humans against cancer, and revealed that propolis has pharmacological properties.[18–21] In Southwestern Algeria, propolis used by beekeepers and little is known about its biological activities. A study of Boufadi et al. (2014) reported that propolis harvested from different areas of Algeria contained various high concentrations of polyphenolic compounds known as the main active molecules exhibited free radical scavenging activity.[22] The toxicity of Cd increased oxidative stress and affected urogenital tissues.[23,24] The decrease in body weight and an increase in prostate gland weight, blood-PSA and Cd^{2+} suggest the Cd-toxicity. This study also showed marked histopathology changes in the prostate tissue. Prostate and testis are the target tissues and are highly sensitive to Cd.[25,26] Cd, at high dose, induces prostate epithelial cell damage associated with the irregular acini forms. Cd triggers a necrosis of stroma associated with the solid parenchyma areas. The results of this study are compared to other studies performed on the testis in which Cd causes degeneration in spermatogenic cells and the disruption of the connection

complex between Sertoli cells.[27,28] Other negative effects as high blood testosterone, an increase in blood PSA levels and prostate lesions, were recorded in rats exposed to Cd.[27,28] Studies of toxicology suggested that Cd is a risk factor associated with prostate cancer.[20,28,29] The cellular mechanism of Cd toxicity was already elucidated. After Cd absorption, Cd is transported by albumin and hemoglobin to reach the liver. In the liver cells, Cd conjugates to glutathione (GSH) and metallothioneins (MT). The metalloprotein complexes Cd-GSH are excreted in the bile and Cd-MT are stored in the liver or convoyed to the kidney. The Cd-MT complex, in the proximal tubules, leads to 50% excretion of Cd-MT and 50% endocytosis reabsorption. The Cd-MT is transformed by lysosomes thus releasing Cd, which interacts with cellular components, and damage them. High Cd-dose exposure may induce prostate cancer and increase blood PSA.[20] Propolis becomes the subject of increasing scientific interest due to its diverse biological properties. It has been shown that propolis have antibacterial, antiviral, and antitumoral activities.[21,30] This study revealed the protective effect of propolis against Cd-toxicity. Propolis, from different geographic areas and source plants, displays different chemical profiles. Main constituents of European propolis are flavonoid and phenolic acids whereas Mediterranean propolis contains diterpenic acids. This study indicates that propolis treatment showed lower blood PSA and Ca^{2+} levels, a decrease in prostate weight-body weight ratio and less marked prostate necrosis. Caffeic acid phenethyl ester (CAPE), a main active component extracted from propolis, is a strong antioxidant.[31] CAPE is a specific inhibitor of NF-jB.[31] Recent studies suggested that CAPE treatment suppressed the proliferation of used metastatic prostate cancer cell lines such as LNCaP and PC-3 cells. Propolis treatment enhances apoptosis in prostate cancer cells.[32] Propolis reduces the angiogenesis process.[33] This occurs by modulating the expression of growth factors such as VEGF and TNF.[34] Studies, carried out on the antitumor activity of propolis,[35] showed an antiproliferative effect against tumor lines (blood, colon, breast, prostate, lung, liver, brain, kidney).[36] Various studies showed that propolis alcohol extract was able to modulate the expression and activity of factors involved in the carcinogenesis process. The antiproliferative effect results from a restoration of the apoptosis signal.[37] Cell molecular mechanism of propolis remains unclear. Moreover, more studies are needed to investigate the correlation between propolis intake and prostate cancer incidence.

5. CONCLUSIONS

This study showed that propolis has preventive role against the Cd-toxicity. Propolis reduced accumulation of Cd in the prostate gland and prevents the increase of blood PSA. Though the molecular mechanism of the action of the propolis is unclear, propolis contributes widely to involve the scavenging of free radicals, increasing antioxidant status and metal-chelating abilities.

Conflict of interest

There is no conflict of interest for all authors.

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Original article

Glucocorticoids safety administration in multiple sclerosis treatment: A focus on physicians' adherence to avoid side effect

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ABSTRACT

Introduction: The problems of GCs administration safety in MS patients have not been solved yet because of their side effects, absence of the alternative treatment for acute relapse onset and its rapid progression.

Aim: To analyze clinical and pharmaceutical aspects of GCs rational use in practical treatment of MS patients throughout studying of physicians' adherence to follow the recommendation of avoiding their side effects.

Material and methods: This is a retrospective study of 50 randomized MS case histories.

Results and discussion: Twenty two (44 %) of MS patients had clinical and anamnestic risk factors for GCs use. However, GCs have been prescribed in 27 cases (54 %) of current hospitalization, in 26 (52 %) of patients' anamnesis, and 38 (76 %) of patients, totally. During a hospital stage 44.44 % received pulse therapy, 59.26 % - oral GCs and 11.11 % - endolumbal administration. GCs were frequently used in MS onset during current hospitalization and in SPMS in pre-hospital period. Approximately 91 % with EDSS 5-6 were treated with GCs.
We have observed possible side effects of GCs in 31.58 % among 38 MS cases treated with CGs, however, the patients have not been properly examined for their estimation. We have discovered that physicians paid more attention to prevention of gastrointestinal side effect of GCs (51.85 %), than osteoporosis. We also found 3 cases (11.11 %) of irrational combinations of GCs with NSAIDs.

Conclusions: GCs are frequently and effectively prescribed to MS patients, their side effects are still under proper control in clinical practice.

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1. INTRODUCTION

Glucocorticoids (GCs) are considered reserve or unreplaceable medicines used in therapeutically difficult and sometimes desperate situations. They are effective in treatment of autoimmune diseases with unknown etiology, such as rheumatoid arthritis (RA), acute interstitial pneumonitis, multiple sclerosis (MS).[1,2] GCs are widely used in allergic diseases, i.e. bronchial asthma, psoriasis, atopic dermatitis, etc.[3–5] Furthermore, they are prescribed to prevent rejection after transplantation and to correct adrenal cortical hormone insufficiency.[6] The mechanism of their actions is connected with suppression of immune reactions by lymphocytolysis, acceleration of immunoglobulins destruction, decrease of proinflammatory cytokines such as interleukin-2 production.[2]

The significance of GCs in clinical practice is impossible to underestimate. However, in some cases a number of side effects of GCs associated with a longterm usage or a high dose limit their prescriptions.[7] The GCs therapy leads to osteoporosis, obesity, diabetes mellitus (DM), adrenal insufficiency, peptic ulcers and gastrointestinal bleeding, hypertension, behavior and cognitive changes, super infections due to immune suppression.[8,9] Their side effect also are depended on route of administration and the drug, which exactly is used.

There are some recommendations for prevention and reduction of GCs' side effects.[7,10,11] However, the question is whether physicians consider them in their daily practice.

We choose MS patients to analyze the side effect of GCs, considering their administration as a gold standard for acute relapse treatment.[12] Despite numerous studies of MS, GCs therapy remains the first-line in any of its clinical forms' aggravation. Not only it inhibits the autoimmune processes, but it is also used as a substitute therapy due to the development of GCs insufficiency in MS, which changes immunological reactivity by exacerbating allergic manifestations and promoting the process of demyelination.[13] Although GCs has been used in MS treatment for years, the problems of their prescription in different types of MS course and prevention of their side effects have not been resolved yet.[14]

2. AIM

The aim of our study is to analyze clinical and pharmaceutical aspects of GCs' rational use in practical treatment of MS patients throughout studying of physicians' adherence to follow the recommendation of avoiding their side effects.

3. MATERIAL AND METHODS

This is a retrospective study of 50 MS case histories from 2007 to 2015. The cases were received by a randomized method at the Multiple Sclerosis Department of the State Institution 'Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine' in Ukraine. In all cases anamnestic and physical examination data, as well as prescription lists have been analyzed. Administration of GCs at a prehospital stage and/or during the period of current hospitalization has been taken into consideration. The next issues were studying of presence of contraindications for GCs prescription, occurrence of possible side effects or adverse reactions, and use of non-advisable combination of GCs with other drugs in the observed case histories. We have also studied whether doctors follow the recommendations for prevention and reduction of GCs side effects. For statistics, we use absolute and percent data.

4. RESULTS AND DISCUSSION

We have discovered that the majority of MS patients received GCs, some of them had anamnestic data for GCs contraindication and others had signs of possible GCs side effects during hospitalization. We divided all the results according to the mentioned issues.

4.1. Present clinical and anamnestic factors in the observed cases that could be considered as contraindications for GCs prescriptions

We have learnt whether the following factors have been presented in case histories of the MS patients: obesity, hypertension, DM, osteoporosis, chronic gastritis and peptic ulcer, etc.

There were 5 (10%) patients with abnormal weight: 3 (6%) of them were overweight and 2 (4%) were obese. General cholesterol and its fractions' level have not been checked in the cases. Two (4%) patients had DM type 2. Blood glucose level baseline and after OTTG was checked only in 5 (10%) of total cases, while glycosylated HbA1c level was not defined in the patients at all. Hypertension was discovered in 7 (14%) of the studied cases (Table 1).

According to literature, GCs do not affect lipid profile,[15] but has influence on glucose metabolism, increases blood pressure[16] and leads to sinus bradycardia,[17] gain weight and emotional instability.[18] Thus, the GCs prescriptions should be debated in this clinical group of patients.

Chronic gastritis and peptic ulcer have been observed in 5 (10%) and 1 (2%) of patients, respectively (Table 1). Some researchers report that additional risk factors such as previous history of gastrointestinal events should also be considered as contraindication for GCs use.[11] Use of pulse therapy by methylprednisolone alone does not lead to gastric mucosal injury, but not together with nonsteroidal anti-inflammatory drugs (NSAIDs).[19]

There have been 13 (26%) of patients with persistent chronic infection which causes chronic inflammatory diseases such as tonsillitis, rhinosinusitis, pyelonephritis, saplingooforites, prostatitis, persistent mix infection in our research (Table 1). These chronic infections could be activated due to immunosuppression caused by GCs therapy.[20]

There was no information about osteoporosis in the patients because bone mineral density (BMD) measurement

were absent. The literature sources show a significant influence of GCs on bone structures.[21] Even though short course of pulse therapy by methylprednisolone seems to be safe, MS patients have additional risk of osteoporosis because of their inactivity.[22] The researchers underline, BMD measurement of the MS patients should be taken before GCs treatment to determine those at high risk for osteoporosis,[23] and preventive or therapeutic agents should be given.[24]

The patient were not properly checked for cardiovascular contraindications before starting pulse therapy by methylprednisolone despite on some authors had claimed of severe adverse effect on heart.[9,16,17] First of all, nobody has been consulted by cardiologist and echocardiogram has not been done for anyone, despite of 8 (16%) patients have different changes in electrocardiogram. Repolarization disorder was found in 2 (4%) cases, bradycardia in 2 (4%) patients, tachycardia in 1 (2%) case, myocardial hypertrophy of left ventricular in 3 (6%) cases (Table 1). We believe the bradycardia and myocardial hypertrophy of left ventricular should be considered as contraindication for pulse therapy by methylprednisolone.[16,17] Moreover, they were the same patients who have abnormal weight and hypertension.

Table 1. Clinical and anamnestic data, which could be considered as contraindication for of GCs prescription.

Possible contraindication for GCs prescriptions	Number of MS patients, *n* (%)
Overweight and obese	5 (10%)
DM type 2	2 (4%)
Hypertension	7 (14%)
Peptic ulcer and gastritis	6 (12%)
Persistent chronic infection	13 (26%)
Bradycardia	2 (4%)
Myocardial hypertrophy of left ventricular	3 (6%)
Total amount of patients, who might have contraindication	22 (44%)

A total number of patients with one or more clinical and anamnestic factors that could be interpreted as risk factors for the GCs use was 22 (44%). We suppose the real number of these patients was significantly higher due to the lack of necessary examination included in the case histories.

4.2. Study of GCs administration ways in MS patients during current hospitalization and at the prehospital stage

GCs have been prescribed in 27 (54%) cases during current hospitalization, and in 26 (52%) of prehospital stage. The total number of patients treated with GCs was 38 (76%) (Table 2).

During the current hospital treatment, the patients have received GCs in three schemes. Almost half of them were prescribed intravenous pulse therapy by methylprednisolone (solumedrol) 500–1000 mg daily for 3–5 days (Table 2). Actually, the use of pulse therapy allowed to effectively relieve severe recurrence in relapsing-remitting type of MS (RRMS) and rapid progression rates in secondary progressive type (SPMS). This contributes to a significant regression of 'neurological deficit' and to prolonged clinical remission in RRMS, or it leads to stabilization in MS onset.[12,25,26]

Another 16 patients received oral methylprednisolone (Medrol) in dose 40–80 mg for alternating scheme every other day (Table 2). One patient was treated with oral methylprednisolone after finishing pulse therapy to achieve therapeutic effect. According to the literature sources, oral administration of GCs shows the most effective results in RRMS patients with relapses of moderate severity with Expanded Disability Status Scale (EDSS) 3–4. At the MS onset, this tactics leads to stabilization with a partial regression. In general, oral administration of GCs is less effective than pulse therapy in acute period.[14,27]

We observed some new methods for GCs application of endolumbal injection of dexamethasone (dexazone) in 3 (11.11%) patients (Table 2). It is provided by neurologists from the State Institution 'Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine'. They proved the effectiveness and expediency of this administration in severe cases of MS progredient forms, proceeding mainly with spinal symptoms.[13]

Table 2. Number of GCs prescriptions depending on the way of administration.

GCs therapy	Total number of GCs prescription	Pulse therapy	Oral administration	Endolumbal injection
Prehospital stage	26 (52%)	19 (73.08%)	13 (50.00%)	1 (3.84%)
Current hospitalization	27 (54%)	12 (44.44%)	16 (59.26%)	3 (11.11%)
Both pre- and hospital	38 (76%)	26 (68.42%)	22 (57.89%)	4 (10.52%)

The average duration of MS in investigated cases was 9.54 ± 8.32 years. MS onset was diagnosed in 9 (18%) of patients, and an aggravation was found in 41 (82%) of patients. Maximal duration of MS took 27 years. Anamnestic data show the GCs pulse therapy applied in 19 (73.08%) cases. Oral GCs administration at prehospital stage was found in 13 (50 %) patients. At prehospital stage, mostly methylprednisolone was used. However, we found prescription of oral prednisolone in 3 (11.52 %) cases and oral dexamethasone in 4 (15.36 %) cases retrospectively. Endolumbal administration of GCs was in anamnesis of 1 patient (3.84 %). Analysis of general GCs prescriptions at hospital and prehospital stages shows the pulse therapy in 68.42 % of total GCs prescriptions in MS patients, and oral GCs administration found in 57.89 %, respectively (Table 2).

The researchers reported of GCs longterm treatment effectivity in intravenous pulse therapy by high dose methylprednisolone. It is associated with a significant disability risk progression reduction for 5 years in RRMS, while oral

continuous low dose prednisolone is not correlated with any risk reduction in disability progression for 18 months. Risk of experiencing at least one exacerbation at the end of follow-up is not significantly reduced with GCs therapy.[28]

4.3. Study of GCs prescription frequency in MS cases depending on course and 'neurological deficit' severity

Total 50 cases were split into groups due to the clinical course of MS to study the condition of GCs prescriptions. There were 9 (18%) MS onset cases, 33 (66%) of the RRMS cases and 8 (16%) of the SPMS cases. Patients with primary-progressive type of MS (PPMS) were not considered in our research as there were few of them.

The GCs were prescribed during current hospitalization to 77.77% of MS onset patients, 51.51% of RRMS and 37.50% of SPMS cases (Table 3). As we see, GCs were most frequently used in hospital period in the group of MS onset patients. Anamnestic data show the most frequent GCs prescriptions at the prehospital stage in SPMS patients. Particular attention was paid to 3 patients with MS onset, treated with GCs before hospitalization. These were cases with repeated hospitalization during a shot period. The cases might evidence unsuccessful previous GCs therapy of the MS onset with repeated prescription.

Table 3. Number of GCs prescriptions depending on clinical course of MS.

GCs therapy	MS onset (n = 9)	RRMS, (n = 33)	SPMS (n = 8)
Prehospital stage	3 (33.33%)	18 (54.54%)	5 (62.5%)
Current hospitalization	7 (77.77%)	17 (51.51%)	3 (37.5%)
Both pre- and hospital	8 (88.88%)	23 (69.69%)	7 (87.5%)

Next, we study GCs prescriptions frequency depending on 'neurological deficit', which was estimated by EDSS. There were 7 (14%) cases with EDSS 1–2, 32 (62%) with EDSS 3–4, and 11 (22%) with EDSS 5–6 from total 50 cases.

Table 4 shows that the most frequent prescription of GCs was in patients with maximum EDSS 5–6. Approximately 90% of the patients with the severest 'neurological deficiency' have received GCs at the prehospital stage, and 80% – during current hospitalization. This also proves the efficiency of the GCs.

Table 4. Number of GCs prescriptions depending on EDSS.

GCs therapy	Number of GCs prescriptions in different EDSS		
	1–2, (n = 7)	3–4, (n = 32)	5–6, (n = 11)
Prehospital stage	3 (42.86%)	13 (40.62%)	10 (90.91%)
During current hospitalization	4 (57.14%)	14 (43.75%)	9 (81.81%)
Both hospital and prehospital period	6 (85.71%)	22 (68.75%)	10 (90.91%)

4.4. Control of GCs side effects occurrence in MS patients

GCs remain the most powerful and effective medication for acute exacerbations and severe cases of MS with high EDSS. Thus, the MS patients have to take them for a long time, repeat the scheme of treatment and change one of GCs to another. This undeniably leads to the side effect occurrence, which is indication for GCs discontinuation. Withdrawal syndrome might be common in such situations.[25] The biggest problem is absence of the pharmacological group that could totally replace GCs in MS exacerbation treatment.

Scientists continue to search for solution to the problem of GCs side effects. Recently it has been reported about new classes of medicines: selective glucocorticoid receptor agonists and modulators (SEGRAMs), which might replace GCs in future MS treatment.[29] However, there is still not enough clinical research on this issue. Doctors are more likely to continue the 'therapy of despair', than start thinking about possible side effects of GCs.

There were 38 patients (76%) in our study, who have received GCs at the prehospital stage and during current hospitalization. We found neither any information on registration of GCs side effects, nor withdrawal of medicine due to the side effects' registration. However, we have carefully studied clinical and anamnestic data of patients who have ever received GCs therapy.

We suppose that signs of GCs side effects might occur in 12 cases (31.58%) among 38 patients who have received GCs therapy both at a prehospital stage and in current hospitalization (Table 5). There were 4 cases, in which patients noted that they had increased blood pressure recently. It might be explained by the age of patients over 40 years. However, one of them was 30 years old. Another possible side effect was gaining weight by 2 patients, who believed that overweight was the result of GCs therapy. Two patients reported on becoming DM due to longterm GCs therapy. We observed chronic inflammatory diseases aggravation such as acute pyelonephritis, acute rhinopharyngitis, subacute rhinitis in 3 cases in one week after the start of pulse therapy by solumedrol in hospital. One patient refused to receive GCs, which might also be due to some unidirectional side effects of GCs (Table 5).

Table 5. Possible side effect of the GCs.

Signs of possible side effects	Number of patients GCs treated	Data source
Increased blood pressure	4 (10.53%)	Anamnestic data
Weight gain	2 (5.26%)	Anamnestic data
DM onset	2 (5.26%)	Anamnestic data
Aggravation of chronic infection	3 (7.89%)	Clinical data
Refusal of the GCs	1 (2.63%)	Clinical data
Total	12 (31.58%)	

Our data on possible side effect of GCs in 31.58% of MS cases correspond to another research, where side effects of GCs have been observed in 38.2% of RA patients.[30] Among MS patients from NARCOMS registered 17% indicated serious adverse effects after a long-period of GCs treatment, the majority completed treatment; only 0.8% stopped therapy because of adverse effects.[31] In our study nobody was refused the GCs therapy.

Registration of the GCs side effects should be proved by certain methods of control. Nevertheless, we have discovered absence of blood glucose level data baseline and after OTTG in 90% of total case histories, glycosylated hemoglobin level in 100%, blood cholesterol level in 85%, BMD measurement in 100%, Echocardiography in 100% of the all cases. Thus, it becomes obvious why no side effects have been reported in investigated cases. In general, we have found out that the MS patients under study were extremely rarely consulted by related specialists. There were consultation of otorhinolaryngologist in 13 (26%), internist in 19 (38%), cardiologist in 0%, dermatologist in 0%, gynecologist in 1 (2%), urologist in 0%, ophthalmologist in 27 (54%), vertebrologist in 1 (2%), endocrinologist in 1 (2%) and gastroenterologist in 0% of studied cases. This also limited both registration of GCs side effects and prevention of risk for GCs prescriptions.

We absolutely agree with researchers, who think that physicians must pay attention to risks of the side effects related to GCs treatment and be familiar with guidelines to manage them.[11]

4.5. The search for evidence of the physicians' tendencies to prevent GCs side effects

We have discovered GCs in 27 (54%) lists of prescription during the current hospitalization. The doctors pay attention to side effects from gastrointestinal tract, which often occur in GCs treatment.[11,19,32] They use anti-secretory and antacid medicines in 14 (51.85%) cases of GCs prescription. The most 'popular' was combination of aluminum hydroxide and omeprazole in 9 (33.33%) cases. In some cases, there was also prescription of ranitidine, lansoprazole, magnum hydroxide.

However, we observed irrational combinations of GCs with NSAIDs in 3 cases (11.11%) and with nicotinic acid in one case (3.7%), which could increase gastrointestinal side effects. The number of irrational combinations is high in our study, but it is still lower than in another research, where the irrational prescription of GCs with NSAIDs was 22.3% of RA patients.[30]

We found prescriptions of some unusual combinations of GCs with spironolactone in 12 cases (44.44%). Some authors have reported that spironolactone has an anti-inflammatory effect, which has been preclinically studied.[33] The spironolactone-based composition has been recently patented for treatment of MS.[34] However, the combination of GCs with spironolactone is to be studied in future research.

Finally, we did not notice the physicians' adherence to prevent the development of osteoporosis. The American College of Rheumatology recommends using calcium and vitamin D for as long as the patient receives GCs.[10] We have not found any prescription of these medications in case histories.

There is strong evidence for prevention and treatment of osteoporosis and the use of proton pump inhibitors in GCs treatment.[35] The researchers advise to investigate presence of comorbidities and to evaluate the risk factors of GCs side effects occurrence. During GCs therapy, monitoring of body weight and waist circumference, blood pressure, blood glucose, lipid profile, BMD, electrocardiogram control, and vaccinations should be provided.[36] Irrational combinations should be avoided.[30,32]

5. CONCLUSIONS

GCs prescriptions could not be underestimated in MS treatment due to high effectiveness in MS relapses and in 'neurological deficiency' progression. They have been prescribed to 76% of MS patients. On the other hand, this can cause a large number of GCs side effects, such as hypertension, glucose metabolism impairment, weight gain, osteoporosis, gastropathy, aggravation of chronic infection and others. This indicates the necessity to have a strict GCs safety administration control at before-, during- and after-prescription stages. Check-ups to prevent and treat GCs side effects are poorly provided by physicians, that is shown a lack of clinicians' compliance with the evident-based guidelines. First of all, incomplete MS patient's examination does not reveal the full list of possible risk factors for GCs use and occurrence of side effects at an early stage. Secondly, preventive GCs effect pharmacotherapy is weakly prescribed: gastropathy is avoided in half of cases, but osteoporosis – in none.

Clinical perspectives

Our research allowed us to look deep insight into the conditions of GCs safety administration in MS treatment. We tried to indicate the main issues of the incorrect tactics of the GCs prescription. We believe our study will help physicians-practitioners to avoid GCs side effects more effectively. The anticipation of GCs side effects in physicians' daily practice is the right way to GCs safety administration.

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Original article

Increased TNF-α and TGF-β concentrations in rat liver after intense exercise

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ABSTRACT

Introduction: Intense exercise can cause cellular damage, resulting in activation of inflammatory and fibrotic reactions.

Aim: The aim of the present study was to investigate how one session of intense exercise affected liver gene expression and concentrations of tumor necrosis factor α (TNF-α) and profibrotic transforming growth factor β (TGF-β) in untrained and trained rats.

Material and methods: Here we investigated the impact of intense exercise on liver gene expression and concentrations of TNF-α and TGF-β in untrained and trained healthy rats (n = 30 each). The trained rats underwent 6 weeks of endurance training with increasing load. From each group, liver samples were collected before, immediately after, and 3 h after one session of intense exercise. Gene expression was evaluated with quantitative real-time polymerase chain reaction. Protein content was measured by enzyme immunoassay.

Results and discussion: One session of intense exercise did not influence gene expression at any time point. In trained rats TNF-α and TGF-β was increased immediately after exercise (P = 0.011 and P = 0.009, respectively). The increase in TGF-β persisted 3 h post exercise (P = 0.045). In untrained rats the concentration of TNF-α did not change in any time point, while TGF-β was decreased both immediately and 3 h after intense exercise (P = 0.01 and P = 0.03, respectively).

Conclusions: Intense exercise led to increased proinflammatory and profibrotic activity in the liver of trained rats.

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1. INTRODUCTION

Physical activity induces the production and release of wide range of cytokines. They exert their effects in autocrine, paracrine, and endocrine manners and play an important role in driving adaptive changes to physical exercise.[1] Such changes occur mainly in muscles,[2] but physical exercise also influences many other organs and tissues in the organism, including liver, which serves as a very important energy source during exercise. While moderate activity provides health benefits, intense exercise can negatively affect metabolic processes, cause cellular damage,[3] and provoke transient inflammatory responses.[4] It has been shown in human studies that strenuous exercise is a strong stressor and could result in splanchnic hypoperfusion with subsequent disturbances in liver homeostasis and energy.[5,6] Rats that run on a treadmill to exhaustion exhibit liver damage marked by increased serum levels of aspartate transaminase (AST) and alanine transaminase (ALT). These animals also show increased serum levels of the proinflammatory cytokine tumor necrosis factor α (TNF-α), and histological evaluation reveals periportal leukocyte infiltration and hepatocyte vacuolization.[7,8]

2. AIM

The aim of the present study was to investigate how one session of intense exercise affected liver gene expression and concentrations of TNF-α and profibrotic transforming growth factor-β (TGF-β) in untrained and trained rats.

3. MATERIAL AND METHODS

3.1. Rats and exercise protocol

The experimental protocol was approved by the Ethics Committee of the Medical University in Bialystok, and was performed according to EU regulations governing laboratory animal treatment.

This study included 60 male Wistar rats that were randomly assigned to the untrained (UT, $n = 30$) or trained (T, $n = 30$) group. The exercise protocol was previously described.[9] Trained rats were subjected to endurance training (treadmill running, 5 days per week, 6 weeks). During week 1, the speed was 1200 m/h. The initial running time was 10 min/day and was increased by 10 minutes each day. Over the remaining 5 weeks, the exercise time was 60 min/day. The speed was 1500 m/h for week 2, and 1680 m/h for weeks 3–6. The untrained rats stayed sedentary during the training period.

At 24 h after training cessation, each group was randomly divided into 3 subgroups (each $n = 10$). Two subgroups (UTpre and Tpre) were sacrificed before exercise. The remaining subgroups performed 60 minutes of treadmill running at 1680 m/h. Two subgroups (UT0h and T0h) were sacrificed immediately after this exercise session. The remaining subgroups (UT3h and T3h) were sacrificed 3 h after exercise. Liver tissue samples were collected under anesthesia with intraperitoneal chloral hydrate (1 mL/100 mg body mass).

3.2. Tissue homogenization

About 25 mg of tissue was homogenized with a steel ball (diameter 5 mm) in the TissueLyser (Qiagen, Germany). Homogenization was performed at room temperature at a frequency of 25 Hz for 5 minutes. The tissues intended for real-time polymerase chain reaction (RT-PCR) were homogenized in 750 μL of QIAzol Lysis Reagent (Qiagen, Germany). The tissues used to determine tissue protein levels were homogenized in 1 mL of 1 × PBS. Samples used to determine protein concentrations were subjected to two cycles of freezing at –20°C and thawing at room temperature, then centrifuging at 5000 × g for 5 minutes at 4°C.

3.3. Isolation of total RNA

We isolated total RNA from rat liver tissue with a BioRobot EZ1 (Qiagen, Germany) and an EZ1 RNA Universal Tissue Kit (Qiagen, Germany), according to the manufacturer's instructions. RNA quality and quantity were evaluated with a camera ND-1000 (NanoDrop Technologies, Wilmington, Delaware, USA). Then, total RNA samples were stored at –80°C.

3.4. Quantitative, real-time reverse-transcription polymerase chain reaction

RT-PCR reactions were performed with an ABI 7500 (Applied Biosystems, Waltham, Massachusetts, USA) and MicroAmp Optical 96-Well Reaction Plates with Barcodes (Applied Biosystems, Waltham, Massachusetts, USA). To each well, we added the reaction mixture, which included the TaqMan RNA-to-CT 1-Step Kit (Applied Biosystems, Waltham, Massachusetts, USA) and primers appropriately selected for the TaqMan Gene Expression Assay (Applied Biosystems, Waltham, Massachusetts, USA). Primers specifically targeted sequences of the following genes: *TNF-α*, *TGF-β1*, and the control gene, glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*). Next, we added total RNA to the reaction mixture in all wells, except the no template control (NTC), which received water instead of RNA (Sigma-Aldrich, Saint Louis, Missouri, USA). The test samples and control were assayed in duplicate, and the NTC was assayed in triplicate.

Gene expression levels were calculated with the comparative cycle threshold (C_T) method. The C_T of each sample was normalized to the C_T of GAPDH as follows:

$$\Delta C_T = C_T\text{research gene} - C_T\text{GAPDH}.$$

The relative gene expression levels (ΔΔCT) were calculated by subtracting normalized C_T values for the trained group from those of the untrained group, as follows:

$$\Delta\Delta CT = \Delta CT\text{trained} - \Delta CT\text{untrained}.$$

Finally, the fold change in the mRNA level after treatment was calculated as $2^{-\Delta\Delta CT}$.

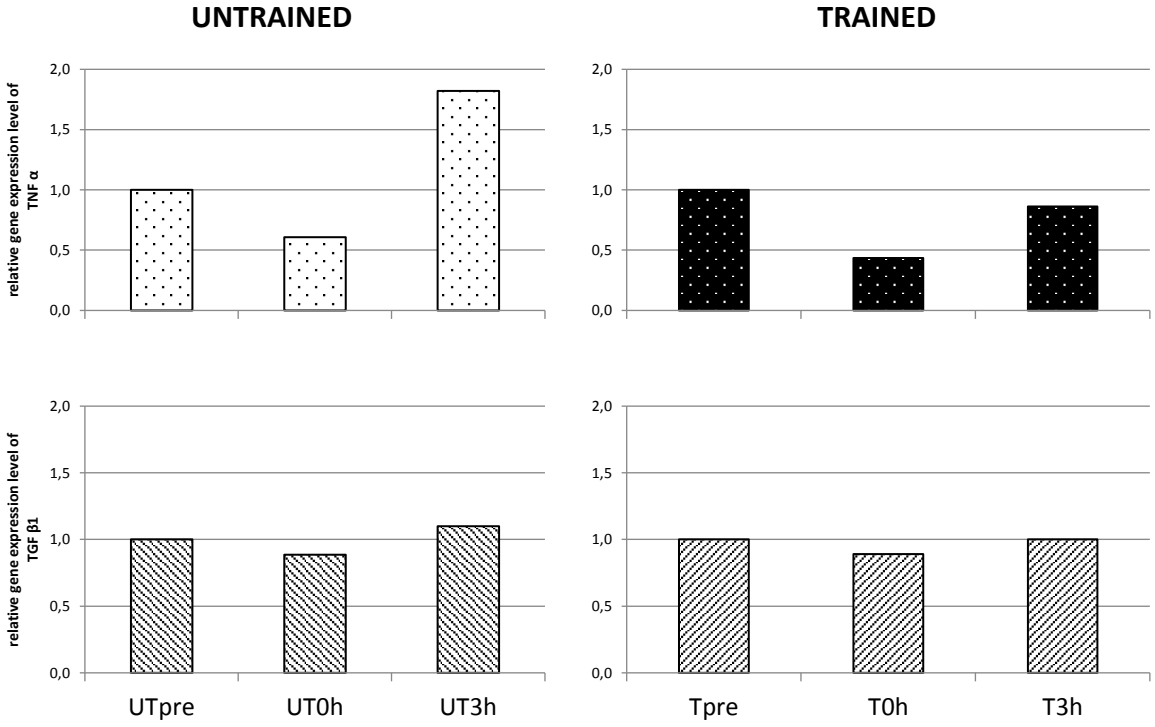

Figure 1. Relative changes in liver mRNA expression with exercise. Relative mRNA levels (dCt) of *TNF-α* and *TGF-β* were measured in livers of UT and T rats prior to exercise (UTpre, $n = 10$; Tpre, $n = 10$) and immediately after (UT0h, $n = 10$; T0h, $n = 10$) and 3 h after (UT3h, $n = 10$; T3h, $n = 10$) one session of exercise. There were no statistical differences between investigated groups.

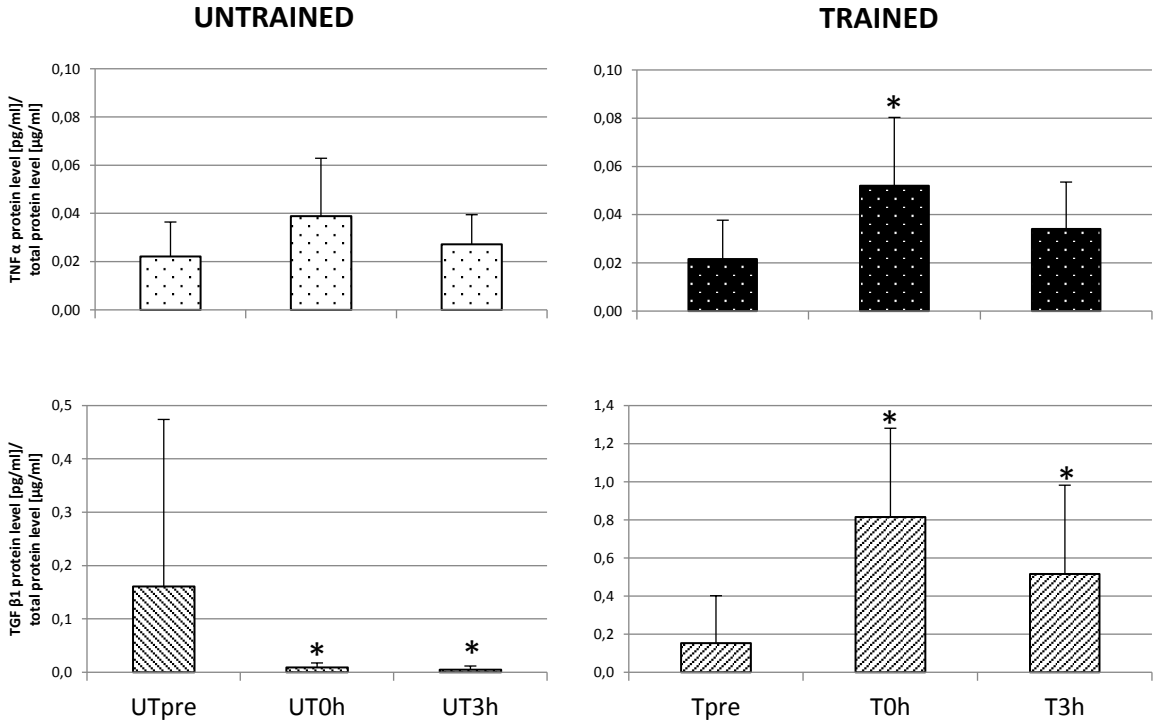

Figure 2. Levels of TNF-α and TGF-β proteins, relative to total proteins, were measured in UT and T rats prior to exercise (UTpre, $n = 10$; Tpre, $n = 10$), immediately after exercise (UT0h, $n = 10$; T0h, $n = 10$) and 3 h after exercise (UT3h, $n = 10$; T3h, $n = 10$). *$P < 0.05$.

3.5. Measuring TNF-α and TGF-β1 levels

TNF-α concentration was measured using the Rat TNF-alpha Quantikine ELISA Kit (R&D Systems, McKinley, Minnesota, USA). TGF-β1 concentrations were measured using the Mouse/Rat/Porcine/Canine TGF-beta1 Quantikine ELISA Kit (R&D Systems, McKinley, Minnesota, USA).

3.6. Measuring of total protein contain

Total protein contents of samples were measured using a colorimetric method (Pierce BCA Protein Assay Kit; Thermo Fisher Scientific, Waltham, Massachusetts, USA). All solutions were measured at 450 nm (total protein contents at 562 nm) using a BioTek Power Wave XS spectrophotometer (BioTek Instruments, Winooski, Vermont, USA).

3.7. Statistical analysis

Results are provided as the median with minimum and maximum values. In figures, the mean ±standard deviations are presented. mRNA levels (for statistics, ΔC_T was used) and protein levels in investigated groups were compared with the non-parametric Mann-Whitney *U* test. *P* less than 0.05 was considered statistically significant.

4. RESULTS

One session of exercise did not influence the gene expression of any of the investigated cytokines at any investigated time point (Figure 1).

The effects of one session of exercise on protein concentrations are presented in Figure 2.

In UT rats, TNF-α protein concentrations did not differ between UTpre and UT0h or UT3h, while TGF-β concentrations significantly decreased from UTpre to UT0h ($P = 0.01$) and UT3h ($P = 0.03$). In trained rats, TNF-α concentrations significantly increased from Tpre to T0h ($P = 0.011$), but not T3h, while TGF-β concentrations significantly increased from Tpre to T0h ($P = 0.009$) and T3h ($P = 0.045$).

5. DISCUSSION

We investigated the influences of physical exercise on the generation of selected cytokines in the liver at the mRNA and protein levels. Our results suggested that one session of intense exercise could not influence gene expression of TNF-α and TGF-β. However, one session of intense exercise influenced the liver protein content of these cytokines. The difference could be due to post-transcriptional modifications. It is estimated, that the correlation between mRNA and protein levels is lower than 0.5.[10] The fact that intense exercise suppressed toll-like receptor-4 production might, at least in part, explain the lack of change in pro-inflammatory cytokine gene expression.[11]

Intense exercise induces liver damage, resulting in aminotransferase release, oxidative stress, and ultrastructural abnormalities.[7] Here we showed that liver inflammation subsequent to such damage was driven by increased TNF-α concentration. TNF-α, a primary biomarker of tissue injury, activates T cells and macrophages and upregulates other proinflammatory cytokines. Intense exercise also led to increased liver concentrations of TGF-β, which plays a crucial role in hepatic fibrosis. TGF-β induces transdifferentiation of hepatic stellate cells into myofibroblasts, and promotes production and inhibits degradation of extracellular matrix. Hepatocytes affected by TGF-β eventually become pre-neoplastic hepatocytes.[12,13]

Interestingly, TNF-α and TGF-β levels only increased in trained animals. Gornicka et al. demonstrated that endurance training increased oxidative damage in rat livers and decreased concentrations of the antioxidant α-tocopherol.[14] We hypothesize that untrained animals had sufficient antioxidant levels to protect from oxidative stress and subsequent damage after one session of intense exercise. However, antioxidants may have been partly consumed in the trained animals, potentially resulting in more pronounced damage and induction of inflammatory and fibrotic reactions. The results in trained animals could also be related to overtraining syndrome, defined as maladapted physiology following excessive exercise without adequate rest. The etiology of this syndrome is unknown, but overtraining is reportedly accompanied by immunologic abnormalities.[15]

6. CONCLUSIONS

Notably, our findings suggest that intense exercise increases liver concentration of TNF-α and TGF-β, and these cytokines could drive liver damage after intense exercise. The intensity of one session of exercise and rest between sessions should be carefully planned to reduce the risk of potentially harmful and even cancerogenic reactions in the liver.

Conflict of interest

The authors declare that there is no conflict of interest.

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Original article

Effectiveness of air pulsed cryotherapy on delayed onset muscle soreness of elbow flexors following eccentric exercise

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ABSTRACT

Introduction: Cryotherapy is widely used in sports to facilitate recovery from exercise-induced muscle damage that often results from strenuous training and/or competition. However, a paucity of evidence exists on the therapeutic values of repeated air pulsed cryotherapy (CRYO) application to suggest its usefulness to clinicians, coaches, sports scientists and athletes in the field of sports and rehabilitation.

Aim: This study investigates the effectiveness of CRYO on the recovery from delayed onset of muscle soreness (DOMS) induced by eccentric exercise.

Material and methods: Thirty-two participants (21.31 ± 1.03 years, height 1.72 ± 0.05 m, BMI 22.15 ± 1.69 kg/cm^2) were equally randomized into CRYO group and control group (CONT). DOMS was induced by eccentric contractions of elbow flexors. Visual analogue scale score (VAS), mid arm circumference (MAC), pressure pain threshold (PPT), range of motion of active elbow flexion (ROM-AF), passive elbow flexion (ROM-PF), active elbow extension (ROM-AE), passive elbow extension (ROM-PE) and isometric peak torque of elbow flexors (IPT) were measured at pre-exercise (PRE), immediately, 1, 2, 3, 4, and 7 days post exercise.

Results and discussion: There were significant interactions effect (group X time) with ($P < 0.05$) for VAS, MAC, PPT, ROM-PF, ROM-AE, and ROM-PE. Additionally, all outcome measures (except for ROM-AF and IPT) demonstrated a significant improvement ($P < 0.05$) in DOMS recovery in the CRYO group compared to CONT group.

Conclusions: A 20 minutes (4 session × 5 minutes) session for 5 consecutive days of repeated air pulsed cryotherapy has beneficial effects on the recovery of DOMS on elbow flexors from eccentric exercise.

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1. INTRODUCTION

Delayed onset muscle soreness (DOMS) due to exercise induced muscle damage (EIMD) is a common problem among elite and novice athletes as a result of excessive or unaccustomed training.[1] The mechanism underlying DOMS remains inconclusive, as the physiological events that cause exercise-induced micro-tears in the muscle fibres and resultant damage involves a combination of mechanical or biochemical factors.[1,2] Researchers have identified several causative factors of DOMS that include lactic acid accumulation in muscle, muscle spasm, connective tissue damage, inflammation, enzyme efflux, and free radicals.[3,4] DOMS describes the inflammatory response and oxidative stress in a muscle which trigger the release of several chemical mediators that are responsible for pain, and local elevation of inflammatory substances like histamine, prostaglandin and leukotriene.[1] These inflammatory substances stimulate directly the sensation of pain by sensitizing type III and IV pain afferents free nerve ending.[5]

DOMS is commonly characterized by muscle pain, swelling, loss of muscle function that includes decreased range of motion (ROM) and strength deficits.[6] Symptoms are usually first evident within 24 h post exercise, reaching the peak occurrence between 24 h and 72 h, and gradually dissipating between 7 and 10 days.[7] Furthermore, the muscle pain may be associated with decreased muscle performance in the form of decreased rapid force capacity and maximal muscle strength.[6] DOMS is usually cited by coaches and athletes as being detrimental to recovery and performance, the rapid reversion of DOMS in athletes is essential for both function restoration and regain of sports performance.[6,7] Therefore, several modalities of recovery have been used to hasten the recovery period from DOMS which include warm-up and cool-down,[8] soft tissue massage,[3] stretching exercise,[9] electrotherapy,[10] thermotherapy[11] and cryotherapy.[7,12] However, the efficacy of such interventions on exercise induced muscle damage remains equivocal.[13]

Cryotherapy is one of a standard care for acute inflammation.[14] Cryotherapy is proposed to decrease skin-tissue temperature, reduce secondary hypoxic injury, and reduce inflammation consequently decreases edema.[14,16] However, the effect of cryotherapy on recovery of DOMS remains inconclusive.[12,14] There is still controversy over what constitutes the optimal modality, frequency and duration of cryotherapy application for DOMS.[12] Available scientific evidences from a meta-analysis and systematic review suggest that no standard guidelines for a target temperature for optimal therapeutic effects have been established.[17,18] However, the current practice based treatment guidelines for acute tissue injury recommend intermittent cryotherapy application several times a day for approximately 15–20 minutes throughout 72 h retrieval period after injury or until the tendency for swelling has resolved.[15] Previous studies which investigates the effect of cooling on symptoms associated with DOMS conclude that cryotherapy has been shown to reduce the signs and symptoms of DOMS.[19–22] On the other hand, evidences from studies do not support any effect on muscle recovery after cryotherapy.[7,12,23–25] Such discrepancies in the effect may originate due to differences in exercise protocol to induce DOMS, different cooling applications, small sample size and lack of consistency in dosage and frequency for the cryotherapy, which generally consists of a single application, inadequate duration,[13] all of which may have contributed to lack of uncertain findings for effectiveness.

A novel modality of cryotherapy is the air-pulsed cryotherapy, a treatment involving very short exposures to extreme cold (–30°C) to treatment area, and it is getting popular among athletes and coaches.[26] Air-pulsed cryotherapy involves repeatedly exposing very cold air on skin and the sub-epidermal tissues to withdraw heat energy by convection from treatment area.[23] The very cold air exposure is reported to cause a greater decrease in skin temperature than other cryotherapy technique.[27] To our knowledge, there is no study that evaluated the effect of repeated air pulsed cryotherapy on DOMS as per the clinical recommendations made by standard guidelines for cryotherapy application.[15] Therefore, the current study attempts to answer the question about clinical effectiveness of the repeated air pulsed cryotherapy treatment for DOMS. Such information is useful for the clinicians in the field of sports medicine, and rehabilitation as well as to the sports scientists, athletes and coaches towards managing and training any individuals with DOMS.

2. AIM

The main aim of the current study is to investigate the effect of 20 minutes per day (4 session × 5 minutes) of air pulsed cryotherapy application on DOMS induced on elbow flexor muscle (biceps brachii) by eccentric exercise.

3. MATERIAL AND METHODS

3.1. Participants

A total of 32 volunteers (32 males), aged 18 to 25 years (21.31 ± 1.03 years, height 1.72 ± 0.05 m, BMI 22.15 ± 1.69 kg/cm^2) participated in the study. All participants were healthy volunteers who were recruited from campus and community settings around the university. Any volunteer with history of alcohol consumption and with reported contraindications to cryotherapy treatment were excluded from the study. The inclusion criteria required the participants with no history of musculoskeletal and neurological disorders of upper limb, no recent injuries to upper limb over the last 12 months and with no history of any form of resistance training to upper limb over the last 3 months of time period. The participants were randomly assigned into one of the two groups namely repeated air pulsed cryotherapy intervention (CRYO group, $n = 16$) and control group (CONT, $n = 16$). The ethical approval of

the study was granted by an institutional ethics committee and all the participants signed a written informed consent form prior to the start of the study.

3.2. Eccentric exercise induction protocol

The eccentric exercise of elbow flexor muscle was performed using isokinetic dynamometer (Con-Trex CMV AG, Dubendorf, Switzerland). Prior to the exercise performance, the machine was calibrated as per the recommendations of the manufacturer. Each participants performed a bout of 3 sets of 20 maximal eccentric contractions of elbow flexors of the nondominant arm. For each eccentric contraction, the elbow joint was forcibly extended from a flexed (60°) to a fully extended position (180°) in 1 s at an angular velocity of 120°/s in a supinated arm position and the arm was passively repositioned at 60° (at rate of 30° deg/s). The subjects were verbally encouraged to generate maximal force against resistance from flexed position towards extension during the elbow extending action throughout range of motion, with a 3 minutes rest allowed in between each set.[23]

3.3. Intervention protocol

Air pulsed cryotherapy was administered to all the participants in the CRYO group by a trained research assistant, who used a Cryo^6 skin cooling system (Zimmer Medizin Systems, Neu-Ulm, Germany). All the participants in the CRYO group received 4 repeated applications of cryotherapy each session lasting for a duration of 5 minutes. A rest period of 1 minute was given between each sessions to avoid any cold burns due to extreme cold.[23] The cold pulsed air was applied 2 cm above the distal tendon of biceps brachii to the nondominant arm with a maximal available air flow intensity of 9 over a 4 × 10 cm area. The scanning of the cold air was performed through vertical and horizontal motions with a 5-cm distance kept between the tube nozzle and skin. An infrared thermometer (DT –480, China) was used to confirm skin temperature during cryotherapy treatments for a sufficient effect of cold therapy (5°C–15°C).[28] The CONT group participants were rested in supine position without cryotherapy treatment and were given general advice to take rest and not to carry any heavy weight. All of the participants were requested to avoid any kind of vigorous physical activity.

3.4. Data collection

A total of eight separate outcome measures which include visual analogue scale score (VAS), mid arm circumference (MAC), pressure pain threshold (PPT), range of motion of active elbow flexion (ROM-AF), passive elbow flexion (ROM-PF), active elbow extension (ROM-AE), passive elbow extension (ROM-PE) and isometric peak torque (IPT) of elbow flexors were measured in random order. All the outcome measures were evaluated repeatedly over 7 different points at baseline (PRE) taken prior to the eccentric exercise induction of DOMS, immediately (Imm), and on 1, 2, 3, 4, and 7 day (1D, 2D, 3D, 4D, and 7D) respectively.

3.5. Visual analogue scale

The pain intensity perceived by the participants was assessed using a VAS score. The VAS consists of a 10-cm line labelled with 0 at the left endpoint representing no pain and 10 at the right endpoint representing unbearable pain. The subjects were asked to mark the level of perceived pain on VAS as the participants stood in an upright position, flexed their forearm slowly to a 90° angle and returned to the initial position of full elbow extension.[23]

3.6. Pressure pain threshold

PPT was assessed to measure peripheral sensitization using a digital pressure algometer (Somedic AB, Sollentuna, Sweden) with a probe size of 1.0 cm^2. After calibration with a 100 kPa calibrating weight, the probe was placed perpendicularly over the mid-belly of the biceps muscle and force was gradually applied at a rate of 40 kPa/s. The participants pressed a button when they started to feel pain as a result of applied pressure. This protocol was performed three times with 30 s interval between measurements and an average value (in kPa) of the three measures was used for further analysis.[29,30] The point of measurement at the skin was marked with a semipermanent marker for the consistency of the subsequent measurements.

3.7. Mid arm circumference

An anthropometric tape measure was used to measure the elbow flexors circumference at the level of mid-belly of the biceps brachii muscle.[21] The skin was marked with a semipermanent marker to maintain consistency of measurement for the subsequent days. The measurements were taken while the participant was in the sitting position with arm relaxed and hanging by the side. An average of the three measures was recorded in centimetres for further analysis with a 30 s of interval between each measurement.

3.8. Range of motion

A standard goniometer was used to measure the total ROM for the elbow joint with active ROM (AROM) assessed before passive ROM (PROM) and flexion measured before extension. All measurements were taken in the supine position. The measurement procedure was standardized for both measurements with the fulcrum of the goniometer centred over the lateral epicondyle of the humerus and the stationary arm was placed parallel to the humerus pointing towards the acromion process. The moving arm was parallel to the radius pointing to the styloid process of the radius. The active flexion angle was defined as the angle at the elbow when participant performed flexion movement at the elbow joint to touch the shoulder with the palm and the active extension angle was the angle when participants extended the elbow joint as much as possible. The pain-free AROM was determined by instructing participant to stop at the position where the initial pain was perceived. For the PROM, the participant was then instructed to relax the arm and the movement was performed by the investigator.[31] The participant notified the investigator when he first perceived pain. Three measurements

were taken for each angle with a 30 s of interval between each measures. The average of the three measures was recorded in degree for further analysis

3.9. Isometric peak torque

IPT measurement of the elbow flexors was carried out at a joint angle of 90° using an isokinetic dynamometer (Con-Trex CMV AG, Dubendorf, Switzerland). The participants were instructed to pull the forearm towards the shoulder to induce elbow flexion and to sustain the maximal effort for 5 s at a fixed elbow angle. A total of three measurements were taken with 30 s of interval between each measures.[23] An average value of torque from the three measures was recorded in Newton meters (Nm) for further analysis.

3.10. Statistical analysis

A sample size calculation was estimated from a previous study with DOMS as the primary clinical outcome at a power at 0.80 and an effect size of 0.46. Data were analysed using the SPSS 22.0 for Windows Statistical Package (SPSS Inc, Chicago, IL). All variables were tested for normality using the Shapiro–Wilk test. Changes in variables over time were compared between groups using a mixed model repeated measures ANOVA (group × time) on normalized data. Bonferroni test analysis was followed up to detect differences in the main effect. The Greenhouse–Geisser epsilon was used to adjust the degrees of freedom to increase the critical value of the F ratio. Level of significance was set at $P < 0.05$ for all analyses.

4. RESULTS

There was no significant difference in the mean age, weight and BMI between groups, except height. The changes in absolute values (mean ± SD) for the outcome measures at pre-exercise (Pre), immediately (Imm) and days 1 to 7 (1D–7D) post exercise for the groups (CRYO, $n = 16$) and control (CONT, $n = 16$) are presented in Table 1.

Table 1. Changes in outcome measures from pre exercise (Baseline), immediately (Imm) and days 1 to 7 (1D–7D) for the cryotherapy (CRYO, $n = 16$) and control (CONT, $n = 16$) groups.

Measures	Pre	Imm	1D	2D	3D	4D	7D
VAS, cm							
CONT	0	0.012 ± 0.05	3.47 ± 0.74[a]	4.47 ± 0.96[a]	4.51 ± 1.42a	2.91 ± 1.14[a]	0.51 ± 0.46[a]
CRYO	0	0.018 ± 0.07	2.57 ± 0.35[a,b]	3.20 ± 0.76[a,b]	2.26 ± 0.93[a,b]	0.41 ± 0.40[b]	0.06 ± 0.12[b]
Mean diff (95%CI)	0	0 (–0.05–0.04)	0.9 (–0.48–1.32)	1.27(–0.64–1.90)	2.25(–1.38–3.11)	2.50(–1.9–3.08)	0.45(–0.64–0.2)
PPT, kPa							
CONT	339.19 ± 56.8	287.69 ± 52.99[a]	243.02 ± 46.17[a]	251.48 ± 57.07[a]	279.09 ± 55.49[a]	304.38 ± 48.81[a]	336.00 ± 59.42
CRYO	330.7 ± 39.52	282.56 ± 49.25[a]	258.92 ± 35.27[a]	278.52 ± 41.98[a,b]	310.0 ± 45.68[a,b]	330.25 ± 41.35[b]	338.19 ± 40.40
Mean diff (95%CI)	8.48 (–27.04–44.00)	5.13 (–31.81–42.07)	15.90 (–45.65–13.85)	27.04 (–63.35–9.27)	30.85 (–67.57–5.90)	25.87 (–58.57–6.83)	2.18 (–39.08–34.70)
MAC, cm							
CONT	29.21± 3.55[a]	29.41(3.56)	29.64 ± 3.64[a]	29.81 ± 3.77[a]	29.84 ± 3.79[a]	29.48 ± 3.63[a]	29.25 ± 3.58
CRYO	28.26 ± 2.40	28.38(2.37)	28.50 ± 2.41[a,b]	28.49 ± 2.44[a,b]	28.36 ± 2.41[b]	28.29 ± 2.41[b]	28.27 ± 2.39
Mean diff (95%CI)	0.95(–1.2–3.1)	1.02(–1.1–3.2)	1.1(–1.1–3.3)	1.3(–0.9–3.6)	1.49(–0.8–3.7)	1.18(–1.0–3.4)	0.98(–1.2–3.2)
ROM-AF, °							
CONT	145.94 ± 3.05	143.27 ± 3.75[a]	134.0 ± 4.48[a]	131.71 ± 6.51[a]	134.19 ± 5.59[a]	139.08 ± 3.80[a]	145.92 ± 2.73
CRYO	146.79 ± 3.44	143.79 ± 4.26[a]	135.41 ± 5.12[a]	134.64 ± 5.34[a]	138.17 ± 4.95[a]	141.19 ± 3.53[a]	147.15 ± 3.30
Mean diff (95%CI)	0.8 (–3.2–1.5)	0.52(–3.4–2.4)	–1.42(–4.9–2.0)	–2.93(–7.2–1.4)	–3.9(–7.8–0.16)	–2.1(–4.7–0.54)	–1.2(–3.4–0.96)
ROM-AE, °							
CONT	–2.08 ± 4.53	9.75 ± 6.81[a]	32.39 ± 8.00[a]	51.35 ± 7.44[a]	35.44 ± 10.38[a]	18.21 ± 7.77[a]	1.814 ± .36
CRYO	–2.66 ± 5.20	8.00 ± 9.14[a]	23.13 ± 8.30[a,b]	28.95 ± 9.03[a,b]	15.40 ± 6.10[a,b]	2.41 ± 6.78[a,b]	–2.44 ± 4.97
Mean diff (95%CI)	0.6(–2.9–4.1)	1.75(–4.1–7.6)	9.3(3.4–15.1)	22.39(16.4–28.4)	20.04(13.8–26.2)	15.8(10.5–21.1)	4.25 (–0.8–7.6)
ROM-PF, °							
CONT	147.90 ± 3.12	144.46 ± 4.06[a]	136.57 ± 4.01[a]	133.56 ± 4.12[a]	135.55 ± 4.37[a]	141.81 ± 2.85[a]	147.91 ± 2.91
CRYO	148.62 ± 2.80	145.42 ± 3.21[a]	142.81 ± 3.47[a,b]	142.39 ± 3.08[a,b]	145.79 ± 3.50[b]	147.71 ± 3.35[b]	148.79 ± 3.20
Mean diff (95%CI)	0.7(–2.8–1.4)	0.96(–3.6–1.7)	6.24 (–8.9–3.5)	8.83(–11.4–6.2)	10.25(–13.1–7.4)	5.90(–8.1–3.6)	0.88(–3.1–1.3)
ROM-PE, °							
CONT	–2.96 ± 4.97	4.39 ± 6.19[a]	17.71 ± 6.81[a]	27.13 ± 8.77[a]	25.73 ± 11.73[a]	8.94 ± 7.03[a]	–2.64(4.99)
CRYO	–3.60 ± 3.92	3.42 ± 8.20[a]	9.51 ± 9.64[a,b]	13.84 ± 11.33[a,b]	6.73 ± 7.04[a,b]	–3.25 ± 4.29[b]	–3.64(3.89)
Mean diff (95%CI)	0.6(–2.6–3.9)	0.9(–4.3–6.2)	8.2(2.14–14.2)	13.3(5.9–20.6)	19(11.9–26.0)	12.2(7.9–16.4)	1(–2.2–4.2)
IPT, Nm							
CONT	42.82 ± 9.77	33.02 ± 5.86[a]	29.63 ± 5.44[a]	30.97 ± 5.21[a]	32.74 ± 5.82[a]	35.42 ± 6.18[a]	38.12 ± 8.32[a]
CRYO	39.78 ± 6.58	30.875 ± .60[a]	28.72 ± 5.39[a]	30.66 ± 5.34[a]	32.44 ± 5.81[a]	35.11 ± 5.74 [a]	36.75 ± 6.12[a]
Mean diff (95%CI)	3.0 (–3–9)	2.1(–1.9–6.3)	3.0(–3–9)	0.9(–1.9–6.2)	0.64(–2.9–4.8)	0.87(–3.5–4.1)	0.88(–3.9–4.6)

Comments: No significant differences between groups at the baseline; values are mean ± SD, [a] Significant compared with PRE, [b] Significant compared with CONT.

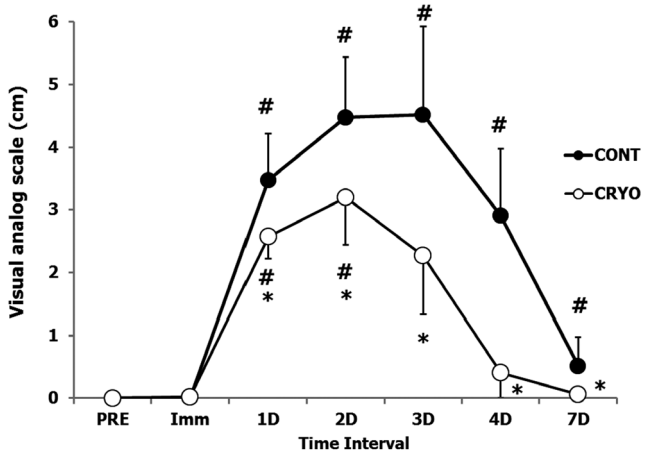

Figure 1a. Changes of VAS: PRE, Imm, and 1D–7D post exercise for the CRYO and CONT groups. Comments: Values are the mean ± SD. * Significant compared with PRE ($P < 0.05$), # Significant between groups ($P < 0.05$).

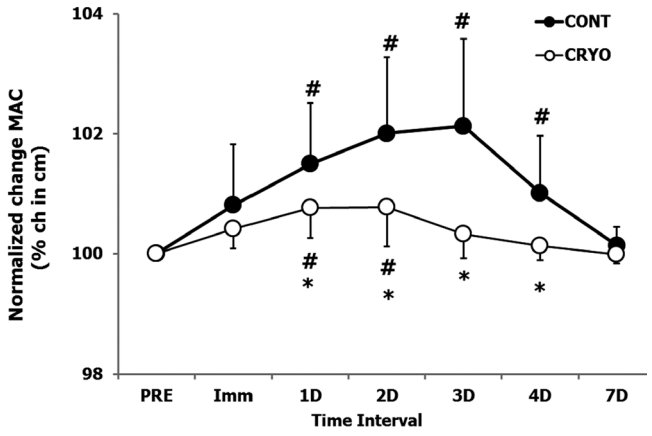

Figure 1b. Normalized changes in MAC: PRE, Imm, and 1D–7D post exercise for the CRYO and CONT groups. Comments: * Significant compared with PRE ($P < 0.05$), # Significant between groups ($P < 0.05$).

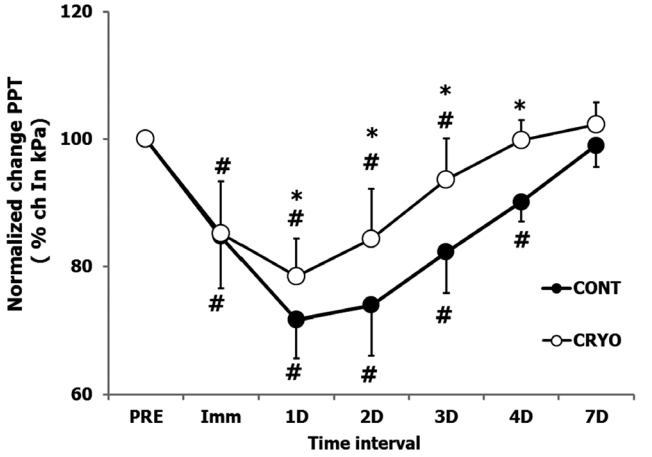

Figure 1c. Normalized changes in PPT: PPRE, Imm, and 1D–7D post exercise for the CRYO and CONT groups. Comments: * Significant compared with PRE ($P < 0.05$), # Significant between groups ($P < 0.05$).

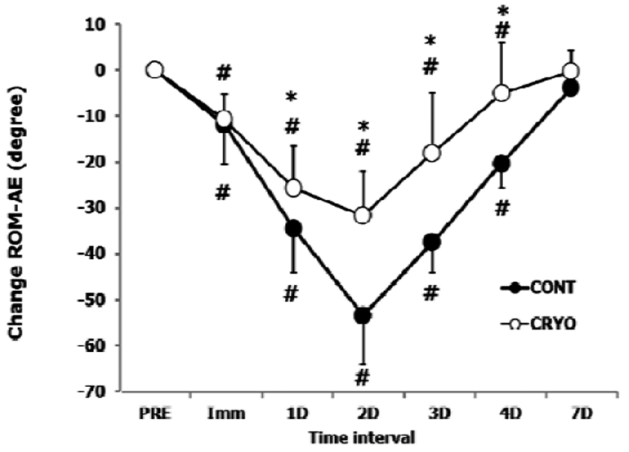

Figure 2a. Changes in ROM-AE: PRE, Imm, and 1D–7D post exercise for the CRYO and CONT groups. Comments: * Significant compared with PRE ($P < 0.05$), # Significant between groups ($P < 0.05$).

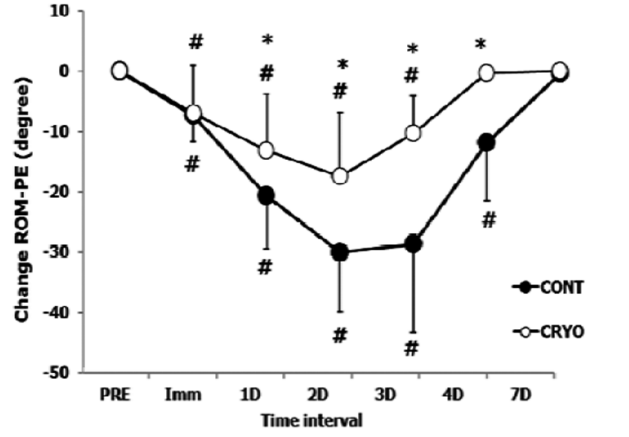

Figure 2b. Changes in ROM-PE: PRE, Imm, and 1D–7D post exercise for the CRYO and CONT groups. Comments: * Significant compared with PRE ($P < 0.05$), # Significant between groups ($P < 0.05$).

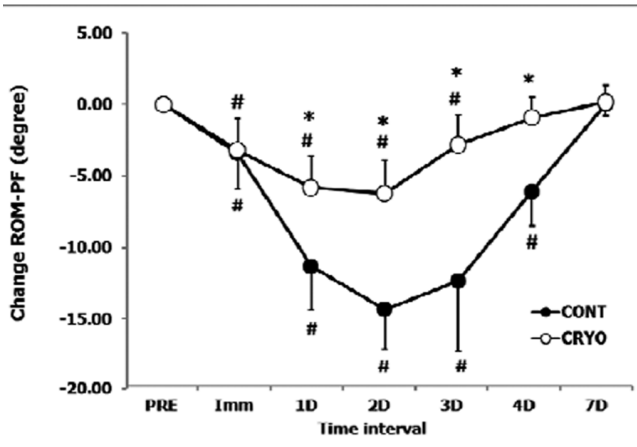

Figure 2c. Changes in ROM-PF: PRE, Imm, and 1D–7D post exercise for the CRYO and CONT groups. Comments: * Significant compared with PRE ($P < 0.05$), # Significant between groups ($P < 0.05$).

4.1 Pain intensity

The results showed a significant main effect of time for VAS (changes within the participants between baseline and repeated measures) with ($F_{1.99, 59.76} = 332.62$, $P = 0.001$, $\eta^2 = 0.91$) and significant main effect of condition (changes between CRYO and CONT group) with ($F_{1, 30} = 38.18$, $P = 0.001$, $\eta^2 = 0.56$). A significant main effect on interaction between time and conditions (within and between differences across the time of measures between the groups) was also observed with ($F_{1.99, 59.76} = 29.62$, $P = 0.001$, $\eta^2 = 0.49$). DOMS peaked 4.51+1.42 for CONT group at 3D and 3.20+0.76 for CRYO group at 2D (Figure 1b) The effect size was larger for all the significant effects which ranged $\eta^2 = 0.49$–0.91).

4.2. Pain pressure threshold

A significant main effect of time on PPT was observed in both groups ($F_{3.18, 95.56} = 113.91$, $P = 0.001$, $\eta^2 = 0.80$). Similarly, the main group effect was also significant between groups ($F_{1, 30} = 23.43$, $P = 0.002$, $\eta^2 = 0.43$) on 1D ($P = 0.007$), 2D ($P = 0.002$), 3D ($P = 0.001$), and 4D ($P = 0.001$) respectively. PPT returned to PRE for CRYO group at 4D compared with 7D for CONT return to PRE levels (Figure 1b). ANOVA revealed a significant group × time interaction ($F_{3.18, 95.56} = 6.40$, $P < 0.003$, $\eta^2 = 0.18$) with a larger effect size.

4.3. Mid arm circumference

The results showed a significant main effect of time in both groups ($F_{3.08, 92.60} = 32.23$, $P = 0.001$, 2= 0.52) and a significant main effect between groups ($F_{1, 30} = 18.48$, $P = 0.001$, $\eta^2 = 0.38$). The main effect of interaction (group × time) was also significant ($F_{3.08, 92.60} = 10.59$, $P = 0.001$, $\eta^2 = 0.26$). All the observed changes are clinically significant with large effect size ($\eta^2 = 0.26$–0.52). Figure 1c shows the main effect of interaction where MAC return to PRE values for the CRYO group at 3D compared with CONT at 7D.

4.4. Active range of motion

There was a significant main effect of time on ROM-AF in both groups ($F_{2.14, 64.35} = 204.62$, $P = 0.001$, $\eta^2 = 0.87$), however no significant effect was established between groups and interaction of group × time ($P > 0.05$). For ROM-AE, there was a significant main effect of time ($F_{3.53, 106.03} = 202.48$, $P < 0.001$, $\eta^2 = 0.87$) and group ($F_{1, 30} = 24.47$, $P = 0.001$, $\eta^2 = 0.48$) with a significant interaction effect of group × time ($F_{3.53, 106.03} = 16.16$, $P = 0.001$, $\eta^2 = 0.35$). CRYO group demonstrated significant lower deficit in ROM-AE than CONT group at 2D ($P = 0.015$), 3D ($P = 0.001$), 4D ($P = 0.001$), and 5D ($P = 0.001$) as indicated in Figure 2a.

4.5. Passive range of motion

For ROM-PF, a significant effect of time ($F_{3.24, 97.31} = 134.20$, $P = 0.001$, $\eta^2 = 0.82$), group ($F_{1, 30} = 66.24$, $P = 0.001$, $\eta^2 = 0.48$) and main interaction of group X time ($F_{3.24, 97.31} = 31.29$, $P = 0.001$, $\eta^2 = 0.51$) was observed respectively with larger effect size. The CRYO group demonstrated a significantly lower deficit in ROM-PF than CONT group on 1D to 4D post-exercise ($P = 0.001$) (Figure 2b). Similar results of significance were obtained for ROM-PE on time effect ($F_{2.77, 83.11} = 78.66$, $P < 0.001$, $\eta^2 = 0.72$), group effect ($F_{1, 30} = 16.43$, $P = 0.001$, $\eta^2 = 0.35$) and interaction of group × time ($F_{2.77, 83.11} = 11.49$, $P < 0.001$, $\eta^2 = 0.27$). CRYO group demonstrated a significantly lower deficit in ROM-PE than CONT group on 1D ($P = 0.026$), 2D ($P = 0.001$), 3D ($P = 0.001$) and 4D post-exercise ($P = 0.001$) (Figure 2b).

4.6. Isometric peak torque

The results showed a significant main effect of time in both groups ($F_{4.26, 156.66} = 282.19$, $P = 0.001$, $\eta^2 = 0.90$), and a significant time X group interaction effect ($F_{4.26, 127.88} = 2.79$, $P = 0.026$). However, there was no significant effect observed between groups ($P = 0.084$, $\eta^2 = 0.09$). Table 1 shows that the IPT remained lower than the PRE value after 7D.

5. DISCUSSION

The study results demonstrated that repeated air pulse cryotherapy significantly enhanced the recovery process of DOMS following eccentric exercise to a greater extent than the CONT group. Past studies suggested that the muscle needs to be eccentrically engaged to optimal and adequate intensity of muscle work in order to create a DOMS phenomenon before any effect on DOMS to be investigated.[23,32] In current study, an eccentric exercise protocol successfully induced DOMS which had been confirmed by significant changes in all dependent variables over time (Table 1). The pattern of changes observed in dependent variables after DOMS by eccentric exercise were similar to the trend reported in previous studies.[23,32]

In current study, muscle soreness peaked at 2D–3D post exercise which is consistent with previous studies.[21,23,24,33] The CRYO group had significantly reduced VAS rating than CONT groups at 1D to 7D ($P < 0.001$). While the change in VAS rating in CRYO group from 4D to 5D (2.26+0.93 cm to 0.41+0.40 cm) was superior to minimally clinical important difference (1.7 to 2.0 cm),[34] the muscle soreness returned to PRE level for the CRYO group at 4D compared with 7D for the CONT (Table 1, Figure 1a). Therefore, it can be suggested that air pulsed cryotherapy might effectively relieves pain after 24 h of application. Our result was similar to Ingram et al.[20] who reported a significant reduction in soreness of quadriceps muscle among participants at 24 h with two 5-minutes immersions in 10°C water. Similarly, Oakley et al.[19] also found a significant pain reduction of hamstring muscle with 20 minutes of cold application three times a day throughout 72 h post exercise. In contrast, numerous cryotherapy studies had no significant change in muscle soreness.[23,24,35–37]

The CRYO group had a significant increase of PPT value at 2D, 3D and 4D and return to PRE level at 4D (Table 1, Figure 1c) suggested that air pulsed cryotherapy was more effective than CONT group in mechanical pain reduction. The course of change in PPT observed over time was similar to previous studies[32,38] where PPT showed a largest decline 24 h

after DOMS following eccentric exercise. These results suggested that air pulsed cryotherapy reduced pain and increased PPT contributed by rapid reduction in skin temperature. As low skin temperature is shown to induce a local analgesic effect (<13.6°C) and reduced nerve conduction velocity (<12.5°C),[39] it might explain the mechanism on how repeated air pulsed cryotherapy reduced pain and increased PPT. In current study, 5 minutes air pulsed cryotherapy (–30°C) reduced the skin temperature to 7.44±1.32°C which was more cooler than a previous study[23] (9.±0.8°C) during 20 minutes application and the temperature remained lower than 18°C among the participants for at least for 10 minutes even after cooling application.

The CRYO group had a significant relief in swelling as measured by MAC after 1D–4D compared to the CONT group and MAC returned to PRE level at 3D (Table 1, Figure 1b). The findings were similar to Eston and Peter who reported that cold water immersion (every 12 h for a total of 7 sessions) following eccentric biceps exercise showed a significant reduction in stiffness and swelling.[21] In contrast, few other studies[23,26] demonstrated that cryotherapy did not significantly affect swelling which could be explained due to differences in protocols such as modality of cryotherapy, duration of treatment and lack of continuation of treatment associated with DOMS. Therefore, the repeated air pulsed cryotherapy protocol used in current study carefully considered the above differences together with clinical recommendations by increasing the treatment time to 20 minutes with increased frequency of treatment application.

The decreases in ROM-AF, ROM-PF, ROM-AE and ROM-PE following DOMS induced by eccentric exercise might be as a result of muscle stiffness. The stiffness might occur due to connective tissue damage, tissue edema which increased mechanical sensitivity of muscle receptors to discomfort as activated by pressure or stretching.[1,21] As a result of DOMS, ROM-AE and ROM-PE might cause more pain particularly due to eccentric action of the damaged elbow flexor muscle which might lead to reduced movements. Nevertheless, ROM-AE and ROM-PE in CRYO group showed significantly lesser reduction than CONT group which could be attributed to positive effect of repeated air pulsed cryotherapy application. The significant reduction of ROM-PF in CRYO group was lesser than the CONT group. Therefore, it was possible that air pulsed cryotherapy could accelerate the recovery in ROM-PF, ROM-AE and ROM-PE by reducing pain, inflammatory process and muscle tightness. However, no significant change in ROM-AF between groups was observed. Past study suggested that cold application might increase local blood viscosity and tissue stiffness interrupting active exercise[15] which might explain why no change in the ROM-AF occurred.

The current study showed a large decline (approximately 31%) in strength of elbow flexors in 1D post exercise DOMS and the strength remained below the baseline even at day 7. The possible explanations for loss of muscle strength may include rupture of the myofibril, sarcolemma, t-tubules and consequent failure of action potential conduction and excitation-contraction coupling, which may have resulted to an inability to generate force.[40] In our study, IPT had no significant difference between groups. The pattern of strength loss and recovery observed in current study is similar to Guilhem et al.[23] who reported that maximal isometric torque of elbow flexors strength decreased by 33% in 24 h after exercise and the eccentric exercise protocol used were similar to the present study (3 × 20 eccentric contractions). Therefore, it might be argued that repeated air pressured cryotherapy did not have any effect on the muscle strength. To our knowledge, no studies showed significant improvement in strength of elbow flexors after eccentric exercise from cryotherapy.[23,36,41]

There are few limitations present in the study. The study considered only healthy male participants and hence, the external validity of the study findings may not be applicable to other groups of population (e.g., females, elderly individuals, clinical population). As gender is reported to affect the pain outcome measures, the researchers recruited only the male participants. No measurement of subcutaneous fat tissue was considered which could be another limitation as presence of sub cutaneous fat might act as an insulator and inhibit effects on tissue cooling. Nevertheless, BMI data showed that the participants did not have obesity which might minimize the effects of sub cutaneous tissue to cooling effects. Further research should focus on testing the study findings in other populations involving different muscle groups before applying the positive effects of the study to day to day clinical practice. Applications of cold for short period (<10 minutes) are reported to be ineffective in DOMS recovery[42] and hence, a duration of 20 minutes was considered as optimal duration for repeated air pulsed cryotherapy application.

6. CONCLUSIONS

A 20 minutes (4 session × 5 minutes) session for 5 consecutive days of repeated air pulsed cryotherapy has beneficial effects on the recovery of DOMS on elbow flexors following eccentric exercise. Future studies are required to investigate the effects of repeated air pulsed cryotherapy in multiple muscle groups among athletes.

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Conflict of interest

None declared.

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Original article

Factors associated with severe stigma among patients living with HIV/AIDS in Port Harcourt

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ABSTRACT

Introduction: Human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) have been known as a stigmatizing illness. HIV/AIDS-related stigma, in its severe form, compromises the well-being of persons living with HIV/AIDS (PLWHA).

Aim: To identify the factors associated with severe stigma among PLWHA in Port Harcourt.

Material and methods: This was a hospital-based cross sectional study involving PLWHA attending anti-retroviral clinic of the University of Port Harcourt Teaching Hospital (UPTH) in Port Harcourt. Data on sociodemographic characteristics and stigma were obtained from 302 participants selected by systematic random sampling. Bivariate and multivariate analyses were performed to explore factors associated with severe stigma among PLWHA.

Results: Eighty-seven of the 302 respondents (28.8%) had severe stigma. PLWHA who were males, non-Christians, who had no formal education, and had no source of income had the highest proportion of severe stigma. Multivariate analysis revealed that source of income was a predictor for severe stigma among PLWHA (odds ratio 3.59; CI95% 1.45–8.90; $P = 0.006$).

Discussion: The findings in this study expose the negative influence of lack of income on the psychological being of PLWHA as those who had no source of income were more likely to experience severe stigma than those with a source of income.

Conclusions: Severe stigma is prevalent among PLWHA in Port Harcourt. The need for stigma prevention strategies among PLWHA is advocated especially among those with no source of income. Financial empowerment and creation of employment opportunities by Nigerian government in collaboration with non-governmental organizations could mitigate stigma among PLWHA.

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1. INTRODUCTION

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) is an emerging disease that has remained a major public health crisis in Nigeria, a country with a high number of people living with HIV second only to South Africa.[1] HIV and AIDS stigma has been identified as a significant challenge to the success of achieving universal access to HIV prevention, treatment, care and support.[2,3] Also, HIV and AIDS are relatively more stigmatizing than other illnesses as the society views it as a behaviorally acquired and contagious disease.[4]

Stigma has emerged as a 'hidden epidemic' ravaging the society and it is promoted by socially-shared ignorance, fear, misinformation, and denial.[5] It refers to attitudes and beliefs that lead people to reject, avoid, or fear those they perceive as being different.[6] Severe stigma as perceived by the victims affects their self-esteem, disrupts their family relationships and limits their ability to socialize and obtain housing and jobs.[7] Hence, adversely affecting the mental health of the victim.[8]

In Nigeria, a hospital based study carried out among persons living with HIV or AIDS (PLWHA) noted that 57.7% and 80% of the clients did not disclose their status to people outside their immediate families and employers respectively due to perceived stigma.[9] Also, another study in South Africa among PLWHA, noted that almost all participants (95.8%) had experienced stigma.[10] Stigma seem to occur pervasively among PLWHA. High stigma consciousness have been linked to lower CD4 count in PLWHA.[11] Furthermore, stigma in its severest form has been linked to poor mental health of the victims.[7] Although studies have been done on stigma among PLWHA, scarcely is there any study that has elucidated the predictors of the severe form of stigma among this population. Hence, the need to explore factors associated with severe stigma among PLWHA. Identifying determinants of severe stigma among PLWHA could serve as a basis for instituting evidence based stigma preventive strategies among PLWHA.

2. AIM

This study therefore aimed to identify factors associated with severe stigma among PLWHA in Port Harcourt, Nigeria.

3. MATERIAL AND METHODS

This study was carried out in Port Harcourt, the capital of Rivers State. Rivers State is one of the 36 states in Nigeria. It is located in the south-south region of Nigeria and has a population of 5,185,400.[12] A hospital-based cross sectional study design was adopted in this study. The study population comprised of PLWHA attending the ante-retroviral (ARV) clinic in the University of Port Harcourt Teaching Hospital (UPTH).

The research and ethics committees of the University of Port Harcourt granted ethical approval for this research work. Written informed consent was obtained from the clients prior to their inclusion into the study. Anonymity and confidentiality of information were upheld in this study. Sample size was calculated based on the formula for cross sectional studies,[13] based on the state prevalence of HIV of 15.2%, [14] precision of 0.05 and α level of 0.05. Systematic sampling method was used to select the 302 participants in the study.

Data on stigma were obtained from a three-item validated tool modified for HIV and AIDS.[15–17] The tool comprised of uncomfortable component (do you feel other people are uncomfortable with you because of your disease?), avoidance component (do you feel other people are avoiding you because of your disease?) and inferior component (do you feel other people treat you like an inferior person because of your disease?). A 'yes' response was scored as 1 and a 'no' response scored as 0. The scores from each of the items are scored to obtain the total score, which ranges from 0 to 3. A score of 3 depicts severe stigma.[15–17] Data on sociodemographic characteristics of age, sex, marital status, educational level, religion, source of income and category of income were obtained from the respondents.

The Statistical Package for Social Sciences (SPSS) version 20 was used in data analysis. Bivariate analysis was employed using χ^2 tests or Fisher's exact as appropriate. Variables with statistical significance of $P < 0.25$ were entered into multivariate analysis model in order to accommodate more variables in the model. Multivariate analysis was performed using unconditional binary logistic regression to determine predictors of severe stigma among PLWHA. P less than 0.05 was considered statistically significant. Odds ratio and 95% confidence intervals were calculated to determine the strength of association.

4. RESULTS

A total of 200 females (66.2%) and 102 males (33.8%) were involved in this study. The age range of respondents was 20 to 76 years. The mean ages of male and female respondents were 43.3 ± 9.6 years and 36.7 ± 9.1 years, respectively. The difference in the mean age was significant ($P < 0.001$) as shown in Table 1.

Eighty-seven of the 302 respondents had severe stigma giving a prevalence of 28.8%. The cross tabulation of severe stigma across sociodemographic characteristics showed that

Table 1. Mean ages of male and female respondents.

Gender	*N*	Age in years	
		Mean	SD
Male	102	43.26	9.627
Female	200	36.67	9.149

Comments: $t = 5.820$; $P < 0.001$.

Table 2. Bivariate analysis of severe stigma and sociodemographic factors.

Sociodemographic factors	Severe stigma: Yes *n* (%)	Severe stigma: No *n* (%)	Total *n* (%)	
Age (years)				
20–29	15 (35.7)	27 (64.3)	42 (100.0)	$\chi^2 = 3.859$ $P = 0.425$
30–39	37 (27.4)	98 (72.6)	135 (100.0)	
40–49	24 (28.9)	59 (71.1)	83 (100.0)	
50–59	10 (33.3)	20 (66.7)	30 (100.0)	
≥ 60	1 (8.3)	11 (91.7)	12 (100.0)	
Sex				
Male	35 (34.3)	67 (65.7)	102 (100.0)	$\chi^2 = 2.277$ $P = 0.131$*
Female	52 (26.0)	148 (74.0)	200 (100.0)	
Marital Status				
Currently single	31 (32.0)	66 (68.0)	97 (100.0)	$\chi^2 = 0.692$ $P = 0.406$
Currently married	56 (27.3)	149 (72.7)	205 (100.0)	
Educational level				
None	1 (100.0)	0 (0.0)	1 (100.0)	*Fisher's Exact* = 8.200 $P = 0.029$*
Primary	14 (28.0)	36 (72.0)	50 (100.0)	
Secondary	35 (23.0)	117 (77.0)	152 (100.0)	
Tertiary	37 (37.4)	62 (62.6)	99 (100.0)	
Religion				
Christians	84 (28.1)	215 (71.9)	299 (100.0)	*Fisher's Exact* $P = 0.023$*
Non-Christians	3 (100.0)	0 (0.0)	3 (100.0)	
Income				
Without source of income	12 (57.1)	9 (42.9)	21 (100.0)	$\chi^2 = 8.835$ $P = 0.003$*
With source of income	75 (26.7)	206 (73.3)	281 (100.0)	

Comments: * Statistically significant $P < 0.25$.

Table 3. Multivariate analysis of severe stigma (dependent variable) and sociodemographic factors (independent variables) using binary logistic regression model.

Independent variables*	Coefficient *B*	Odds ratio (95% CI)	*P*
Gender			
Male	0.379	1.46 (0.86–2.47)	0.157
Female**			
Educational level			
(In ordinal scale)	–0.234	0.79 (0.55–1.14)	0.214
Income			
Without source of income	1.277	3.59 (1.45–8.90)	0.006***
With source of income**			
Constant	–0.002		0.998

Comments: Hosmer and Lemeshow tests: $P = 0.864$, * Religion was not included in the model as one of the cells contained a zero value, ** Reference category, *** Statistically significant $P < 0.05$.

the highest proportions of severe stigma occurred among those aged 20 to 29 years (35.7%), males (34.3%), currently single (32%), with no formal education (100%), non-Christians (100%) and those with no source of income (57.1%) as shown in Table 2. Bivariate analysis showed that sex, educational level, religion and source of income were significantly associated with severe stigma at statistical significance of $P < 0.25$.

Multivariate analysis using binary logistic regression showed that source of income was the only independent variable associated with severe stigma. PLWHA who had no source of income were approximately four times more likely to experience severe stigma than those with a source of income (OR 3.59; 95%CI 1.45–8.90; $P = 0.006$) as shown in Table 3.

5. DISCUSSION

Similar to present study, several studies[18–21] across the globe have also explored sociodemographic factors associated with the experience of stigma among PLWHA. This is not surprising as these factors could serve as basis for instituting interventions aimed at limiting and preventing severe stigma among PLWHA. Curtailing stigma among PLWHA is vital for their optimal mental health.[8]

The finding that sex of PLWHA was not significantly associated with the occurrence of severe stigma in present study is consistent with studies by Abrahams and Jewkes in South Africa[10] and Berkley-Patton et al. in USA.[22] However, it contrasts with a study by Nattabi et al. in Uganda,[23] which found an association between sex and experience of stigma, noting that female PLWHA had significantly higher prevalence of stigma than male PLWHA. Also female gender was closely associated with HIV related stigma in a longitudinal study carried out in five cities in USA by Martinez et al.[4] Moreover, these other studies focused on occurrence of stigma generally while this study focused on the occurrence of severe stigma. In spite of the differences reported, there is a dire need to institute measures to prevent the occurrence of stigma among persons living with HIV irrespective of their gender.

The age of PLWHA was not related to the experience of stigma unlike a study in Uganda, which reported that PLWHA who were above 30 years were significantly more likely to experience stigma than those aged 30 years and below.[23] The dissimilarities in the study population could account for the observed differences; while the study in Uganda comprised of PLWHA who were less than 49 years in age, the present study had a wider age range of respondents with the maximum age being 76 years. Also, cultural differences could be attributed to the disparity of findings. However, the findings of present study implies that individual counseling programs on reducing perceived stigma among PLWHA should be non-age specific that is, all age groups should be involved.

This study found that non-Christians had significantly higher prevalence of severe stigma than Christians. The

location of this study which comprised of a predominantly Christian population could contribute to this disparity. Noteworthy, most people living with HIV or AIDS express faith as important in coping with HIV.[24] However, there is need for health care providers to put into cognizance the religion of their clients when rendering services to PLWHA in order to offer targeted counseling on prevention of stigma. The present study found that PLWHA who had no source of income were approximately four times more likely to experience severe stigma than those with source of income. This subtly exposes the protective influence of the presence of source of income on the occurrence of severe stigma among PLWHA. Therefore, empowerment programs for PLWHA who have no source of income could reduce the impact of stigma amongst them.

Although the present study has added to the existing literature on the factors associated with severe stigma among PLWHA, the cross sectional design of the study is a limitation as the identified factors do not reveal causality. Also, the hospital based nature of the study may limit the generalizability of the findings. The authors therefore advocate for more studies using community based population and the employment of analytical study designs.

6. CONCLUSIONS

Severe stigma occurs among PLWHA attending the ARV clinic in UPTH, Port Harcourt. Age, sex, education and marital status were not significantly related to the occurrence of severe stigma while source of income was significantly associated with severe stigma in this study. Stigma prevention strategies should include financial empowerment and provision of employment opportunities for PLWHA with no source of income, through the collaborative efforts of government and non-governmental organizations.

Conflict of interest

None declared.

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Case report

Bicoronal approach in managing frontal sinus osteoma – case report

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ABSTRACT

Introduction: Giant osteomas of paranasal sinuses occur rarely, therefore there is no clearly stated surgical management, with varied approaches being reported in literature.

Aim: The aim of this study is to present the bicoronal approach as a treatment option for giant osteoma of the frontal sinus.

Case study: This paper presents the case of 61-year-old female patient who was admitted to the hospital with a giant osteoma of the left frontal sinus. The patient was complaining of recurrent headaches, most often in the frontal region. The computed tomography showed a giant osteoma of left frontal sinus (36 × 30 × 24 mm). Due to the osteoma's size and limitations of the intranasal technique, an external surgical approach was chosen. The tumor was resected from bicoronal incision, which enabled full visualization of the tumor and minimized the complication risk.

Results and discussion: Giant osteomas of the frontal sinus frequently spread intracranially or into the orbit, which may lead to serious complications. The only course of action is surgery, and although endoscopic methods play a leading role today, giant osteomas often require external incisions. In the presented case, we describe the bicoronal approach as favorable for the surgeon as well as for the patient.

Conclusions: The advantage of the bicoronal approach as one of the surgical methods used to treat giant osteoma of the frontal sinus is to provide good access to pathologies within the frontal sinus that are impossible to remove endoscopically, together with a satisfactory aesthetic result.

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1. INTRODUCTION

Osteomas most commonly appear in the head and neck region, especially within mandible and paranasal sinuses. Osteoma is a benign, slow-growing tumor that affects 1% of population. Approximately 80%–96% of all paranasal sinus's osteomas occur in frontal sinuses, 2%–15% in ethmoidal sinuses.[1] In most cases, osteomas are asymptomatic and the diagnosis is made accidentally. Due to their localization, ethmoidal osteomas are presenting symptoms earlier than frontal ones. Patients complain of face- and headaches. The term 'giant osteoma' is used to describe osteomas larger than 30 mm in at least one diameter and/or with weight over 110 g.[2] Giant osteomas often spread intracranially and into the orbit, which may lead to serious complications. The only treatment is surgery. Due to the rarity of giant osteomas, there is no definite method of treatment. Both, intranasal and external approaches are recommended in literature.[1,3–6]

2. AIM

The aim of this study is to present the bicoronal approach as a treatment option for giant osteoma of the frontal sinus.

3. CASE STUDY

A 61-year-old female patient was admitted to our clinic to perform surgical treatment of the left frontal sinus osteoma. The patient suffered from headaches but denied anosmia, nasal obstruction or any vision problems. Nasofiberoscopy showed normal nasal patency and normal nasopharynx. Cone beam computer tomography (CBCT) revealed giant osteoma occupying entire lumen of the left frontal sinus, connected to the posterior wall and limited to the frontal sinus (Figure 1). Osteoma caused dehiscence of the anterior sinus wall and the upper-medial wall of orbit. Due to the size of the tumor (36 × 30 × 24 mm), the external approach was chosen for surgical treatment. Bicoronal incision was performed 2 cm behind the hairline, between temporal muscles. Skin and frontal muscles were dissected to the upper margin of orbit and to the nasion point in horizontal line (Figure 2). Periosteum flap was prepared that did not overlap the envisaged cut of the frontal bone. The periosteum pedicle was inserted to the upper margin of orbit. A 'window' cut was made in the anterior wall of the frontal sinus by the piezoelectric (oscillating) knife. The visualized tumor filled the whole sinus. The tumor was cut by diamond burr towards its posterior insertion. The insertion of osteoma was located on the inferior part of the septum between frontal sinuses. After the tumor's removal, mucous membrane of the frontal sinus was unchanged. The next important step of surgery was to close the bone defect. The bone loss in the anterior wall of the frontal sinus was covered by previously removed bone fragment using the titanium microplate Synthes and titanium microscrews. The shape of

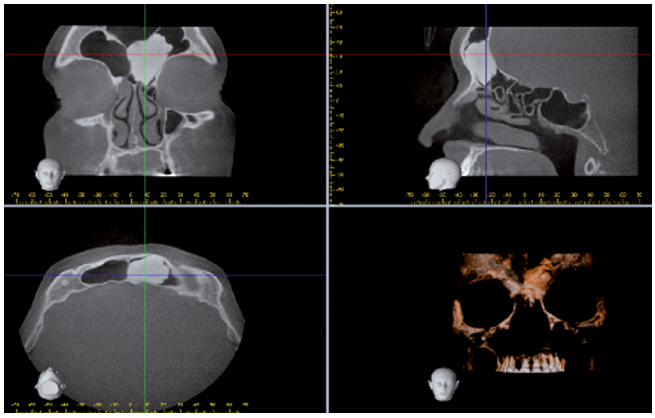

Figure 1. Giant osteoma of left frontal sinus.

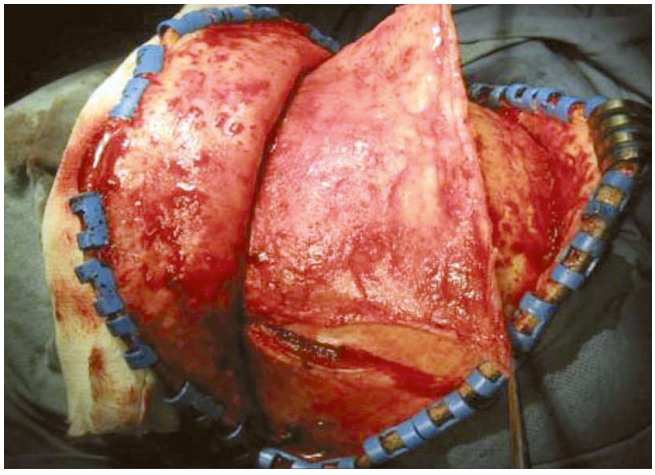

Figure 2. Bicoronal incision with visible periosteum flap.

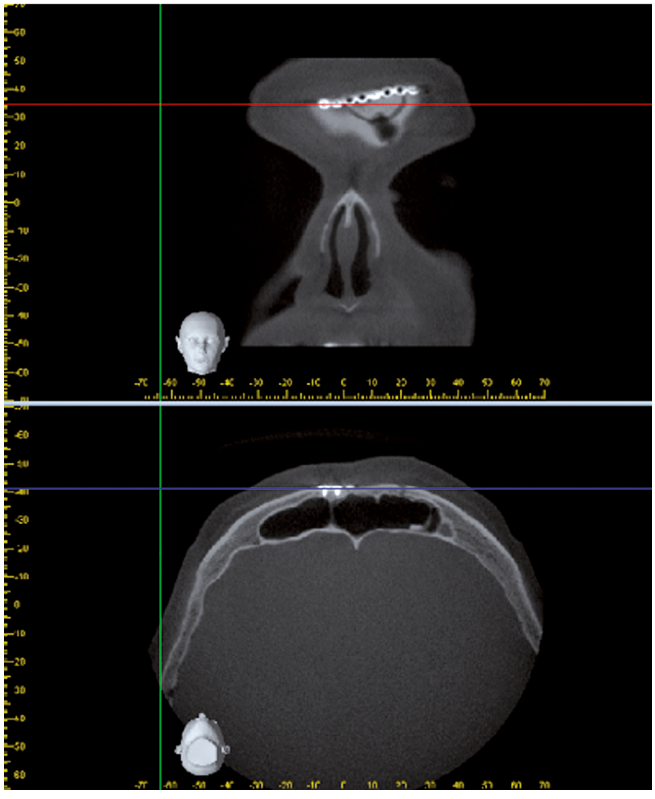

Figure 3. Postoperative CT scan.

the frontal bone was reconstructed, its anterior wall covered with periosteum flap. The procedure lasted 3.5 h. The subcutaneous cavity drainage was removed 2 days after the surgery, skin stitches 8 days after the surgery. The control CT scan confirmed complete removal of osteoma and the correct positioning of the microplate (Figure 3). No nasal bleeding was observed in the postoperative period. We have not identified any deformation of the frontal bone. We could not sense the presence of the microplate in palpation. Normal nasal patency, proper sense of smell, hair regrowth, full mobility of the eyeballs and no vision disorders were observed. The patient reported that all previous symptoms had passed.

4. RESULTS AND DISCUSSION

Osteomas of paranasal sinuses are benign, slowly growing tumors, most commonly within frontal and ethmoidal sinuses. Usually, they are asymptomatic and diagnosed incidentally. Although osteomas appear in 1% of population, giant osteomas are extremely rare and cause symptoms. Ethmoidal sinus osteomas often lead to orbital symptoms, such as eye motor dysfunction, double vision, exophtalmus and/or epiphora. Frontal sinus osteomas often cause headaches or face deformities. Due to obstruction of the sinus ostium and mucosal dysfunction, the patient often develops mucocele.

The etiology of osteomas is still unclear. One of the theories mentions osteoblasts within mucoperiostium as the cause of pathological growth.[7] Some authors connect osteomas to Gardner's syndrome.[8]

There are three histological types of osteomas: ivory osteoma (dense compact bone), mature osteoma (trabecular bone) and mixed type.

The main therapeutic proceeding in the case of osteomas is surgical treatment, either endoscopic or external approach. There is no clear indication when surgery is recommended. Because of the tumor's slow growth and relatively rare number of recurrences, some authors suggest their incomplete removal in difficult cases. Treatment of asymptomatic osteomas remains controversial; most authors prefer conservative treatment limited to observation with regular radiological studies.[5] However, surgery should be performed in cases of asymptomatic osteomas involving at least half of the sinus's lumen or fast-growing osteomas (more than 1 mm per year). The same applies to osteomas of the frontal recess, sphenoid and those spreading into the orbit.[9]

The choice of surgical treatment of osteomas, endoscopic or external, should be based on localization and the size of the tumor. Possible complications during the procedure should also be taken under consideration. With respect to frontal osteomas, endoscopic treatment often involves DRAF II or DRAF III procedure and 70° endoscope, which sometimes is not sufficient to remove giant osteoma.[10] Then the external approach or combined techniques remain as the alternative.[9] A decision can be made after grouping the tumor by the Chiu grading system (Table 1),[2] where tumor type I and II qualifies for endoscopic treatment.[9]

Table 1. Frontal sinus osteoma grading system.[2]

Grade	
Grade I	Base of attachment is posterior-inferior along frontal recess Tumor is medial to a virtual sagittal plane through the lamina papyracea Anterior-posterior diameter of the lesion is less than 75% of the anterior-posterior dimension of the frontal recess
Grade II	Base of attachment is posterior-inferior along frontal recess Tumor is medial to a virtual sagittal plane through the lamina papyracea Anterior-posterior diameter of the lesion is more than 75% of the anterior-posterior dimension of the frontal recess
Grade III	Base of attachment is anterior or superiorly located within the frontal sinus AND/OR Tumor extends lateral to avirtual sagittal plane through the lamina papyracea
Grade IV	Tumor fills the entire frontal sinus

In the presented case, the bicoronal approach was chosen as the most favorable for the patient as well as for the surgical team. Selection of the piezoelectric knife for performing the 'window' within the anterior wall of the frontal sinus enabled the preserving of mucous membrane and hence natural sinusal drainage. Thanks to this technique, the risk of uncontrolled CSF leak and/or lesions within natural sinusalostium was avoided. Using titanium microplates and screws to reconstruct the anterior wall of the frontal sinus guarantees the durable osteointegration of bony fragment. The bicoronal cut behind the hairline provided a good aesthetic effect.

5. CONCLUSIONS

Giant osteomas may manifest with severe symptoms and lead to intraorbital and intracranial complications. Surgical treatment should be chosen based on the tumor's size and location as well as the surgeon's experience. Some traditional external approaches remain superior to endoscopy when treating giant osteoma, preserving the sinus's function and giving a satisfactory cosmetic outcome.

Conflict of interest

None declared.

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Case report

Spontaneous cerebral haemorrhage in a young weight lifter: A case report and a review of current literature

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ABSTRACT

Introduction: Intracranial haemorrhage is the leading cause of death related to a head trauma in sports, and spontaneous cerebral bleedings are a very rare condition in young athletes.

Aim: We propose the case of a young weight lifter, androgenic anabolic steroids abuser, who developed a spontaneous massive intracranial haemorrhage during exertion.

Case report: The patient was a weight lifter at a competitive level, who had exercised on a regular basis for the past 5 years, assuming anabolic steroids and proteins for some years. Moreover, he referred a negative family history for spontaneous bleeding in the brain. At the visit time he presented very high blood pressure values.

Results and discussion: In this case report, the side of the cerebral lesion was typical for a hypertensive brain damage. High blood pressure values, and the alteration of sodium and potassium were compatible with hyperaldosteronism; moreover, cardiac ultrasound assessment showed a hypertrophic ventricle condition, secondary to a chronic untreated hypertension.

Conclusions: The chronic use of anabolic steroids could contribute to hypertensive complications, such as intracranial haemorrhages.

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1. INTRODUCTION

The spontaneous intracranial haemorrhage is a very severe condition leading to neurological disability and associated to a high mortality rate.

It is a very rare condition in young subjects; its incidence increases after the age of 55 years, and it doubles after 80 years.[1]

As reported in several studies, the intracranial haemorrhage is the leading cause of death secondary to a head trauma[2] during sport activity.[3]

Moreover, the dissection of cervical artery has been described in association with several sports, such as swimming[4] and also following a trauma to the neck by a sea wave.[5]

Alaraj et al. reported about two young athletes, abusers of anabolic androgenic steroids, who developed a spontaneous subdural haematoma.[6]

2. AIM

We propose the case of a young weight lifter, abuser of androgenic anabolic steroids, who developed a spontaneous massive intracranial haemorrhage during an exertion.

3. CASE REPORT

A 30-years-old, previously healthy, man arrived to the Emergency Department for a severe headache resistant to acetaminophen, associated to nausea, vomiting and neurological abnormalities. In particular, he initially showed an aphasia and then a marked weakness of face, of the left upper limb and of the left lower limb. Neurological symptoms began during a training session. Patient denied any history of head trauma. He referred that, about a year before, he was hospitalized for a persistent headache, associated with elevated blood pressure values; on that occasion, he was positive to drug tests for the detection of anabolic steroids. According to its medical history, the patient was a weight lifter at a competitive level, who had exercised on a regular basis for the past 5 years, assuming anabolic steroids and protein integrators. Moreover, he reported a negative family history for spontaneous cerebral bleedings.

At the visit time, he weighted 105 kg and presented elevated blood pressure values (190/100 mmHg). Physical examination showed bilateral papillaedema and conjunctival haemorrhage. Regarding biochemical parameters, we found high creatinine plasma levels associated to an alteration in sodium and potassium levels. The encephalic CT showed the presence of a right-sided lenticular haemorrhage (Figure 1A). The patient underwent to an echocardiogram, showing a hypertrophic left ventricle; the exam excluded the presence of a patent foramen ovale. Subsequently, we performed a cerebral

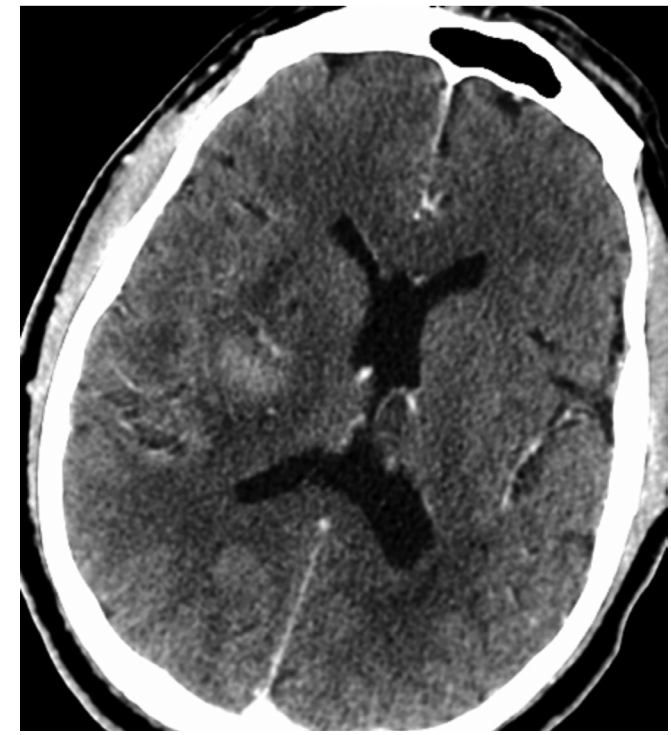

Figure 2. The angiography tomography of the brain excluded arteriovenous malformations or 166 atherosclerosis of internal carotids.

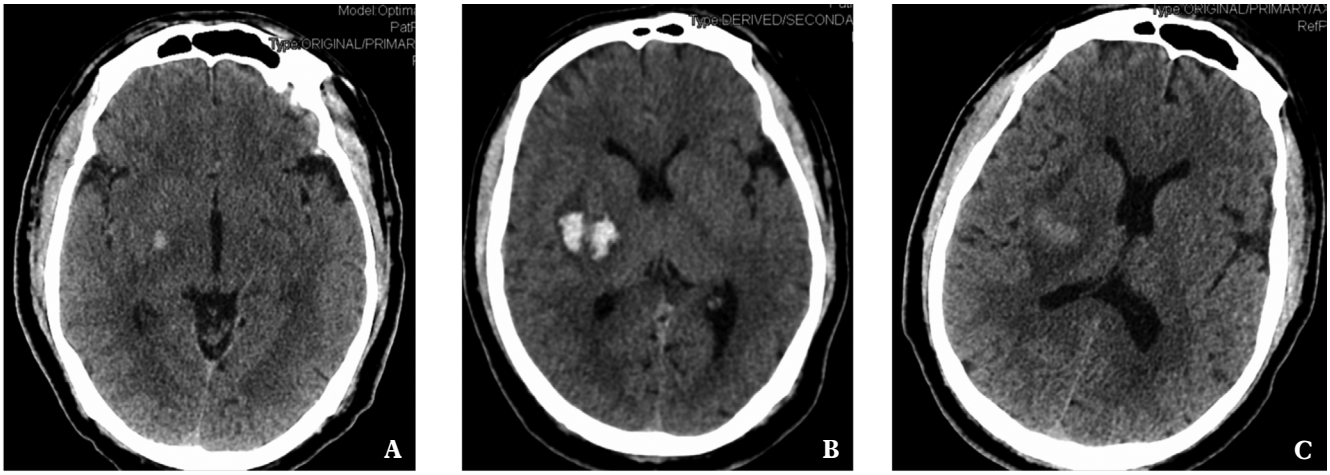

Figure 1. Several CT scans of the brain showing the progression of the haemorrhagic lesion at different times: at baseline (A), at 24 hours (B) and after 1 week (C).

CT angiography, which had excluded intracranial vascular malformations or severe atherosclerosis of internal carotids (Figure 2). The neurosurgeon excluded indications for surgery. At the 24-hours control (Figure 1B), the haemorrhage was significantly increased, showing the development of a large neurogenic oedema. These findings were associated to the progression of neurological abnormalities, with the onset of a complete paralysis of the left side. After a week, a new encephalic CT evidenced a partial reduction of the haemorrhagic area (Figure 1C).

4. RESULTS AND DISCUSSION

Although several cases of cerebral bleedings in sportsmen were reported, only Alaray et al.[6] described two different cases of subdural haematoma in weight lifters.

According to epidemiological data, the anabolic steroid use is growing in the population of young athletes, with special reference to testosterone, nandrolone, stanozolol, or methandienone.[7]

The chronic use of anabolic steroids is widely associated to the development of a pro-thrombotic burden, because of the increase in thrombin and plasmin levels,[8] and because of the deficiency of protein C,[9] predictors of acute myocardial damage and peripheral arterial disease. A case of a young man who presented potentially life-threatening arterial thromboses during anabolic steroid assumption was previously described.[10]

Moreover, the use of anabolic steroids is associated to a significant increase in blood pressure values;[11] this phenomenon is probably related to the sensivity of endothelium to catecolamine levels, to the renin and aldosteron production, or to others pathways.[12] Data from a follow-up study, as reported by Pereira dos Santos et al., showed that these effects appeared to be relatively short lived;[13] currently there is a lack in evidence on the use of steroids in the longer term. A recent study reported the association between recreational of anabolic steroid use and arterial hypertension and hyperlipidemia;[14] Severo et al. reported that changes in lipid profile, were associated to an increase in inflammatory markers and endothelial dysfunction.[15]

In this case report, the side of the cerebral lesion was typical for a brain damage on hypertensive basis.

The elevation in blood pressure values, and the alteration of serum electrolytes, were compatible with the presence of a drug-related hyperaldosteronism; moreover, the cardiac ultrasound assessment showed a hypertrophy of left ventricle, likely secondary to a chronic untreated hypertension.[16,17] A retrospective study, suggested a causative role in the pathogenesis of sudden cardiac deaths of anabolic steroids; in particular, authors identified several pathological changes within the myocardium of the left ventricle, such as interstitial and perivascular fibrosis, and fibroadipous metaplasia and perineural fibrosis.[18] Chronic use of anabolic steroids was associated to a depression in left ventricular function; moreover, steroids-using bodybuilders presented a reduced diastolic functions of both ventricles.[19] A case of a myocardial infarction in a young body builder was previously reported.[20] However, long term effects of weight lifting and of the abuse of anabolic steroids on myocardial fibres and on peripheral vasculature, are still argument of research.[7]

5. CONCLUSIONS

The weightlifting is associated with the increase in blood pressure values and with alterations on myocardial fibres,[7] but these effects seem to be reversible. However, the chronic use of anabolic steroids could contribute to hypertensive complications,[16,17] such as intracranial haemorrhages.

Conflict of interest

None declared.

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Case report

Surgical treatment of central giant cell granuloma of the jaws in children

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ABSTRACT

Introduction: There has been much debate in the literature regarding the preferred method of central giant cell granulom (CGCG) treatment. Non-surgical methods are widely accepted, including intralesional corticosteroid injections, calcitonin therapy and the rarely used interferon therapy but surgical excision is the preferred method of treatment.

Aim: The objective of this study was to describe our experience in the surgical treatment of CGCG in the paediatric population.

Material and methods: A case study of 9 paediatric patients with the average age of 10 years is discussed in this article. Most patients were diagnosed with mandibular CGCG lesions, and multifocal tumours localized in the mandible and the maxilla were noted in 2 cases.

Results and discussion: The surgical procedures performed in our department included enucleation (2 patients), en bloc resection (2 patients) and segmental resection (5 patients). Segmental resections require further reconstruction. A surgically created defect is repaired with the involvement of frozen or autologous bone grafts, distraction osteogenesis and microvascular customized multiple tissue flaps.

Conclusions: Our experience indicates that despite the use of a meticulous surgical technique, patients at risk of tumour recurrence have to remain under strict clinical observation.

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1. INTRODUCTION

The term 'central giant cell granuloma' (CGCG) was introduced in 1953 by Jaffe.[1] This benign osteolytic lesion of the jaw is also referred to as central giant cell lesion (CGCL).[2] Central giant cell granuloma occurs relatively rarely and represents 7% of benign jaw lesions.[3] It is noted in almost every age group, but its incidence is highest in children and adults younger than 30 years. Research suggests that CGCG is nearly three times more prevalent in women than men.[4] In the craniofacial region, CGCG is localized mainly in the mandible, and it can cross the midline.[3] Multifocal lesions are also observed, often in combination with hyperparathyroidism, Noonan syndrome, neurofibromatosis type 1 and cherubism.[2]

According to Chuong et al., CGCG can be subdivided into aggressive and non-aggressive types depending on clinical and radiographic characteristics.[5] The non-aggressive form may be discovered during routine panoramic radiography as a radiolucent mass. This asymptomatic, slow-growing lesion has a low recurrence rate. The aggressive form may demonstrate alarming features upon physical examination, including painful swelling with facial asymmetry and malocclusion. Computed tomography (CT) scans and radiographs reveal cortical bone destruction and, in some cases, root resorption. The aggressive form of CGCG has a higher recurrence rate.[2–4]

The etiology of CGCG remains unknown.[4] Morphologically, CGCL reveals aggregations of multinucleated giant cells, multiple foci of haemorrhage and trabeculae of woven bone, and high vascular density. Histologically, CGCG requires differentiation from bone tumours associated with hyperparathyroidism.[2,6]

Surgical excision is the preferred method of CGCL treatment, and it ranges from curettage with cryotherapy to segmental resection.[4,7,8] The condition is most prevalent in children, therefore, conservative treatment may be required to reduce secondary deformities. Non-surgical methods include intralesional corticosteroid injections, calcitonin therapy and the rarely used interferon therapy.[9] According to De Lange et al., surgical treatment carries the lowest risk of recurrence, and the 5-year disease-free survival rate after surgical curettage is 76.1%.[10]

2. AIM

The objective of this study was to describe our experience in the surgical treatment of CGCG in the paediatric population.

3. MATERIAL AND METHODS

All of the examined patients were analysed with reference to the anatomical location of the tumour, age, gender, clinical status, radiological features, method of treatment, treatment complications and incidence of recurrence. A total of 9 patients received treatment for CGCG in our department between July 2014 and June 2016, including 2 females (22%) and 7 males (78%). Upon admission, the patients' age ranged from 2 to 17 years, with the average age of 10 years. Hyperparathyroidism was excluded in all cases by measuring serum calcium, phosphorus and alkaline phosphatase levels. CGCG was confirmed by histopathology.

4. RESULTS

In our study, lesions were most commonly localized in the mandible (5 patients, 56%) and the maxilla (2 patients, 22%). Multifocal CGCG was observed in 2 patients (22%), where a large bilateral lesion between the left and the right mandible ramus with another focus in the left maxilla was noted in the 1st patient (Figure 1) , and a lesion in the right angle of the mandible, the mandibular body and the left maxilla near the midline was observed in the 2nd patient.

Six patients had received previous treatment in other institutions, 4 patients had been subjected to intralesional corticosteroid injections with curettage, and 2 patients had undergone lesion enucleation. Six patients were admitted for treatment in our department due to residual lesions or recurrence after the first treatment.

Our approach to CGCG involves complete surgical resection for further reconstruction of the missing tissues. Only 2 (22%) patients were qualified for enucleation. To expand surgical margins, the resected area was additionally devitalized and ablated using argon plasma coagulation. In the remaining 7 cases, the lesions were large, and en block excision was the surgical procedure of choice. Monolateral resection of the ramus and the body of the mandible was performed in 3 patients. In 1 case, bilateral resection of the mandible ramus was required (Figure 1). In this patient, both condyles and a small frontal part of the mandible were left (Figure 2). Mandibular reconstruction with free fibular flap was immediately performed in all 3 patients.

Two patients from this group were also diagnosed with CGCL of the maxilla. These lesions were removed after the resection of mandibular tumours. Two recurrent episodes were noted in one of the patients – 1 in the maxilla and 1 in the mandible. Subsequent widening of surgical margins was performed with good result. In the described cases, non-ossifying fibromas of long bones were observed. One patient was diagnosed with a small asymptomatic lesion near the right knee-joint. In the other patient, a large lesion in the left femoral neck was treated by enucleation and stabilization with the use of LCP hip plates and neck screws.

In the following 3 patients, marginal resection of the anterior part of the mandible was performed without disruption of bone continuity. One of the patients had to be reoperated due to recurrence. Surgical margins were widened, CGCL was not detected, and the mandible was reconstructed by alveolar ridge distraction. In the last patient, the lesion was localized in the left frontal part of the maxilla

Figure 1. 9-Years-old patient with multifocal CGCL tumour.

Figure 2. The same patient as in Figure 1 after tumour resection and reconstruction.

under the nasal cavity. It was resected widely and reconstructed with a free fibular flap 4 months later (Table 1).

5. DISCUSSION

CGCG occurs relatively rarely and represents 7% of benign jaw lesions.[3] It is diagnosed in almost every age group, but is most prevalent in children. The diagnosis is made based on physical examination and radiographs, followed by histological confirmation.

In our study, 7 patients were diagnosed with the aggressive form of CGCG, which was associated with rapid lesion growth, facial asymmetry and tooth displacement. CT scans and radiographs revealed large radiolucent masses with cortical bone destruction.

There is mounting evidence to suggest that intralesional corticosteroid injections are effective, especially in aggressive forms of CGCG. Four of our patients were diagnosed with recurring or residual lesions after steroid treatment in other institutions. We found that unsuccessful injections prolong the time from diagnosis to surgery, which contributes to tumour growth.

Despite the growing number of treatment options, surgery remains the gold standard.[4,9] The range of the resection is correlated with age, and its extensiveness generally increases in older patients.

In our department, enucleation and curettage involve devitalization and ablation of the post-resection gap by argon plasma coagulation. This surgical technique was applied in 2 patients who remained under observation for 8 months with no signs of recurrence. Segmental resection is always performed with further reconstruction in mind. Reconstruction is performed with frozen or autologous bone grafts or microvascular, customized multiple tissue flaps. Distraction osteogenesis may be performed when sufficient quantities of tissue are available. The reconstruction modality also depends on a child's age. Treatment can begin with a conservative approach, followed by more advanced surgical techniques.

Table 1. Characteristics of study patients

Case no.	Age, y	Gender	Anatomical location	Clinical status	Radiological features	Method of treatment	Previous treatment	Incidence of recurrence in our Department
1	2	M	Mandible, frontal part	Rapidly growing, painless tumour	Radiolucent masses	En bloc resection with ablation of the post-resection gap using argon plasma coagulation	None	None
2	3	M	Mandible, left body	Painless swelling	Radiolucent masses with cortical bone destruction	En bloc resection with ablation of the post-resection gap using argon plasma coagulation	Enucleation in another institution, followed by recurrence	None
3	7	F	Mandible, left body	Rapidly growing, painful tumour	Radiolucent masses with cortical bone destruction	Enucleation with ablation of the post-resection gap using argon plasma coagulation	None	None
4	9	M	Maxilla, hard palate	Painful tumour	Radiolucent masses with cortical bone destruction	Enucleation with ablation of the post-resection gap using argon plasma coagulation	Enucleation and intralesional corticosteroid injections in another institution, followed by recurrence	None
5	9	M	Mandible, bilateral ramus and body, Maxilla, left side	Rapidly growing, soft tissue swelling	Tooth displacement, Radiolucent masses with cortical bone destruction	Segmental resection	Intralesional corticosteroid injections in another institution with no improvement	None
6	12	F	Maxilla, left, frontal part	Painful, soft tissue swelling	Tooth displacement, Radiolucent masses with cortical bone destruction	Segmental resection	Enucleation in another institution, followed by recurrence	None
7	16	M	Mandible, mental part	Tooth displacement, pain ful tumour	Tooth displacement, Radiolucent masses with cortical bone destruction	Segmental resection	None	One episode of recurrence with subsequent widening of surgical margins
8	16	M	Body of mandible, right side, ramus Maxilla, left, frontal part	Tooth displacement , painful tumour	Tooth displacement, Radiolucent masses with cortical bone destruction	Segmental resection	Intralesional corticosteroid injections in another institution with no improvement	Two episodes of recurrence: one in the maxilla and one in the mandible with subsequent widening of surgical margins
9	17	M	Body of mandible, left side, ramus	Tooth displacement, painful tumour Soft tissue swelling	Tooth displacement, Radiolucent masses with cortical bone destruction	Segmental resection	Intralesional corticosteroid injections in another institution with no improvement	None

Surgery is usually performed during a single-stage procedure, but reconstruction may be delayed when surgical margins are uncertain. CGCG is localized mainly in the mandible, but the observations made in 2 of the studied patients indicate that special attention should be paid to multifocal lesions. The entire skeleton is not routinely scanned for additional lesions. When microvascular reconstruction is needed, the donor site is analysed in a CT scan. In 2 patients, CT revealed non-ossified fibromas in the femur. In 1 of these patients, the lesion was large, therefore, the patient was subjected to enucleation and stabilization with an LCP hip plate and neck screws as well as reconstruction with the use of frozen bone grafts.

Our experience indicates that despite the use of meticulous surgical technique, patients at risk of recurrence have to remain under long-term clinical observation and radiological surveillance.

6. CONCLUSIONS

CGCG occurs relatively rarely and represents 7% of benign jaw lesions.[3] It is diagnosed in almost every age group, but is most prevalent in children. The diagnosis is made based on physical examination and radiographs, followed by histological confirmation.

Non-surgical methods of treatment are widely applied, including intralesional corticosteroid injections, calcitonin therapy and the rarely used interferon therapy. Despite the above, surgery remains the gold standard.

The results of this study indicate that wide resection is relatively safe even in children provided that reconstruction is well planned. Surgeons should be able to choose from a variety of techniques to effectively reconstruct the defect.

The patients should remain under clinical observation due to the high risk of GCGC recurrence.

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Case report

About a degeneration of a colon endometriosis cystic foci

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ABSTRACT

Introduction: Malignant transformation of endometriosis is a rare entity. Its occurrence in the digestive system is exceptional. In fact, due to the atypical symptoms, the diagnosis is often delayed at an advanced stage. So, the treatment strategy should be discussed in a multidisciplinary meeting.

Aim: Our objective was to describe a challenging diagnosis of an in situ carcinoma developed on a cystic foci of endometriosis of the colon in a woman without a particular past medical history.

Case study: A 32-year-old female patient presented with abdominal pain for about six months. The different explorations have concluded to an ovarian cystic tumour. Intraoperatively, the mass seemed to be developped in the right colon. This led to perform a right hemicolectomy. Gross findings consisted in a sub-mucosal 10-centimeters cyst and microscopic features were consistent with an in situ carcinoma developed on a cystic endometriosis foci.

Discussion: This case illustrates the malignant potential of endometriosis especially when it is misdiagnosed.

Conclusions: Besides the fact that this case was illustrated by radiological and microsocpic features, it puts emphasis on the non consensual management of a rare lesion of the colon.

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1. INTRODUCTION

Endometriosis is defined as a localization of hormonereresponse endometrium mucosa outside the endometrium. It can be gonadal or extragonadal.[1–3] The frequency of extragonadal endometriosis in the bowel is estimated to involve 3% to 37% of women with pelvic endometriosis and most lesions are found in the sigmoid colon and rectum.[4,5] The malignant transformation of these lesions accounts for 0.3%–1% of the cases and their diagnosis is based on microscopic features. In fact, no clinical or radiological features are specific.

2. AIM

Our objective was to describe a challenging diagnosis of an in situ carcinoma developed on a cystic foci of endometriosis of the colon in a woman without a particular past medical history.

3. CASE STUDY

A 32-year-old female was admitted to the department of surgery for a 6-month lasting abdominal pain. The patient was multiparous with two pregnancies and she had no history of gynecological surgery. The patient did not report a change in the intestinal transit or catamenial change in symptoms. Moreover, she wasn't using estrogen therapy. Gynecological and abdominal examination was normal. Abdominal ultrasound showed a 10-centemeter pelvic mass with dual solidocystic component (Figure 1). Abdominal and pelvic computed tomography (CT) scan showed a heterogeneous pelvic mass measuring 9 cm with a dual component and a significant contrast enhancement at the wall. According to the radiological features, this mass was supposed to be linked to the right ovary. No distant metastasis was detected (Figure 2). Ovarian tumor markers were negative. A subumbilical midline laparotomy was performed and showed a mass of the right colon

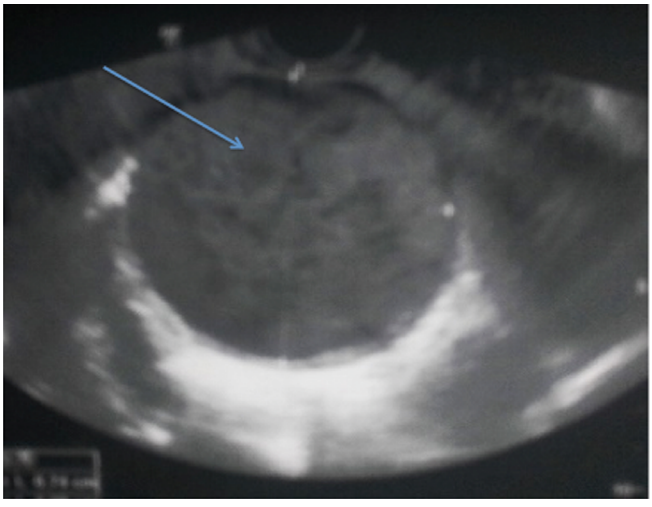

Figure 1. Abdominal and pelvic ultrasound examination showing a pelvic mass with solid and cystic component making 10 cm long axis.

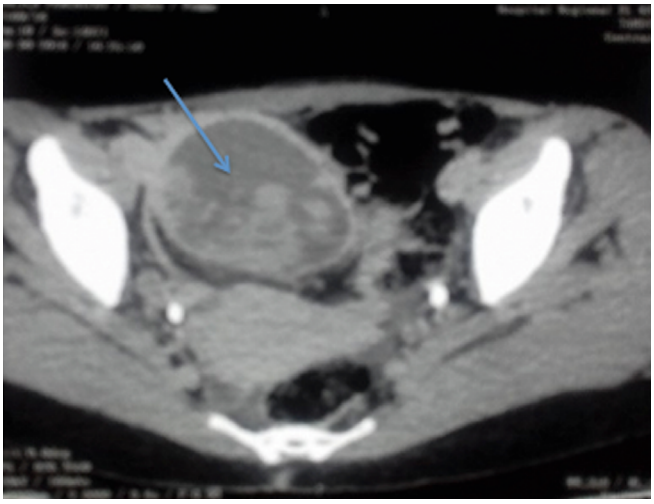

Figure 2. Abdominal and pelvic computed tomography scan showing a heterogeneous pelvic mass of 15 cm long axis, with dual component and significant contrast enhancement at the wall. Its origin was linked to the right ovary.

Figure 3. Gross findings showing a 10-centimeter cystic submucosal lesion (arrow).

with multiple lymph nodes of the right meso-colon. The exploration of the rest of the abdominal cavity did not show other abnormalities. The uterus and the adnexa were normal. A right hemicolectomy with a latero-lateral ileocolic anastomosis was performed. Extemporaneous exam was performed on an ileocolectomy specimen characterized by a sub-mucosal cystic lesion measuring 7 cm and filled with necrotic material and hemorrhage (Figure 3). It concluded to a cystic benign lesion. The definite exam showed a colonic mucosa with a submucosal cystic lesion dilacerating the muscularis mucosa, with a normal colonic layer (Figure 4a). The cystic lesion was covered by a unistratified epithelium mimicking endometrium mucosa (Figure 4b). The epithelium was characterized by focal papillary projections (Figure 4c). These formations were line by atypical epithelial cells characterized by hyperchromatic and atypical nuclei. These atypical cells were limited to

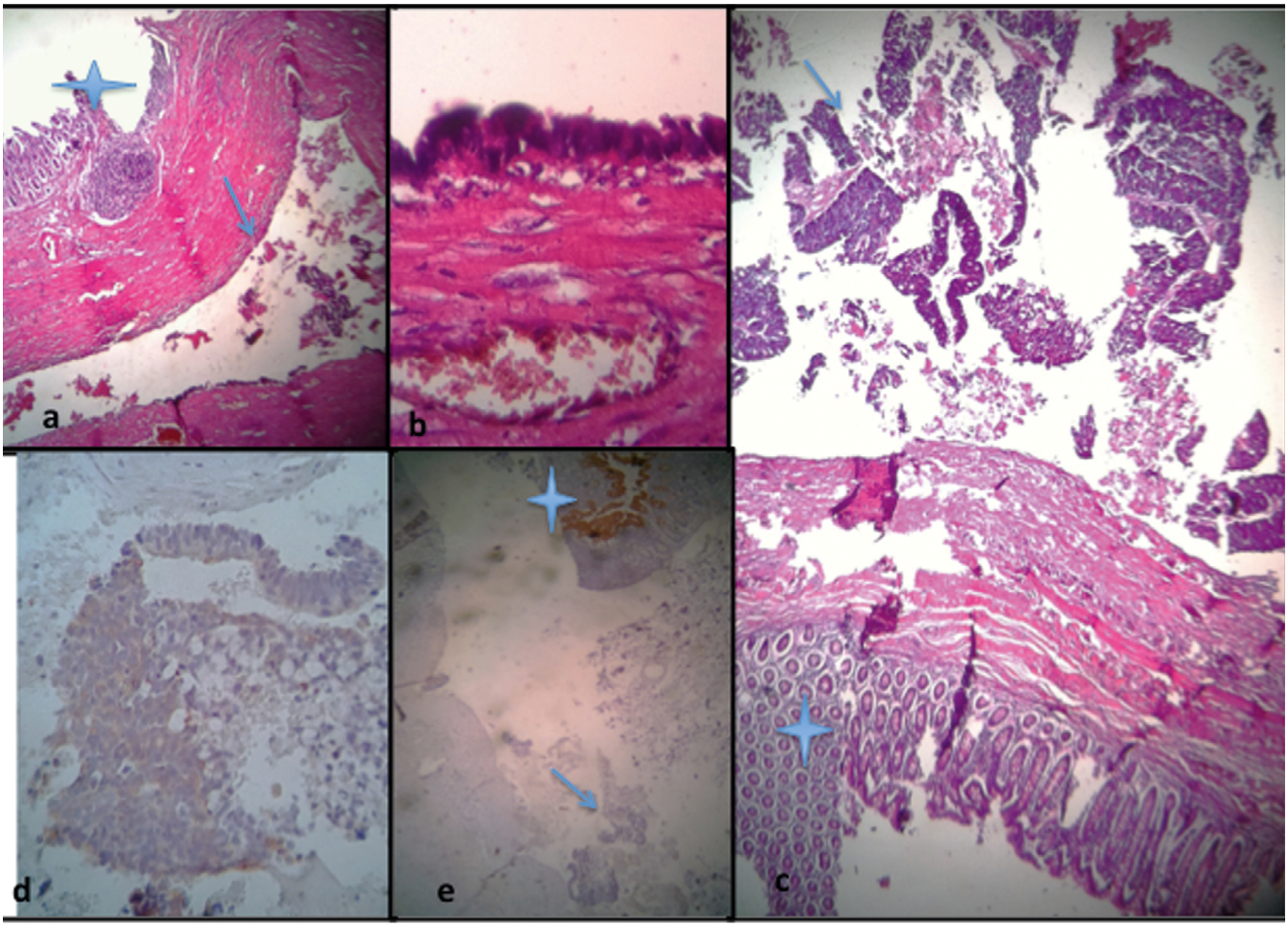

Figure 4. Microscopic findings showing: (a) the localization of the lesion (arrow) beyond the mucosa (star) (HE, ×250), (b) a fibrous cystic lesions lined by atypical cells with hyperchromatic nuclei (HE, ×400), (c) surface cells forming papillary projections (arrow). The upper colonic mucosa is showed using a star (HE, ×400). Immunohistochemical study showing: (d) the expression of CK7 antigen by the tumour cells (HE ×400), (e) the absence of expression of CK 20 antigen by the tumour cells (arrow). The intestinal mucosa expressed the CK20 antigen and highlighted the fiability of the technique (star) (HE, ×400).

the surface and didn't infiltrate the basal lamina. All the cystic lesion were included and studied in order to rule out a possible infiltration. Sixteen lymph nodes were sampled from the meso-colon and were benign. An immunohistochemical study was performed using antibodies againt cytokeratin (CK) 7, CK20, hormonal receptors and mib-1. Tumour cells expressed diffusely and intensely the CK7 (Figure 4d). On the other hand, the tumour cells didn't express the CK20 antigen (Figure 4e). The diagnosis of *in situ* carcinoma developed on a cystic endometrioid foci was retained and a biannual observation of the patient was established without a particular event.

4. DISCUSSION

This case illustrates a rare and challenging cystic lesion of the colon in a young woman without a particular past medical history and especially no endometriosis. The diagnosis of in situ carcinoma developed on a cystic endometriosis foci was established and was particularly challenging.

A few cases of degeneration of endometriosis foci of the colon have been reported in the English literature.[4,5] Almost all patients presenting such a lesion had a past medical history of endometriosis or have a history of cyclic intestinal symptoms during years. Radiologic features aren't specific of these lesions.[6] Transvaginal ultrasound after bowel preparation is reported to be the best initial imaging method for endometriosis, since it can detect foci of deep endometriosis as an irregular hypoechoic mass with or without hypoechoic or hyperechoic foci penetrating into the hypoechoic muscularis propria layer wall. It may also show as long, nodular hypoechoic lesions along the intestinal wall. A number of characteristic appearances of endometriosis of the rectosigmoid area have been reported, including the 'pyramid sign,' the 'comet sign,' and the 'Indian headdress sign.' Ultra-sound examination is also known to be operator-dependent, time-consuming. On contrastenhanced CT imaging, endometrioid foci typically appear as soft-tissue density masses, indistinguishable from other gastrointestinal pathologies either benign or malignant. Magnetic

resonance imaging shows eccentric mass/masses infiltrating into the intestinal wall causing luminal narrowing with associated fibrosis and smooth muscle hyperplasia appearing at times as irregular, speculated, hypo-intense lesions on T2-weighted images. Fat saturated T1-weighted images show a mass or thickening, which is isointense to muscle, possibly with interspersed hyper-intense foci that reflect hemorrhagic blood products.[7] Recently, some authors reported the utility of contrast enhanced MR-colonography in the diagnosis of lesions of endometriosis.[6] Because of the lack of inter-observer agreement and the necessity of very skilled radiologists, the gold standard for diagnosis of endometriosis remains the laparoscopic visualization of suspicious lesions. In our case, the diagnosis was misleading because the lesion was large, cystic and seemed to be linked to the ovary. The colonic localization of the lesion was a peri-operatively discovery. The extemporaneous exam concluded to a benign cystic lesion because of the absence of a stromal invasion and the surgical resection was performed because of the large size of the lesion and in order to avoid complications like intestinal occlusion. Microscopic examination was quite challenging. The diagnosis of endometriosis was easy because of the presence of typical cystic foci of endometrial mucosa. The difficulty in our case was represented by the presence of in situ lesions that were hard to classify. In fact, invasion is defined by an infiltration by the stroma and if present, the lesion is classified as an adenocarcinoma. When establishing the diagnosis of adenocarcinoma, the main challenge faced by pathologists consists in proving the development of such a tumour on lesions of endometriosis and the immunohistochemical study plays a key-role in that case when showing the negativity of CK20 antibody which is quite specific of a primary colonic adenocarcinoma. In our case, there was no infiltration proved despite the inclusion of the totality of the lesion. What was particular to our observation was the atypical cells forming papillary projections on the surface which were characterized by a high proliferative index. This kind of lesion was reported in a patient by Schutz R and colleagues.[8] In fact, they reported a similar non infiltrating lesion classified as an in situ carcinoma. The treatment of digestive endometriosis is mainly based on surgical resection according to many authors.[9] On the other hand, the mainstay treatment of malignant transformation of digestive endometriosis is based on multimodal therapy including surgery resection and chemotherapy. Indeed, only oncologic resection optimizes cure but even though passing on healthy margin, recurrence remains possible. In our case, there was no infiltration, the surgical margins were healthy and all the lymph nodes analysed were benign. These findings made our surgeons and oncologists advocate for a close observation without adjuvant chemotherapy.

Our patient hasn't presented complications since a 2-year follow-up period.

5. CONCLUSIONS

Besides the fact that this case was illustrated by radiological and microsocpic features, it puts emphasis on the non consensual management of a rare lesion of the colon.

Conflict of interest

The authors declare that they have no competing interests and disclose any personal or financial support.

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Case report

Progressive spastic paraparesis in a young male

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ABSTRACT

Introduction: Adrenoleukodystrophy (ALD) is a hereditary genetic disease linked to the X chromosome. It is caused by mutations in ABCD1, a gene that codes for ALD protein, a peroxisomal membrane protein of unclear function. A very large spectrum of symptoms, as well as different degrees of intensity among the members of the same family may be a serious diagnostic challenge.

Aim: To examine current views with respect to ALD pathogenesis and treatment methods and to present the case of its specific variant: adrenomyeloneuropathy. Additionally, we wish to direct attention to the possibility of such a diagnosis in each patient (including women) with progressive paraparesis.

Case study: We present the case of a 29-year-old male patient with progressive paraparesis. The implemented diagnostics procedures (neuroimaging studies and levels of very long chain fatty acids) led to a correct diagnosis: adrenomyeloneuropathy.

Results and discussion: Symptomatology as well as diagnostic and therapeutic methods implemented for patients with ALD are discussed in detail.

Conclusions: Only a very thorough patient interview and family history as well as a detailed physical examination can provide proper direction for diagnostic procedures. This is important due to the necessity of periodic screening for male children in order to earlier detect the cerebral form of ALD. Early diagnosis is associated with better benefits concerning allogeneic hematopoietic stem cell transplants.

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1. INTRODUCTION

Adrenoleukodystrophy (ALD) is a genetically conditioned disease that affects the white matter of the brain, axons, the adrenal cortex and the testes.[1] It leads to progressive demyelination within the central and peripheral nervous system and adrenal failure.[2] The incidence of all phenotypes in hemizygotes (males) and heterozygotes (female carriers) is estimated at approximately 1 : 16 800 births.[3]

The defective gene, ATP binding cassette subfamily D member 1 (ABCD1), that codes for the ALD protein (ALDP), a peroxisomal membrane protein, was mapped on the X chromosome (Xq28).[4,5] ALDP participates in the transportation of very long chain fatty acids C24:0/C26:0-CoA (VLCFA) through the peroxisomal membrane. ALDP mutation prevents VLCFA transport to the peroxisome, and consequently their beta-oxidation. This results in the accumulation of VLCFA in the cytosol.[6] Currently it is postulated that VLCFA may directly damage selected cells (oligodendrocytes and astrocytes) through mitochondrial dysfunction and disturbances of their calcium homeostasis.[7] In the culture of adrenal cortex cells, Whitcomb et al. demonstrated their influence on the microstickiness of the cell membrane and decreased response to the adrenocorticotropic hormone (ACTH). This last effect authors associated with the decreased access to the ACTH receptors.[8] The presence or absence of the cerebral inflammation is a basic feature that differentiates a quickly progressive childhood phenotype from adrenomyeloneuropathy (AMN) and other, milder forms of the disease.[1] In terms of pathology, the standard, initial manifestation of ABCD1 mutation is adrenomyeloneuropathy – a slowly progressing dying back axonopathy that affects both ascending and descending pathways of the spinal cord, and in some cases polyneuropathy. In 60% of male patients, in different periods of life, a conversion to the rapidly progressive cerebral form occurs that is characterized by inflammatory demyelination, histologically similar to that in sclerosis multiplex.[9]

The following clinical phenotypes of ALD have been described:[10,11]

- rapidly progressive childhood phenotype, characterized by progressive demyelination, onset at the age of 5–12 years, which leads to death within a few years,
- adolescent or adult cerebral phenotype,
- AMN, characterized by onset at the age of 15–30 years and slow progression of paraparesis,
- Addison's disease only with no neurological symptoms.

In this paper we present the case of a patient with AMN, and then briefly discuss current knowledge concerning this disease.

2. AIM

The aim of this study is to examine current views with respect to ALD pathogenesis and treatment methods and to present the case of its specific variant – AMN. Additionally, we wish to direct attention to the possibility of such a diagnosis in each patient (including women) with progressive paraparesis.

3. CASE STUDY

A 29-year old man, graduate of the Faculty of Pharmacy, father of two healthy daughters, was referred to the Department of Neurology due to progressive lower limb paresis present for 2 years. Moreover, he reported numbness and tingling sensations in distal sections of the lower limbs, particularly following alcohol consumption. The interview revealed: gynecomastia (the patient underwent a surgical procedure due to this, Figure 1) and hypergonadotropic hypogonadism (the patient had been diagnosed by an endocrinologist in an outpatient clinic). The patient's maternal grandfather exhibited very similar symptoms (mother with-

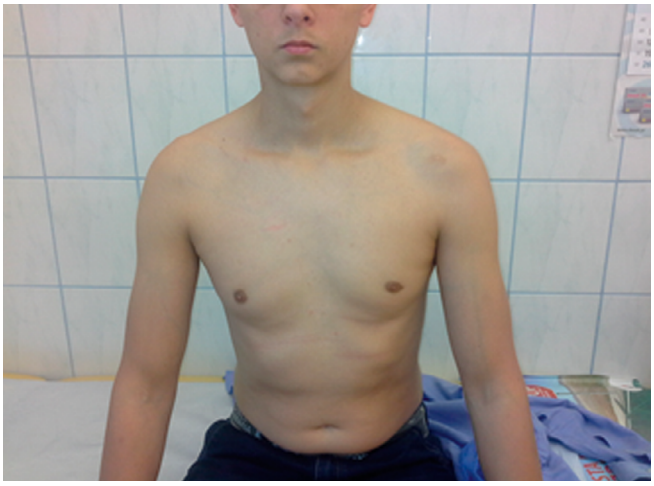

Figure 1. Residual gynecomastia and absence of male type body hair distribution.

Figure 2. Very dark complexion, very thin, scarce hair on the scalp.

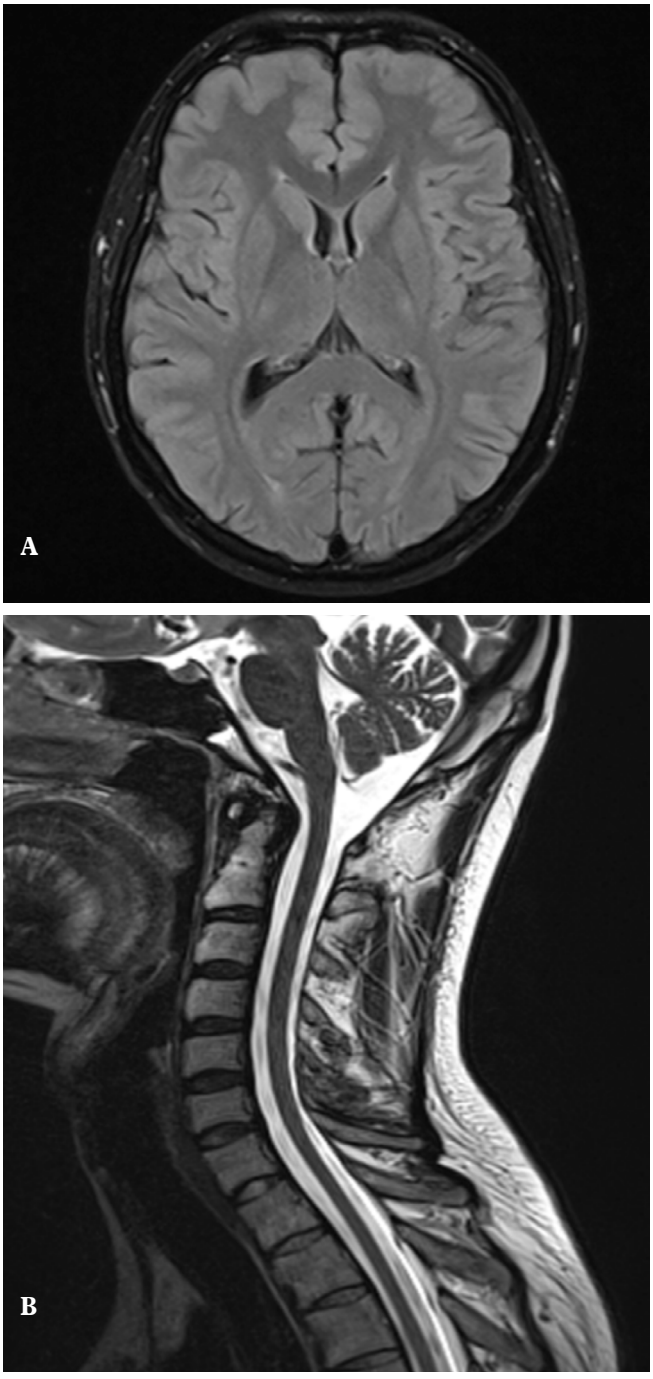

Figure 3. A complete MRI scan of the brain (A) and spinal cord (B) did not reveal focal lesions and features of atrophy.

out symptoms). He was diagnosed with sclerosis multiplex, but died at the age of 80 due to other reasons. Many years before his death he had been wheel-chair bound. The physical examination revealed very dark complexion, absence of male type body hair distribution, very thin, scarce hair on the scalp and testicular atrophy (Figures 1 and 2). The neurological examination detected insignificant (4/5 on the Lovett scale) weakness of the lower limbs muscle strength, both sided increased knee and Achilles tendon reflexes, both sided extensor plantar response (Babinski's sign) and weakened vibratory sensibility in distal sections of the lower limbs. The psychological examination did not reveal any cognitive deficits.

A complete MRI scan of the brain and spinal cord (Figure 1) was performed; it did not reveal focal lesions and features of atrophy. Nerve conduction study (NCS) demonstrated features of sensory-motor polyneuropathy, of an axonal-demyelinating type. The level of ACTH in the morning was determined: the result was at the lower norm threshold 25 ng/L (norm 25–80 ng/L). The level of B12 vitamin was normal.

Based on personal interview, family history and the results of additional tests and examinations, AMN was suspected. Differential diagnosis included Kennedy's disease (in our patient bulbar muscles were not affected and he remained fertile) and hereditary spastic paraplegia (hypergonadotropic hypogonadism with no olfactory impairment).

Blood serum was taken to determine VLCFA levels – the ratio of C24:0/C22:0 = 1.565 was obtained (reference range less than 0.960), and C26:0/C22 = 0.044 (reference range less than 0.030). The result confirmed the values of VLCFA associated with X-ALD. Six months later this patient went to the Mayo Clinic for neurological consultation, where diagnosis based on VLCFA profile was confirmed. Performed genetic examinations revealed mutation p. Gln 157(c.469C>T) in ABCD1 gene. The patient started therapy with Lorenzo's Oil and low C26:0 diet, but he ceased it because of high cost and lack of effect (constant disability progression). Because our patient had two sons (4 and 1 year old), 3 asymptomatic sisters with multiple offspring (9 males) VLCFA profile and subsequent genetic testing for all family members mentioned above was urgently recommended.

4. RESULTS AND DISCUSSION

The clinical picture of AMN includes: progressive paraparesis (upper limbs are not affected at all, or affected insignificantly) with increased tendon reflexes, pyramidal signs, axonal polyneuropathy (panmodal abnormalities, mainly concerning proprioception), features of neurogenic bladder, adrenal failure (loss of body mass, nausea, vomiting, skin hyperpigmentation). Moreover, testicular atrophy, gynecomastia, impotence and reduced scalp hair were observed.[12,13] Testicular dysfunction involving a decreased ratio of the testosterone level to the luteinizing hormone (LH) and/or elevated gonadotropines levels were detected in 81.6%, and adrenal failure in 70% of patients.[14,15] The influence of this disease on baldness seems logical due to the confirmed expression of ABCD1 in the hair follicles.[16] Cognitive disorders, although typical of the cerebral ALD, were revealed in lesser intensity even up to 60% of patients with the AMN phenotype and were manifested as subcortical dementia.[17]

There is no correlation whatsoever between the type of ABCD1 gene mutation and the disease phenotype. In the same family cerebral phenotypes of ALD and AMN may occur.[5,18] AMN is probably the most commonly found phenotype of ALD.[19] AMN may transform itself to the cerebral form of ALD. The risk of such a transformation to occur is

approximately 20% within 10 years 21 and is associated with poor prognosis.

Although ALD mainly affects males, at least half of women, X-ALD heterozygotes, develop symptoms similar to those of AMN, and in approximately 1% symptoms of adrenal failure will occur.[1,18] It should be remembered that neurological symptoms in females appear later in life (65% by the age of 60 years).[18] Moderately severe paraparesis develops in 15% of heterozygotes.[15] Due to considerable differences in the intensity of signs and symptoms in patients with AMN, and also the possibility of transformation to the severe inflammatory form, prognosis is impossible to determine. Each patient is at risk of developing adrenal failure.

Presently, the most recognized diagnostic method for ALD is the biochemical serum analysis. As Moser et al. demonstrated in hemizygotes elevated levels of C26, C25, C24, and C23 fatty acids were present, while the levels of C20 and C22 remained normal.[21] Currently, the basic method is to determine levels of C26 and the ratio of C26/C22 and C24/C22.[18] In heterozygotes, biochemical tests yield negatively false results in approximately 15% of cases. Consequently, in this group, the examination of choice is the analysis of the ABCD1 gene mutation.[10]

MRI techniques serve mainly for differential diagnosis. The MRI scan of the brain of a patient with AMN may not demonstrate abnormalities or may detect a moderately increased signal within pyramidal tracts (internal capsule, brain stem, including the pons) in T2-FLAIR sequences, which is reflected by Wallerian degeneration. The MRI scan of the spinal cord may occasionally reveal its atrophy. The presence of contrast-enhanced lesions or ones that transgress the borders of pyramidal tracts suggests the transformation of AMN into cerebral X- ALD.[13]

In differential diagnostics for AMN, sclerosis multiplex, myelopathy of a different etiology, Kennedy's disease and hereditary spastic paraplegia should always be considered. Kennedy's disease demonstrates some common features with some AMN phenotypes, such as: X-chromosome inheritance, gynecomastia, impotence, features of androgen insufficiency (in this case caused by the androgen insensitivity syndrome). It should be remembered that in Kennedy's disease weakness and atrophy of bulbar and proximal limb muscles dominate. Patients are generally infertile.[22] In the case of hereditary spastic paraplegia, only the coexistence of paraparesis with Kallmann syndrome has been reported (olfactory impairment and hypogonadotropic hypogonadism), and not the presence of hypergonadotropic hypogonadism, which in the case of our patient allowed us to exclude preliminarily this group of diseases.[23]

AMN/ ALD remains an incurable disease. Administration of Lorenzo Oil along with eliminating VLCFA from the diet normalizes their level within a month, but this does not prevent progression of earlier neurological symptoms.[21] This treatment may benefit young boys without neurological symptoms.[24] Despite earlier studies reporting the reduction of VLCFA levels by lovastatin, more current research suggests that this is the effect of reducing the LDL levels that VLCFA are associated with. Hence, currently this drug is not recommended.[25] Allogeneic haematopoietic cell transplantation is recommended for children in an early stage of cerebral ALD.[26] Such treatment may also be effective in adults with an early stage of cerebral ALD, but no studies and reports on this subject exist. Symptomatic treatment is used in AMN. Moreover, periodic check-ups of adrenal function should be performed in order to detect their insufficiency and introduce substitutive therapy[13].

Due to a significant range in the intensity of symptoms among patients with AMN, and also the possibility of transformation into a severe inflammatory form, it is not possible to determine prognosis for any particular patient.

5. CONCLUSIONS

X-ALD is a heterogeneous disease in terms of its phenotypes. Its specific form, AMN, should be always considered in differential diagnosis when symptoms of myelopathy are present, especially in young males. Only a thorough personal interview and family history, as well as searching for discreet clinical features of adrenal dysfunction, testicular dysfunction and other characteristic phenotype features may enable a correct diagnosis. Despite the lack of targeted treatment for adult patients with AMN, correct diagnosis may benefit their sons who, following proper screening, may be candidates for allogeneic haematopoietic cell transplantation.

Conflict of interest

None declared.

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Case report

Posterior reversible encephalopathy syndrome (PRES) in the course of immunosuppressive therapy in a 45-year-old male with normal blood pressure – case study

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ABSTRACT

Introduction: Posterior reversible encephalopathy syndrome (PRES) is an entity characterized by acute neurological symptoms including headache, quantitative disturbances of consciousness or vision and seizures, accompanied by radiological findings. Most of the time it is induced by high blood pressure in predisposed patients.

Aim: The aim of the study is to spread the knowledge of PRES and emphasize its risk factors.

Case study: 45-year-old male with a history of hypertension and nephrotic syndrome was admitted to the emergency department after seizure. Although the patient was normotensive, his numerous risk factors were considered and he was diagnosed with PRES. Initial diagnosis was confirmed in MRI.

Results and discussion: Normotensive patients develop compensatory mechanisms within the central nervous system to ensure constant cerebral blood flow despite blood pressure fluctuations. Abnormal compensatory response in patients with PRES is related to increased permeability of blood vessels and culminates in vasogenic brain oedema, however, chronic hypertension is a relative protective factor in the development of PRES. It is essential to distinguish between PRES, ischaemic cerebral stroke, uremic encephalopathy and cerebral venous sinus thrombosis. The treatment of PRES involves elimination of the predisposing factor and arterial pressure reduction.

Conclusions: PRES is characterized by symptoms resembling stroke which makes the differential diagnosis difficult. Due to the differences in the management of ischemic stroke and PRES, as well as the time factor, which brings forward the preservation of neurological symptoms in both cases, a prompt and accurate diagnosis followed by urgent implementation of therapeutic procedure in the hospital emergency department is essential.

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1. INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinical entity characterized by acute neurological symptoms including headache, quantitative disturbances of consciousness (ranging from somnolence, through stupor, to coma), seizures and vision disturbances (such as blurred vision, visual field defects and cortical blindness), accompanied by radiological findings.[1] Most of the patients diagnosed with PRES are hypertensive, however, incidence of PRES in normotensive patients has been reported.[2]

Neuroimaging, i.e. computed tomography (CT) and magnetic resonance imaging (MRI), is the mainstay in the diagnosis of PRES. The most common CT and MRI findings mainly consist of white matter oedema in the occipital and parietal lobes, sometimes involving also other locations such as the frontal lobes, the cerebellum or the thalamus.[3]

The aim of the treatment is to manage the cause leading to PRES and reduce blood pressure, thus leading to alleviation of the clinical symptoms and normalization of radiological image.

2. AIM

The aim of the study is to spread the knowledge of posterior reversible encephalopathy syndrome and emphasize its risk factors and management in emergency department.

3. CASE STUDY

A 45-year-old male with a history of hypertension and nephrotic syndrome (status after kidney transplantation in 1997, chronically treated with cyclosporine and prednisone) was admitted to the Clinical Emergency Department (ED) of the Regional Specialist Hospital in Olsztyn, Poland, around 9.30 a.m. after the first seizure in his life. As his wife reported, on the same day at work he suffered from dizziness, which lasted for about 30 minutes and preceeded the seizure. At the scene patient was treated with 1 mg of clonazepam by emergency medical team (EMT), which resulted in resolving convulsion. On admission, the patient was conscious, confused but oriented as to the place and himself, with retrograde amnesia. He was complaining of impaired visual acuity of the right eye.

On admission patient was hemodynamically stable. His vital signs were as follows: blood pressure (BP) 136/87 mmHg, heart rate 87 bpm, respiratory rate 12 breaths/min, SpO2 98% while breathing ambient air. On physical examination, the breath sounds were normal. The abdomen was normal, and there was no peripheral oedema at none of lower extremities. On neurological assessment pupils were round, symmetrical and reactive to light, binocular visual defect with predominance of right visual field. Meningeal and Babinski's signs were negative. Muscle strength of both upper and lower limbs was symmetrical and deep tendon reflexes normal. The results of hematologic and other laboratory tests are shown in Table 1.

Table 1. Patient's laboratory test results.

Variable	Results	Normal
Hematocrit, %	44.2	41–53
White blood cells, 103/μL	8.97	4.1–10.9
Platelets, 103/μL	199	150–400
Glucose, mg/dL	130	60–99
Sodium, mmol/L	139	136–145
Potassium, mmol/L	3.8	3.5–5.1
Urea, md/dL	57	10.50
Creatinin, mg/dL	2.0	0.7–1.2
eGFR, mL/min	36.7	>60
CRP, mg/dL	0.62	<0.5
Troponin T, ng/mL	0.006	<0.010
APTT, s	28	26–36
INR	1.02	0.8–1.2
D-dimer, mg/L	1.32	<0.5

The abnormalities observed in laboratory data included increased creatinine and urea levels and decreased eGFR. D-dimer values were requested to rule out cerebral venous thrombosis. Although its range was higher than normal, the patients previous electronic medical records showed that its level had been elevated for the last couple of years and ranged from 1–2 mg/L. Hence the D-dimer value was ruled out as a diagnostic measure for PRES.

Every patient admitted to our hospital after first episode of seizures is having head CT scan taken (with and without contrast enhancement) in order to confirm/exclude any vascular malformations, aneurysms, tumours, hematomas or other abnormalities which can lead to epileptic attacks. However, while confusion following seizures is commonly occurring, impaired vision might indicate stroke episode.

According to the latest AHA Guidelines on ischemic stroke management, given the narrow therapeutic windows for treatment, timely ED diagnosis of ischemic stroke is paramount.[4] Thus, prompt patient evaluation in ED consists of initial examination carried out by emergency physician, collecting blood samples for laboratory tests, performing ECG and initiating stroke team. Door to head CT scan time shouldn't last longer than 20 minutes.

In this case however, history of renal hypertension, nephrotic syndrome, kidney transplantation and long-term treatment with cyclosporine and steroids were major risk factors indicating possibility of PRES occurrence. Taking under consideration short-lasting symptoms and possible causes of patients complaints other than stoke we decided to perform head MRI instead of standard CT scan.

The MRI revealed fingerlike zones of cerebral oedema in the occipital white matter (the bigger one on the left side) pressing against the brain ventricular system in the region of posterior horn of the lateral ventricle (Figure 1).

Based on radiological findings, neurological symptoms and numerous risk factors, patient was diagnosed with PRES. Since his blood pressure was normal, he required no emergency interventions and was transferred directly to the Clinical Neurology Department of the same hospital about an hour after admission to the ED.

Figure 1. Patient's MRI performed on admission to the hospital. Visible white matter oedema in the occipital white matter.

4. RESULTS AND DISCUSSION

PRES was first described in 1996 by Judy Hinchey (initially as reversible posterior leukoencephalopathy syndrome – RPLS), who stated, based on a retrospective observation of 15 patients, that certain diseases and immunosuppressive therapy can result in neurological side-effects like disturbance of consciousness, vision disturbances, headaches and seizures related to white matter oedema. Among the potential causes of RPLS Hinchey enumerated immunosuppressive therapy, eclampsia or renal hypertension.[5]

Currently, there are several theories concerning the pathomechanisms of the development of PRES, however, none of them has found unequivocal confirmation. PRES most frequently occurs in hypertensive patients, with arterial hypertension playing a critical role in the pathogenesis of PRES.[6]

Normotensive patients develop compensatory mechanisms within the central nervous system to ensure constant cerebral blood flow despite blood pressure fluctuations. This phenomenon, known as autoregulation of cerebral blood flow, functions properly for mean arterial pressure (MAP) between 60 mm Hg and 120 mm Hg, preventing fluid leakage from the intravascular space to the interstitium. This autoregulatory mechanism remains under constant influence of metabolic and neurogenic factors, among which the leading role is played by sympathetic innervation of blood vessels, which induces vasoconstriction in response to increased MAP. Abnormal compensatory response, frequently occurring in patients with PRES, is related to increased permeability of blood vessels and culminates in vasogenic brain oedema. Due to poor sympathetic innervation of vasculature originating from the basilar artery, there is an apparent predisposition for oedema to occur in the parietal-occipital lobe region.[7] In patients with chronic arterial hypertension, especially if improperly controlled, the autoregulatory range of MAP values are shifted to the right. As a result of the said shift, normotensive patients present with symptoms of encephalopathy if the pressure suddenly raises above 160/100 mm Hg, while patients with chronic hypertension do not do so until the pressure rises to 220/110 mm Hg or greater.[8] Chronic hypertension is a relative protective factor in the development of PRES because, by causing cerebrovascular hypertrophy, it compromises permeability of the blood-brain barrier.

Apart from the mechanism of vasogenic cerebral oedema, there is also the theory of cytotoxic endothelial damage. The development of PRES is induced by both increased arterial pressure and all kinds of endothelial damage (e.g. in the course of diabetes, dyslipidaemia or nicotine addiction).[1] Both mechanisms are causing blood-brain barrier disturbances and resulting in oedema. Conditions like eclampsia, collagen diseases (systemic lupus erythematosus, multinodular arteritis),[9] sepsis, septic shock or status-post transplantation also predispose to the development of PRES.

There is also a wide variety of medicines which use increases the risk of PRES development. These include glucocorticoids and cytostatic drugs (e.g. cyclosporine, which effect on the development of PRES has been studied since the entity was first described in 1996).

Key role in the differential diagnosis of PRES is played by physical examination, the aim of which is to reveal PRES risk factors, and by neuroimaging: CT and MRI, of which the MRI seems more precise, because of the often occurring false negative results and difficulties to distinguish PRES from acute stroke in CT scans. The nuclear magnetic resonance (NMR) can reveal hyperintense lesions in occipital and parietal white matter in the time T2 FLAIR, DWI that are hypointense at time T1. Using the ADC is reported by some authors to be crucial in differentiating PRES with is-

chemic stroke (in PRES hyperintense, in stroke hypointense lesions). However, there are opinions negating this theory and pointing to the same image in both disease entities.[10]

Due to the clinical picture, it is essential to distinguish between PRES, ischaemic cerebral stroke, uremic encephalopathy, disequilibrium syndrome or cerebral venous sinus thrombosis.

One of the possible diagnoses in the case of aforementioned patient taken under consideration was sinus venous thrombosis since nephrotic syndrome and corticosteroid therapy are major risk factors of this entity. Symptoms such as headache, focal neurologic deficits, seizures and mental status disorders are common in both PRES and sinus venous thrombosis, however thrombosis is most frequently associated with increased intracranial pressure (ICP).[11] In this case however there was no evidence of coagulopathy in laboratory tests and no symptoms of increased ICP, yet differentiation based on clinical features is extremely difficult and final diagnosis had to be confirmed in neuroimaging. MRI in patients suffering from sinus venous thrombosis reveals thrombus in sinuses and, as a result from thrombosis, cerebral oedema with or without associated ischemic or haemorrhagic stroke.[11]

Patients with uremic encephalopathy sometimes show symmetrical changes within the region of basal ganglia, internal capsule and white matter, while patients with PRES present white matter oedema, especially in the occipital and parietal lobes.[12] Although usually typical, the location of oedemic lesions is not enough to make an unequivocal diagnosis, as the literature also describes cerebellar oedema, oedema of the frontal lobes or thalamus oedema in the course of PRES.[3]

The treatment of PRES involves elimination of the predisposing factor and arterial pressure reduction. Thus, it is crucial to properly differentiate ischemic stroke from PRES: in the course of PRES, arterial pressure should be intensely normalized, while in patients presenting with ischemic stroke, the process of reduction of arterial pressure should commence above 220/120 mm Hg or above 185/110 mm Hg – if thrombolysis is planned.[4] An early and accurate diagnosis, followed by appropriate causal and hypotensive treatment, leads to the subsidence of neurological symptoms and, subsequently, of radiological changes. On the other hand, improper or delayed treatment might cause preservation of stroke or PRES symptoms resulting in patient's disability and anxiety.[13]

In the case described, the predisposed patient developed full-blown PRES (chronic arterial hypertension, renal failure, status-post transplantation, chronic immunosuppressive treatment, cyclosporine and glycocorticosteroids), despite the appropriate values of arterial pressure. PRES in normotensive patients is rather rare, however literature describes similar cases.[2] The knowledge of the disease entity and the related symptomatology played the key diagnostic role in the case described and resulted in the appropriate selection of imaging methods (in Poland CT is preferred to MRI in emergency departments in the case of neurological disorders). Quick diagnosis and transfer of the described patient for further treatment in the neurological department led to full subsidence of the clinical symptoms within 24 hours following admission to the department.

5. CONCLUSIONS

Neurological emergencies are among the most frequent diagnoses of patients in hospital emergency departments. The leading cause of neurological disorders are cerebral strokes which, due to the variability of the location of ischemic or haemorrhagic focuses, are characterized by a wide spectre of neurological symptoms. PRES is characterized by symptoms resembling stroke which, when combined with its rare occurrence, makes the differential diagnosis difficult. Due to the differences in the management of ischemic stroke and PRES, as well as the time factor, which brings forward the preservation of neurological symptoms in both cases, a thorough, quick and accurate differential diagnosis followed by urgent implementation of therapeutic procedure in the hospital emergency department is essential. An accurate diagnosis can be put forward based on a thorough physical examination, performed taking into account the occurrence of predisposing factors, and based on radiological examinations. Introduction of the prompt and proper treatment leads to the subsidence of neurological deficit symptoms.

Conflict of interest

None declared.

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Case report

Prolonged mechanical CPR of a 48-year old male patient in severe hypothermia conducted in the emergency department – case report

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ABSTRACT

Introduction: Hypothermia is still one of the major problems of modern emergency medicine. It causes reduction in oxygen consumption by brain tissue, which has neuro- and cardio protective effect. Most of the time, severe hypothermia leads to prolonged resuscitation resulting in decreased quality of cardiopulmonary resuscitation (CPR) due to the rescuers fatigue.

Aim: The aim of this paper is to introduce the case of prolonged resuscitation with the use of mechanical device, conducted in hypothermic patient.

Case study: We report a case study of 48-year-old male in severe hypothermia (19°C) and active gastrointestinal bleeding. We have conducted prolonged CPR for 142 minutes together with noninvasive core warming techniques that resulted in conversion of pulseless electrical activity to ventricular fibrillation and achievement of return of spontaneous circulation. Despite proper treatment, patient died next day in Intensive Care Unit due to the multi-organ failure.

Results and discussion: Cardiac arrest in case of severe hypothermia can lead to survival with good neurologic outcome, however prolonged cardiac arrest results in hypoxic brain injury and severe neurological dysfunction. It is crucial to initiate effective chest compressions to maintain minimal cerebral blood flow. Mechanical devices can be implemented in such situations in order to provide efficient CPR.

Conclusions: Cardiac arrest due to hypothermia can lead to extension of resuscitation. To improve survival of patients in situations requiring prolonged resuscitation, mechanical devices performing chest compressions should be implemented. It is possible to successfully warm up hypothermic cardiac arrest patients through noninvasive methods.

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1. INTRODUCTION

Identification and treatment of reversible causes of sudden cardiac arrest (SCA) are considered to be crucial interventions in the algorithm of advanced life support (ALS).[1] Potentially reversible causes are divided in two groups: 4Hs and 4Ts (Table 1).

Table 1. Reversible causes of cardiac arrest.

4Hs	4Ts
Hypoxia	Tension pneumothorax
Hypo- or hyperkalemia and other electrolyte disorders	Tamponade
Hypo- or hyperthermia	Thrombosis (coronary and pulmonary)
Hypovolemia	Toxins (poisoning)

Hypothermia is still one of the major problems of modern emergency medicine. It is estimated that about 1500 patients suffer and die from accidental hypothermia in United States every year.[2] Poland still lacks exact data on this entity. Hypothermia causes reduction in oxygen consumption which has neuro- and cardio protective effect. In all hypothermic patients with no fatal illness nor lethal injury, cardiopulmonary resuscitation (CPR) should be implemented and conducted until patient's body is rewarmed. Most of the time, severe hypothermia leads to prolonged resuscitation resulting in decrease in quality due to the rescuers fatigue. Mechanical devices can be introduced to the standard ALS algorithm while long-lasting CPR, to maintain high quality chest compressions.

2. AIM

The aim of this paper is to introduce the case of prolonged resuscitation with the use of mechanical device, conducted in hypothermic patient.

3. CASE STUDY

Patient, 48-year old male, was brought by emergency medicine team (EMT) to emergency department (ED) of the Regional Specialist Hospital in Olsztyn, Poland. His neighbor found him unconscious in a garden-plot. The outside temperature didn't exceed 6°C. Patient's body was chilled and his clothing was covered in clotted blood. Rescuers managed to speak with the neighbors, who reported that the day before patient vomited the contents reminding of the coffee grounds. Additionally, patient had history of cerebral palsy, hypertension, heart failure NYHA IV and alcoholic cardiomyopathy. He was admitted to the hospital at 10:38 a.m. in severe condition, with peripheral cyanosis. After opening the airway, there were no signs of normal breathing, only agonal gasping. Due to the lack of pulse in the major arteries and the impossibility of detection of blood pressure (BP), cardiac arrest was diagnosed and CPR started immediately. At the same time, core body temperature was measured and determined at 19°C (at the level of lower one third of the esophagus). Simultaneously basic neurological examination was executed. Patient's pupils were wide and almost not responding to light. On the Glasgow Coma Scale patient received 3 points. While starting CPR, patient was immediately connected to a monitor which showed heart rate of 20–30 bpm. In conjunction with the lack of pulse, mechanism of cardiac arrest was defined as pulseless electrical activity (PEA). Leading cause of cardiac arrest in this case was hypothermia. However, due to the presence of acidosis and hypovolemia, this patient manifested 3 of 8 reversible causes contributing to SCA.

ALS procedures were implemented immediately after recognizing cardiac arrest, according to the hypothermia protocol. In this case, we have promptly introduced both passive and active core rewarming techniques, such as covering patient's trunk with the thermal blanket, infusing warmed fluids and bladder lavage with warm saline solution. After intubation patient was mechanically ventilated with 100% oxygen. Chest compressions were performed by load distributing band (LDB) mechanical device. After about 30 minutes of resuscitation, conversion of the rhythm to VF occurred. Therefore, a single defibrillation was performed. After delivering shock with the energy of 200 J, no return of spontaneous circulation (ROSC) was achieved and

Table 2. Venous/Arterial blood test results in time.

	10:35 a.m. v	12:05 p.m. a	1:20 p.m. a	3:45 p.m. a	9:10 p.m. v	5:35 a.m. v
pH	7.247	7.258	7.209	7.339	7.162	7.196
pCO_2, mm Hg	64.9	42.2	53	40.1	61.2	77.2
pO_2, mm Hg	38.2	173.7	225.5	294	48.7	41.7
BE, mEq/L	-0.5	-8.1	-6.8	-4.3	-6.8	-0.8
Creatinine, mg/dL	0.8			0.8	0.9	1.1
Urea, mg/dL	56			110	96	76
APTT, s	58.8			73.3	61	40.3
INR	3.62			5.34	4.24	1.81
WBC, 103/mgL	1.82		1.0	2.19	1.09	2.31
RBC, 106/mcL	4.25		1.33	1.92	2.89	4.69
Hgb, g/dL	10.6		3.2	5	8.2	13.7
Hct, %	34.9		11.3	16.2	25.1	40.6
PLT, 103/mcL	22		11	13	15	39
K^+, mmol/L	2.8	5.4	3.4	2.5	2.95	4.73
Na^+, mmol/L	141.4	138.4	142.8	145.1	140.0	153.0
Cl^-, mmol/L	101.1	104.0	107.2	106.8	104.0	108.9

Comments: v – venous; a – arterial; pCO_2 – partial pressure of CO_2, pO_2 – partial pressure of O_2, BE – base excess, APTT – activated partial thromboplastin time, INR – international normalized ratio, WBC – white blood cells, RBC – red blood cells, Hgb – hemoglobin, Hct – hematocrit, PLT – platelet count.

CPR (still performed by LDB device) was continued till 1:00 p.m., when ROSC occurred. At that time, central body temperature increased to 22.6°C. Resuscitation lasted for 142 minutes. Results of blood tests pointed to the presence of acidosis with pH of 7.247. Hemoglobin levels maintaining 10.6 g/dL at 10:40 a.m., decreased to 3.2 g/dL in less than 4 hours. Coagulation parameters were also highly elevated. All these disorders combined with history of coffee-ground vomiting, pointed to the features of active upper gastrointestinal bleeding (Table 2).

Figure 1. Patient's chest X-ray performed at 1:20 p.m. Presence of the fluid within the right pleural cavity. Heart is shifted to the left side and its size is magnified.

Gastroenterologist performed emergency gastroscopy, which revealed duodenal ulcer with a diameter of approximately 30 mm (Forrest IIb). Due to the increasing anemia, blood transfusions were initiated (3 units of fresh frozen plasma, 4 units of RBC concentrate, 2 units of PLT concentrate) while resuscitation was still ongoing. We have also administered proton pump inhibitors (esomeprazole a total of 7 ampoules, 40 mg each in continuous infusion), antibiotics (metronidazole 500 mg, ceftriaxone 1.0 g) and fentanyl 100 mcg.

At 7.15 p.m. patient has been transferred to intensive care unit of this same hospital with the BP of 130/74, heart rate of 93 bpm and core body temperature of 29.5°C. Despite of the further treatment conducted in intensive care unit (pharmacotherapy, transfusions of 12 units of PLT concentrate and 4 units of RBC concentrate) multiple organ failure was progressing and at the time of re-arrest, CPR has not been undertaken. Patient was declared dead at 9:45 am of the next day.

4. RESULTS AND DISCUSSION

Accidental hypothermia is an unintentional decrease of core temperature to 35°C or below which is most of the time caused by environmental exposure.[3] There are some conditions and diseases predisposing to excessive drop in body temperature, such as injury, alcohol or drug abuse, elderly or very young age and lowered mental status.[1] We presume that in this case gastrointestinal bleeding led to patient's collapse in garden-plot while the outside temperature was low. Influence of both ambient temperature and unconsciousness resulted in severe hypothermia.

According to the Swiss system,[3] hypothermia is classified in five stages:

(1) mild hypothermia (patient is conscious, his body is shivering: 35°C–32°C)
(2) moderate hypothermia (patients' consciousness is impaired, there is no shivering: 32°C–28°C)
(3) severe hypothermia (patient is unconscious: 28°C–24°C)
(4) profound hypothermia (apparent death: 24°C–13.7°C)
(5) death due to hypothermia (less than 13.7°C).

Temperature of 13.7°C is the lowest recorded temperature in hypothermic patient who was successfully resuscitated.[4]

Low core temperature causes decrease in basic metabolism and neurologic function,[5] which in terms of cardiac arrest can have neuroprotective effect. Although SCA in case of severe hypothermia can lead to survival with good neurologic outcome,[6–9] prolonged cardiac arrest results in hypoxic brain injury and severe neurological dysfunction.[10] It is crucial to initiate effective chest compressions to maintain minimal cerebral blood flow. One way of potentially improving the quality of chest compression is with automatic mechanical devices, which can apply compression more consistently than manual massage. Also, the engineering of such devices may target additional physiological mechanisms to improve circulatory output. Nowadays there are two types of mechanical devices used worldwide: LDB (AutoPulse) and active chest decompression piston device (LUCAS). So far there are no clear evidences on the advantage from the routine use of these mechanical devices.[1] However, ERC guidelines 2015 emphasize the key role of mechanical chest compression in selected patients (e.g. when manual chest compressions are impractical or compromise provider safety). Randomized controlled trials in the field of emergency medicine, especially in the subject of resuscitation, are controversial and difficult to conduct,[11] which makes research on mechanical chest compressions challenging.

The implementation of mechanical chest compression device in case of this patient, has provided good quality chest compressions which was of a great importance considering longlasting CPR. Furthermore, since we have used mechanical ventilation, mechanical chest compressions device and monitored patient's heart rhythm with the use of self – adhesive pads instead of paddles, we've saved a lot of human resources. Two physicians and two paramedics were present on patient's bedside on admission and at the beginning of treat-

ment. After setting everything up only one physician and one paramedic were taking care of the patient. This model of SCA management is, in our opinion, the most effective, especially in circumstances of prolonged resuscitation.

According to the latest guidelines, extracorporeal life support may be helpful in some hypothermic cardiac arrest. At the time of patient's admission to our department we immediate access to that device. However, literature and presented case study, show that it is possible to warm up hypothermic cardiac arrest patients successfully through noninvasive methods, which are both easy to apply and feasible in any hospital.[8]

There are some studies on prognostic factors likely to identify patients in hypothermic cardiac arrest who would probably survive. According to Mair et al. on plasma potassium levels (serum potassium more than 9 mmol/L), central venous pH (pH less than 6.50) and ACT (activated clotting time more than 400 s) on admission can be used to identify hypothermic arrest victims with predicted poor outcome.[12] Mair's paper was a small retrospective study (analysis of 22 patients), however more investigators report connection between high potassium level and death.[13–15] Our patient presented hypokalemia and acidosis, however neither potassium level nor pH were extremely low. Regardless these, seemingly, favorable values, patient's poor general condition, co-morbidities, gastrointestinal bleeding and long-lasting hypothermia prior to arrival of EMT have put him at risk of multi-organ failure which resulted in his death the next day.

5. CONCLUSIONS

Cardiac arrest due to hypothermia can lead to extension of resuscitation. To improve survival of patients in situations requiring prolonged resuscitation, mechanical devices performing chest compressions should be implemented. It is possible to successfully warm up hypothermic cardiac arrest patients through noninvasive methods.

Conflict of interest

None declared.

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Review article

Development and implementation of methods for training doctors and dental surgeons using virtual devices and simulation

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ABSTRACT

Introduction: Simulation is increasingly incorporated in medical education to learn and develop cognitive, psychomotor and behavioural skills at the individual level and in teamwork. An advanced medical simulator SimMan 3G and an e-learning platform were created to develop a new approach towards doctors' training.

Aim: A programme for the development and implementation of training methods for doctors and dental surgeons was created, as exemplified by the Simulation Centre of University Hospital in Olsztyn.

Material and methods: The leading component of the project is the SimMan simulation device, along with specially designed rooms for simulation, debriefing and supervision of the training process. The most distinguishing feature of the entire training programme is a specially designed platform for education and training: www.symulatorymed.pl, consisting of knowledge bases, case reports, training scenarios, and tests ultimately compatible and cooperating with the aforementioned medical simulator.

Results and discussion: Importance of medical simulation has been proven in terms of preservation of knowledge and skills for much longer than did previous training methods. The newly designed e-learning platform gives the opportunity to create specialized databases and check the results of on-simulator training sessions, which serve as 'feedback' to all the information provided on-line. This allows for multi-dimensional comparison of the progress and effectiveness of teaching during the successive testing sessions.

Conclusions: The main goal of the newly created simulation infrastructure is to transfer better results of education from the conditions of the simulation room into reality, in order to improve the survival and effectiveness of treatment of patients.

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1. INTRODUCTION

Simulation is increasingly incorporated in medical education to learn and develop cognitive, psychomotor and behavioural skills at the individual level and in teamwork. The overall objective is to determine the desired results of teaching and training using simulators and then incorporating the results into the curriculum with the aim of achieving the previously established objectives. The advanced medical simulator SimMan 3G, along with an e-learning platform created within the infrastructure, is designed to develop a new approach towards doctors' training, regarding situations that require either sustaining or restoring life functions as well as new methods of conduct, especially concerning difficult cases and the system used to validate them. The new methodology of training will also be an element used for scientific analysis, both in the process of acquiring new skills as well as the validation of these on the basis of so-called partial qualifications. Thanks to the research and development (R&D) infrastructure it will be possible to propose a new approach for acquiring knowledge in terms of both diagnosis and treatment of patients in life or in health threatening situations (according to Polish Qualifications Framework). The new system will be based on clear criteria of validation regarding both formal and informal training methods, and it will enable evaluation in terms of analyzing the effectiveness of different methods of acquiring knowledge and skills in sustaining and restoring life functions.

2. AIM

Within the process of the development and introduction of a new methodology into the region of Warmia and Mazury, it is necessary to create a framework project, based largely on past national and international experience in the fields of creating and introducing elements of simulation into medical education. The effectiveness of learning through simulation depends largely on how well and how thoroughly it is planned and subsequently used. It should be complementary to the existing educational program and its implementation should harmonize with the rest of postgraduate education. For this purpose and based on the guidelines of the Society for Simulation in Healthcare among others, a plan for the development and proper utilization of available infrastructure was created, as exemplified by the Simulation Centre of University Hospital in Olsztyn.

3. MATERIAL AND METHODS

The most important component of the Simulation Centre is the SimMan 3G simulation device (Figure 1), along with a specially designed room for simulation (Figure 2) as well as a debriefing room, and another room used for supervision of the training process. This is where data from conducted training sessions as well as audio-video recordings of training-educational sessions are collected. The simulator is necessary to make sure that it is safe to test new methods of research in addition to dealing with difficult cases in terms of sustaining and restoring life functions by creating opportunities for practical verification of various procedures, which also use the remote transmission of data. The SimMan 3G device represents the next generation of simulators, with the following key advantages: ease of use, durability, and full range of complementary products and services. The SimMan 3G simulator's interface, with three modes of operation, is used intuitively, allowing you to prepare effective simulation. It is also important to those developing scenarios for teaching. Prepared and programmed simulation will look exactly the same every time; therefore, each participant can be trained or examined in a standardized way. In addition, the software for the event scenario may include images or sounds and multimedia graphics, allowing materialization of practiced simulated clinical situations. Reports in the form of videos, systems for monitoring patients, programmed medical cases, and planned scenarios all form

Figure 1. SimMan 3G: an advanced simulation device.

Figure 2. Specially equipped room for simulation in hospital environment

grounds to create a comprehensive simulation system that lets you test all sorts of methods and procedures in terms of sustaining and restoring life functions, while at the same time providing absolute safety when testing new solutions. Thanks to this, the implementation of the system is compatible with both the latest recommendations and guidelines in this regard. Selected features of the SimMan 3G simulator are shown in Table 1. The durable and resistant design of the SimMan 3G mannequin lets you carry out training in various conditions; therefore, the instructor can simulate actual circumstances under which medical procedures are performed: in either a clinic, a hospital, or an ambulance.

Table 1. Specifications of SimMan 3G medical simulator (Laerdal).

Selected functions of the SimMan 3G simulator
Multiple airway skills/features: Controllable open/closed airway; automatically or manually controlled Head tilt / chin lift, jaw thrust (articulation of the mandible) Suction (oral and nasopharyngeal) Bag valve mask ventilation Orotracheal intubation, nasotracheal intubation Combitube, laryngeal mask airway and other devices for opening airways Endotracheal tube intubation, fiberoptic intubation, retrograde intubation Transtracheal jet ventilation Needle cricothyrotomy, surgical cricothyrotomy Variable lung compliance, variable airway resistance
Airway complications and difficulties: Detection of proper head position Can't intubate/Can ventilate Tongue edema, pharyngeal swelling Laryngospasm, decreased cervical range of motion, trismus Right main bronchus intubation Stomach distention
Breathing features: Simulated spontaneous breathing Bilateral and unilateral chest rise and fall Normal and abnormal breathing sounds Oxygen saturation and waveform
Respiratory complications: Cyanosis Needle thoracentesis – bi-lateral and Pneumothorax Unilateral & bilateral chest movement in the course of diseases Unilateral, bilateral & lobar breath sounds
Cardiac features: Extensive ECG library Heart sounds - four anterior locations ECG rhythm monitoring (4 wire) 12-lead ECG display Defibrillation and cardioversion Cardiac pacing.
Cardiovascular features: Blood pressure measured manually by auscultation of Korotkoff sounds Carotid, femoral, brachial, radial, dorsalis pedis, popliteal and posterior tibialis pulses synchronized with ECG Pulse strength adjusting to blood pressure Pulse palpation is detected and recorded by the monitoring system.
Vascular access: Intravenous access (right arm), intraosseous access (tibia and sternum) Automatic Drug Recognition System

The most distinguishing feature of the entire training project, addressed to doctors and dental surgeons, as well as other employees of the healthcare system, is a specially designed platform for education and training: www.symulatorymed.pl, ultimately compatible and cooperating with the aforementioned medical simulator (Figure 3). It is an experimental platform consisting of knowledge bases, case reports, training scenarios, and tests to check the acquired knowledge. Communication with the user occurs via a standard web browser, and uses technological solutions that do not require installation of additional or specialized extensions. Users of the platform are subject to authorization and control, and access to selected elements of the scenarios requires authentication. On the other hand, access to the raw results of R&D is open. The e-learning platform gives the opportunity to create specialized, thematic databases based on the scenarios that can be programmed into the training simulator SimMan 3G. Their proper implementation, in particular the analysis of difficult cases, makes it possible to develop new ways of dealing with them. In addition, the ability to control and check the results of training sessions and educational tests completed by registered users serves as 'feedback' to all the information provided on-line. This allows for comparison of the progress and effectiveness of teaching during the successive testing session.

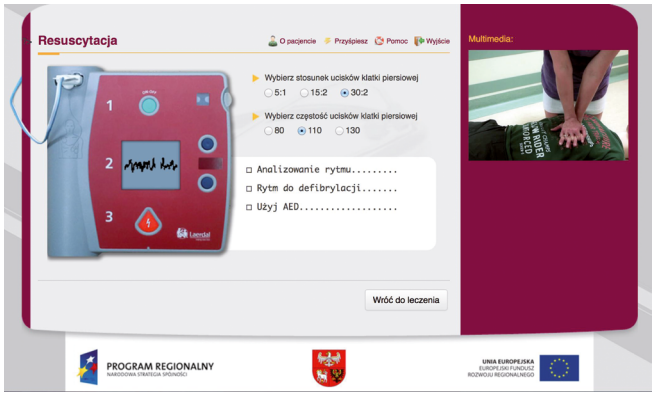

Figure 3. E-learning platform for an online training.

4. RESULTS AND DISCUSSION

Simulation is more often being used in medical education to learn and develop cognitive, psychomotor and behavioural skills not only at the individual level but also in teamwork. The overall objective is to determine the desired results of teaching and training using simulators and subsequent management of education by incorporating simulation into the curriculum with the aim of achieving the previously established objectives.[1] An essential element of education using simulation devices is feedback from trainees and trainers, on the basis of which it is possible to plan further education or verify schemes already created.[2] Conducting simulation sessions should take place in a specific environment, as much as possible, reflecting the environment in which

acquired knowledge and skills are later to be used.[3] Importance of 'mastery learning' based on medical simulation has been proven in terms of improving and achieving high level skills by trainees, which in turn leads to the preservation of knowledge and skills for much longer than did previous training methods.[4] In order to achieve better results during training of medical personnel while making use of simulation applications and devices, more research is needed to confirm the efficacy of scientific methods and those developing new aspects of training based on events observed during the learning process.[1,5] The developed R&D infrastructure will use scientifically-tested and proven training methods in the education process. This will be used to formulate and test new training methods 'in difficult cases' on the basis of planned and conducted scientific research.[5] Every doctor and dental surgeon who is registered to conduct business activity, and the entity of the medical industry, can benefit from the project results and take part in scientific research, provided they have generated both a login and a password to access the website and the learning platform with required written or electronic notification of their desire to participate in the Warmia and Mazury Chamber of Physicians. The programme of the incorporation of the developed R&D infrastructure into the process of instruction and development of skills of practitioners registered to conduct business activity in the area covered by the Warmia and Mazury Chamber of Physicians is very important. The inclusion of simulation and scientific research in the existing training program should greatly improve learning outcome.[6] Determination of the expected results at the end of the project, e.g. to improve the skills of medical personnel of various specialties in sustaining and restoring life functions of patients with sudden occurrence of threats to health or life in different healthcare units, e.g. outpatient clinics, specialist clinics, hospitals of various specialties and profiles, will translate into improved patient safety.[7] It is necessary to precisely identify results, the attainment of which is possible with the simulation in individual research groups, e.g. reduction in response time and appropriate diagnostic and therapeutic procedure in acute pulmonary embolism in patients undergoing orthopaedic surgery or surgery during hospitalization in surgical wards. The target group of trainees requires the determination of the type of chosen simulation - in this case, the use of both the e-learning platform and the medical SimMan simulator to improve access to selected training methods.[8] Original determination of how to conduct training using simulation is also significant. The first stage, for instance, is solving cases available on the e-learning platform, and in the next stage there are exercises using the simulator, which can be done in groups of 3–5 or smaller, of 1–2 persons. Selection of appropriate training groups consisting of only doctors, or of doctors and nurses, depends on the desired effect.[9,10] Logistics of conducting scientific research, as well as sharing research results with the possibility of access granted to economic entities carrying out medical activities, also needs to be developed. As it has been demonstrated repeatedly, only a well-planned simulation leads to successful outcomes.[11] Therefore, the rules of use of feedback coming from the entities involved in the development of new training methods and those participating in education are currently being established, and the pre-established initial training program for a 'test group' is being implemented as a pilot study. Analysis of all the positive and negative experiences of the study, conducted in a pilot group with multiple attempts made in order to best fit the available simulation tools to the actual situation, is to allow for a reliable initial assessment of learning outcomes in the pilot group and for verification of the initial assumptions in order to develop the most effective and efficient training methods for sustaining and restoring life functions as well as procedures applicable to difficult clinical situations.[12] The evaluation of the degree of satisfaction of business entities taking part in both the course of scientific research and the training process will occur through appropriate and validated questionnaires. One of the components of programme adjustment is also the assessment of satisfaction corresponding to the implementation of the curriculum and supervision of the process of scientific research.[13] Based on the results of work analyses carried out, there will be re-verification of the established goals as well as ways to incorporate simulation into the training program. The types of simulation itself, particularly the use of the e-learning platform and getting appropriate feedback from people involved in the programme and analyses, will also be verified. Ideally, it would be a continuous process, regardless of the duration of the project and the results obtained so far.[14,15] The involvement of entities conducting medical business activity involved in scientific research requires close cooperation between the University Hospital and the Warmia and Mazury Chamber of Physicians as well as the Faculty of Medical Sciences at University of Warmia and Mazury. The previous experience with students training gives a stable background for establishing such a network between the subjects interested in medical teaching and professional development. Swamy et al. proved, that working with a simulation device improves significantly students' knowledge and confidence.[16] The major challenge to medical simulation was the fact, that evidence to date was weak in methodology and it was difficult to transfer the knowledge and experience from the students' training room to already practicing professionals. It has not been adequately tested, that learning by simulation is directly transferable to the clinical context,[17] although a few studies have shown a direct positive impact in the clinical outcome from the use of simulation for medical training.[18] Therefore, a great role of the presented programme of R&D infrastructure in establishing methodology for simulation incorporation in professional development is expected.

5. CONCLUSIONS

The main goal of the newly created R&D infrastructure should not only be to support knowledge in sustaining and restoring life functions and final achievement of a satisfac-

tory learning outcome using the simulation device, but also to transfer better results of education from the conditions of the simulation room, in order to improve the survival and effectiveness of the treatment of patients in reality.

Conflict of interest

The authors declare no conflict of interest.

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Review article

Paravertebral blockade using a catheter implanted under visual control during thoracosurgical procedure as an ideal expedient for treating postoperative pain

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ABSTRACT

Introduction: Postoperative pain is a natural occurrence after surgery, and its severity significantly affects the overall condition and likely recovery time of the patient. Because postoperative thoracic pain is one of the most severe postoperative, the physician must repeatedly administer medication from all levels of painkillers. Use may involve potential risks of further complications.

Aim: The aim is to describe some pathophysiological aspects of pain, some methods of pain therapy, anatomy of paravertebral space (PVS) and methods of performing a paravertebral blockade, especially the implementation of a catheter to the PVS, during operation from lateroposterial access.

Material and methods: This work was based on the available literature and the experience of the authors.

Results and discussion: This method was implemented on 38 patients over a 10 month span. On 3 of the patients, the analgesic effect was not obtained. In the author's opinion this was due to the intercostal being opened too wide with the same PVS resulting in the administered medication reaching the pleura, hence not making the desired impact. On the remaining patients the analgesic effect was obtained at a level of 3–5 PVS, without the necessity of administrating opioids in the case of breakthrough pain. After the first 24 h following surgical procedure the patients showed positive signs of recovery and were able to start rehabilitation.

Conclusions: Intraoperatively implanting a catheter to the PVS following thoracosurgical procedure in order to conduct continuous, regional postoperative anaesthesia is a safe and effective method of treating postoperative pain in thoracic surgery.

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1. INTRODUCTION

Postoperative pain is a natural occurrence following surgical procedures and its severity substantially influences the overall condition and likely recovery time of the patient. As pain intensifies following a thoracosurgical procedure, the physician is forced to repeatedly administer medication from all levels of analgesics. The application of which may be associated with a potential risk of further complications.

This thesis introduces a method of pain therapy based on the administration of drugs to the paravertebral space (PVS) under visual control through an intraoperatively placed catheter. Based on both the author's personal experience and published research, this process is considered an effective and safety method of alleviating postoperative pain. Considered as an alternative to epidural anaesthesia commonly used in many branches of thoracic surgery, the process simultaneously avoids the complications related to the use of opioids and non-steroidal anti-inflammatory drugs.

2. AIM

The aim of this paper is to describe some pathophysiological aspects of pain, some methods of pain therapy, anatomy of PVS and methods of performing a paravertebral blockade (PVB), especially the implementation of a catheter to the PVS, during operation from lateroposterial access.

3. MATERIAL AND METHODS

This work is based on the available literature and the experience of the authors.

4. RESULTS AND DISCUSSION

Postoperative pain is caused by an intraoperative trauma to the tissues and organs and its intensity is proportional to the type, extent and duration of the surgical procedure. In the instance of a planned surgical procedure, the physiological role of pain and the benefits resulting from short-term pain stimulation after contingent injuries no longer apply. Postoperative pain merely evokes phenomena unfavorable to the patient and maintaining long-termed pain stimulation develops a cascade of unfavorable pathophysiological processes, even causing neuroplastic changes to the central nervous system (CNS) leading to chronic pain syndrome. This causes an increase of sensitivity in the spinal cord and brain during the synthesis and activation of various receptor systems (i.e. NMDA) and also the formation of various compounds modifying pain perception. If the peripheral stimulus is strong enough or repeated – as in the instance of inflammatory pain or protracted pain – the pain transduction in the spinal cord becomes complex. During the release of endogenous substances, whose purpose it is to inhibit the pain stimulus, the same stimulus is simultaneously being 'intensified' and 'fixed.'[1] The modulation of reactivity in the CNS clinically manifests itself in a long lasting *hyperalgesia allodynia*, which can last longer than the nociceptive stimulation (receptor) and the healing process of the wound. It is believed that the 'plastic' reactivity of the CNS determines the formation of the central sensitization, which lasts 10–200 times longer than the flow of information from the peripheral receptors. The process of central sensitization is probably the cause of secondary hyperalgesia, referred pain, pain memory and 'second pain' (tied to the emergence of a series of offloading in neighboring neurons).[2] Back pain also postoperative, is a major health problem and a leading cause of disability. It generates work absenteeism and great costs for the society.[3]

Thoracosurgical procedures are part of a group of procedures causing the highest level of discomfort regarding postoperative pain. Following a thoracotomy, pain which limits chest movement leads to respiratory system dysfunctions. These are based on: vital lung capacity reduction, a limiting in coughing and a less effective removal of secretions. Thoracosurgical procedures can also cause arterial hypoxemia, atelectasis and pneumonia.[4]

The general administration of opioids represents the traditional method of treating postoperative pain in thoracic surgery – that they are most effective when administered intravenously, preferably through a patient-controlled analgesia (PCA) pump. Due to ineffectiveness, non-steroidal anti-inflammatory drugs (NSAIDs) used in monotherapy do not apply in thoracic surgery. They have a different target than opioid drugs; therefore it is possible and even indicated to combine medication from the two mentioned groups.

NSAIDs exhibit a ceiling effect. Exceeding the recommended dose does not enhance the therapeutic effects, but instead can possibly result in unwanted side effects. Therefore combining two NSAIDs is not recommended. Through reduction in the production of prostaglandins in the CNS, non-opioid analgesics (paracetamol and metamizole) have an analgesic and antipyretic effect. They do not have anti-inflammatory characteristics and due to the effect they have on different areas; they can be associated with 'typical' NSAIDs. A combined administration with opioids is again recommended.

A thoracotomy is an immense injury linked to a strong stimulation of the sympathetic nervous system. The most effective way to avoid adverse reactions is through the use of multimodal analgesia adopting the techniques associated with conduction anaesthesia.[5]

Over the years, an epidural was considered the 'golden standard' in pain therapy following thoracosurgical procedures due to its excellent, early analgesic effect.[6] However on considering the method's limitations and possibilities, its unsuitability is easily seen.

According to current guidelines outlined by a committee of experts concerning the treatment of postoperative pain, continuous paravertebral analgesia (PVB) is the recommended technique following surgical procedures within the chest. In comparison to an epidural it guarantees; effective control of pain both during coughing and at a rest, a

reduced need for opioids, improved ventilation, less chance of developing postoperative nausea and vomiting, and stable blood pressure. Prescribing anticoagulants after implanting an epidural catheter is contraindicated, whereas being harmless when applied after PVB.[7]

In a meta-analysis performed on 520 patients including 10 comparative theses between thoracic epidural analgesia (TEA) and PBV, Davies et al. conclude both methods' analgesic equivalence, but with a significantly lower amount of complications arising with PBV.[8]

In a more recent meta-analysis released in 2014 – including 12 trials and a group of 542 patients who had undergone a thoracosurgical procedure – Baidya et al. came to a similar conclusion, qualifying both methods (TEA and PVB) as equally effective in treating postoperative pain, with a smaller amount of side effects and complications in favour of PVB.[9] Also in 2014, Ding published a meta-analysis based on 18 independent theses – where 777 patients were taken into treatment - comparing the analgesic effects of TEA and PVB after a thoracotomy, concluding that while being comparable (VPS; 4-6), the frequency of occurring nausea, vomiting and incontinency after PVB was lower, with a smaller percentage of ineffective anaesthesia.[10]

4.1. Anatomy of the PVS

The PVS is a cuneal formation in the chest area lacking definition within anatomy textbooks. Located on both sides of the spine, it is filled with loose connective tissue. It is limited at the front by parietal pleura and on the medial side by the vertebral body, and both the intervertebral disc and foramen (neural exit). Finally it is bound at the back by the superior costotransverse ligament (*ligamentum costotransversarium superius*) and the intercostal membrane. The lack of an upper and lower wall favours the communication between the areas located directly above and below the PVS. It is however assumed that the level Th12 serves as the lower, axial border, paravertebrally limited by m. psoas major.[11]

Due to the lack of solid boundaries on the sides, it reaches intercostal spaces. The endothoracic fascia (*fascia endothoracica*) divides the paravertebral area into the extra pleural and subendothoracic compartment, whose purposes are not explained.[12]

The extra pleural (front) compartment contains the sympathetic ganglion, and the subendothoracic (rear) compartment the spinal nerve. The identification of the endothoracic fascia dividing the sympathetic and rear ganglion plus the compartments can be helpful in understanding the blockade's spread and common diversity.[13]

Administrating an anaesthetic to PVB consequently causes its spread; sideways into the endothoracic fascia, medially into the intervertebral foramen and epidural space, and upwards and downwards into neighboring paravertebral parts. On the level of the thoracic vertebrae this area contains: the spinal nerve (endothoracic, lacking a myelin sheath in the paravertebral section), the intercostal nerve's dorsal branches, connective branches (white and grey) and the sympathetic trunk (in the front part) (Figure 1).[14]

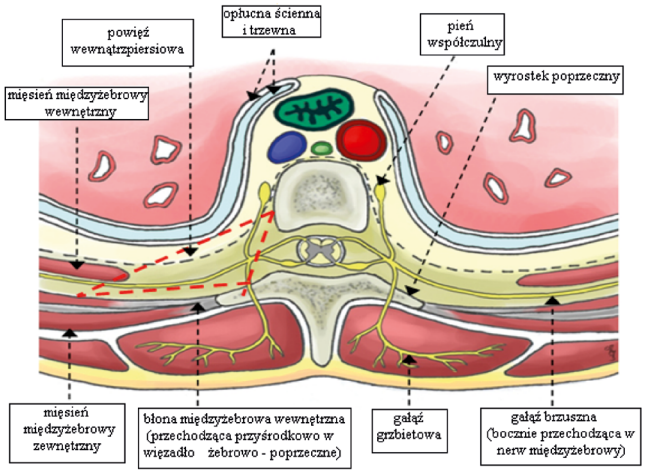

Figure 1. Anatomy of the endothoracic fascia.[15]

Administrating a local anaesthetic to PVS causes a direct effect on the nervous structures mentioned above. The anaesthetic effect is a combination of a somatic, physical and sensory blockade, as well as a one-sided sympathetic blockade in a number of contiguous dermatomes. The anaesthesia's extent depends on its volume and concentration.[16]

Eason and Wyatt deemed that 15 mL of 0.375% bupivacain should desensitize at least 4 neighboring dermatomes. Today it is assumed that 15 mL of 0.5% bupivacain injected in the PVS space inhibits somatic nerves on a range of more than 5 dermatomes (1–9), while a sympathetic blockade affects more than 8 (6–10).[17]

In accordance with many authors, a continuous postoperative infusion should be at 0.1 mL/kg per hour.[18]

4.2. Methods of performing a PVB

Various methods of performing a PVB are described in clinical practice. These include methods based on: identification with the help of losing resistance, recognition of anatomical points, help of a neurostimulator, using ultrasonography, the opening of the chest during surgical procedures.

According to Davies, the implementation of a catheter to the PVS by the operating surgeon represents the most logical procedure in thoracic surgery, allowing the avoidance of complications and the anaesthetic's administration to the desired place.[8] Other authors[19] also suggest this solution because possible complications are few and far between. Yet, and for no apparent reason, it is a rarely practiced method deserving of more propagation due to its easy execution, slim chance of causing serious complications, and vast analgesic efficiency.

The procedure is based on the insertion of a Touhy needle (most commonly a 16G) to the front of the thoraxes closure and the area surrounding the wound's paraspinal pole after finishing the surgical procedure on the same level or one intercostal above (Figure 2).

Through this needle, the catheter for the permanent local anaesthesia is induced cranially at a distance of several centimeters and placed under visual control below the pari-

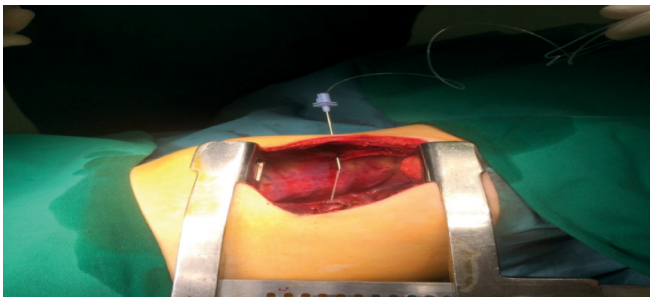

Figure 2. Catheter 16G inserted through a Touhy needle into the postoperative wound's paraspinal pole.

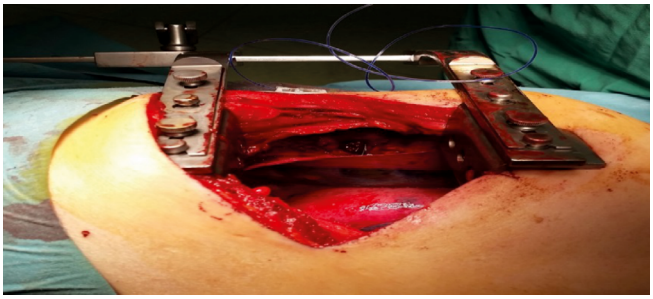

Figure 3. State after the catheter's implantation to the PVS, colored with a methylene blue solution for a better visualization.

etal pleura in the PVS. Berrisford and Sebanathan recommend the paraspinal section to be at least 10 cm long.[20]

To avoid undesired movement, the subpleural section is being tunneled subcutaneously. After installing the filter at the end of the catheter, a solution of physiological salt can be administered ensuring its proper localization and the liquid's spread below the parietal pleura (Figures 3 and 4).

For the purpose of teaching given to the paravertebral methylene blue solution (Figure 4).

A major intercostal opening at the posteolateral access can be a particular problem, touching the parietal pleura too closely in the paraspinal area, which can result in the anaesthesia pouring through the emerged wound into the pleural cavity. The closure of the intercostal at least results in partial sealing and an effective anaesthesia, as evidenced by the author's experience.

The correctness of catheter insertion to PVS, can be checked postoperatively providing water contrast agent through the catheter (Figure 5).

4.3. Used medication

There is a lack of an unequivocal and categorical algorithm determining the dosage of drugs that should be used in PVB. According to many authors, bupivacain at a concentration of either 0.25% or 0.5%, and ropivacain at a concentration 0.5% should be used alongside the occasional addition of adrenaline. Both drugs are dosed in a bolus of 10–20 mL and a subsequent, continuous infusion at the speed of 0.1 mL/kg per hour.[16,18,21]

The author uses a bolus of 0.5% bupivacain infused to the intraoperatively implanted catheter at the moment of

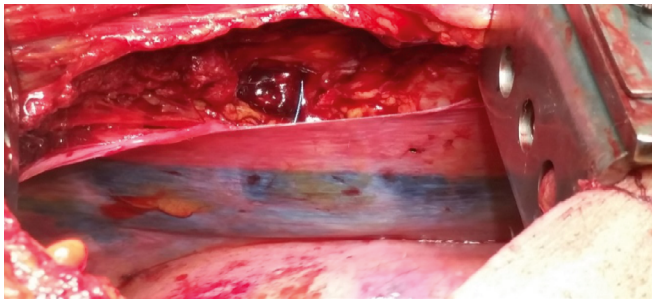

Figure 4. Paravertebral space colored in the distance of 4–5 intercostal.

closing the coating of the chest and a subsequent continuous infusion of 0.25% bupivacain by elastomeric pump at a speed of 5 mL/h, usually obtaining the analgesic effect on a level of 3–5 PVS. This removes the need to administrate opioids in the occurrence of breakthrough pain.

Pain intensity was assessed on the basis of VPS (visual pain score). Patients filled out Pain-Scale Questionnaire surveys on a 0–10 scale, in the first, 2nd, and 3rd postoperative days. Drug administration to PVS was continued 3 days after surgery (until the 3rd postoperative day). Complications of this method are rare. These include: infectious complications, hematoma, toxicity of topical anaesthetic subarachnoid or epidural anaesthesia, neurological complications, damage to nervous structures, puncture large vessels, haemorrhage, blood pressure drop. We have not experienced any complications during this postoperative pain treatment.

Figure 5. PVS contrasted with an Ultravist 350 solution, administered through the intraoperatively implanted catheter.

This method was implemented on 38 patients over a 10 month span. On 3 of the patients, the analgesic effect was not obtained. In the author's opinion and considering the intraoperative picture, this was due to the intercostal being opened too wide with the same PVS resulting in the administered medication reaching the pleura, hence not making the desired impact. On the remaining patients the analgesic effect was obtained at a level of 3–5 PVS, without the necessity of administrating opioids in the case of breakthrough pain. After the first 24 h following surgical procedure the patients showed positive signs of recovery and were able to start rehabilitation.

According to Richardson, the optimal solution is the use of 'pre-emptive analgesia' under multimodal therapy, using the dose of the anaesthetic infused to PVS before incision to the skin, supplemented by further proceedings as described above, decreasing postoperative pain to 0.5 cm on a scale of 0–10 cm.[18]

5. CONCLUSIONS

Intraoperatively implanting a catheter to the PVS following thoracosurgical procedure in order to conduct continuous, regional postoperative anaesthesia is a safe and effective method of treating postoperative pain in thoracic surgery.

Conflict of interest

None declared.

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Review article

Therapeutic properties of lactoferrin

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ABSTRACT

Introduction: For many years, milk and colostrum proteins have been the object of scientists' interest. A group of whey proteins, including lactoferrin (Lf) are credited with special features that promote health and wellbeing.

Aim: The purpose of this paper is to disseminate health and medical properties of lactoferrin originating from the cow's milk and bovine ncolostrum.

Discussion: Extensive research (clinical as well) proves that lactoferrin is beneficial for the human organism. Moreover, no harmful side-effects have been reported following its application. Effective antibacterial function against intestinal pathogenic bacteria and simultaneous stimulation of beneficial microflora are the main functions of this compound. Lactoferrin can also be used in management of cancer and numerous viral infections (i.e. herpes virus or rotavirus) as it stimulates the immune system.

Conclusions: In summary, lactoferrin is a milk protein increasingly more appreciated in medicine. Interest in this protein is rising, which is reflected in numerous scientific and clinical studies that underline its medical importance. Furthermore, research will surely contribute to the understanding of its function and ultimately, it will play a significant role on the market.

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1. INTRODUCTION

Recently, milk and colostrum proteins, as well as their derivatives, have become the objects of scientists' interest. Beside obvious nutritional functions, it is mainly because of their biological role.[1–4] Colostrum and milk are the most complete and wholesome of all meals – especially to a newborn.[5,6] It is because of the health supporting properties of the protein, which on average accounts for 4% of milk composition.[7] The principle milk protein is casein, but it is its allergenic properties that are mostly emphasized on.[8,9] On the contrary, whey proteins are praised for their exceptional functions. They comprise an average of 20%–25% out of total protein content.[2,4,10] They are composed of α-lactalbumin, β-lactoglobulin, plasma albumin, as well as: immunoglobulins, lactoperoxidase, lysozyme and lactoferrin.[11] The abovementioned proteins are detrimental for the correct immune reaction of the organism. Therefore, more and more food preparations for newborns, convalescents or athletes are enriched by those proteins.[12]

2. AIM

The aim of this paper is to underline the properties of lactoferrin and its application in medicine, on the basis of current scientific and overview data. Special attention was paid to the prophylactic values of lactoferrin and its use in treatment of various diseases.

3. DISCUSSION

3.1. Short characteristic of lactoferrin

Recently, significance of bovine colostrum in functional products has diametrically increased.[13] It is all due to lactoferrin (Lf), which content in colostrum is significantly higher than in milk.[14,15] Lactoferrin is a secreted protein, present in milk and colostrum, but also in body fluids as well as tears and saliva. Its content in bovine milk ranges 50–120 mg/dm^3.[10] Whereas Zander et al.[16] present the following content range: 0.1–0.3 mg/cm^3, which stands for 1% of total whey protein content. Lactoferrin name is derived from Latin. *Lac* – means milk, whereas *lacto* – milky and *ferrum* – iron. Thus, milk protein of high affinity to iron was created.[17] Lactoferrin is a glycoprotein, built from 689 amino acids, which molecular weight is about 80 kDa. It consists of a single polypeptide chain with two homological lobes. Each of these lobes has one binding area that can coordinate with one iron ion on the third degree of oxidation (Fe^{3+}).[17–19] Through chelating abilities, lactoferrin lowers the availability of iron to pathogens.[20] It stops their growth as well.[21,22] Complexes of lactoferrin with ions such as: Ga^{3+}, Al^{3+}, Mn^{2+}, Cu^{2+}, Co^{3+} have been reported so far.[17]

Biologically active peptides, which can be obtained by the enzymatic cutting of lactoferrin, are possible to be distinguished.[23] The cut is performed thanks to the enzymatic digestion of lactoferrin by pepsin. In result the created peptide is called lactoferricin.[24,25]

3.2. General lactoferrin properties

Lactoferrin is the so called immunoregulator. This means that its function involves inducing growth of precursor T-cells into mature helper cells as well as differentiation of immature B-cells.[18] In result B-cells become cells effectively producing antigens.[26] Beside the fact of immune system stimulation, antibacterial, antiviral, anti-inflammatory and antifungal properties are worth noting. It is also credited with anticancer features. Lactoferrin is described by scientists as a multipotential protein.[16,17,28]

3.3. Antibacterial activity

Antibacterial activity of lactoferrin can be direct (damage of cell walls or change in bacterial metabolism) or indirect (stimulation of organism's defense – faster response to infection).[6] Especially the effective antibacterial activity is shown in case of *Escherichia coli* strain or other pathogenic intestinal bacteria. At the same time, it stimulates the activity of beneficial microflora of *Bifidobacterium* species (selective lactoferrin activity).[29] Furthermore, lactoferrin increases sensitivity of bacteria to some antibiotics (vancomycin, penicillin) and influences the decrease of their effective doses. For example, as Diarra et al.[14] report the combination of penicillin with lactoferrin doubled the inhibitory activity of antibiotic against *Staphylococcus aureus*. Defensive activity of lactoferrin was presented in systemic infection of mouse with *S. aureus*, while whey protein was used as an addition to drinking water (in the amount of 2%). A decrease in bacterial count in kidneys 5–12 times was observed.[30] Additionally, Haversen et al.[31] proved that in case of urinary tract infections with *E. coli* in mice, lactoferrin and its peptides were found in urine 2 hours after oral intake. It is highly suggestive that lactoferrin may be active at the infection site as well. Trumpler et al.[32] clinically confirmed the effectivity of lactoferrin in alleviating the course of infection in in patients with neutropenia to whom chemotherapy was applied.

3.4. Antiviral properties

The presence of sialic acid and modification of compound structure that appears during iron ions binding process (as well as manganese and zinc) may have an impact on antiviral lactoferrin activity. Herpes virus (HSV), human immunodeficiency virus (HIV), hepatitis type B and C virus (HCV) or rotavirus all turned to be sensitive to lactoferrin activity.[6,33] Zimecki and Artym[6] underline that the synergistic activity of lactoferrin (as well as lactoferricin) with some antiviral compounds may lower the dose of applied medications, which are toxic to organism. Synergistic activity was observed during lactoferrin application with acyclovir in Herpes Simplex-1 (HSV-1) infection. It allowed to lower the dose of medication 2–7 times.[34] Nozaki et al.[35] showed simi-

lar effects using lactoferrin and interferons (IFN) in HCV infections of people. Lactoferrin can be used as a selective drug carrier because it has an ability to penetrate to the cellular viral receptors.[6,32]

3.5. Anticancer properties

Lactoferrin and its peptide – lactoferricin effectiveness in the treatment of cancer is confirmed by *in vitro* and *in vivo* studies. Eliassen et al.[36] state that lactoferrin had a significant antiviral activity directly on cancer line cells of fibrosarcoma, melanoma and colon cancer. Zimecki and Artym[6] confirm the cytotoxic activity of lactoferrin. Mechanism includes damage to cell membrane and lysis of cell *in vitro*, what reduces tumors *in vivo*. In Shimamura et al.[37] studies lewis lung carcinoma cells were applied to mice thus inducing angiogenesis, after which the lactoferrin was applied to them which inhibited tumor growth. Such function of lactoferrin results from the direct inhibitive impact on endothelial proliferation as well as indirect impact on IFN release.

3.6. Immuno-stimulating activities

Multipotential protein has also the fundamental function in immune system – it stimulates immune response. As studies conducted on several experimental models by Zimecki et al.[38] report, lactoferrin has been applied to New Zealand Black mice for several months, in which the autoimmunological hemolytic disease has been developing and it caused lowering of positive Coombs reaction percentage. It means that IgG antibody titers engaged in autoimmunological reactions decreased.[38] Additionally, after the pre-incubation of peritoneal lymphocytes of examined mice with lactoferrin, the decrease in number of erythrocyte antigen recognizing cells was noticed.[6,38]

One of very interesting aspects connected with the discussed protein is the fact that lactoferrin alone can act as an analgesic agent or can cooperate with morphine.[39] Analgesic activity of lactoferrin is mediated by nitrous oxide. Earlier statements confirm studies conducted on mice by Narayan Raju et al.[40] Authors report that after reversal of lactoferrin activity by the opioid receptor antagonist (naloxone) the inhibition of psychical stress symptoms in the examined animals was observed. What is more, the analysis of formalin test in rats confirmed the effectiveness of increase of morphine analgesic activity.[39]

4. CONCLUSIONS

1. Lactoferrin has been an object of scientists' interest for several years. First of all, its popularity was gained by the high content in bovine colostrum but also many invaluable properties. Surely, next decade will bring further studies which will allow to use it and its derivatives potential to full extent.
2. Lactoferrin is a multipotential protein which isolated from milk or colostrum is effective, safe and easily digested. Therefore, it can be used with many substances creating products that can be easily used in treatment but also in prevention of some diseases.
3. Thanks to chelating abilities, lactoferrin has a number of antibacterial, antiviral, anticancer properties as well as directly and indirectly influences human immune system. Thankfully to its selectivity, it inhibits pathogenic bacteria growth, simultaneously creating good environment for growth of proper intestinal microflora. It is worth to underline the possible use of lactoferrin as an analgesic substance.

Conflict of interest

None declared

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Review article

Advances in diagnosis and treatment of obstructive sleep apnea

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is a sleep disorder which is very common among obese patients, and which is mostly observed in highly developed societies.

Aim: The purpose of this article is to present the methods of OSA treatment.

Material and methods: Medline searches were conducted in context of OSA, basing on literature from 2014 and 2015.

Results and discussion: We can divide OSA treatment methods into three groups. There are methods based on positive airway pressure (PAP), which are proved to be the most efficient, but are often hardly accepted by patients due to the need of wearing an uncomfortable mask during sleep. The second group are methods based on the use of the mandibular repositioning devices, which are less efficient than positive airway pressure, but more willingly accepted by patients; these methods have proven quite successful in treating mild to moderate OSA. The third group are surgical methods which can be very efficient, but at the same time, can cause danger to the patient's life.

Conclusions: Using intraoral devices is recommended to patients with mild to moderate OSA symptoms and to patients with a severe form of the disorder who cannot cope with the PAP treatment. The surgical treatments of OSA are not recommended despite being efficient, since they produce many dangerous side effects.

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1. INTRODUCTION

The definition of obstructive sleep apnea (OSA) is a partial or complete airway obstruction which takes place during sleep and lasts for at least 10 s.[1] It is caused by airway expansion muscles which cannot withstand the underpressure created by the breathing muscles. OSA is determined to affect approximately 4% of middle-aged men and 2% of adult women; the figures climb up to the age of 60 to 70 years old.

The causes of OSA need to be differentiated among muscles disorders, respiratory reflexes disorders and the central causes.[2] While waking up, these muscles are activated by the pharyngeal and laryngeal mechanoreceptor reflexes. In OSA patients, these reflexes are weakened due to the lesser innervation and smaller susceptibility to temperature changes and vibrations.[3] OSA is associated with obesity which is a common disorder in developed countries. This phenomenon is to be seen in over 50% of patients with body mass index (BMI) of over 40 kg/m^2. OSA is also clearly associated with cardiologic and metabolic disorders or opioid medication. Research on OSA helped develop a group of anatomic and physiologic disorders which create a higher risk of OSA prevalence. The group consists of adenotonsilar enlargement, laryngopharyngic disorders, macroglossia, acromegaly, midface hypoplasia and retrognathia.[4] Breathing disorders during sleep may also be caused by central neurological system disorders like the Cheyne-Stokes syndrome or arousal disorders. They can also result from the larynx nerves stimulation during upper airway infection.[4] It was suggested that OSA is connected with a low adiponectin level, but research did not demonstrate a correlation between the continuous positive airway pressure (CPAP) treatment and adiponectin level changes.[5]

One of the most typical signs of the upper airway contraction is snoring which is caused by the soft palatal tissue vibration. OSA also causes partial hypoxemia and sleep laceration which is particularly dangerous for it may resolve in lack of concentration leading to traffic accidents.[4,6] Research conducted on a group of Canadian drivers revealed that drivers suffering from OSA had a higher traffic accidents factor than healthy drivers during a 3 year period.[7] Other OSA symptoms are xerostomia, increased saliva secretion, change in sleep rituals and dyspnea. Daytime symptoms usually include headaches, irritability and stomach reflux.

The diagnosis of OSA is based on polysomnography or nighttime heart work and breathing diagnostics.[1,8] It shows the quality of the sleep, the airflow in the upper airways, the number of awakenings during sleep, sleep position, electrocardiogram and blood saturation.

The severness of OSA is measured with the apopnea/hypopnea index (AHI) which shows how many times during an hour of sleep the patient suffers from partial or complete upper airway obturation lasting for at least 10 s. AHI of 5–15 represents a benign/mild form of OSA, 16–30 is moderate, and 30 and higher is defined as a severe form of the disorder.[1]

2. AIM

The purpose of this article is to present the methods of OSA treatment.

3. MATERIAL AND METHODS

Medline searches were conducted in context of OSA, basing on literature from 2014 and 2015.

4. RESULTS AND DISCUSSION

Treatment methods of OSA can be divided into three groups. There are methods based on positive airway pressure delivered to the patient's airway through a mask, surgical treatment and treatment based on using intraoral devices which are supposed to move the mandibula and/or the tongue forward to reduce the pressure on the patient's airway. Other ways of treating OSA are reducing the patient's body weight and phrenic and glossopharyngic nerve stimulation.[4] Based on 17 articles from 2014–2015, this review shows the most popular methods of treating OSA.

CPAP – the device treats OSA by delivering air to the patient's airway under pressure which is higher than the pressure which causes the patient's soft palatal tissues to collapse. The air is provided by a nasal mask or a nasomouth mask. A higher pressure is needed throughout the rapid eyes movement (REM) sleep phase and in obese patients.[8] The CPAP shows good results in sleepiness, tiredness and concentration disorders treatment; however, 20% to 50% of patients are unable to cope with the therapy due to the associated discomfort. Common side effects are air leaks and uncomfortable face squeeze. The side effects are mostly caused by the airpressure and can be removed by device adjustment.[3] Patients often complain about airways mucosa dryness thus the devices are often equipped with air warmers and humidifiers.[9] Other limitations include the fact that these devices need electricity to work, which makes them impossible to use in some environments.[6,10] According to research,[11] phone coaching can help the patients with motivation and instructions on how to use the CPAP device. As a result, patients may be more willing to wear the mask for a longer time during the night. Other methods of helping the patients to cope with the CPAP are sleeping medications, medical education and behavioral therapy.[9] CPAP is one of the most popular methods of treating OSA and there are many modifications of it which are to help reduce the percentage of treatment failures.

Bi-level positive airway pressure (BPAP) is characterized by different airway pressure – it is reduced during the exhale, which helps the patient to exhale.[9]

Adaptive servo-ventilation (ASV) is a BPAP device modification in which the inhale and exhale pressures are not consistent, but they change during the sleep.[9]

Auto-titrating positive airway pressure (APAP) are the devices which, contrary to CPAP, are not set on one particular pressure value. Instead, they constantly check the patient's sleep to establish the optimum minimal pressure needed to keep the patient's airways open. Correct pressure is changing through the night and depends on several conditions, such as the body position or sleep phase. Different producers have developed different algorithms which are responsible for maintaining the correct pressure at a given moment. Compared to CPAP, APAP shows a small but significant advantage in the time it takes a patient to get used to the device (11 minutes), and also in reducing daytime sleepiness. On the other hand, CPAP is more efficient in reducing the patient's blood pressure and helping other cardiometabolic disorders. Another advantage of the APAP device is reducing the cost of the diagnostics, while the device does not require many therapist appointments to be set on the correct working pressure.[9]

Another device which is to help the patients to use the positive airway pressure (PAP) devices is expiratory pressure relief (EPR). It is similar to the BPAP device, but it does not have a set air pressure for the exhale. With every exhale, it measures the airflow and according to its value, it lowers the air pressure for early exhale opposite to the late exhale.[9]

Expiratory positive airway pressure (EPAP) is a device placed on the patient's nose and consisting of a flap which lets a free inhale, and at the same time, lets an exhale only when the exhale air pressure is high enough. At first, the device showed good results, but later research on the group of patients who had previously used CPAP showed that the EPAP results were not significantly better than the placebo.[9]

One of the suggested ways of treating OSA is to stimulate the airways expanding muscles by constantly providing air pressure at high frequency and low amplitude. On that basis, an oscillating positive airway pressure (OPAP) device prototype was created. The device was planned to be used with CPAP, but clinical research showed that there were no significant differences between using CPAP with and without OPAP.[3]

Intraoral devices are the optimal treatment option for patients with mild to moderate OSA form and also for patients with severe OSA who cannot cope with CPAP devices. Intraoral devices work by changing the position of the lower jaw and/or the tongue to relieve the pressure they can put on the airways by obstructing it. The most important advantages of these devices are low price, working without the need of electrical charging, easiness of transportation due to their small size and weight, as well as immediate effects. Their most considerable disadvantage is smaller efficiency in comparison to the PAP devices.[4,6,10]

Mandibular advancement device (MAD) is an intraoral device used in treatment of OSA and snoring. By changing the position of the lower jaw to a more protruded and open one, it increases the airflow in the patient's airways. Additionally, MAD stabilizes the jaws and the hyoid bone position, preventing the airways obturation. The hyoid bone becomes more protruded, which changes the suprahyoid muscles equilibrium position and additionally increases the airflow. A 75% mandible protrusion shows to be the most efficient in OSA treatment.[10] Setting the MAD is usually done with the use of the inch by inch method to set the optimal mandible position. The mandible position is set by the screws located on the palatal side of the device or in the front in the midline. It can also be equipped with two regulation levers located on the sides of the device. Some MADs allow the jaw to be open, some set it fixed. Using MAD may cause side effects, such as jaw pains, teeth hypersensitivity and increased saliva secretion. Some patients may require an adaptation time of up to a few months. MAD users should have at least 10 teeth in one dental arch to provide a correct anchorage for the device; however, using MAD with dental prosthesis shows satisfying results.[12] In edentulous patients, the best support is provided by dental implants; however, patients often refuse to accept such treatment due to its high cost and the need of a surgical treatment. When MAD is used with partial or complete dentures, it is highly recommended to perform systematic dental examinations due to the possibility of jaw process resorption. Some researchers also question the safety of occlusion in MAD users. Authors[13] claim that intraoral devices made without the correct central relation registration may lead to teeth and mandibular position disorders. Research conducted in France also shows that the intraoral devices therapy is mostly performed in patients with a high socioeconomic status, which means it is hardly available to the less wealthy part of the society.[14] The research from 2014 suggests that there may be a relation between cephalometric factors and the percentage of intraoral devices treatment success.[15]

Devices which are based on tongue protrusion are mostly recommended for edentulous patients. These devices also have disadvantages. They do not fit very well, they may cause bruising of the mucosa and they increase saliva secretion.

Surgical methods of treating OSA are mostly uvulopalatopharyngoplasty (UPPP) which involves a tonsillectomy, excision of the uvula and posterior palate and trimming of the posterior pillars. This procedure provides satisfying results only in 33% patients and it can also cause the patient to be non-compliant with/for the PAP devices in the future.[9]

Surgical maxilla and mandible protrusion provides the AHI decrease to an average level of 7.7 per hour; however, due to high mortality, the procedure is rarely conducted. Similarly, the tracheostomy is very efficient providing the full upper airway bypass; nevertheless, due to complications, such as recurring lungs inflammations, near stomy complications, psychologic trauma and high morbidity, it is rarely performed.[9]

In 2011 a new idea of OSA treatment emerged. Strollo and associates proved that bilateral hypoglossal muscles stimulation with a surgically mounted neurostimulator is efficient in reducing OSA symptoms, such as daytime sleepiness.[16] Disadvantages of this treatment are high cost and the need of performing a surgical procedure. A continuous transcutaneous electrical stimulation (CTES) might become an alternative, but the efficiency of this method is still to be confirmed.[16]

5. CONCLUSIONS

All the authors of the cited publications agree that there is a need to continue the research on OSA, as it may have a considerable influence on the public health/ health level in society. There is still no agreement on what the right tool to establish the OSA severeness in a patient. On what method should be used for OSA severeness diagnosis. Some authors[17] suggest that AHI should be replaced with the length of the airways obturation index, blood saturation level index or awakening length index. The CPAP therapy remains the official standard of OSA treatment. Using intraoral devices is recommended to patients with mild to moderate OSA symptoms and to patients with a severe form of the disorder who cannot cope with the PAP treatment. The surgical treatments are not recommended despite being efficient, since they produce many dangerous side effects.

Conflict of interest

None declared.

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Review article

The potential benefits of plant cyclitols in the treatment of psoriasis

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ABSTRACT

Introduction: Cyclitols, the hydroxylated cycloalkanes biosynthetically derived from glucose, occur in all living cells and express a broad spectrum of biological activity and participate in many cellular processes including membrane biogenesis, signal transduction, ion channel physiology, osmoregulation, and antioxidation. They have several health-promoting and therapeutic properties such as: improving lipid profile in decresing of serum triglicerydes and total cholesterol, as well as having an insulin-mimetic effect. Moreover, they have antioxidative, anti-inflammatory and anti-cancer properties.

Aim: Revision the literature and analysis of available studies on the potential beneficial effects of cyclitols on inflammatory processes in psoriasis.

Results and discussion: This article discusses the potential anti-inflammatory properties of cyclitols affecting the individual elements of the pathophysiology of psoriatic inflammation: inhibits the expression of MHC class I and MHC class II of mature dendritic cells, resulting in a decrease of IL-12, IL-23, which are necessary to differentiation of naive lymphocytes in Th1 and Th17 line; inhibits NF-κB, a major signaling pathway activated by TNF-α with reducing of inflammation; inhibits the angiogenic factor VEGF, with reducing epidermal hyperproliferation and enhance of the activity of antioxidants.

Conclusions: The anti-inflammatory effects of cyclitols suggest that they can be used for treatment of psoriasis.

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1. INTRODUCTION

Cyclitols, the hydroxylated cycloalkanes, biosynthetically derived from glucose, occur in all living cells and express a broad spectrum of biological activity. They participate in many cellular processes including membrane biogenesis, signal transduction, ion channel physiology, osmoregulation, and antioxidation.[1] They are responsible for the tolerance to abiotic stresses such as salinity, cold or high temperature.[1,2] Cyclitols are converted in plants via methylation of myo-Inositol, the major and ubiquitous inositol among all live organisms.[3] The most common cyclitols are: D-chiro-inositol, D-ononitol, D-pinitol and D-sequoitol.[4] They are present in seeds of many plant species (legumes, buckwheat, Cucurbitaceae), mostly in legumes and therefore are common constituents of human diet and feed for livestock.[5] Moreover, free cyclitols present in food or released during degradation of galactosyl cyclitols by bacteria (in digestive tract) can be absorb by endothelial cells indicating some physiological benefits.[6,7]

Myo-Inositol and other cyclitols indicate several health-promoting and therapeutic properties.[8] They can improve lipid profile in decresing of serum triglicerydes and total cholesterol after oral using pinitol[9] and myo-inositol.[10] The mostly studied and well documented is the insulin-mimetic effect of D-pinitol,[11] D-chiro-inositol – isomer of myo-inositol[12] and sequoitol.[13] Myo-Inositol indicates antioxidative,[6] anti-inflammatory[14] and anti-cancer properties.[15] Cyclitols can improve osteogenesis with bone mineral density, together with D-chiro-inositol, which inhibits osteoclastogenesis.[16] Antioxidant properties have protective effects on the nervous system and developing of Alzheimer's disease.[17] Furthermore myo-inositol has the effect of supporting normal ovulatory activity and sperm motility (Figure 1).[18] The immunomodulatory effects of D-pinitol[14,19] lead us to suggestion that some cyclitols can be used for treatment of psoriasis. Moreover, plant-derived food containing cyclitols can play an additional role in prevention of development of this disease.

Because of the unsatisfactory efficacy of psoriasis treatment, patients are constantly looking for new formulations, often turning to alternative medicine. Moreover, psoriasis is a systemic disease. Studies indicate its association with metabolic disorders: obesity, diabetes and cardiovascular disease compared with the general population. Psoriasis is an independent risk factor for atherosclerosis.[20,21] Severe psoriasis can shortens life expectancy about 3–4 years.[22] The appropriate treatment of psoriatic patients can prevent the development of comorbidities. The prevalence of the disease and its consequences should be treated as a serious social and economic problem. Cyclitols have anti-inflammatory effect and may be an effective alternative treatment for psoriasis, both topically and systemically, also reducing the risk of developing metabolic disorders in patients.

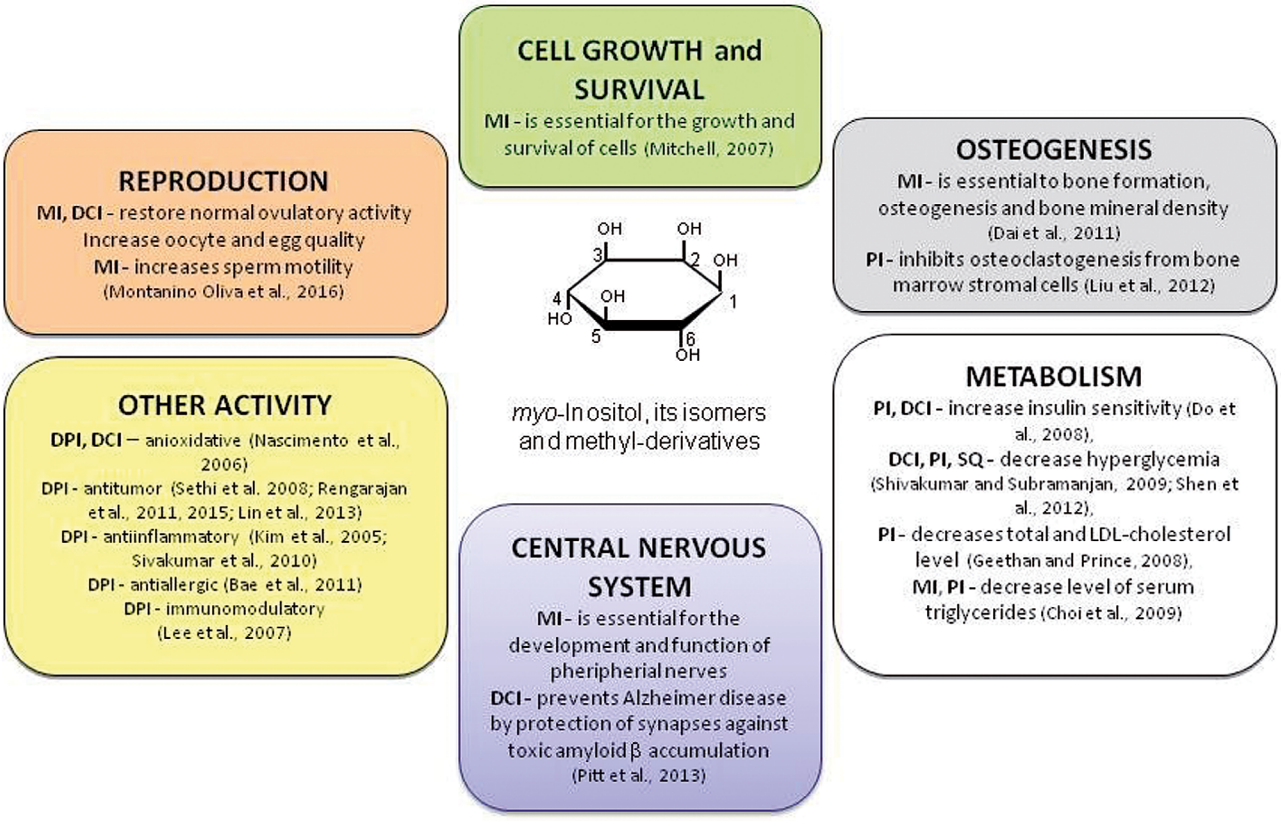

Figure 1. Biological and therapeutic activity of myo-inositol, its isomers and methyl-derivatives. Comments: MI – myo-inositol, PI – D-pinitol, DCI – D-chiro-inositol, SQ – D-sequoitol (by Croze MJ and Soulage CO, [8] modified).

2. AIM

The aim of this paper is to review the literature and analysis the data about cyclitols, taking into account their properties hypothetically affecting inflammatory processes of psoriasis.

3. RESULTS AND DISCUSSION

3.1. Cyclitols and Th1, Th17

Psoriasis is a disease mediated by Th1 and Th17. Lymphocytes Th1 secrete IL-2, IL-3, IFN-γ, TNF-α, and Th17 IL-17A, IL-17F, IL-21, IL-22, IL-25, IL-26, TNF-α. These cytokines drive and sustain inflammation, stimulate keratinocytes to excessive 'vicious circle' proliferation mechanism.[23–25]

D-pinitol inhibits the expression of MHC class I and MHC class II of mature dendritic cells (DCs), resulting in a decrease of IL-12, IL-23, which are necessary to differentiation of naive lymphocytes in Th1 and Th17 line.[25,26] The scientific results of Lee et al., suggest that the D-pinitol is a potent inhibitor of dendritic cell maturation, thereby blocking activation of IL-12/Th1/IFN-γ and Th17/ IL-23 axes – the most important keys in the development of psoriatic inflammation.[26,27] By weakening the activity of Th1 decreasing production of pro-inflammatory cytokines TNF-α, IL-1 and IL-6 is observed[14]. Moreover, D-pinitol affects the growth of expression of the GATA transcription protein 3, which regulates the Th1/Th2 balance.[19]

3.2. Cyclitols and proinflammatory cytokines

The main inflammatory cytokine in psoriasis is TNF-α, which stimulates endothelial cells to express adhesion molecules, resulting in the migration of neutrophils to the skin and to produce microabscesses and formation of elongated, dilated blood vessels (loops) in the dermal papillae in psoriasis lesions.[24]

Nuclear factor κB (NF-κB) is responsible for the activation of Th1 and transcription of a numerous genes, which are involved in the pathogenesis of psoriasis, for the production of the proinflammatory cytokines (TNF-a, IL-6, IL-8, IL-12, cyclin D). It is believed that dysfunction of NF-κB may contribute to the worsening of psoriasis.[26,28]

Lee et al. observed that D-pinitol inhibits NF-κB, a major signaling pathway activated by TNF-α with reducing of inflammation.[26] Geller et al., noted a significant reduction of TNF-α production by human monocytes, stimulated with bacterial lipopolysaccharide with the ethanolic extract of *Hancornia speciosa*, comprising bornesitol.[29]

Inhibition of TNF-α by pinitol has a great importance in suppressing the insulin resistance.[10,30] This is very important because the hyperinsulinemia accompanying insulin resistance, leading to faster development of atherosclerosis, destruct the endothelial cells and macrophages.[31] Insulin regulates gene expression of TNF-α in macrophages, exacerbating the inflammatory process, favoring the formation of oxidized low density lipoprotein (ox-LDL). This leads to excessive ox-LDL accumulation as lipid droplets in macrophages, thereby contributing to the formation of foam cells.[32] Pinitol, in a dose-dependent manner, inhibits the formation of foam cells and the lipid storage processes in atherosclerotic plaques.[33,34] Choi et al., demonstrated a significant reduction in TNF-α production, monocyte chemotactic protein-1, IL-1, IL-8 and the metalloproteinase-9 expression, during administration of pinitol into human macrophages.[10] Summarizing, pinitol can inhibits the formation of foam cells, and thus the formation of atherosclerotic plaques. Atherosclerosis is observed in patients with psoriasis because of the common pathogenic mechanism.[10,30,35]

Chauhan et al., showed immunosuppressive properties of D-pinitol, which inhibits the expression of CD3, CD19, CD4 and CD8 of splenocytes and secretion of proinflammatory cytokines Th1 and Th2, without toxic effect in vitro and in vivo. The immunosuppressive properties of D-pinitol were better in comparison to cyclophosphamide.[36]

3.3. Cyclitols and apoptosis

Psoriasis is characterized by excessive proliferation and abnormal differentiation of epidermal keratinocytes, leading to parakeratosis. One of the factors responsible for this phenomenon are abnormal apoptosis. The index of apoptotic keratinocytes in the basal layer of epidermis is 0.12% in the normal epidermis, 0,035% in psoriatic papules and 0.31% in the outgoing lesions.[37] This confirms the observation that psoriatic keratinocytes are particularly resistant to apoptosis, in psoriatic lesions where overexpressed Bcl-XL, stimulated by TNF-α were found.[38] NF-κB plays an important role in the growth, differentiation and apoptosis of epidermal cells. Its activation is one of the mechanisms of anti-apoptotic, initiated during the differentiation of keratinocytes.[39]

D-pinitol inhibits NF-κB, a major signaling pathway activated by TNF-α and reduce inflammation.[28] TNF-α effect on keratinocyte proliferation, reducing their sensitivity to apoptosis, stimulates T-cell activity, stimulates the expression of adhesion molecules and other proinflammatory cytokines.[40] Inhibition of NF-κB reduces expression of antyapototic proteins (Bcl-2 and Bcl-XL).[26] Sethi et al., demonstrated that pinitol completely inhibits TNF-induced activation pathway of NF-κB in various cell types cancer and embryonic.[28]

3.4. Cyclitols and angiogenesis

An important element supporting the inflammation and hyperproliferation of the epidermis in psoriatic plaque is angiogenesis. Immune cells and activated keratinocytes produce angiogenic factor – VEGF, which maintains the activity of angiogenesis and endothelial cells. Its concentration correlates with the severity of psoriasis.[41] VEGF stimulates mitosis of endothelial cells, vascular permeability, and also contributes to the chemotaxis of neutrophils and activation of monocytes. It is synthesized in keratinocytes, and its in-

creased concentrations in plasma and psoriatic lesions, correlating with disease activity.[42]

Elevated levels of VEGF which are the main source of adipocytes can be noted in hyperinsulinemia accompanying obesity and metabolic syndrome.[43] Therefore, it is possible that hyperinsulinemia can provoke psoriasis or aggravate existing lesions not only by promoting inflammation, but also by stimulation of VEGF secretion.[44]

It has been proven in Sethi et al. research, that D-pinitol inhibits the angiogenic factor VEGF, with reducing epidermal hyperproliferation.[28] Inositol has similar properties.[6]

3.5. Cyclitols and oxidative stress

Chronic inflammation in psoriatic lesions affects the formation of reactive oxygen species (ROS) leading to 'oxidative stress.'[45] They cause damage to endothelial cells, increase permeability of small blood and allow the migration of inflammatory cells. Oxidative stress increases the production of eicosanoids (by activation of phospholipase A) which have proinflammatory and chemoattractant properties.

In psoriasis during the penetration of the neutrophils to the epidermis and for microabscesses formation, the production of large amounts of ROS observed, which cause damage of proteins and lipids and disrupt the integrity of the epidermal barrier.[20]

Oxidative stress plays a key role in the development of diabetes and its complications due to hyperinsulinemia. ROS production leads to endothelial dysfunction, observed already in the early stages of the disease and atherosclerosis.[21] Hyperglycemia leads to increased ROS production in mitochondria of endothelial cells. It causes an activation of protein kinase C, increased production of glycation finish products, an increase in the concentration of glucose via activation pathway of the aldose reductase, enhanced activity of fructose-6-phosphate, which contributes to insulin resistance and NF-κB pathway activation resulting in transcription of pro-inflammatory cytokines. In addition, it decreases the production of vasodilatative NO.[6,46]

In the study of Sivakumar et al., rats with streptozotocin-induced diabetes and secondary renal failure got orally d-pinitol for 30 days with improvements in the laboratory tests (lower the concentration of urea, uric acid, creatinine, glycation finish products and pro-inflammatory cytokines – TNF-α, IL-1, IL-6, NF-κB).[14] Furthermore, D-pinitol produce substantial weakening of the activity of antioxidants as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, with concomitantly decreased oxidation products in the kidneys (lipid peroxides, hydroperoxides and carbonyls protein), which proves its nephroprotective character.[14,47]

3.6. Clinical experience of cyclitols use in patients with psoriasis

Only inosytol is mentioned in the literature to have the beneficial effect in psoriasis. There is only one described case of the effectiveness of inositol in the treatment of a patient with bipolar disorder and severe psoriasis provoked by lithium.[48] Interestingly, it is reported that the apperance of psoriasis during the lithium treatment is associated with decreased levels of inositol in the skin.[49] In addition, besides mood stabilization, relief of psoriasis was achieved, which did not occur after the withdrawal of lithum and using immunosupresive systemic treatment.[48] Allan et al., applied the supplementation of inositol in 15 patients with bipolar disorder, who also suffered from psoriasis. Supplementation resulted in a reduction in PASI, despite lithium therapy, including patients who did not use lithium. Therefore it can be concluded that inositol has positive influence on the psoriatic process.[50]

4. CONCLUSIONS

Anti-inflammatory properties of cyclitols may be a good therapeutic options for topical and systemic treatment of psoriasis, as well as reduce metabolically induced inflammation – metainflammation, which leads to more frequent development of metabolic disorders and atherosclerosis in patients with severe psoriasis. However, clinical studies are needed to confirm their beneficial effect on psoriasis.

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