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ORIGINAL PAPER

ASSOCIATIONS BETWEEN HLA CLASS II HAPLOTYPES, ENVIRONMENTAL FACTORS AND TYPE 1 DIABETES MELLITUS IN LITHUANIAN CHILDREN WITH TYPE 1 DIABETES AND CONTROLS

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ABSTRACT

Introduction. The onset of type 1 diabetes (T1D) is determined by genetic predisposition and environmental factors.

Aim. The aim of our work was to identify associations between human leukocytes antigen (HLA) class II alleles, environmental factors and T1D in Lithuania.

Materials and methods. Our case-control study included 124 diabetic children (mean age 9.19±3.94 years) and 78 controls (mean age 10.77±3.36 years). The age ranged from 0 to 15 years. HLA–DRB1, DQA1 and DQB1 alleles were genotyped using polymerase chain reaction. Information concerning the environmental factors was collected via questionnaires.

Results. Logistic regression model indicated that three haplotypes: (DR3)––DQA1*0501–DQB1*0201, (DR4)–DQA1*0301–DQB1*0302 and (DR1)–DQA1*010––04–DQB1*0501, increased the T1D risk statistically significantly 18.1, 12.3 and 3.4 times, respectively, while (DR11/12/13)–DQA1*05–DQB1*0301 haplotype decreased the risk of T1D 9.1 times.

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Several different regression models included environmental factors and different sets of risk and protective haplotypes. The results suggest that living in a remote area with lower population density during pregnancy increased the risk of T1D, as well as short breastfeeding, introduction of eggs before 5th month of age and infections during the last 6 months before diagnosis. Smoking during pregnancy as well as rubella and varicella virus infections seemed to decrease the risk of T1D. These associations were revealed while evaluating only environmental factors and when different HLA haplotypes together with environmental factors were included in the regression model.

Discussion. The HLA typing shows that the differences in the incidence of T1D between Lithuania and neighboring countries cannot be explained only by genetics, but lifestyle and/or environmental factors should be considered. A number of studies presented here, have shown conflicting results regarding environmental factors and their associations with T1D.

Conclusions. Both genetic and environmental factors play a major role in diabetes development and protection. However, even quite rapidly ongoing changes of environmental factors and lifestyle in Lithuania have not helped us to reveal any clear picture.

Key words: type 1 diabetes (T1D), children, human leukocytes antigens (HLA), environmental risk factors, case-control study.

INTRODUCTION

Type 1 diabetes mellitus (T1D) is a slowly progressive autoimmune disease caused by a selective destruction of the insulin-producing pancreatic beta cells. Genetic predisposition is important, but not sufficient, for the disease to develop. Human leukocytes antigen (HLA) genes contribute the most to genetic susceptibility for T1D, although other genes are also likely to be involved but with much less importance [12]. Certain HLA genes can also provide protection from diabetes. Among Caucasians, T1D is positively associated with DR3–DQ2 and DR4–DQ8 haplotypes and negatively associated with DR2–DQ6 [9, 24]. Together with genetic predisposition, several facts, such as the rapidly increasing incidence, prove that environmental factors play a crucial role for the development of T1D [10]. Prenatal events, growth during the first years of life, nutrition early in life and rapid weight gain are those factors which can cause beta cell stress [2, 14]. Several studies have observed that non-breast-fed infants gain weight more rapidly than breast-fed children. This fact may explain the protective effect of breast-feeding against T1D [14]. Viral infections, social factors, psychological stress, etc., can also modify the risk for the disease [4, 16].

Thus, T1D develops in genetically susceptible individuals as a response to the interaction with lifestyle and/or environmental agents. However, convincing evidence

for some major environmental factors to be the initiators of the disease process has so far not been presented. Being aware of many extensive studies in this field, we still thought that studies on this topic in Lithuania might yield additional new information. In Lithuania, the incidence of T1D is rather low – 14.2 per 100 000 children in a year [28] – as compared to neighboring countries: 64.2 per 100 000 in a year in Finland [7], 37.8 per 100 000 in a year in Sweden [27] and 22.7 per 100 000 in a year in Norway [1]. The incidence is increasing year by year on average from 1.3% in Norway to 3.3% per year in Sweden [21], where in 2008–2009, the incidence amounted to more than 40 cases per 100 000 in a year (Samuelsson U., Sweden; unpublished data, 2009).

AIM

The aim of our work was to identify associations between HLA class II alleles, environmental factors and T1D in Lithuania against the background of rapid changes in lifestyle and environmental factors in Lithuania.

MATERIALS AND METHODS

Our study is part of a larger study (Diabetes and Environment at the Baltic Sea, DEBS) which was designed as a case-control study. The group consisting of 286 children with newly diagnosed T1D during the period of 1 August, 1996, and 1 August, 2000, in Lithuania and 813 age and sex matched double randomly selected healthy controls participated in that study, which has been presented earlier [23].

All parents, together with their children, filled in the questionnaires about nutrition in early life, duration of exclusive and total breast-feeding, time of introduction of cow's milk based formula, cereal, eggs and other solid foods. There were questions regarding exposure during pregnancy, neonatal period and first year of life, social factors such as living conditions and residence, mother's education, occupation, employment, child attendance to kindergarten, infections and vaccinations. The questionnaire has been described previously [23].

HLA testing was performed in 124 diabetic children (55 male and 69 female, mean age 9.19±3.94 years) and compared with 78 controls (43 males and 35 females, mean age 10.77±3.36 years). The ages ranged from 0 to 15 years. Blood samples were obtained from children with diabetes as well as control children and stored at -20°C. DNA was extracted from blood leukocytes by the standard phenol-chloroform method and then was dissolved in sterile double-distillate water. HLA–DRB1, DQA1 and DQB1 alleles for diabetic children were genotyped using polymerase chain reaction (PCR) with amplification of the second exon of the genes as described earlier [25]. Amplified product was manually dot blotted onto nylon membranes. Synthetic sequence-specific oligonucleotide (SSO) probes were 3'-end labeled with (αP^{32})dCTP and used for hybridization followed by stringency washes and autoradiography. Laboratory analysis was carried out in the Department of Molecular Immunogenetics, Karolinska Institute, Sweden.

HLA–DRB1, DQA1 and DQB1 alleles for control children were genotyped using PCR with sequence-specific primers (SSP–PCR) supplied by Protrans and following manufacturer's recommendations (Protrans, Germany). The amplified products were determined by means of agarose gel electrophoresis. Laboratory analysis was carried out in the Laboratory of Immunology and Genetics, Kaunas Medical University Hospital, Lithuania.

The study was approved by the Research Ethics Committee of Kaunas University of Medicine, Lithuania.

Statistical analysis

Comparisons of means between the groups of cases and controls were performed by the Student's *t*-test or Mann-Whitney *U*-test (non-parametric values). Proportions were compared using Pearson's χ^2 or Fisher's exact test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Risk factors' models were analyzed using logistic regression analysis. Differences were considered significant at $P < 0.05$.

RESULTS

A binary logistic regression model was performed to assess the importance of different haplotypes and environmental factors on T1D development. We tried several logistic regression models that included the previously mentioned environmental factors and HLA haplotypes.

The first logistic regression model (Tab.1) indicated that three haplotypes: (DR3)–DQA1*0501–DQB1*0201, (DR4)–DQA1*0301–DQB1*0302 and (DR1)––DQA1*0101–04–DQB1*0501, increased the risk of diabetes statistically significantly 18.1, 12.3 and 3.4 times, respectively, while (DR11/12/13)–DQA1*05–DQB1*0301 haplotype decreased the risk of T1D 9.1 times.

Tab. 1. Logistic regression model for haplotypes predicting the likelihood of T1D mellitus

Haplotype	OR	95% CI	*P*
(DR1)–DQA1*0101–04–DQB1*0501	3.36	(1.27–8.86)	0.014
[DR2(DR15)]–DQA1*0102–DQB1*0602	0.000	–	0.998
(DR3)–DQA1*0501–DQB1*0201	18.06	(5.07–64.36)	< 0.001
(DR4)–DQA1*0301–DQB1*0302	12.31	(4.25–35.61)	< 0.001
(DR11/12/13)–DQA1*05–DQB1*0301	0.11	(0.03–0.38)	0.001

$\chi^2 = 134.53$, $df = 5$, n = 202; $P < 0.001$

In other logistic regression models, we included all environmental factors mentioned above that had significant associations with diabetes. The final logistic re-

gression model including environmental factors is shown in Tab. 2. The mother's residence during pregnancy in a village or remote house, eggs introduction in infant nutrition before 5th month of age and child infections during the last 6 months before diabetes onset significantly increased diabetes risk. Viral infectious such as rubella and varicella seemed to decrease the risk of T1D.

Tab. 2. Logistic regression model for environmental factors predicting or protecting the likelihood of T1D mellitus

Environmental factor	OR	95% CI	*P*
Mother's residence during pregnancy in village or remote house	6.46	1.74–23.94	0.005
Egg introduction before 5th month of age	3.70	1.77–7.75	0.001
Tetanus, diphtheria and pertussis vaccine	4.02	0.99–16.32	0.052
Varicella infection	0.47	0.22–0.97	0.042
Rubella infection	0.33	0.14–0.77	0.011
Infection during the last 6 months before diagnosis of T1D	3.85	1.79–8.27	0.001
Stressful event previous 6 months before diagnosis	2.38	0.85–6.62	0.097

$\chi^2 = 57.09$, $df = 7$, n = 187; $P < 0.001$

Finally, to several different regression models, we included environmental factors and different sets of risk and protective haplotypes (Tab. 3–5). These results are based on a quite small sample and show heterogeneous pictures of associations. Although sometimes statistically significant, they are difficult to interpret. Logistic regression analysis showed that living in a remote area with lower population density during pregnancy seemed to increase the risk, as well as short breast-feeding. Smoking during pregnancy as well as rubella and varicella infections rather seemed to decrease the risk of T1D. These associations were observed while evaluating only environmental factors and when different HLA haplotypes together with environmental factors were included in the regression model.

Tab. 3. Logistic regression model for protective haplotypes and environmental risk factors influencing the likelihood of T1D mellitus

Environmental factor	OR	95% CI	*P*
Mother's residence during pregnancy in a village or remote house	12.68	0.82–197.18	0.07
Total breast-feeding less than 3 months	3.41	1.09–10.62	0.035
At least one of the protective HLA haplotypes	0.003	0.001–0.03	<0.001

$\chi^2 = 104.59$, $df = 3$, $n = 145$; $P < 0.001$

Tab. 4. Logistic regression model for risk haplotypes and environmental protective factors influencing the likelihood of T1D mellitus

Environmental factor	Odds ratio	95% CI	*P*
Mother's smoking during pregnancy	0.07	0.01–0.93	0.04
Varicella infection	0.35	0.15–0.80	0.013
Rubella infection	0.33	0.13–0.82	0.017
At least one of the risk HLA haplotypes	23.30	9.37–57.93	< 0.001

χ^2=90.05, *df*=7, n=193; *P*<0.001

Tab. 5. Logistic regression model for grouped haplotypes and environmental factors predicting or protecting the likelihood of T1D mellitus

Environmental factor	Odds ratio	95% CI	*P*
Mother's residence during pregnancy in a village or remote house	17.74	1.41–222.99	0.026
Total breast-feeding less than 3 months	3.46	1.14–10.50	0.028
Rubella infection	0.19	0.06–0.64	0.007
Infection during the last 6 months before diagnosis of T1D	2.49	0.86–7.22	0.09
At least one of the risk HLA haplotypes	12.48	4.31–36.16	< 0.001
At least one of the protective HLA haplotypes	0.03	0.01–0.11	< 0.001

χ^2 = 151.39, *df* = 6, n = 191; *P* < 0.001

DISCUSSION

This study is important because of the specific situation in Lithuania regarding the low incidence of T1D as compared with other European, especially neighboring, countries. Even considering some limitations of this study, such as small sample size and the retrospective data collection with the risk of bias, the present study provides useful and essential information about T1D etiology.

The HLA typing shows that the differences in the incidence of T1D between Lithuania and neighboring European countries such as Sweden, Finland, Norway or Estonia [1, 7, 19, 28] cannot be explained only by genetics, but lifestyle and/or environmental factors should be considered. A number of studies have shown conflicting results regarding environmental factors and their associations with T1D. In some studies, long-term breast-feeding has been shown to have a protective effect [22], while other studies have not found such association [18]. Our study confirms that total breast-feeding for three months or less increased the risk of T1D only when other environmental factors and HLA haplotypes were included in logistic regression analyses. Some recent studies have confirmed associations between the early

introduction of cow's milk and development of diabetes [23, 30]. Other studies do not support such associations [18]. Early introduction of cereal, eggs and other solid foods may increase the risk of T1D too [20]. Our study showed no impact of early introduction of cow's milk or any solid food except for early introduction of eggs on the development of T1D. We found that living in an area with low population density was the factor increasing the risk of T1D mostly, which might fit into the "hygiene hypothesis" suggesting that less exposure to certain infection/antigens early in life might counteract the maturation of the immune system and increase the risk of autoimmune disease like T1D [5]. Anyhow, early contact with microbial antigens may prevent autoimmune diabetes [15]. However, data from other studies show conflicting results. Some studies proposed that residence in urban areas increased the risk of diabetes [8], while other studies found the lowest incidence of T1D in urban areas [11]. Possibly, our finding that smoking during pregnancy has a protective effect is related to the "hygiene hypothesis", or smoking has a direct effect on the maturation of the immune system [13]. Our results are in concordance with those of Svensson et al., who found that maternal smoking during pregnancy was associated with a decreased risk of T1D in the offspring [26].

Exposure to common infections during the first half year of life has been reported to be associated with reduced diabetes risk [15]. However, some viruses such as rubella and enteroviruses could directly destroy beta cells in susceptible individuals. Similarly, another study showed that only one of the childhood infections (morbilli, pertussis, rubella, etc.) was not related to diabetes risk [3]. In our study, we found that varicella and rubella infections in association with at least one of the risk HLA haplotypes in early childhood decreased diabetes risk. However, infections during the last six months before the onset of diabetes may increase diabetes risk [29]. Other studies have shown that only the most common infections may influence diabetes development [3].

Vaccinations have been proposed to protect against diabetes [4, 15] or increase the risk of diabetes [17]. No association between the risk of T1D and any of routinely recommended childhood vaccines was found.

Stressful events in early life or stress during the last half year have also been associated with an increased risk of T1D [6, 29]. Such events have been hypothesized to accelerate a pre-existing autoimmune process [6]. However, no associations between the development of diabetes and stressful events were observed in our study.

CONCLUSIONS

Environmental factors and lifestyle together with genetic predisposition certainly play an important role in the development of T1D, so etiology is complex. Our study showed that nutrition in early life as well as factors related to increased hygiene might contribute to T1D development. However, even quite rapidly ongoing changes of environmental factors and lifestyle in Lithuania have not helped us to reveal any clear picture.

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ORIGINAL PAPER

ERYTHROPOIETIN INCREASES Epo AND EpoR EXPRESSION IN DLD-1 CELLS

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ABSTRACT

Introduction. Supplementation of recombinant human erythropoietin (rHuEpo) is one of the methods for the treatment of anemia for patients with colon cancer. However, the results of *in vitro* studies investigating the influence of rHuEpo on cancer cells are contradictory.

Aim. The aim of the present study was an assessment of the effect of rHuEpo on proliferation, as well as Epo and EpoR protein expressions in normoxia and hypoxia conditions on human colon adenocarcinoma cells (DLD-1).

Materials and methods. The cells were cultured in medium with rHuEpo in concentrations of 1 and 3 IU without (normoxia) or with (hypoxia) cadmium chloride for 48 hours. Cell viability was counted using a haematocytometer and trypan blue 0.4% (w/v) dye. Expression of Epo and EpoR protein was assessed by western blot.

Results and Discussion. We observed a decrease in the number of colon cancer cells in hypoxia. Addition of rHuEpo did not modify cell numbers in normoxia and hypoxia. We found a significant increase of EpoR expression in all cells growing in medium with cobalt chloride in comparison with respective normoxic cells. We also noted that rHuEpo in concentration of 3 IU significantly increased expression of Epo and EpoR protein in colon cancer cells in normoxia and hypoxia conditions.

Conclusions. We concluded that Epo and EpoR are constitutively expressed in DLD-1 cells. In hypoxia as well as in the presence of rHuEpo the increase of Epo and EpoR protein was found. However, the expression of Epo and EpoR protein in these cells does not seem essential to their growth.

Key words: erythropoietin (Epo), erythropoietin receptor (EpoR), recombinant human erythropoietin (rHuEpo), colon cancer cells.

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INTRODUCTION

Erythropoietin (Epo) is a 30.4-kDa glycoprotein hormone produced and secreted in the kidneys of adults and in fetal liver in response to hypoxia as a 166-amino acid peptide [13]. During maturation a carboxy-terminal arginine in position 166 is removed resulting in a circulatory mature 165-amino acid protein. Endogenous as well as exogenous peptide (recombinant human Epo, rHuEpo) has the same composition [15]. The main physiological role of Epo is the stimulation of erythropoiesis. However, the results of numerous *in vivo* studies have shown that Epo protects against ischemia and trauma of the brain, retina, and spinal cord in animals [7, 8, 10]. Moreover, in *in vitro* studies it has been shown to stimulate angiogenesis, cell proliferations and vessel formation [15].

The effect of Epo is mediated by binding to the erythropoietin receptor (EpoR), the expression of which has been shown in nonhematopoietic cells and tissues such as endothelial cells, brain, female genital tract, placenta, myoblasts, kidney, intestine and various cancers [13]. EpoR is a transmembrane protein. The presence of EpoR in these cells may suggest the participation of Epo in autocrine or paracrine mechanisms. The binding of Epo to EpoR activates also others cascades that lead to the enhancement of proliferation, differentiation and survival [13, 16]. Thus, an endogenous Epo/EpoR system plays a prominent role in developing many tissues, including cancers.

In solid cancers, including colon cancer, Epo and EpoR expressions are mainly regulated by hypoxia via hypoxia inducible factors-1 (HIF-1) [1]. HIF-1 is composed of HIF-1A and HIF-1B and under normoxic as well as hypoxic conditions mRNA in both of them are constantly expressed in a number of mammalian cell lines. However, HIF-1A protein is markedly increased by hypoxia, whereas HIF-1B protein is constantly present regardless of oxygen tension [9]. Then, HIF-1A is the main regulator of Epo and EpoR expressions in hypoxic cancer cells.

In vitro studies investigating the role of Epo and Epo–EpoR signaling in tumor growth and angiogenesis have yielded contradictory results. Yasuda et al. observed the inhibition of angiogenesis and tumor cell survival in stomach and melanoma xenografts following the blockade of Epo–EpoR signaling [25]. These results are in opposition to the findings of Hardee et al. who did not observe any effects on angiogenesis and tumor growth in colon and head and neck xenografts after Epo administration [12].

AIM

At present in literature there have been no reports describing the influence of rHuEpo on human colon adenocarcinoma cells (DLD-1). Thus, the aim of our study was to estimate whether rHuEpo might directly affect human colon cells in normoxia and hypoxia. We also assayed the influence of rHuEpo on Epo and EpoR protein expressions in DLD-1 cells in normoxia and hypoxia conditions.

MATERIALS AND METHODS

Reagents

RPMI-1640 medium, fetal bovine serum, penicillin and streptomycin were obtained from ATCC (American Type Culture Collection, Manassas, VA, USA), RhEpo beta (NeoRecormon, Roche) was purchased from Roche (Basel, Switzerland) and cadmium chloride was provided by Sigma (Sigma-Aldrich, St. Louis, MO, USA).

Cell culture

DLD-1 cells were obtained from American Type Culture Collection (ATCC) and cultured in RPMI-1640 medium, supplemented with 10% fetal bovine serum (ATCC), penicillin (50 IU), streptomycin (50 μg/L) in humidified atmosphere (90% relative humidity) with 5% CO_2 at 37°C. The culture media were changed every two days. Cells were generally maintained in 75 cm^2 flasks (Sarstedt Inc., Newton, NC, USA) but for the experiments, they were plated onto 100-mm dishes (Sarstedt) with 6 mL of medium. The cells were incubated for a 24-hour period prior to treatment and allowed to proliferate to 70–80% confluence before the commencement of each experiment, without serum in RPMI-1640 medium. The control was media with PBS only. For all experiments, cells at the 5^{th} to 9^{th} passages were used.

Drug treatment

Prior to each treatment, DLD-1 cells were grown until they reached 50–60% confluence. Then the cells were treated with rHuEpo in the final concentration of 1 IU and 3 IU. Untreated cells were used as control. The incubation time was 48 hours.

Cell number

The DLD-1 cells (5×10^5 cells) were plated on 6-well cluster plates (Nunck, Denmark) in 2 mL medium, and cultured for up to 96 hours at 37°C. Cells were harvested by 0.25% trypsin treatment, and counted at each time point using haematocytometer. Samples were analyzed in triplicate at 48 hours after cell culture was initiated. Cell viability was expressed as a number of viable cells counted using a haematocytometer and trypan blue 0.4% (w/v) dye.

Western blot analysis for Epo, EpoR, and β-actin

Cells were lysed in NP-40 buffer consisting of 50 mmolar Tris-HCL (pH 8.0), 150 mmolar NaCl, 1% Triton X-100 and protease inhibitor cocktail (Roche). The lysate was centrifuged at $10\,000 \times g$ for 20 minutes at 4°C. An aliquot (10 μL) of supernatant was subjected to electrophoresis on a 10% SDS-PAGE, followed by transfer to 0.2 μm pore-sized nitrocellulose membrane (Bio-Rad) according to the method described in the manual accompanying the unit. Blots were blocked for 1 hour at room temperature with 5% non-fat milk (Bio-Rad) in Tris-buffered saline, pH 8.0 (Sigma-Aldrich).

The nitrocellulose was incubated overnight with: mouse anti-Epo (1:400), goat anti--EpoR (1:500), mouse anti-Actin (1:3000) antibodies from Sigma-Aldrich in TBS-T (20 mmol/L Tris–HCl buffer, pH 7.4, containing 150 mmol/L NaCl and 0.05% Tween 20). Secondary antibodies alkaline phosphatase conjugated were goat anti-mouse or rabbit anti-goat conjugated antibodies (Sigma-Aldrich) were added at concentration of 1:10 000 in TBS-T and incubated for 1 hour by slowly shaking. Then nitrocellulose was washed with TBS-T (2×10 min) and submitted to Sigma-Fast BCIP/NBT reagent. The intensity of the bands was quantified by densitometric analysis using Image J 1.37a software (National Institutes of Health, USA).

Statistical analysis

Shapiro–Wilk's *W*-test for normality was used for data distribution analysis. In all experiments, the mean values for six assays with standard deviation were calculated unless otherwise indicated. The differences between groups were estimated with the Tukey–Kramer Multiple Comparisons Test. If *P* value was less than 0.05, it was considered statistically significant.

RESULTS

We observed a significant decrease in the number of cancer cells in hypoxia in comparison to normoxia conditions. Medium with rHuEpo in concentrations of 1 and 3 IU did not indicate a significant impact on a number of these cells growing up under normoxia as well as hypoxia conditions. Also, no differences in the number of cancer cells were found in DLD-1 cells growing in medium with solvent of rHuEpo and control (Fig. 1).

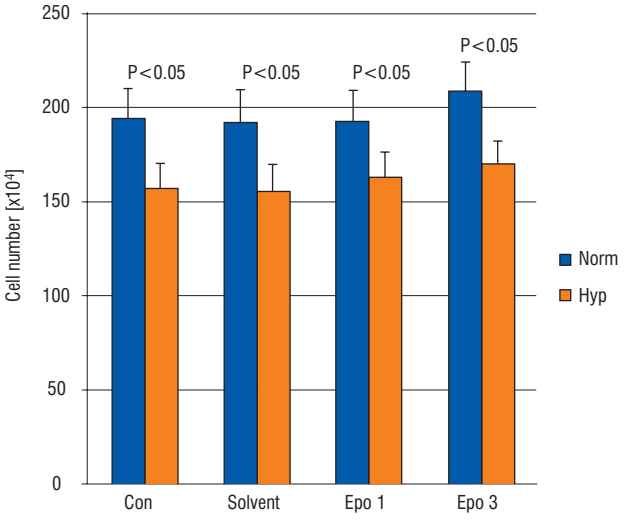

Fig. 1. Effect of rHuEpo on cell number in normoxia (21% of O_2) and hypoxia (250 μmolar $CoCl_2$).

A significant increase of Epo expression was observed in the cells growing in medium with 3 IU rHuEpo in comparison to control. The addition of $CoCl_2$ to medium also caused an increase of Epo expression in comparison to control as well as in comparison to group of cells growing in medium with rHuEpo in concentration of 3 IU in normoxia conditions (Fig. 2).

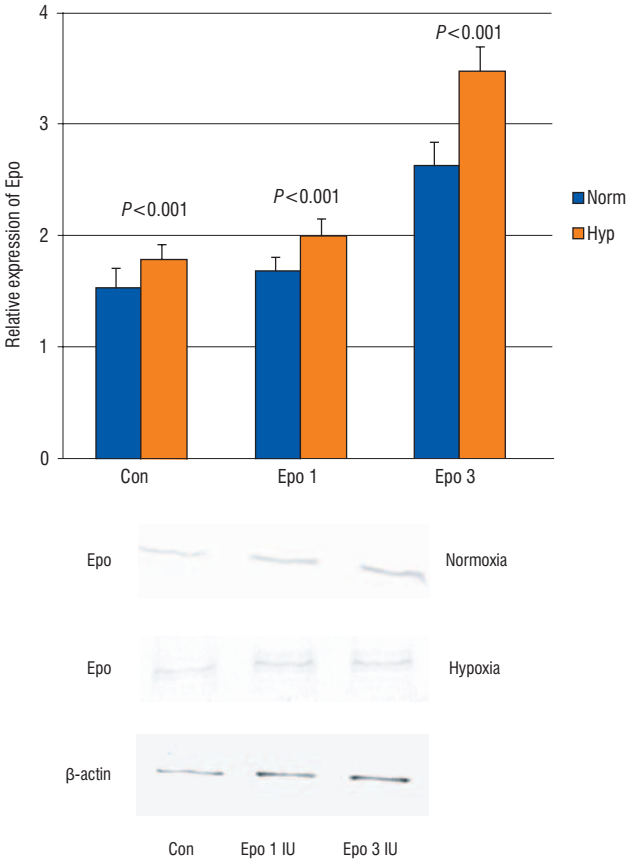

Fig. 2. Epo expression in DLD-1 cells treated with rhEpo in concentrations of 1 and 3 IU for 48 hours in normoxia (21% of O_2) and hypoxia (250 μmolar $CoCl_2$) conditions by western immunobloting.

In normoxia, an increase in EpoR expression was observed in cells growing in medium with 3 IU of rHuEpo in comparison to control. In all DLD-1 cells growing in hypoxia a significant increase of EpoR expression was found in comparison to the expression observed in cells growing without $CoCl_2$. In hypoxia, an increase in EpoR expression in cells growing in medium with rHuEpo in concentration of 3 IU was observed in comparison to control as well as to expression of EpoR occurrence in cells growing in medium with 1 IU of rHuEpo (Fig. 3).

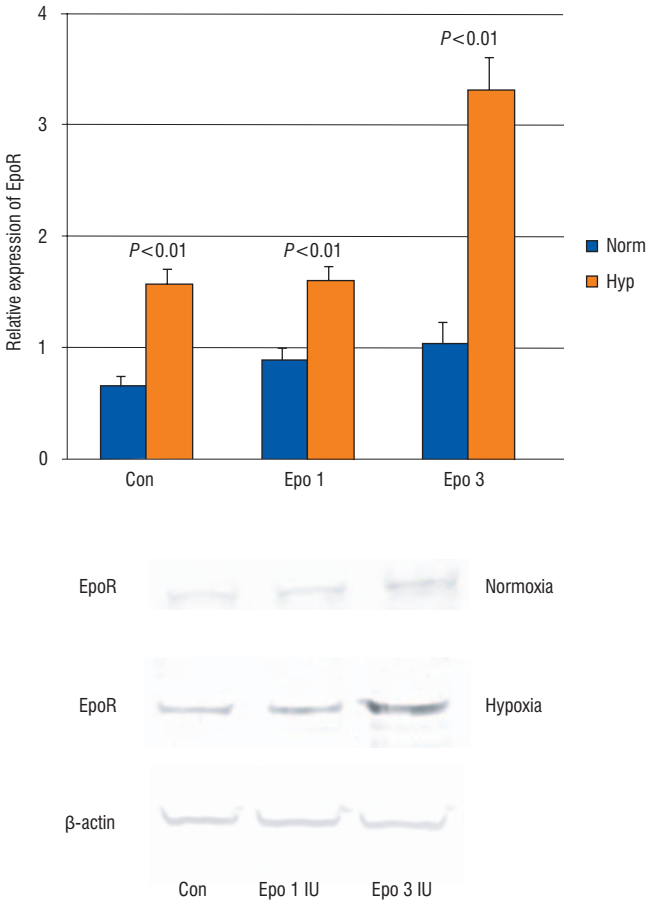

Fig. 3. EpoR expression in DLD-1 cells treated with rHuEpo in concentrations of 1 IU and 3 IU for 48 hours in normoxia (21% of O_2) and hypoxia (250 μmolar $CoCl_2$) conditions by western immunobloting.

DISCUSSION

The influence of rHuEpo on DLD-1 cells in normoxia and hypoxia conditions has not been studied yet. In the present study we observed that induction of hypoxia conditions by cobalt chloride caused a significant decrease in the number of colon cancer cells. The addition of rHuEpo did not modify the cell numbers in normoxia and hypoxia. In all cells growing in medium with cobalt chloride we observed a significant increase of EpoR expression in comparison with respective normoxic cells. We also found that rHuEpo in concentration of 3 IU significantly increased the expression of Epo and EpoR protein in colon cancer cells in normoxia. The same effect was observed in hypoxia conditions.

Our results are in line with the study of Song at al. who demonstrated that hypoxia inhibits cell proliferation. They postulated that the expression of HIF-1A and caspase-3 resulted in the production of the apoptosis of periodontal ligament cells [19]. Moreover, Yamamoto et al. showed translocation of a pro-apoptotic factor, Bax, from the cytoplasm to the mitochondrial membrane and induction by caspase-3--like activity-dependent apoptosis in response to hypoxia. At the same time, they observed a significant decrease in anti-apoptotic factors such as Bcl-2 and Bcl-xL in epithelial cells under hypoxic conditions [23]. However, the influence of hypoxia on the proliferation of cancer cells is not clear and some of the published results are apparently conflicting. Sahai et al. demonstrated that chronic hypoxia induces proliferation of proximal tubule cells mediated by the activation of protein kinase C (PKC) [17]. Yang and Kang found that suppression of HIF-1A gene results in a decrease of pancreatic cancer cell proliferation [24]. In turn, Volm and Koomägi did not observe a relationship between HIF-1A or HIF-1B and proliferation, but found a significant correlation between HIF-1 expression, apoptosis and the pro-apoptotic factors caspase-3, Fas, and Fas ligand [20].

In the next set of experiments, our objective was to determine the expression of Epo and EpoR protein. We proved the presence of Epo and EpoR protein in DLD-1 cells in normoxia and hypoxia conditions. The literature data showed no significant measurable Epo-specific binding activity on the surface of the head and neck squamous carcinoma cells in normoxia and a significant increase of EpoR expression in hypoxia and rHuEpo treatment [14]. On the other hand, another study reported EpoR expression in DLD-1 cells in normoxia conditions [4].

The presence of EpoR on the cancer cell surface may suggest a potential role of Epo in the activation of specific signal transduction of these cells. Indeed, Hammerling et al. demonstrated a 650% increase in the proliferation of erythroid cell line after administration of rHuEpo in pharmacologically relevant doses (0.01–0.4 IU) [11]. However, 68 tumor cell lines with no observed biological response to rHuEpo have been described [18]. Moreover, rHuEpo (dose range 0.01–100 IU) did not have an impact on human solid tumors (head and neck, lung, breast, stomach, colorectal, hepatocellular, pancreas, ovary, choriocarcinoma, osteogenic sarcoma, glioblastoma, neuroblastoma, prostate, renal) in *in vitro* experiments [6]. Further, another study demonstrated the absence of biological response of cancer cells to this peptide [5]. Therefore, in the next part of the experiments we studied the influence of rHuEpo on cell number as well as Epo and EpoR expressions. In our *in vitro* study we showed the lack of effect of rHuEpo in concentrations of 1 and 3 IU on DLD-1 cells in normoxia and hypoxia conditions. Similar results were achieved by Wang et al. who demonstrated no toxicity under normal conditions over a 48-hour period in retinal pigment epithelium cells treated with rHuEpo at concentrations of 0.001–100 IU/mL compared with control [21]. Also results of another study show that in hypoxia con-

ditions rHuEpo in concentration of 30 IU had no effect on head and neck squamous cells survival [14]. Thus, it seems that rHuEpo stimulates proliferation of hematological cancers but in the case of other tumors its effect depends on the types of cells and probably also on conditions of culture.

However, we found that an addition of rHuEpo to the growth medium led to an increase of Epo and EpoR expressions both in normoxia and hypoxia conditions. This observation is in line with findings published by Lo Nigro et al., who demonstrated that the addition of rHuEpo in culture medium increased EpoR expression [14]. Moreover, in an *in vivo* study a positive correlation between the semi-quantitative EPO score and the EPOR score in breast cancer tumor cells [2] and prostate cancer [3] was found.

In our *in vitro* study we proved the presence of EpoR in DLD-1 cells, but we did not observe evidence of the biological action of rHuEpo on these cells except for an enhancement of Epo and EpoR expressions. Westphal et al. suggested that only 60% of the newly synthesized EpoR is processed to the glycosylated receptor protein in the Golgi apparatus. It is possible that the performed staining showed both mature and also premature protein [22]. Thus, not all receptors detected by western blot possess biological activity and, despite an increase of EpoR expression, we did not observe any effects of rHuEpo.

CONCLUSIONS

We conclude that Epo and EpoR are constitutively expressed in DLD-1 cells. In hypoxia, as well as in the presence of rHuEpo, the increase of Epo and EpoR protein was found. However, the expression of Epo and EpoR protein in these cells does not seem essential to their growth.

ACKNOWLEDGMENTS

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ORIGINAL PAPER

INDIRECT COSTS OF BREAST CANCER IN LITHUANIA IN 2008

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ABSTRACT

Introduction. The costs of breast cancer constitute a huge economic impact on society. Indirect costs associated with breast cancer present a significant challenge to the health care system as well. This is primarily due to temporary and permanent disability, disability allowances and pensions or premature death.

Aim. The objective of this study was to estimate annual indirect costs of breast cancer from a societal perspective in Lithuania for the year 2008.

Materials and methods. A survey of 379 women treated in five major Lithuanian hospitals was conducted in the period of October 2008 – March 2009. Economic data concerning sick-leave and disability due to illness was gathered via survey; data on breast cancer mortality was obtained from the Lithuanian Health Information Center.

Results and Discussion. Productivity loss due to premature death reached €14.280 million, productivity loss due to morbidity amounted to €27.036 million – the major portion of these costs accounted for a production loss due to permanent disability. Temporary disability allowances and permanent disability pensions were estimated at €6.116 million and €8.550 million, respectively.

The paper also highlights the impact of the disease on the whole society and upon survivors personally. Decreasing the production losses due to breast cancer should be emphasized. Effective treatment strategies should be implemented in order to balance the costs of the disease.

Conclusions. Total indirect breast cancer costs, estimated from a societal perspective, reached €55.982 million in 2008 in Lithuania with an average annual amount

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of €5500 per breast cancer patient. Lithuanian budget losses in 2008 due to breast cancer morbidity amounted to €41.7 million, while €14.3 million were associated with premature deaths.

Key words: breast canceer, morbidity costs, mortality costs, cost-of-illnes study.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women worldwide, constituting approximately 23% of all cancer forms. According to WHO reports, over 1 000 000 new cases of cancer are annually diagnosed worldwide. The mean prevalence of breast cancer globally is 66.7 cases per 100 000 women. The highest morbidity is registered in the developed countries – especially in the U.S., whereas in Asian and African countries it is at the lowest level. In the year 2000 there were 350 000 new breast cancer cases in Europe, while the number of deaths from breast cancer was estimated at 130 000. Breast cancer is responsible for 26.5% of all new cancer cases among women in Europe, and 17.5% of cancer deaths [18]. According to the Lithuanian Cancer Registry, the respective number in Lithuania is approximately 1300 cases [11, 18]. Mortality from breast cancer in Lithuania reaches approximately 32 cases per 100 000 of the population.

Most often early-stage breast cancer is diagnosed in the developed countries. For a long time, the following trends predominated in Lithuania: in about 60% of patients – breast cancer was diagnosed in the early stage, and in about 40% of women – in the late stage [8]. Due to the implementation of the mammography screening program these rates have improved by 10% [15].

Increased incidence and declining mortality resulting from effective early diagnostics and modern treatment technologies generate huge expenditures. It is estimated that the costs for breast cancer treatment is increasing constantly and the costs of follow-up medical care, ongoing pharmaceutical needs and recurrences are also predicted to increase [3].

One of the most important tasks in health care system management is to reduce the economic burden of illness. It is obvious that health care system resources should not be allocated on the basis of disease costs, but rather according to the benefits of applied interventions. However, cost-of-illness studies provide essential information for a more thorough health economics evaluation analysis.

Cost-of-illness studies of a specific disease provide information on the cost structure related to that disease for a specific population in a well-defined geographical area (typically a one-year period) [7]. Cost-of-illness studies can track the current costs and predict future costs of the disease, demonstrate if disease requires increased allocation of prevention or treatment resources. They also represent an important

analytical tool in public health policy and may lead to an improved quality of health care [13]. Cost-of-illness study usually includes direct and indirect costs. The term of indirect costs in health economics mainly involves the quantification of lost productivity due to illness, premature retirement and death. This means that we have to deal with the economic impact of disease on society and the national economy.

In breast cancer, indirect costs are substantial and can be significantly larger than direct costs – depending upon the country, they may constitute up to 70% of total costs [9]. Due to the high disease incidence rate in women under 65 years of age and the correspondingly high indirect costs resulting from disability, disability pensions or premature death, indirect costs associated with breast cancer present a significant challenge to the health care systems [4]. Thus, annual cost estimates are very important in evaluating the burden of the disease and educating policy-makers.

Published research for the years 2000–2010 on breast cancer costs vary widely in methodology, perspective, patient populations and time horizon. Some studies have measured all costs of breast cancer [9, 12, 16], other concentrated on breast cancer direct treatment costs [1, 10, 17, 19] and only a few analyzed the indirect burden of illness to society and patients [5, 14]. The latter studies show that indirect costs cover a substantial part of total costs due to disease onset at a relatively young age and related disability.

To our knowledge, there are no studies covering the Baltic states estimating the indirect costs of breast cancer. Such a study would offer valuable information for health authorities concerning the impact of the disease and would serve as part of the framework for upcoming breast cancer economic evaluations.

AIM

The objective of this study was to estimate annual indirect costs of breast cancer from a societal perspective in Lithuania for the year 2008.

MATERIALS AND METHODS

Study type and participants

A cross-sectional observational survey in five major Lithuanian hospitals was conducted from October 2008 to March 2009. Target population and inclusion criteria were as follows: breast cancer patients who attended hospitals or outpatient clinics for treatment or consultations, having been diagnosed with breast cancer at least six months prior to participation in the study. Prevalence based sample size was calculated referring to breast cancer morbidity rates in Lithuania in 2005 (10 178 breast cancer patients in 2005 – the latest information available at the time of the study) and general population size in Lithuania in 2005. Study response rate was 95% – 379 out of 400 randomly chosen women from hospital registries agreed to participate in the study. Instrument used: a self-administered economic data questionnaire, developed by the authors.

Data collection methods

This study estimated indirect breast cancer costs from a societal perspective in Lithuanian for 2008. The costs presented here are annual prevalence-based costs, based on data obtained from the survey, the Lithuanian Health Information Center, the Department of Statistics to the Government of the Republic of Lithuania and the State Social Insurance Fund Board.

The cost-of-illness analysis included an estimation of annual indirect costs from a societal perspective – labor productivity loss due to illness (stemming from early mortality and morbidity). We decided to interpret the concept of indirect costs as follows: the monetary expression of time lost due to treatment, morbidity and mortality.

The study was carried out using the human capital approach, assuming that when a worker is leaving a labor market, productivity is lost until the return to work (in case of temporary disability) or until the end of a working life (in case of permanent disability) and the value of production of an individual is considered at market price [6].

Costing

The data for estimating breast cancer morbidity and mortality costs was gathered from the survey. The estimation of budget losses due to temporary sickness was based on average sickness allowances for 2008 from the same source as above. Then, the survey data was extrapolated to the national level, relying upon breast cancer morbidity data from the National Cancer Registry. The estimation of budget losses due to permanent disability allowances was based on average work incapacity pensions for 2008 from the State Social Insurance Fund Board. The valuation of lost production due to morbidity was based on gross domestic product (GDP) values for Lithuanian inhabitants for 2008.

Morbidity Costs

Morbidity associated costs were assessed by questionnaire in the sample of breast cancer patients. The questionnaire included questions about the breast cancer stage, employment status, permanent disability status, work capacity level, average number of days lost due to breast cancer and others. The obtained data enabled us to calculate the societal burden – annual production quantities that were not created due to illness – lost of GDP value due to decreased activity in the labor market and disability allowances from the State Social Insurance Fund Board due to temporary and permanent disability.

GDP value loss due to temporary disability was calculated in the following way: women of employable age, active in the labor market and missing some days of work due to breast cancer, were identified from the whole survey population – 233 out of 379 (61.48%) were of employable age, 186 out of 233 (79.83%) were employed, and 135 women out of 186 (72.58%) confirmed having sick-leave due to breast cancer. Then, these numbers were extrapolated to the national basis and the presumption was made that 3 625 working breast cancer survivors of employable age might be ex-

periencing sick-leave and missing some days of work due to illness. Next, the average number of missed days per year was multiplied by average GDP value per inhabitant in a year in Lithuania for 2008 (GDP value in 2008 was €9 590).

GDP value loss due to permanent disability was calculated in a similar way: according to survey results, 208 (54.88%) out of 379 women confirmed having permanent disability. 164 women out of 208 (78.78%) were of employable age, and 36 out of 164 (21.95%) were not active in the labor market and not contributing to GDP. Accordingly, survey data was extrapolated to the national level and the presumption was made that 2 234 women of employable age with permanent disability were not active in the labor market in Lithuania in 2008. Then, this number was multiplied by the average GDP value per inhabitant in a year in Lithuania for 2008.

Budget loss due to permanent disability pensions was estimated as follows. According to survey results – 208 (54.88%) out of 379 women confirmed having permanent disability and receiving permanent disability pensions, 161 out of 208 (77.40%) were of employable age. This means that nationally 4 323 breast cancer patients might have had permanent disability in Lithuania in 2008. Next, the sample was distributed according to permanent disability levels. Average pensions due to disability are categorized into three groups: 75–100% of decreased work capacity (I level), 60–70% of decreased work capacity (II level) and 45–55% of decreased work capacity (III level). In 2008 average permanent disability pensions accordingly were €151, €131 and €71 per month. The number of persons with permanent disability in each disability level was multiplied by average disability pensions.

Budget loss due to temporary disability allowances was estimated, based on information about average sick-leave allowances, adjusted by number of workdays missed due to illness and the average female gross wage in Lithuania for 2008 (€585.22). 186 (or 49.08% out of 379) women reported that they were active in the labor market, 135 (or 72.58% out of 186) reported that they missed some workdays during the past month and 75 (55.55%) of them reported that they missed more than 2 days – the rest were excluded from the analysis, because the first 2 days of sick-leave are not covered in the insurance fund. Accordingly, an extrapolated number of 2 774 patients was analyzed. The average number of workdays lost was evaluated using survey results and then the data was extrapolated to the national level. Temporary disability allowances were estimated, controlling the figures by a different allowance range (it depends on the number of workdays missed) and average female gross wage. Also, due to the fact that temporary disability allowances are rewarded from the 3rd day of illness, patients who missed 1 or 2 days in a month, were excluded from the analysis. The remaining data was categorized in two levels: patients, who missed 3–7 workdays (receiving 40% of average monthly wage) and patients, who missed more than 7 workdays (receiving 80% of average monthly wage).

Mortality costs

Data on deaths caused by breast cancer was obtained from the Lithuanian Health Information Center under the Ministry of Health. The total number of breast cancer death cases in Lithuania in 2008 was 602.

Years of potential life lost (YPLL) were estimated. The calculation was based on women's average life expectancy (77 years in Lithuania for 2008). We also estimated the years of potential productive life lost (YPPLL) based on a retirement age of 60, average female wages, standardized by employment rates by age groups in 2008. After the age of 60, YPPLL were not estimated. The total number of deaths including patients who died before the age of 60 in Lithuania in 2008 was adjusted by age groups and employment rates in Lithuania for 2008, and the loss of possible GDP value was estimated by multiplying YPPLL by the average GDP value per inhabitant, per year. Societal costs due to early mortality were estimated by adjusting the number of deaths by female employment rate according to the National Residents Employment Study data. All costs due to early mortality or sickness were estimated as the present monetary value of the lost productive time.

RESULTS

The analysis of production losses due to temporary and permanent disability was intended to be exploratory. The response rate to different questions in individual economics survey ranged from 80 to 95%. For our sample of 379 women, the weighted mean age was 57 (SD ±19) years. Regarding education, 61.5% of the study participants confirmed to have basic education and 25.1% had a university education. Occupation characteristics were distributed in the following way: almost equal numbers of women were identified as full-time employees and retirees – 24% and 31%, respectively. According to breast cancer stage distribution, 76.1% of studied samples were diagnosed with early stage (0–II) and only 23.9% were in an advanced stage (III–IV) of breast cancer.

Morbidity costs (temporary and permanent disability costs)

GDP value loss due to temporary and permanent disability costs was estimated according to estimation methods described in the Costing section. The results of calculations are presented in Tab. 1 and Tab. 2. GDP value loss in 2008 due to temporary and permanent disabilities, reached a total amount of €5.612 million and €21.424 million, respectively.

Tab. 1. Lost GDP value due to temporary disability in Lithuania for the year 2008

Estimated rates	Results
Number of women of employable age, active in the labor market – extrapolated data	4995
Number of employed women, who missed some workdays due to illness during the past month of survey – extrapolated data	3625

Average number of workdays missed – per patient/ per year	58.92
Average GDP per inhabitant in 2008	9590
Average lost state capital due to temporary illness per year – extrapolated data, without discount rate	€5.612 million

Tab. 2. Lost GDP value due to permanent disability in Lithuania for the year 2008

Estimated rates	Results
Number of women of employable age, with permanent disability – extrapolated data	5586
Number of women of employable age, with permanent disability, not active in the labor market – extrapolated data	2234
Average GDP per inhabitant/ per year	9590
Average lost state capital due to permanent disability per year – extrapolated data, without discount rate	€21.424 million

Estimations of budget losses due to temporary disability allowances and permanent disability pensions are presented Tab. 3 and Tab. 4. Annual societal burden of breast cancer in this situation is quite significant, making a total amount of €14.5 million, covered from the State Social Insurance Fund Board. Based on survey data, women, receiving temporary disability allowances due to breast cancer, tend to have a shorter sick-leave – 74.67% of the breast cancer population is absent from work for an average number of 4.88 days per month. Almost €4.5 million per year is paid for temporary disability allowances for a selected group of women missing more than 7 days of work per month.

Tab. 3. Average temporary disability allowances (from the State Social Insurance Fund perspective) due to illness for the year 2008

Number of cases of temporary disability adjusted to number of missed workdays per month due to illness – according to survey (out of 75)	Average temporary disability allowances per person, per year – according to average gross female wage in 2008 (€)	Estimated number of women with temporary disability according to number of missed workdays due to illness per month in Lithuania (out of 2774) – extrapolated data	Average total temporary disability allowances in 2008 – extrapolated data (€)
56 or 74.67%*	760.80	2 071 or 74.67%*	1.578 million
19 or 25.33%**	6455.88	703 or 25.33%**	4.538 million
Total: €6.116 million			

* missing 3–7 workdays per month, 40% salary coverage; ** missing more than 7 workdays per month, 80% salary coverage

Tab. 4. Average permanent disability pensions in Lithuania due to breast cancer, for the year 2008

Number of women with permanent disability due to breast cancer (out of 208) – survey results	Estimated number of women with permanent disability due to breast cancer in Lithuania (out of 5585) – extrapolated data	Assigned disability group, decreased work capacity level (%)	Budget losses due to paid permanent disability allowances (€)
22 (10.58%)	590 (10.58%)	I level (0–25% work)	1.069 million
167 (80.28%)	4483 (80.28%)	II level (30–55%)	7.047 million
19 (9.13%)	509 (9.13%)	III level (60–100%)	433.668
Total: €8.550 million			

Presumably, almost half of all breast cancer patients have been awarded with permanent disability pensions in Lithuania, 2008. The greatest number of them (about 80%) have been assigned with 30–55% work capacity level and received a total amount of €7 million permanent disability pensions per year.

Mortality costs

In Lithuania 602 patients died from breast cancer in 2008. The distribution of deceased breast cancer patients by age in Lithuania in 2008 revealed that most of deaths occurred in patients aged 45–64 years (242 or 40.2%). A woman's average life expectancy was 77 years in Lithuania in 2008 [23]. Considering the total number of life years lost due to premature death from breast cancer, the YPLL were estimated. The number of YPLL constituted an average of 12.5 years for each prematurely dead breast cancer patient. The total number of YPLL reached 7526 in Lithuania for 2008. Calculating YPLL, all premature deaths of employment age were included in the analysis, starting from the death at the youngest age (the youngest productive person who died from breast cancer in 2008 was 31 years old), and ending with the age of legal retirement (60 years old). After the age of 60, YPPLL were not estimated. The total number of deaths including patients who died before the age of 60 in Lithuania in 2008 was 201.

Indirect costs due to early mortality were estimated by adjusting data by female occupation rates in certain age groups. This is essential, because not all persons with breast cancer at an employable age are active in the labor market. According to our study, the employment rate decreased with increasing age – about 82% of women of employable age were active in the age group 30–49, but only 65% were working in the age group of 55–59 years. For breast cancer, average additional indirect costs due to premature mortality adjusted by employable age, employment rate within age groups in Lithuania, 2008 (data from the Department of Statistics to the Government of the

Republic of Lithuania) were 9.86 YPPLL and €69 249 per patient. The total number of deaths adjusted by occupation rate within age groups reached 151, forming a total amount of 1489 YPPLL. The monetary value of these results is presented in Tab. 5.

Tab. 5. Indirect costs due to early mortality from breast cancer in Lithuania in 2008

Estimated rates	Results
Number of deaths of women of employable age	151
YPPLL – calculated till the end of employable age of 59 years, adjusted by occupation rate within age groups	1489
Average GDP per inhabitant in 2008 (€)	9590
Production loss due to premature death (€)	14.280 million

Total indirect breast cancer costs in Lithuania reached €55.982 million in 2008 and an average annual amount of €5 500 per breast cancer patient (Tab. 6). Productivity loss due to morbidity had the most significant impact on the structure of costs, forming about 50% of all indirect costs.

Tab. 6. Indirect costs due to breast cancer in Lithuania for 2008

Source of indirect costs	Average indirect costs for Lithuanian breast cancer population – extrapolated data, discounted value of money (€)
Productivity loss due to premature death	14.280 million
Productivity loss due to morbidity	27.036 million
Budget loss for temporary disability allowances	6.116 million
Budget loss for permanent disability pensions	8.550 million
Total: €55.982 million	

DISCUSSION

This is the first breast cancer economic evaluation in Lithuania. This study calculated annual additional indirect costs from a societal perspective in Lithuania for 2008. Our analysis, based on different data sources, quantified the socio-economic impact of breast cancer. The study followed the most common definitions of indirect costs, used in health economics theory. We recognize a variety of methodological difficulties and limitations in the study. The evaluation of indirect costs due to permanent and temporary illness might have been estimated more accurately if the data had

been obtained from the National Social Security Fund information system instead of the survey. Also, in order to estimate unbiased additional indirect costs of work absence due to disease, it would be advisable to compare the production loss of the breast cancer population with the standard population. The representative sample studied was based on women who were treated or consulted in hospitals during the time of the study, omitting patients from nursing homes – therefore, some limitations to precise sample sizing may be possible.

According to our study, total indirect breast cancer costs in Lithuania reached €55.982 million. Budget losses from a societal perspective associated with breast cancer morbidity were three times higher than those associated with premature deaths (€27.036 million and €14.280 million, respectively). Budget losses due to temporary disability allowances and permanent disability pensions accounted for the total amount of €14.5 million. The major part of the money spent on temporary disability allowances is paid to patients missing more than 7 days of work per month – almost €4.5 million per year are spent from the budget for this reason. This might be explained by the fact that the surveyed women, active in the labor market, and having a sick-leave for more than 7 days, reach an average number of 20.26 days missed from work. Early diagnostics, modern cancer treatment technologies and health care system organization should assist in improving this situation, by enabling women to reach a better health status and to live full-quality lives in an occupational sense as well.

Our study results highlighted the fact that breast cancer GDP value loss due to permanent disability in Lithuania in 2008 was four times higher than the loss due to temporary disability. There might be a reason explaining this situation: breast cancer survivors assigned with permanent disability level and not working at all, were not creating production for the whole year, meaning that the losses were increasing day to day.

It is very difficult to compare the study results with other studies due to differences in methodologies used, breast cancer population size and socio-economic settings. Studies, estimating indirect costs of breast cancer revealed the following results: amount of $1.15 billion for premature mortality losses was stated for California in 2001 [12], €288.73 million associated with total indirect costs (costs of premature mortality, temporary and permanent illness included) for Spain in 2003 [14], and estimations at 2.1 billion kronors for breast cancer indirect costs for Sweden in 2001 [9]. Indirect costs per one breast cancer patient in different studies range from $4221 in Australia in 2005 [5] up to €15 903 in Flanders during 1998–2003 [2] and €5500 according to our analysis. The study, performed in Flanders, revealed that the average number of workdays lost due to disease, was 47.2 per patient/ per year, and 58.9 days respectively according to our analysis. Costs, estimated in our analysis, may be used for determining priorities in health care policy and may serve as a framework for further economic evaluation. The paper highlights the impact of the disease on the whole society and upon survivors personally. Decreasing the production losses

due to breast cancer should be emphasized. Effective treatment strategies should be implemented in order to balance the costs of the disease.

CONCLUSIONS

Total indirect breast cancer costs, estimated from a societal perspective, in Lithuania, reached €55.982 million in 2008 with an average annual amount of €5500 per breast cancer patient. Budget losses in 2008 due to breast cancer morbidity were €41.7 million, while €14.3 million were associated with breast cancer premature deaths.

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ORIGINAL PAPER

THE INFLUENCE OF SPECIALIST KINESITHERAPY ON THE SPINAL FUNCTION AFTER FENESTRATION SURGERIES

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ABSTRACT

Introduction. Back pain is a significant social problem. Etiology of back pain is multifactor. The majority of pathologies resulting in neurological symptoms lead to a surgical procedure. One of the most frequently used surgical procedures for the lumbar region of the spine is fenestration. A surgery resolves a mechanical problem, but often does not improve the functional one. A large group of patients, if not treated with specialist rehabilitation, continue to feel pain in the lumbar region or in the lower extremity.
Aim. The aim of this work was to point to the necessity of applying modern kinesitherapy for relieving pain after fenestration surgeries performed on the spine.
Materials and methods. Group of 18 patients, including 15 women and 3 men, within ages ranging from 25–59 (mean age 39.1) were qualified for individual therapies. The patients came to the Rehabilitation Outpatient Clinic complaining of pain after fenestration surgeries performed at the University Hospital in Olsztyn. All patients underwent spine surgery and the interval period between the procedure and coming to the Clinic was from 0.5 to 1 year. The procedure was performed at L4–L5 level in 13 patients, and at L5–S1 level in 5 cases. Lasègue's sign, numerical pain rating scale (NRS), finger-to-floor test (spinal flexion) were analyzed.
Discussion. Our study indicates that surgery should be followed by specialist therapy focused on regaining stability of the lumbar region via involving deep muscles: transversus abdominis muscle and multifidus muscle and stimulating nerve and muscle fibers to be mobilized in the ailing extremity in order to improve motor control of the lower back.

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Results. On release from hospital, in terms of neurosurgical and orthopedic recommendations, the patients were advised to exercise in the gym and go to the swimming pool 2–3 times a week, whereas no specialist rehabilitation was recommended. As a result, 3 months following their surgeries, all studied patients reported lower extremity weakness, pain when walking down stairs, numb sensation in toes, pain in the L–S area when seated longer than one hour. The performed examinations revealed that before the therapy, Lasègue's sign was 30–60° (mean 51.9°), whereas after a 3-month long therapy, the range of motion was about 45–90° (mean 68.6°). According to the NRS, patients evaluated their pain levels before the therapy as 4–8 points (mean 6.11 points), whereas after therapy as 2–6 (mean 3.44). Before the therapy, a finger-to-floor test yielded the floor distance of 26–54 cm (mean 37.8 cm), after therapy the distance decreased to 17–48 cm (mean 28.6 cm). Due to the employed specialist therapy, in 17 patients pain ailments relief was observed. The patients did not report problems when moving about on uneven ground. They observed a functional improvement concerning everyday life activities. Functioning at work was easier in a sitting position and the efficiency of performed activities less burdensome than before specialist kinesitherapy.
Conclusions. The 3-month long specialist kinesitherapy relieves pain and improves the range of motion in the lower extremity. The suggested program of kinesitherapy improves spinal flexion and static efficiency in a sitting position. Recommending specialist rehabilitation after neurosurgical procedures is essential.

Key words: spine, fenestration, kinesitherapy, pain.

INTRODUCTION

Back pain is a significant social problem. Etiology of back pain is multi-factor. Some authors claim that the reason involves overloading changes leading to muscle and ligament insufficiency [2]. Others believe that the development of pain is closely correlated with the intervertebral disc pathology [8, 9]. Advanced pathologies of the intervertebral disc or anulus fibrosus lead to functional disorders of the neuromuscular system in the damaged area, to neurological pain radiating to a particular dermatome, as well as to dermatomal exteroceptive sensibility disorders, and deep reflex weakening or loss [7]. The majority of pathologies resulting in neurological symptoms lead to a surgical procedure. One of the most frequently used surgical procedures for the lumbar region of the spine is fenestration. This surgery resolves a mechanical problem, but often does not improve the functional one. A large group of patients, if not treated with specialist rehabilitation, continue to feel pain in the lumbar region or in the lower extremity [7, 13].

AIM

The aim of this work is to point to the necessity of applying modern kinesitherapy for relieving pain after fenestration surgeries performed on the spine.

MATERIALS AND METHODS

Group of 18 patients, including 15 women and 3 men, within ages ranging from 25–59 years (mean age 39.1) were qualified for individual therapies. These patients came to the Rehabilitation Outpatient Clinic complaining of pain after fenestration surgeries performed at the University Hospital in Olsztyn. All patients underwent spine surgery and the interval period between the procedure and coming to the Clinic was 0.5–1 year. The procedure was performed at L4–L5 level in 13 patients, and at L5–S1 level in 5 cases. Patients complained of pain involving the spine and lower extremity.

Medical histories indicated that before surgeries all patients suffered from neurological pain radiating to the lower extremities combined with neurological symptoms and strong pain assessed to be 7–9 in the numerical rating scale (NRS). Before surgical treatment no neurological deficits, such as foot drop, were noted. Immediately following the surgeries, patients noticed pain relief in the lower extremities and back. On release from hospital, in terms of neurosurgical and orthopedic recommendations, the patients were advised to exercise in the gym and go to the swimming pool 2–3 times a week, whereas no specialist rehabilitation was recommended. As a result, three months following their surgeries, all studied patients reported lower extremity weakness, pain when walking down stairs and moving about on uneven ground, numb sensation in toes, pain in the L–S area when seated longer than 1 hour. Pain ailments significantly intensified after the return to professional work. Because of the reported symptoms, patients were qualified for specialist kinesitherapy.

During their first visit before undertaking therapy, patients were tested with Lasègue's test to assess their range of mobility and the sensitivity of nervous structures in the lumbar and sacrum regions of the spine. Patients were lying on their backs, while their lower healthy extremities were lifted by the examiner, followed by a lifting of the ailing ones, while the knee was straight. The lower extremity was lifted until the first pain sensation or excessive symptoms of stretching in the entire limb were felt. The range of mobility was evaluated by a goniometer and noted on the examination form in degrees. After noting the Lasègue's sign for all patients, we performed the flexion of the knee and hip in order to detect problems signaling hip joint pathology. In all the studied patients, after the flexion of the ailing extremity in the knee and hip joints, ailments decreased or were entirely relieved. In the study group deficits in the ailing lower extremity were noticed. The range of pain was evaluated via the NRS, in which self-assessment of pain was rated from 0 to 10 points. In this scale, lack of pain is rated as 0, whereas 10 refers to pain of the highest intensity. The finger-to-floor test was also applied to measure spinal mobility and mobility in the hip joints, as well as functional

possibilities for patients in the flexed position. Patients were told to bend forward as far as they could or until they felt the first pain sensation. While bending, the distance between the middle finger and floor was measured in centimeters. All the parameters were taken again after the completed therapy.

After the examinations, the patients were offered a 3-month long specialist therapy. They were to practice personally customized exercises at home every 3 hours (Fig. 1). Twice a week, therapeutic progress was consulted at a specialist outpatient clinic, and functional improvement was controlled.

1

2

3

Fig. 4. Personally customized exercises consisted of: 1. Sensomotor exercises with a corrective cushion; 2. Mobilization of the pelvis on the Pezzi ball; 3. Strengthening the lower extremity with Thera bands

The 3-month long specialist therapy involved:
- patient's education;
- internal stabilization via transversus abdominis muscle and multifidus muscle training, introduced as one of the first and key elements of the therapy;
- exercises mobilizing the ischiadic nerve;
- postisometric relaxation exercises of the biceps femoris muscles, semimembranosus muscles, semitendinosus muscles, piriformis muscle and iliopsoas muscle;
- exercises improving spinal mobility, initially directed at the scar, i.e. hyperextension movement, followed by an opposite direction movement, i.e. flexion movement;
- external stabilization via postural muscles training, from low positions to middle and erect;
- sensomotoric training on mobile ground (corrective cushions, balls);
- functional training with erect positions to prepare for professional work.

RESULTS

The performed examinations indicated that before the therapy, Lasègue's sign was 30–60° (mean 51.9°), whereas after a 3-month long therapy, the range of motion was about 45–90° (mean 68.6°) (Fig. 2).

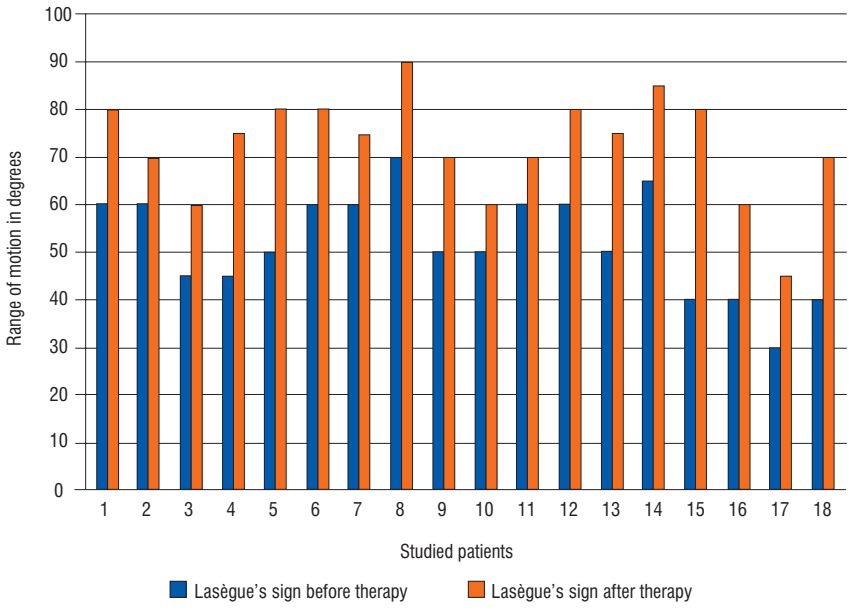

Fig. 2. Lasègue's sign before and after therapy

According to the NRS, patients evaluated their pain levels before the therapy as 4–8 points (mean 6.11 points), whereas after therapy as 2–6 (mean 3.44) (Fig. 3).

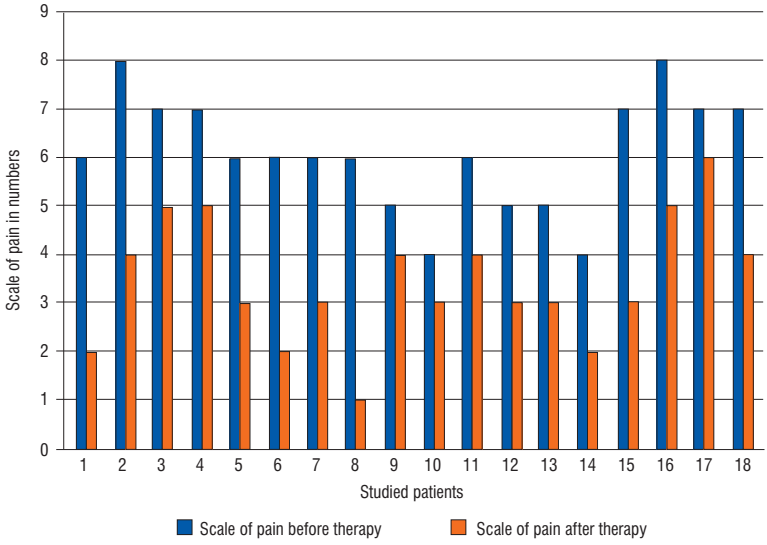

Fig. 3. Numerical rating scale of pain before and after therapy.

Functional possibilities in the flexed position were measured by a finger-to-floor test. The first pain sensations were observed when the floor distance was 26–54 cm (mean 37.8 cm), after therapy this distance decreased to 17–48 cm (mean 28.6 cm) (Fig 4.).

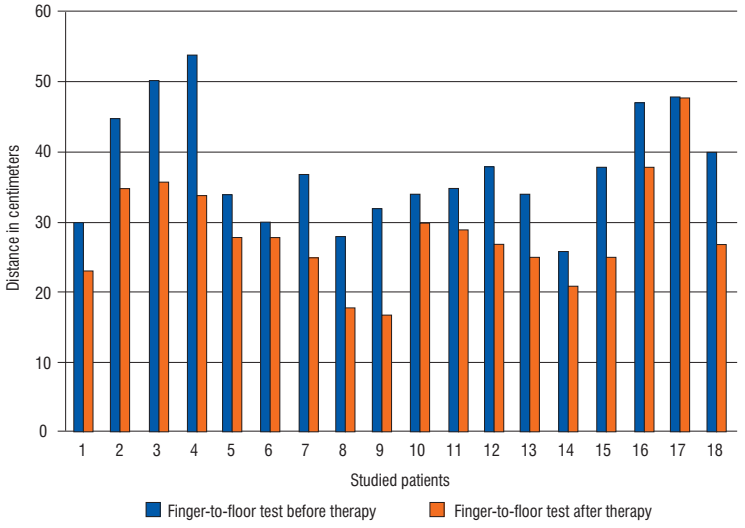

Fig. 4. Finger-to-floor test before and after therapy.

Due to the employed specialist therapy, in 17 patients pain ailments relief was observed. The patients did not report problems with moving about on uneven ground.

They observed a functional improvement concerning everyday life activities. Functioning at work was easier in a sitting position and the efficiency of performed activities less burdensome than before specialist kinesitherapy.

DISCUSSION

Due to a more thorough diagnostics and availability of imaging examinations a large number of patients are operated on in an early stage of discopathy [4, 7]. Many patients, while deciding upon a surgery, believe that pain ailments will disappear directly as a result of a surgical procedure. Frequently, rehabilitation ordered by neurologists and orthopedists in hospital is limited to tilting a patient to an erect position or providing some advice to educate a patient concerning everyday life functioning [5]. The most frequently advised activities involve swimming and general conditioning exercises. Many authors believe [2, 3, 6, 10], that the transversus abdominis muscle is very important in stabilizing the lower region of the back. The transverse plane picture of this muscle changes as soon as the first pain sensations appear. The mechanism of this muscle atrophy begins much earlier. Before a surgery, pain leads to the weakening of low back motor control, delayed activation or weakening of the transversus abdominis muscle, and, consequently, an ineffective muscular stability of the spine. As a result of these pathological changes, spinal cord reflexes are also weakened [3, 4].

Our study indicates that surgery should be followed by specialist therapy focused on regaining stability of the lumbar region via, in the first place, involving deep muscles: transversus abdominis muscle and multifidus muscle. It is also important to stimulate nerve and muscle fibers to be mobilized in the ailing extremity in order to improve motor control of the lower back. The inclusion of exercises which force the stability of deep muscles and improve lower extremity muscles strength enhances the sensation of lumbar region stability as felt by patients. Striving for movement symmetry and activating sensomotor functions make it possible to integrate the neuromuscular system faster and more efficiently, and consequently, to improve the everyday functioning of patients who have undergone fenestration surgeries. Sensomotor exercises improve back stability, coordination and movement efficiency. Sensomotorics is an important element of kinesitherapy because it forces additional work on a body in movement to account for gravitation [10].

The analysis of our study results indicates that an adequate kinesitherapy program improves patients' static efficiency in a sitting position. Before therapy, patients could adopt a sitting position without intensifying pain ailments on average for about 1 hour. After a 3-month specialist kinesitherapy this period was prolonged to 3 hours. After the therapy 5 patients did not feel any pain in everyday functioning. Periodically, a pulling pain in the lumbar region appeared in three patients. In 4 cases, a pulling pain was reported in the calf area, along the peroneus muscles, and in 2 patients there appeared, sometimes, short-time pulling in the hallux; 1 patient in the study group complained of

frequent calf cramps at night. Night cramps intensified at the time when more difficult exercises were introduced. 1 patient in the study group did not make almost any visible therapeutic progress and did not wish to continue the therapy.

CONCLUSIONS

1. The 3-month long specialist kinesitherapy relieves pain and improves the range of motion in the lower extremity.
2. The suggested program of kinesitherapy improves spinal flexion and static efficiency in a sitting position.
3. Recommending specialist rehabilitation after neurosurgical procedures is essential.

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ORIGINAL PAPER

EVALUATION OF THE EFFECTIVENESS OF CHÊNEAU BRACE TREATMENT FOR IDIOPATHIC SCOLIOSIS – OWN OBSERVATIONS

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ABSTRACT

Introduction. Progressive nature of scoliosis significantly affects the development and functioning of a young organism. The extensive interest of medical experts in spinal deformities stems from their high incidence in the population of youth (2–3%), health consequences resulting from the disease progression as well as high economic and social costs.

Aim. Evaluation of the effectiveness of the Chêneau brace in the treatment of idiopathic scoliosis**.**

Materials and methods. The research material comprised 302 patients treated in the Chair and Teaching Hospital of Rehabilitation and the Provincial Children's Hospital in Ameryka near Olsztyn, for idiopathic scoliosis, ranging in ages from 8 to 17. The observation period was from 2 to 5 years. Qualification for orthopedic brace was conducted according to the recommendations of an international group of experts. We analyzed radiograms in the antero-posterior projection taken during the treatment and assessed the Cobb angles. The treatment was finished after skeletal maturity was achieved.

Results. At the stage of research material analysis some patients were excluded for the following reasons: lack of skeletal maturity – 66 (21.8%), interrupted treatment – 110 (36.4%), co-existing diseases impacting on the clinical course of scoliosis – 47 (15.5%). The study group, i.e. 79 patients, who completed their treatment, were

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divided into sub-groups depending on the effect of their treatment. 20 patients improved (24.7%), 18 (22.2%) were stable, 9 (11.1%) worsened, and 32 (41.9%) were qualified for surgical procedure.

Discussion. Meta-analyses of international literature have shown that bracing is an effective therapeutic method for idiopathic scoliosis. However, our studies have shown that a large number of patients decide to finish their therapy too early or do not undertake brace treatment at all.

Conclusions. A large number of patients in the lowest mean age group (12.4 years) who were eventually qualified for surgical procedure is disconcerting. The best outcome of the Chêneau brace treatment was achieved in the group of the highest mean age of 14.3.

Key words: idiopathic scoliosis, Chêneau brace, treatment effectiveness.

INTRODUCTION

Scoliosis is a progressive condition, which significantly affects the development and functioning of a young organism. The extensive interest of medical experts in spinal deformities stems from their high incidence in the population of youth (2–3%), health consequences resulting from the disease progression as well as high social and economic costs [6, 10, 24, 26, 28]. At present, we have at our disposal conservative therapeutic methods of a determined efficiency: kinesitherapy, electrostimulation and bracing. Each of these methods has undergone a specific evolution and currently modifications of the original procedures are applied. In the case of II degree scoliosis, braces from the TLSO group (Thoraco-Lumbo-Sacral Orthosis) are most frequently used clinically. Among them, the Chêneau brace, due to its high effectiveness, occupies a special position. The major function of this orthosis is to correct a 3-dimensional deformity of the spine and back by multipoint pressure zones and inhibiting the disease progression [11, 26]. Studies carried out so far have shown that wearing a brace changes the natural course of scoliosis [8, 16, 26] and allows the patient to avoid a surgical procedure [20, 26, 27, 28].

AIM

The aim of the research was the evaluation of the Chêneau brace treatment results in the management of idiopathic scoliosis.

MATERIALS AND METHODS

To evaluate scoliosis correction achieved with the Chêneau orthopedic brace in patients treated in the Department of Rehabilitation and the Provincial Children's Rehabilitation Hospital in Ameryka near Olsztyn we analyzed the course of therapies of

302 patients. Patients qualified for the research were treated between 2003 and 2008, and their medical documentation was stored in the computer system Q-Klinika. At the stage of detailed analysis, we excluded from the research 66 (21.8%) patients in whom full skeletal maturity had not been observed, i.e. they continued treatment, and 110 (36.4%) patients who had not completed their treatment, i.e. they had not shown up for check-ups despite medical recommendations. The latter group is rather numerous and this is unexpected. Some of these patients, i.e. 54 (17.8%), having received the recommendation for the brace, never came for a control examination. Thus, we can assume that this form of therapy was not acceptable for them, despite the information provided both to the patients and their parents by the ordering physician concerning the consequences of not undertaking the treatment. We also excluded those patients who had co-existing diseases affecting the progression of scoliosis, namely: paresis, Scheuermann's disease, muscular dystrophy, genetic syndromes (Tab. 1).

Tab. 1. Patients excluded during research material analysis

Cause	number
No skeletal maturity	66 (21.7%)
Interrupted treatment	110 (36.1%)
Co-existing diseases	47 (15.4%)

79 patients qualified for bracing completed their treatment. Qualifying procedure carried out at the Department was consistent with the recommendations of the international group of experts from SOSORT (Society on Spinal Orthopaedic and Rehabilitation Treatment) [18]. These recommendations concern the skill and experience of the physician recommending a brace, cooperation of the rehabilitation team – physician, physiotherapist and, in this case, a technician fabricating the brace, choosing one center fabricating braces and systematic control examinations of patients and braces. When analyzing this group of patients, we examined radiograms taken in the antero-posterior projection in order to assess spinal curvature measured according to the Cobb method, skeletal maturity (the Risser sign) and vertebral rotation according to the Nash-Moe method. Girls comprised the majority of patients in this group – 58 (73.4%), there were 23 (29.1%) boys.

Depending on the therapeutic results this group of patients was divided into sub-groups, i.e. patients who: 1) improved, 2) were stable, 3) progressed, 4) were qualified for surgery (Tab. 2). Improvement was defined as the decrease of the curvature angle by more than 5° measured by the Cobb method using X-ray image; stabilization was assumed when the change of the angle amounted to ±5°; whereas progression when after treatment the curvature angle progressed beyond 5° in com-

parison to the initial one, but the final Cobb angle did not exceed 40°. Patients qualified for surgical procedure showed the Cobb angle exceeding 40° after treatment. All patients, simultaneously to bracing, underwent kinesitherapy based on asymmetric exercises with elements of proprioceptive neuromuscular facilitation (PNF). The introduction to the exercises was carried out in hospital environment during at least 21-days rehabilitation courses in the Teaching Hospital and at the Rehabilitation Department. All patients were recommended to wear the brace for 20–23 hours a day, with a break for exercises and personal care activities. Systematic check-ups of the braces and patients were carried out within the out-patient system, and, when necessary, the brace was modified in the center in which it had been fabricated.

Tab. 2. Treatment results

Group of patients	Number
Total	79
Improvement	20 (25,3%)
Stabilization	18 (22.7%)
Progression	9 (11.3%)
Qualification for surgery	32 (40.5%)

RESULTS

Patients in whom improvement was observed comprised 20 patients, ranging in ages from 12 to 16. At the out-set of the treatment the mean age of the patients was 14.35, mean Cobb angle was 33.5° (23–45°), median rotation was 3 (1–4) and skeletal maturity according to the Risser sign was 3 (0–4). The observation period was on average 2.6 years (2–5). The Cobb angle decreased on average by 9.8° (4–27°), leading to the mean curvature angle of 21.8° at the completion of the treatment (Tab. 3). In this group of patients, single curve scoliosis appeared in 7 cases, out of which 6 were thoraco-lumbar (4 right-sided and 3 left-sided), and 1 was a typical right thoracic scoliosis. In the remaining 13 cases, scoliosis was assessed as double curve, and the analysis concerned the primary curve. The group in which stabilization was observed consisted of 18 patients, 7 of whom had single curve scoliosis and 11 double curve scoliosis. At qualifying for treatment the mean age of the patients was 13.8 years (13–17), mean Cobb angle was 32.6° (22–39°), median rotation 2 (1–3), median skeletal maturity 2 (0–4) and observation period on average was 2.4 years (1–4) (Tab. 4). Patients in whom bracing did not produce expected results were, on purpose, divided into two groups: patients who progressed and the therapeutic result did not exceed 40° and patients qualified for surgical procedure.

Tab. 3. Description of group with improvement

Factor	Number
Patient's Mean age in years	14.3 (12–16)
Mean curvature angle in degrees	33.5
Median rotation	3
Median skeletal maturity	3
Mean observation period in years	2.6 (2–5)

Tab. 4. Description of the group with stabilization

Factor	Number
Patients' mean age in years	13.8 (13–17)
Mean curvature angle in degrees	32.6 (22–39)
Median rotation	2 (1–3)
Median skeletal maturity	2 (0–4)
Mean observation period in years	2.4 (1–4)

The mean age in the group which progressed was 13.7 (13–15), mean Cobb angle progression 7.7° (4–12°), median initial rotation 3 (2–4), median rotation after completed treatment 3 (3–4), median initial skeletal maturity 0 (0–3) mean observation period 3.7 years (2–5) (Tab. 5). The completion of treatment in this group was connected with a larger curvature angle than at qualifying for bracing, but the final result allowed the patients to avoid surgery, which should be seen as a therapeutic success.

Tab. 5. Treatment results of in the group with progression

Factor	Number
Patients' mean age in years	13.7 (13–15)
Mean progression angle in degrees	7.7 (4–12)
Median initial rotation	3 (2–4)
Median rotation after completed treatment	3 (3–4)
Median initial skeletal maturity	0 (0–3)
Mean observation period in years	3.7 (2–5)

Patients qualified for surgery comprised the largest group (32) of the youngest patients – mean age 12.4 years (6–15), with a low degree of skeletal maturity – the median initial Risser sign was 0 (0–3) and with the largest progression – mean progression angle 15° (1–37°) (Tab. 6).

Tab. 6. Description of the group finally qualified for surgery

Factor	Number
Patients' mean age in years	12.4 (6–15)
Mean progression angle in degrees	15 (1–37)
Median initial rotation	3 (1–4)
Median rotation after completed treatment	3 (2–4)
Median initial skeletal maturity	0 (0–3)
Mean observation period in years	2.3 (1–4)

DISCUSSION

Chêneau brace is an orthosis unwillingly accepted by youth in adolescence because of esthetic and functional reasons. Patients' and their parents' awareness of the consequences of not treating scoliosis is frequently insufficient and the brace is considered as an element making every day life activities difficult, especially by girls. This results in not undertaking treatment, no determination to wear braces and not observing medical recommendations [28]. Attempts to install pressure detectors within the brace walls, which measured the contact time of the pads and the body, were an interesting and innovative solution towards the verification of the brace wearing time. Unfortunately, technical problems prevented a common application of such solutions [2, 9]. A physician supervising the treatment has no possibility to control kinesitherapy the patient is required to do. A therapeutic success to a large degree depends on adjusting kinesitherapy to the degree and type of scoliosis, doing the exercises systematically, as well as on patients' and their families' awareness and motivation. Meta-analyses of international literature have shown that bracing is an effective therapeutic method for idiopathic scoliosis [21, 28]. Brace, as any other type of orthosis used for a long time, disturbs bathyesthesia and changes proprioception. The pads correct spinal deformities. However, they do not enable the patient to mobilize deep muscles and intercostal muscles. They also do not impact on the elongation of the spine. Frequent stimulation of the neuromuscular system by specific movement patterns and breathing exercises should be an integral part of brace therapy. The more frequent stimulation in the form of short movement or breathing sequences during the day is, the higher the probability of posture deformity correction or stabilization. In order to analyze the treatment course precisely, it is worthwhile to introduce a thorough supervision of kinesitherapy

and to modify physiotherapists' work with the patients wearing orthopedic braces. Further, it is important to verify patients' and their families' active involvement in a movement therapy and the wearing of braces systematically. This can be done by employing control protocols.

Our studies have shown that a large number of patients (36.4%) decide to finish their therapy too early, i.e. before achieving skeletal maturity, or do not undertake brace treatment at all. These results may have been influenced by changing the physician and the treatment center by the patients. Informing the physician who issues the recommendation for the brace about changing the center providing the treatment should be considered as a good practice. It would contribute to collecting more reliable statistical data. Some patients do not accept the diagnosis they just learned about or actually deny that their disease exists. According to the literature such reactions may be manifested by as many as 50% of patients [4]. A large percentage of patients in whom the intended therapeutic effect was not achieved is a disturbing result. The group of patients finally qualified for surgical treatment comprises the largest and youngest group, as well as least advanced with respect to skeletal maturity (Risser sign). Rapid progression, and consequently a short observation period, point to a significant instability of curvatures in this group.

International literature on this subject is not uniform. Publications concerning the efficiency of braces are of diverse scientific value and reliability because of not observing EBM (Evidence Based Medicine) principles and SRS (Scoliosis Research Society) recommendations concerning research conducted on braces used in scoliosis. The SRS recommendations concern qualifying patients for a study group so that groups compared from various centers were homogenous because it is significant for the analysis and reliability of the research.

Inclusion criteria for the research on the effectiveness of conservative treatment according to SRS are as follows: minimum age 10, Risser sign 0–2, initial curvature 25–40°, no previous bracing treatment, girls before puberty, or maximum one year following the first menstruation [19]. Our study does not meet the above mentioned criteria; however, qualifying patients for bracing is performed according to the recommendations formulated by SOSORT.

In 2005 a meta-analysis of international literature was carried out focusing on evaluating the effectiveness of conservative treatment methods for scoliosis, including bracing. Out of 436 articles only 3 discussed randomized studies and 10 with a control group. However, only 5 referred to bracing [13]. A comparison of a group treated with bracing with the control group without treatment showed a significant improvement with bracing, from 50% to 70% [16]. Research on the effectiveness of braces (Charleston Bending Brace, Milwaukee, USA) as a supplementary treatment for exercising did not show a therapeutic effect. The results of both groups did not differ statistically [22]. A comparison of bracing only with exercises did not show any difference between the compared groups [1]. However, a comparison of bracing with electrostimulation showed a higher

effectiveness of the former therapy [23]. A comparison of various braces did not point to a significant advantage for any of them [5, 15, 28].

Comparison of results of research comparable methodologically, carried out globally and in Europe

USA: In 1995 studies performed by SRS showed that wearing a brace gave better therapeutic results than observation alone and no therapeutic intervention [16].

IRLAND: Research conducted by Goldberg [7] on the effectiveness of braces, both the Milwaukee brace and American equivalent of the Chêneau brace (TLSO group), showed that bracing had no impact on the number of performed surgical procedures. The research was carried out with a control group. In the control group the number of performed surgeries amounted to 28.1%, whereas in the group treated with bracing to 24%, which is not a statistically significant difference.

JAPAN: Japanese studies were carried out on a large group of 328 patients. In 20 (6.1%) patients, scoliosis progression exceeding 50° was observed. They were qualified for surgery. The mean age of initiating bracing treatment in the group qualified for surgery was 13.4, the Cobb angle was 48.5°, and the age when surgery was performed was 16.0, whereas the angle of curvature after the completed treatment with bracing was 62.2° [14].

SPAIN: Research carried out in Spain comprised a group of 157 children qualified for bracing. During the observation period, 13 patients did not complete the therapy, whereas 6 were qualified for surgical treatment. Thus, the frequency of surgery was at the level of 3.8%. Assuming that the patients who did not complete the therapy would also undergo surgical treatment, the need to perform surgery was at the level of 12.1% [20].

ITALY: Studies conducted in Italy were prospective. The groups were carefully analyzed according to the degree of curvature and with respect to achieving a minimal and maximal aim. A group of 112 patients was analyzed. The studies were completed by 108 patients, ages: 13.2 ± 1.8, with the Cobb angle of 23.4° ± 11.5°. 1 person underwent a corrective procedure, which makes for the frequency of surgery at the level of 0.9%, and assuming that the patients who did not complete the treatment would also undergo surgery – at the level of 4.5%. The minimal aim was achieved in 99%, and the maximal in 84% [17].

GERMANY: Retrospective studies of the patients treated with the Chêneau brace between 1993 and 1996 in the Clinic in Bad Soberheim comprised 343 girls, with the mean curvature angle of 33.4°, 41 patients underwent surgery, which makes for 11.9% [27, 28] (Tab. 7).

Tab. 7. Percentage of patients treated surgically for idiopathic scoliosis in the cited articles

Country	Italy	Japan	Germany	Spain	USA	Poland – own research
Number of patients	112	328	343	157	153	79
Percent of surgeries (%)	4.5	6.1	11.9	12.1	24.0	41.9

When evaluating the factors which contribute to a positive therapeutic effect of treating idiopathic scoliosis with a brace, most authors point to a proper fitting of the brace as a necessary condition to achieve correction [3, 20, 25]. A good initial correction with the brace is listed as the second factor. In order to evaluate an initial correction, X-ray should be taken and the Cobb angle assessed – the correction of the Cobb angle should amount to approximately 50% of its initial value. This allows us to assume that a positive final effect will be achieved. A very interesting study was published by researchers from Austria. They showed that fitting a brace properly and a good correction with it, is associated with a positive final effect. Proper fitting, but poor initial correction with the brace is associated with stabilization, whilst poor fitting is always associated with progression of the condition [12].

CONCLUSIONS

1. A large group of patients does not accept the Chêneau brace treatment and they do not undertake treatment by his method.
2. A significant group of patients does not observe the principles of using the Chêneau brace.
3. A large percentage of patients in the lowest mean age group of 12.4 qualified finally for surgical treatment is a disturbing phenomenon.
4. The best therapeutic results with the Chêneau orthosis were achieved in patients in the highest mean age group of 14.3 years.
5. Treatment with the Chêneau orthosis is associated with a natural development of idiopathic scoliosis and results in a worsening therapeutic effect in the periods of the disease progression.

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CASE STUDY

DEMONSTRATION OF A POSITIVE EFFECT OF EMOTIONAL EXPRESSION ON BLOOD COAGULATION IS POSSIBLE WITH DARK FIELD MICROSCOPY

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ABSTRACT

Introduction. Effects of psychological stress on blood hypercoagulation have been shown by a number of authors. In healthy subjects acute mental stress simultaneously activates coagulation and fibrinolysis within a physiological range. However, in patients with atherosclerosis or in healthy subjects under acute or chronic psychosocial stressors (e.g. exam, earthquake, blood donation, job strain, low socioeconomic status, social isolation) hypercoagulable states reflected by an increased number of procoagulant molecules and by reduced fibrinolytic capacity might develop. There is also evidence that points to hypercoagulability in depression.

Aim. The aim of this paper was to demonstrate the positive effect of emotional expression on blood coagulation using dark field microscopy.

Materials and methods. Cases of three patients suffering from psychological stress are presented. Humaniversity therapy was applied for all cases integrating a variety of therapeutic techniques, such as: emotional expression, cognitive change, integrity of a holistic approach, touch and positivity. Dark field microscopy was used before and after the sessions to evaluate the effect of therapeutic work on blood coagulation.

Results and Discussion. The results of three cases showed the immediate effect of emotional release on blood coagulation. After the sessions lasting from 1–1.5 hours, all three cases reported improved emotional well-being with changes in blood clotting from levels 4 and 5 (light severe and severe clotting) to no clotting at all.

Conclusions. A positive objective effect of emotional expression on blood coagulation can be demonstrated using dark field microscopy.

Key words: psychological stress, emotional expression, blood coagulation, dark field microscopy.

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INTRODUCTION

Effects of psychological stress on blood hypercoagulation have been shown by a number of authors [1, 2, 7, 8, 11, 13]. In healthy subjects acute mental stress simultaneously activates coagulation and fibrinolysis within a physiological range. However, in patients with atherosclerosis or in healthy subjects under acute or chronic psychosocial stressors (e.g. exam, earthquake, blood donation, job strain, low socio-economic status, social isolation) hypercoagulable states reflected by an increased number of procoagulant molecules and by reduced fibrinolytic capacity might develop. There is also evidence that points to hypercoagulability in depression [8]. Other authors suggest that superimposed life stress on top of chronic stress (as seen in Alzheimer caregivers) may elicit a hypercoagulable state that could contribute to coronary heart disease and to an increased overall mortality rate in this population [7]. The relationship between vital exhaustion and a risk of myocardial infarction shown by researchers [11] may be mediated in part by an imbalance between blood coagulation and fibrinolysis. Older age has been shown to be an additional risk factor for hypercoagulation [13].

The Humaniversity institut specialize in helping patients via Humaniversity Therapy (emotional expression, awareness and healing, etc.) to deal with acute and chronic psychological stress, depression and addictions [4]. The criteria for an evaluation of success using Humaniversity Therapy are rather subjective – patients' satisfaction with their health, mental and physical well-being, improved capacity to deal with daily stressors, etc. Therefore, an objective method to demonstrate the effectiveness of the emotional work offered by Humaniversity institute was sought-after. Dark field microscopy (DFM) was selected – a method with an easy set up for a patient and a therapist that can be immediately evaluated by both and reconstructed by others [6].

AIM

The aim of this paper is to demonstrate the positive effect of emotional expression on blood coagulation using DFM.

MATERIALS AND METHODS

Humaniversity therapy

This therapy integrates a variety of therapeutic techniques that can be applied to group or individual therapy. Each treatment includes emotional expression, cognitive change, integrity of a holistic approach, touch and positivity. Depending on a patient's needs, other forms may be used as well: encounter, catharsis, creativity, etc. [4].

Psychokinesiology

This method is used to detect emotional stress via muscle testing. It allows the practitioner to discover the details of stress mainly resulting from unresolved conflicts and trauma from the past such as time, place, experienced feelings [7].

Mental field therapy

This method is used to assist in trauma healing and cognitive change. It is based on stress reduction through the use of acupressure points while saying stress reducing sentences [10]. This technique was originally discovered by Roger Callahan, and then developed by Dietrich Klinghardt. Similar techniques are therefore known as TFT (Thought Field Therapy) by Roger Callahan, and EFT (Emotional Freedom Technique) by Gary Craight [3, 5, 10].

DFM

The advantage of DFM is that indirect light created by a special condenser focuses on the object and creates a picture with light structures on a dark background. The outlines of the object are better seen than with the usual light field microscope [12].

Blood taking procedure

Blood is taken on an empty stomach. The intake of water or herb tea is permitted. Blood testing and individual session time starts at 9.00 a.m. A recheck is conducted after the session lasting from 1–1.5 hours after the first blood taking. The patient does not eat meanwhile. Drinking herb tea or water is admitted. A drop of blood is taken without squeezing or pushing the blood out of the finger, or ear lobe if preferred. The first drop is removed into a tissue. The second drop is transferred to a glass without touching it and than is put on the objective glass. This sample is taken just in case the firt one is unable to be used. The photos are taken from the center part of the sample.

Levels of blood clotting

Using DFM we can see five different levels of blood clotting – from light to severe. These levels are used as a standard measurement for this research (Fig. 1–5). To simplify the results no attention will be given to the conditions of white blood cells or plasma.

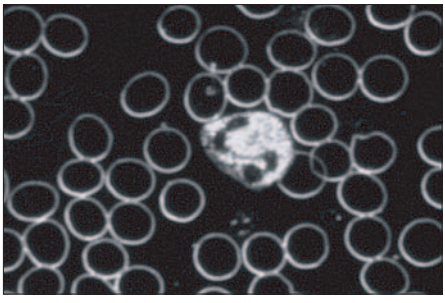


Fig. 1. Level 1 – no blood clotting

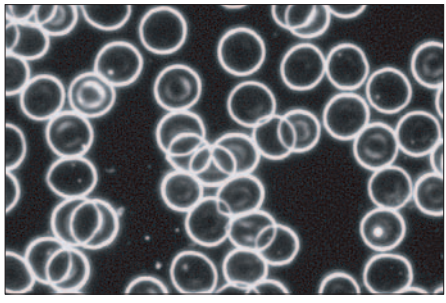


Fig. 2. Level 2 –light blood clotting

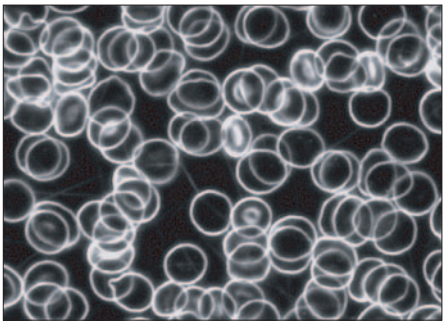


Fig. 3. Level 3. – medium blood clotting

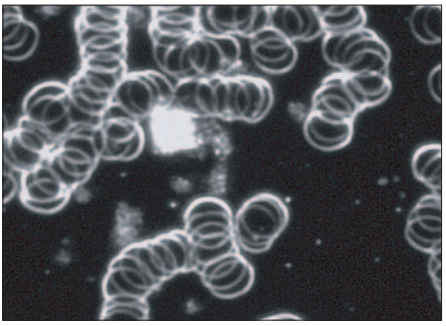


Fig. 4. Level 4 – light severe blood clotting

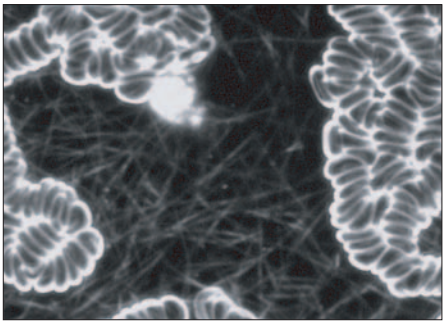


Fig. 5. Level 5 – severe blood clotting

These photos illustrate how erythrocytes can get closer and clump until they form so called "money rolls" [6]. Figure 2 shows just a little departure from the healthy state (Fig. 1). Level 3 shows that self-regulatory functions of the body are getting disturbed, and the clotting of erythrocytes starts to dominate (Fig. 3). Levels 4 and 5 (Fig. 4, 5, respectively) show the formation of "money rolls" and the twisting of "money rolls".

RESULTS

In this paper three cases are presented. As described in the methodology, the therapy consisted of emotional expression. Patients were encouraged to discover and express the repressed emotional content of events connected to their conflicts, followed by a healing phase involving expression of love and care in that situation, and positive affirmations.

Case 1
Complaint: Mrs. B. has a good intention to lose weight and to follow a healthy diet, but after a while she goes back to eating sweets and foods high in calories and low in nutrients (e.g. cakes). She feels that she cannot stop worrying about her family. The blood analysis shows a picture with blood clotting levels 4 and 5 (Fig. 6, 7).

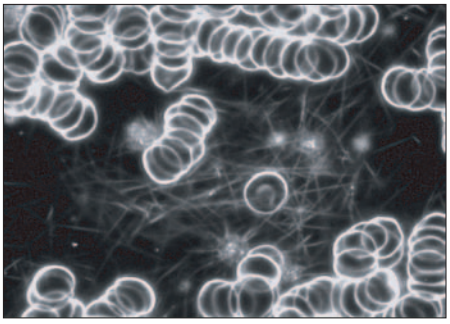
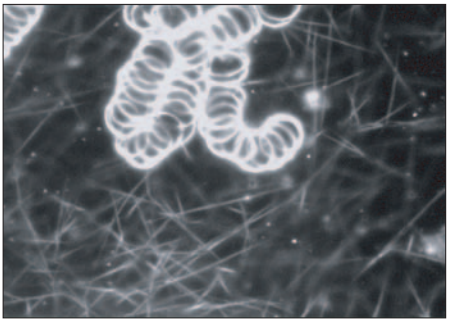



Fig. 6, 7. Levels 4 and 5 of blood clotting before therapeutic work in Case 1

During the session the emotional conflicts were addressed to her. The issue of putting herself under too much pressure appeared. She kept complaining that nothing was good enough and that it was her fault. The talk was started about the time when she was separated from her mother, due to hospitalization with pneumonia at three years old. During this time she felt the pressure of the entire situation, but never expressed anything. She recognized a lot of sadness developing, and saw that she sought for situations in life, which put her under more pressure. After the release of the sadness she soon felt a lot lighter and her worries disappeared. She felt that she was fine the way she was. A photo after the session showed that blood clotting levels changed from 4 and 5 into level 1 (Fig. 8, 9).

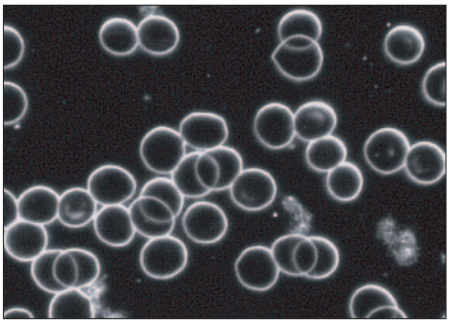
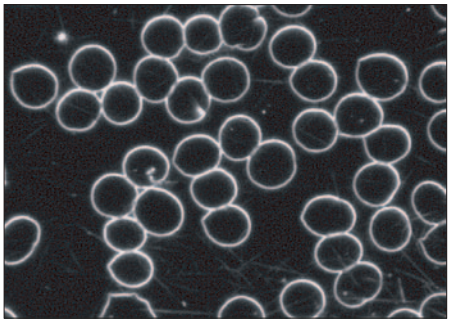
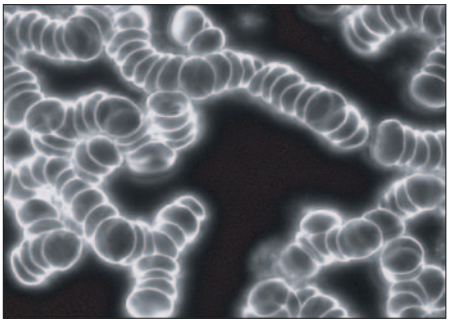



Fig. 8, 9. Level 1 blood clotting after therapeutic work in Case 1

Case 2

Complaint: the patient (Mrs. C. H.) has hives all over her body; she does not use medication in general, except histamines occasionally. Presently it is an acute problem. DFM indicates blood clotting level 5 (Fig. 10, 11).



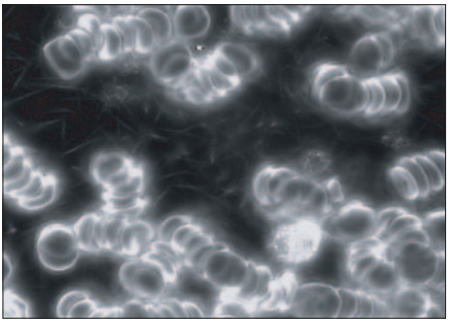
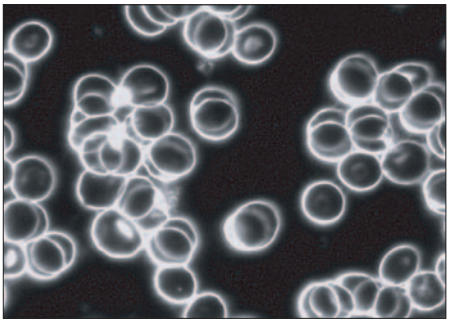


Fig. 10, 11. Levels 4 and 5 of blood clotting before therapeutic work in Case 2

During the session the emotional issues concerning her relationship with husband were discussed, as well as the emotions caused by the loss of her child. After the session she felt emotionally light and open. DFM picture after the session demonstrated reduced clotting to levels 2 and 3 (Fig. 12, 13).



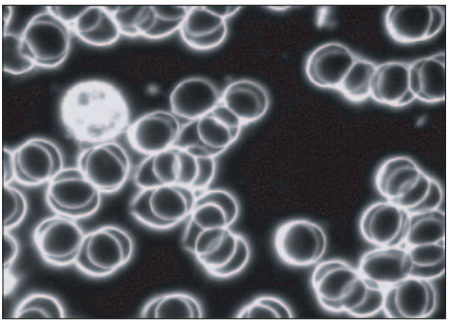


Fig. 12, 13. Level 1 of blood clotting after therapeutic work in Case 2

Case 3

Mrs. A. R. complains of: tensions in body, water retention in ankles, knee pain, fatigue during the day. She feels anxious about starting the weekend course in personal growth, afraid that she will be unable to follow. DFM indicates blood clotting levels 3 and 4 (Fig. 14).

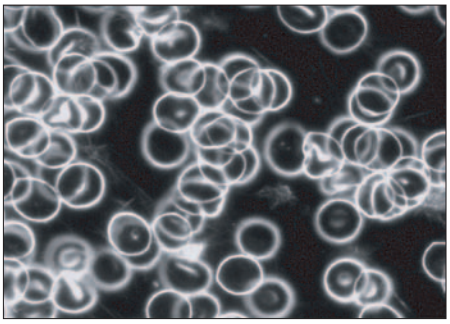


Fig. 14. Levels 4 and 5 of blood clotting before therapeutic work in Case 3

During the session the emotional issues concerning difficulties to obey her father's commands and situations of punishment and humiliation connected to her resisting his will were discussed. She also became aware of a pattern of control and manipulation to get things her way, and she released anger and frustrations. After the session no blood clotting was observed (Fig. 15). Mrs. A. R. felt relieved and confident enough to begin the workshop.

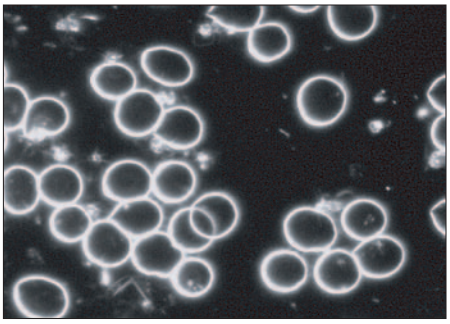


Fig. 15. No blood clotting after therapeutic work in Case 3

DISCUSSION

Usually the effects of therapeutic techniques (such as emotional expression) are not evaluated using objective methods. The patient assesses the immediate and lasting effect of therapy as a subjective feeling of relief, relaxation, increased awareness, centeredness, etc. Therefore, it was interesting whether these subjective evaluations of a rapid change in emotional well-being had any effects on blood clotting. Therefore, DFM method was used to look at changes in hypercoagulation which is reported to be a consequence of acute and chronic psychological stresses [1, 2, 7, 8, 11, 13].

DFM allows one to evaluate the shapes and other properties of individual blood cells, indicating nutritional and other conditions which can adversely af-

fect health. The advantage of this analysis over standard blood tests, which detect chemical changes in the blood, is the possibility to detect disorders sooner, when problems are in their infancy stages. By monitoring the blood's condition, a medical professional can assist in "balancing" the blood by giving dietary and lifestyle recommendations which can enhance health, or eliminate any factors that might increase blood clotting.

The results of cases presented here show an immediate effect of emotional release on blood clotting. After sessions lasting from 1–1.5 hours all three cases reported an improved emotional well-being with impressive changes in blood clotting from levels 4 and 5 to no clotting at all.

Many factors might cause hypercoagulation (e.g. electromagnetic field disturbances, smoking, alcohol, emotional stress, constipation, medication, fatty food and acid-forming food such as excessive proteins, toxic stress due to heavy metals, xenobiotics, excitotoxins) [12]. It is interesting that when releasing just one of them (emotional stress), immediate objective changes were observed. It is also impressive that red blood cells that were clotting together could detach from each other within such a short time without any medical intervention, just as a result of changing the emotional state of a person. Using the available evidence some explanation for these observations will be provided .

Rau et al. [12] has discovered that the formation of "money rolls" of erythrocytes is a consequence of a lack of their electromagnetic charge. Erythrocytes are normally positively charged on the surface, so in order for them to clump they must become neutralized. Neutralization might be caused by excessive protein consumption, etc. The proteins cover erythrocytes and neutralize the surface charge. Without this magnetic repulsion red blood cells clump together. Furthermore, erythrocytes do not respond to the magnetic input of the conductive system of the heart. In a healthy body the conductive system lets red blood cells pulsate charging them with a voltage. A protein-reduced (e.g. vegetarian) diet over a period of time might clear the blood and red blood cells from excess protein and erythrocytes might regain their ability to detach. However, it is not clear how their detaching is connected to emotional work.

For further research, it would be interesting to assess the duration of the positive effect of emotional expression on blood clotting. Apart from a subjective evaluation of impaired emotional well-being, DFM as a cheap and easy method might be used to establish the frequency of therapy needed in individual cases.

CONCLUSIONS

A positive objective effect of emotional expression on blood coagulation can be demonstrated using DFM.

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CASE STUDY

DIAGNOSTIC PROBLEMS OF CYTOMEGALOVIRUS INFECTIONS IN PREMATURE NEWBORNS

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ABSTRACT

Introduction. Cytomegaly is an infectious**,** widespread viral disease. It is caused by *Cytomegalovirus* (CMV), which belongs to the DNA viruses group from the *Herpesviridae* family. The virus is human specific. Once infected, a person remains seropositive to the end of life and the virus remains latent particularly in leukocytes, which are its main reservoir. Many different disease manifestations, which depend partially on a patient's age, but mostly on an immunological state, may be caused by CMV.

Aim. The aim of this work was the assessment and histoclinical analysis of CMV infection in a male newborn with a congenital anomaly syndrome.

Case study and examination results. A male newborn, born in the 30th week of gestation, diagnosed with congenital anomaly syndrome, Apgar score was 2. In the neonatal period hypertrophic cardiomyopathy involving the right ventricle, esophageal atresion, esophagotracheal fistula, hepatosplenomegaly, respiratory insufficiency and hyperechogenic periventricular structures in the brain were diagnosed. During the entire hospitalization period a progression of inflammatory changes in the lungs was observed. The results of serological tests to detect anti-CMV and toxoplasmosis specific antibodies were: CMV–IgG 21.00 IU/mL; CMV–IgM negative; Toxo–IgG 4.0 IU/mL; Toxo–IgM negative. Restoration of esophageal continuity and repair of the fistula were performed surgically. Follow-up serological test was positive for anti-CMV antibodies in the IgG and IgM classes. The patient died on the 79th day following hospital admission. Autopsy and histopathological tests confirmed generalized cytomegalovirus infection.

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Discussion. Most advanced histopathological changes were observed in lungs, liver, spleen and brain. Characteristically changed cells, confirming generalized cytomegalovirus infection were found in all the aforementioned organs.
Conclusions. CMV infections, particularly congenital infections in premature newborns are challenging diagnostic and therapeutic problems. Routine diagnostic procedures to detect CMV infections seem to be necessary in risk groups, particularly for premature infants. Negative anti-CMV antibodies result in patients with an insufficient immune system, does not exclude the presence of this infection. Early diagnosis and treatment of congenital cytomegaly may positively affect a patient's clinical condition and prolonged prognosis.

Key words: cytomegaly, premature newborn, infection

INTRODUCTION

Cytomegaly is an infectious**,** globally widespread viral disease. It is caused by *Cytomegalovirus* (CMV), which belongs to the DNA viruses group from the *Herpesviridae* family [8, 10]. The virus is human specific. It remains in a human organism in a latent form for a long time [1]. In the reactivation period it penetrates into bodily fluids and consequently is easily transmitted into the host environment [6].

The name of the virus comes from the changes which it causes in a cell. An infected cell is markedly enlarged, with characteristic intranuclear and cytoplasmic inclusion bodies.

Cytomegaly may be manifested in many various ways, depending on a patient's age and immunological state. In adults and older children, with a normally functioning immune system, its course is usually asymptomatic, rarely mononucleosis-like [3, 6]. However, in people with a lowered immunity, i.e. in patients with immunodeficiency, patients undergoing immunosuppressive treatment, patients who have undergone surgical treatment, and in fetuses and newborns, CMV infection poses a serious threat which may lead to death.

CMV infection may occur via a number of mechanisms, among others, intraplacental mechanism (congenital cytomegaly), via secretion from the female reproductive tract and mother's milk (perinatal cytomegaly), saliva, sexual intercourse, secretion form respiratory tract, "dirty hands", and iatrogenic transmission [2, 4, 5].

Infections during pregnancy are especially dangerous because the virus may lead to serious congenital abnormalities of the fetus. Complications involving newborns most frequently include: generalized infection (sometimes fatal) with enlarged liver and spleen (hepatosplenomegaly), jaundice, thrombocytopenia, hemolytic anemia, rash, loss of hearing, retinitis, choroiditis, optic nerve atrophy, hepatitis, pneumonia, mental retardation of various degrees, microcephaly, periventricular calcifications and intracranial hemorrhages [10].

Due to its common prevalence and a wide range of adverse manifestations, cytomegaly is a serious clinical challenge.

AIM

The aim of this work is the assessment and histoclinical analysis of CMV infection in a male newborn with a congenital anomaly syndrome.

CASE STUDY AND EXAMINATION RESULTS

A male newborn, birth weight of 1300 g, born in the first pregnancy, single birth, in the 30th week of gestation, by caesarean section due to the risk of fetal asphyxia, preterm outflow of amniotic fluid, and a risk of intrauterine infection. Apgar score was 2. In the neonatal period, the newborn was diagnosed with: hypertrophic cardiomyopathy involving the right ventricle, esophageal atresion, suspicion of esophagotracheal fistula, hepatosplenomegaly, respiratory insufficiency and hyperechogenic periventricular structures in the brain. Antibiotic therapy of a wide spectrum was administered. For further diagnostic procedures and specialist treatment, the newborn was transferred on the 3rd day of life to the Provincial Specialist Children's Hospital in Olsztyn. After admission several examinations were performed which confirmed esophageal atresion and changes to the brain structures in the form of numerous calcifications of periventricular structures and 2nd degree left-sided hemorrhage. A cyst within the spleen was detected. Changes in the liver were not observed. Immunochemical tests to detect anti-CMV and toxoplasmosis specific antibodies in the IgG and IgM classes were ordered. The results were as follows: CMV–IgG 21.00 IU/mL; CMV–IgM negative; Toxo–IgG 4.0 IU/mL; Toxo–IgM negative. On the 3rd day of hospitalization the newborn underwent a procedure to restore esophageal continuity. Throughout the entire hospitalization the patient's condition was unstable, with periodic improvements. However, after 37 days of hospitalization the baby's condition "broke down". Further examinations were carried out which revealed parenchymal density of an inflammatory nature. Within the following days, the patient's condition worsened, the skin became grey, edema appeared as well as meteorism and hardness of the abdomen. The presence of right-sided pneumothorax and tracheoesophageal fistula were revealed. USG of the abdominal cavity showed markedly enlarged liver and spleen. After 68 days of treatment it was decided to close the fistula. Within the following days the baby's condition exacerbated progressively. After a careful analysis of clinical data and the course of disease, fungal superinfection and cytomegaly infection were proposed, despite the first serological test in the IgM class being negative. Immunochemical diagnostic tests were performed again and this time the following results were obtained: CMV–IgG 13 IU/mL; CMV–IgM –2.27 TV. The patient died on the 79th day following admission.

DISCUSSION

Congenital cytomegalovirus infection is diagnosed on average in 1% of newborns, and it is the most frequent infection in humans [2, 6, 8]. In the majority of adults its course is mild and asymptomatic. However, in people with a lowered immunity it may cause serious health problems, not infrequently leading to death, as in the aforementioned described case. In pregnant women a risk of passing the infection to the fetus is estimated to be 40–50%, while the development of a fully symptomatous disease is estimated to be 10–15%. The remaining 85–90% of newborns infected with the virus *in utero* are at risk of delayed manifestations of the peripheral nervous system defects as well as sight and hearing defects [9, 10]. The most serious course is observed in infections acquired in the I trimester of pregnancy. They are characterized by an increased incidence of congenital anomalies, including: microcephaly, intracranial calcifications, low birth weight. Acquiring an infection in the last period of pregnancy increases the risk of an acute form of the disease with intraorgan localization, interstitial pneumonia, interstitial myocarditis, hepatocellular damage, spleen damage, thrombocytopenia and purpura. Changes in the organs in the case observed by us indicate the mother's infection in an early period of pregnancy.

Perinatal infections are generally asymptomatic. However, after some months or even years neurological consequences may appear involving a delayed onset of mental retardation and hearing impairments [9]. The course of the disease in the herein described case indicates that perinatal infection could not have occurred.

The course of infection correlates with the gestation period: the more immature the fetus, the higher probability of developing a fully symptomatous disease, requiring a long-term, multi-directional treatment. It is necessary for the CMV diagnosis to be established as soon as possible after birth. In our case, diagnostic procedures were correct, however the fact that the disease did not manifest itself in the first examination hindered the therapeutic process.

Considering the prevalence of the virus in the European population, all pregnant women should be examined in the III trimester so that the initial status of the newborn is established when some non-specific symptoms appear. In newborns and babies an abnormal course of inogenous jaundice, intestinal disorders, non-specific skin rash, and mostly systemic infections should be seen as indicators for performing examinations. Moreover, manifestations of congenital anomalies already described (as in the discussed case – *esophageal atresia*), hepatosplenomegaly or intracranial calcifications should also lead to examinations to detect the virus's presence. It should be a routine examination in diagnostics involving prematurity, fetus defects and abortions.

Detecting the infection is based on serological tests. The presence of specific antibodies in the IgM class indicates a primary infection. However, serological methods

are of less significance presently, because in order to confirm cytomegaly consecutive tests should be carried out in 2-week intervals, whereas a rapid therapeutic intervention is of vital importance. Only the detection of specific antibodies in the IgM class allows for establishing the diagnosis. It should be remembered that antibodies for other viruses from the *Herpesviridae* family may produce cross-reactions with CMV antigens and give false positive results [10].

In the remaining cases more modern examinations detecting the virus or an element of its structure should be carried out – antigens with the use of various methods of molecular biology. One of them is the polymerase chain reaction (PCR) method which involves multiplication and then identification of the genetic material of the virus in blood, saliva or cerebrospinal fluid. Detecting the virus in amniotic fluid, or antibodies of the IgM class in blood confirms the diagnosis, although negative results of these tests do not always exclude this diagnosis [10].

In the discussed case we deal with a congenital CMV infection. Diagnosing symptomatous cytomegaly was indicated by the changing picture of liver and spleen. During hospitalization the liver displayed disconcerting changeability in USG images, alternately from sizes indicating pathology to those within norm. Spleen displayed a picture of enlarging hyperechogenic changes. Another reason for diagnosing the viral infection were hyperechogenic foci that repeatedly appeared in transfontanelle ultrasonography of the brain, suggesting calcifications or necrotic foci.

Autopsy and histopathological tests of the specimens revealed changes indicating a generalized CMV infection. Histopathological tests revealed the presence of characteristic, enlarged cells with intranuclear inclusion bodies – "owl's eye" in: lungs, liver, spleen, kidneys and pancreas (Fig. 1–6).

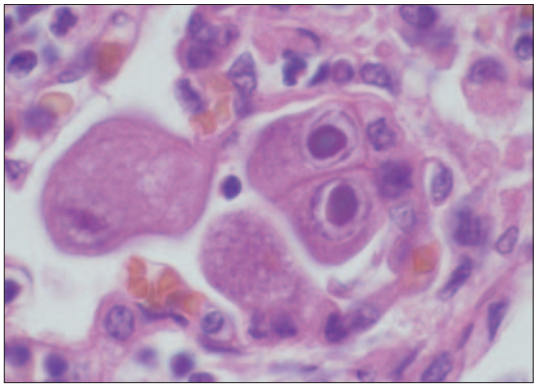

Fig. 1. Intranuclear viral inclusions in alveolar lung cells [HE 400×]

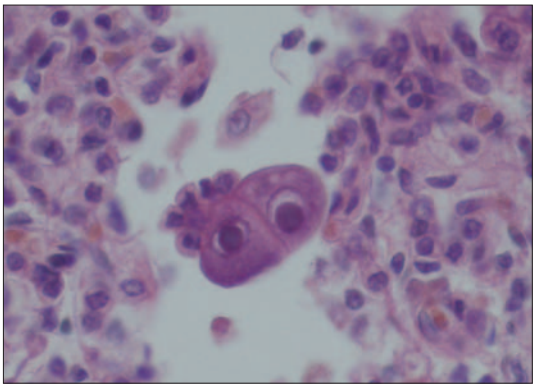

Fig. 2. Intranuclear viral inclusions in spleen cells [HE 400×]

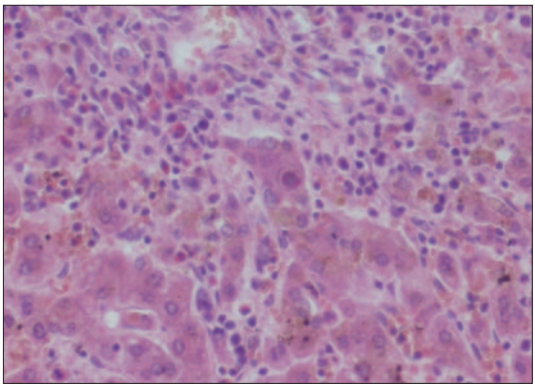

Fig. 3. Intranuclear viral inclusions in liver cells [HE 200×]

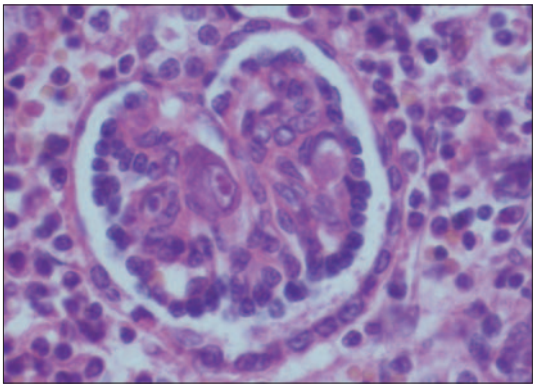

Fig. 4. Characteristic intranuclear viral inclusions in mesangial kidney cells [HE 400×]

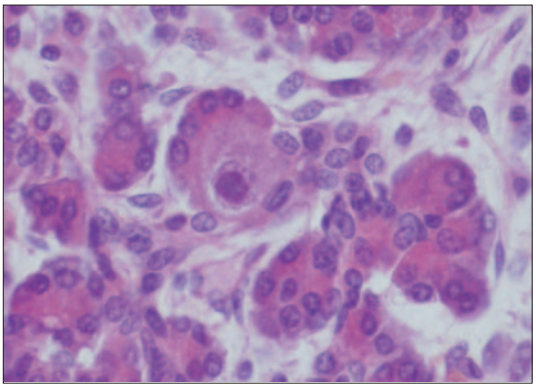

Fig. 5. Intranuclear viral inclusions in pancreas cells [HE 400×]

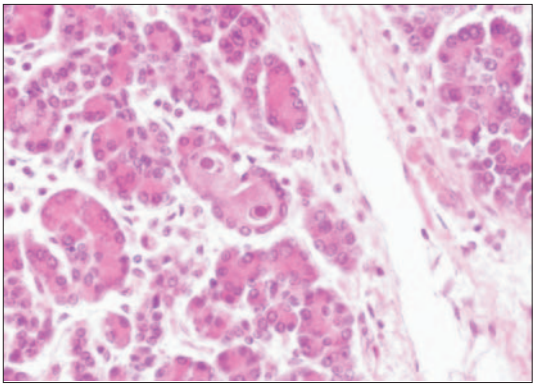

Fig. 6. Inflammation and fibrosis in the pancreas [HE 200×]

Autopsy detected: interstitial pneumonia, hepatitis, splenitis, interstitial nephritis and glomerulonephritis, as well as pancreatitis. In the generalized course of the cytomegovirus infection all parenchymal organs were involved, which was the major cause of death.

There is no vaccine thus far, or a fully effective, safe medication for this disease. Past disease does not prevent reinfection. It is a major cause of congenital infections in newborns, and also the most frequent cause of mental retardation, deafness, and many other developmental defects. All these factors make it a common but underestimated medical problem which warrants further studies.

In Poland compulsory, systematic serological tests to detect cytomegaly in the entire population of pregnant women have not been introduced thus far. Sporadically performed examinations are not consulted by physicians specializing in infectious

diseases. At the time of compulsory screening performed routinely in newborns with the use of just a few drops of blood on filter paper, correlating the detection of cytomegaly with tests focused on more than 20 various metabolic and genetic defects seems to be the modern 3rd degree preventive method, recommended globally [7].

CONCLUSIONS

1. A clinical course of CMV in children is correlated with the route of transmission to the organism and with an age when the infection occurs.
2. It seems that introducing routine diagnostic procedures to detect CMV infections in risk groups, especially for premature newborns, is justifiable.
3. Negative anti-CMV antibodies result in patients with insufficient immune system, does not exclude the presence of infection.
4. Early diagnosis and treatment of congenital cytomegaly may positively affect a patient's clinical condition and prolonged prognosis.
5. Pathomorphologic evaluation of the specimen or a biopsy of a lymph node or parenchymal organs enables the establishment of a final diagnosis.

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CASE STUDY

DIAGNOSTIC DIFFICULTIES IN RECOGNIZING B-CELL LYMPHOMAS IN MEDIASTINAL TUMORS – THREE CASE STUDIES

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ABSTRACT

Introduction. The most frequently diagnosed mediastinal lymphomas include: Nodular Sclerosis Classical Hodgkin Lymphoma (NSCHL) and Primary Mediastinal Large B-cell Lymphoma (PMBL). In the new, 4th edition of the *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue of 2008*, a new category was created: "B-cell Lymphoma, Unclassifiable, with Features Intermediate Between Diffuse Large B-cell Lymphoma and Classical Hodgkin Lymphoma". It has also been referred to as "Mediastinal Grey Zone Lymphoma".

Aim. The aim of this paper was to analyze morphological and phenotypic characteristics of three diagnostically difficult cases of mediastinal and lymph nodes lymphomas.

Materials and methods. Immunohistochemical analysis was performed in two stages: 1) LCA, CD20, CD3, CD30, CD15, Ki67; 2) the panel was extended to include: antibodies Bcl2, Bcl6, CD10, MUM1, CD23, Fascin, transcription factors – PAX5, Oct2, BOB1; LCA/CD45, CD20, CD30, CD15, CD3, CD23.

Case studies. The examination encompassed: 2 cases that demonstrated a discordance between the morphology and the phenotype, and 1 case in which two apparently independent neoplastic growths – PMBL and NSCHL – were diagnosed within 4 months. Patients: 2 women (22 and 31 years old) and 1 man (27 years old) – presented large mediastinal masses of diameter larger than 10 cm.

Discussion. Differential diagnosis between NSCHL and PMBL is sometimes very difficult. However, NSCHL and PMBL demand different therapeutic strategies. In

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the case of PMBL treatment is more intensive. Thus, unambiguous diagnosis is necessary: either NSCHL or PMBL. In some cases, diagnostic difficulties may occur, sometimes it is even impossible to establish diagnosis.
Conclusions. Among B-cell lymphomas in mediastinal tumors there are cases of untypical clinical course and untypical morphological and phenotypic characteristics. Thus, it is necessary to re-examine recurrences, including localizations other than the primary one. An adequate, i.e. large enough, specimen taken during mediastinoscopy is the basis for the correct diagnosis. In diagnostically complicated cases, it is necessary to extend the immunohistochemistry panel to include: CD23 and transcription factors: PAX5, Oct2 and BOB1.

Key words: nodular sclerosis classical Hodgkin lymphoma (NSCHL), primary mediastinal large B-cell lymphoma (PMBL), mediastinal grey zone lymphoma (MGZL), histopathological diagnosis.

INTRODUCTION

One of the most frequently diagnosed mediastinal lymphomas include nodular sclerosis classical Hodgkin lymphoma (NSCHL) and primary mediastinal large B-cell lymphoma (PMBL). NSCHL occurs primarily in young adults, with the peak of incidence between 15 and 34 years of age, slightly more frequently in women. It develops in neck and supraclavicular lymph nodes and in approximately 80% of the cases in the anterior mediastinum. Morphological characteristics include "collagenous" fibrosis, the presence of Hodgkin's cells and lacunar Reed–Stenberg cells (H/RS cells) localized among numerous inflammatory cells.

In the syncytial variant, neoplastic cells form infused areas, especially at the necrosis margins, and mimic neoplasm metastasis or large cell lymphoma metastasis. H/RS cells have a characteristic phenotype and in the majority of cases are: CD30+, CD15+, LCA–, CD3– and CD20– [3, 5, 11, 15]. Prognosis, at the time of modern chemotherapy and radiotherapy, is relatively positive and approximately 75% of patients may be cured [11].

PMBL is a subtype of diffuse large B-cells lymphoma (DLBCL) and accounts for 6–10% of all diagnosed cases [6]. It occurs mostly in young adults, median age – 35 years, twice more often in women. The disease develops as a tumor in the anterosuperior mediastinum. Neck and supraclavicular lymph nodes may be involved. Morphological features of PMBL are diversified. The common features include: diffused proliferation of B-cells of various sizes, from medium to large, fibrosis and compartmentalization [13, 14]. PMBL cells display a positive, strong reaction to CD20+, in approximately 75% of cases the cells show the expression of CD23+, and in about 80% of cases a low expression of CD30+, and are CD15– [6, 12, 16, 18]. Retrospective data covering large numbers of patients indicate a similar or better prognosis in PMBL in comparison to

DLBCL. Recently, common features linking NSCHL with PMBL have been noted, i.e. localization of the tumor mass in anterior mediastinum, frequent involvement of supraclavicular lymph nodes, predominance in young adults, mostly women, fibrotic stroma of the tumor, and many common molecular and genetic features [2, 4, 9, 17, 18, 20]. Sharing common biological and clinical features by NSCHL and PMBL is not surprising, H/RS cells in about 90% of cases are abnormal B-lymphocytes [10, 15]. NSCHL and PMBL are, however, treated differently. The application of a proper therapy from the beginning of the treatment greatly affects survival. Consequently, unambiguous diagnosis is necessary: either NSCHL or PMBL. Sometimes there occur diagnostic difficulties and differential diagnosis may be impossible. For such clinical pictures a new category was created in the new, 4th edition of the WHO Classification of 2008: "B-cell Lymphoma, Unclassifiable, with Features Intermediate Between Diffuse Large B-cell Lymphoma and Classical Hodgkin Lymphoma". Generally it refers to a large mediastinal tumor, thus, this entity is also known in literature as "mediastinal grey zone lymphoma" (MGZL). It occurs in young adults, more frequently in men 20–40 years old. A large tumor mass in the mediastinum leads to symptoms of superior vena cava syndrome and respiratory failure. Morphological and phenotypic characteristics are varied, and as follows from the definition of this entity, morphological and phenotypic features of classical Hodgkin lymphoma (CHL) and PMBL overlap [8, 17, 18, 20]. Clinical course is not as yet certain, but it seems to be more aggressive than CHL and PMBL, and with a worse prognosis. There are no standard treatment methods, but in some cases chemotherapy like the one used in aggressive B-cell lymphomas is recommended [9].

AIM

The aim of this paper is to analyze morphological and phenotypic characteristics of three diagnostically difficult cases of mediastinal and lymph nodes lymphomas**.**

MATERIALS AND METHODS

The examination encompassed: 2 cases that demonstrated a discordance between the morphology and the phenotype, and 1 case in which two apparently independent neoplastic growths – PMBL and NSCHL – were diagnosed within 4 months. Patients: 2 women (22 and 31 years old), 1 man (27 years old) – presented large mediastinal masses of diameter larger than 10 cm. The women also revealed enlarged lymph nodes. The specimens taken for examination were obtained from patients treated in the Ministry of Internal Affairs and Administration Hospital in Olsztyn and diagnosed in the Pathomorphology Unit of the Provincial Specialist Hospital in Olsztyn.

The specimens were taken from the mediastinal tumors and lymph nodes, fixed in 10% buffered formalin solution, routinely treated and sunk in paraffin. Paraffin blocks were sliced into 4 μm sections, which were transferred to microscope slides and stained with hematoxylin and eosine.

Immunohistochemical analysis was performed in two stages. In the 1st stage the following tests were carried out: LCA, CD20, CD3, CD30, CD15, Ki67.
In the 2nd stage the panel was extended to include:
- antibodies Bcl2, Bcl6, CD10, MUM1, CD23, Fascin, transcription factors – PAX5, Oct2, BOB1;
- LCA/CD45 – common lymphocyte marker;
- CD20, Bcl2, Bcl6, CD10, MUM1 – common B-cells markers and/ or their functional stages;
- PAX5, BOB1, Oct2 – transcription factors of B-cells differentiation;
- CD30 – lymphocyte activation marker, H/RS cells marker in HL;
- CD15 – H/RS cells marker in CHL and myeloid cells marker, occurring in some DLBCL;
- CD3 – T-lymphocyte marker;
- CD23 – thymic B-cells marker;
- Fascin – dendritic cell and RS cell marker.

CASE STUDIES

Case 1

The patient, M.D., 22 years old, was admitted to the Ministry of Internal Affairs and Administration Hospital in Olsztyn in April 2006, diagnosed in December 2005 with Hodgkin lymphoma NSII CS IIXB. The patient had previously received three courses of chemotherapy according to the ABVD scheme, leading to disease stabilization (DS). On admission it was revealed: left supraclavicular lymph nodes in fixed packages (35 mm), and in computed tomography (CT) of the chest a nodular mass in the mediastinum (88 × 63 × 126 mm). In laboratory tests: ESR 110mm/h, LDH – not assayed. In the 1st stage of treatment, the patient received chemotherapy, 3 × ABVD/ADM, leading to disease stabilization (DS). Supraclavicular lymph node was taken to verify diagnosis. Morphological characteristics of the node were in line with the CHL, nodular sclerosis NSII, syncytial variant. Layers of collagen divided the node tissue into nodules. Some nodules showed infused areas of atypical, large cells with acidophile nucleoli. Some of these cells might have been morphologically in line with H/RS cells. Inflammatory cells were numerous. Diffused necrosis areas with large, atypical cells forming infused areas around them were noticeable. Immunohistochemical characteristics were different from what we had expected. Tumor cells showed CD20+ expression. The intensity of reactivity varied in various areas of the node. Around necrosis foci, the majority of large cells were CD20+, but their reactivity was weaker than that of B-lymphocytes. There were also nodules where all tumor cells showed uniform, high CD20+ reactivity. The expression of CD15+ was also noticeable; it was strong, on the membrane and perinuclear, alike in all cells; whereas the expression of CD30+ (on the membrane and perinuclear) was very weak in selected cells. On the basis of the morphological and

phenotypic characteristics (CD15+, CD30+) in the lymph node we diagnosed Hodgkin lymphoma, nodular sclerosis with atypical phenotype CD20+. In the 2nd stage, patient was qualified for HDT + ASCT. She received chemotherapy according to the following schemes:

a) May 8–22, 2006: 2 × ICE. CT revealed progression of the mediastinal mass to 110 × 65 × 140 mm; liquid in the left pleural cavity; left supraclavicular node 23 × 24 mm with disintegration;
b) June 12 – August 16, 2006: 4 × EPOCH. CT showed progression in the form of mediastinal tumor enlargement, nodular progression in the right and left supraclavicular areas, metastasis foci in lungs;
c) 1 × CN3OP. Clinically, general symptoms intensified (fever, night sweats, itching) and did not cease despite steroid therapy.

The patient was disqualified from non-standard treatment with CD34+ cells transplantation from non-related donor. Due to a rapid, symptomatous progression of lesions in the mediastinum, the patient received palliative radiotherapy focused on the tumor area. After 3 months, further progression occurred. The patient died in February 2007, 3 months after the completion of radiotherapy and 15 months after diagnosis. When it was possible to perform more detailed immunohistochemical tests in November 2009, the antibodies panel was extended to include transcription factors and Bcl2, Bcl6, MUM1, CD23, Fascin and Ki67. Neoplastic CD20+ cells showed also positive reactions to PAX5 and Oct2, with the intensity comparable to that of B-lymphocytes reactivity. The cells did not display staining when reacting with BOB1. In reacting with Fascin, all neoplastic cells showed a strong, cytoplasmic positive reaction. A positive, strong reaction to MUM1 and Bcl2 was revealed in the majority of the cells. And, what should be emphasized a strong, positive reaction to CD23 was displayed. The last reaction is more typical of PMBL, where it occurs in about 75% of the cases [1]. It has been also described to occur in CHL, but far more rarely. Mitotic activity – Ki67 occurred in about 50% of the neoplastic cells. The cells showed negative reactions to CD10, Bcl6, CD3 markers.

In the described case, a discordance between the morphological characteristics indicating NSCHL and phenotypic characteristics with a strong expression of CD20 in line with large B-cells lymphoma can be noticed. Finally, the case was qualified as MGZL (Fig. 1, 2).

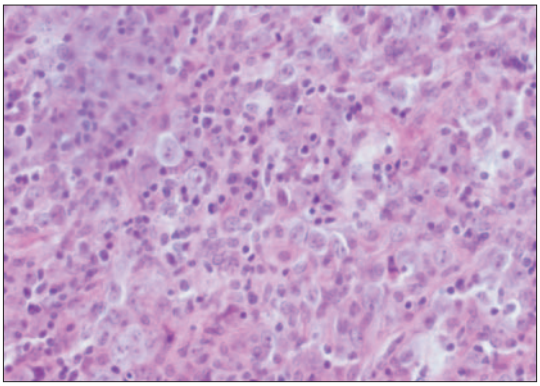

Fig. 1. Case 1. Lacunar cells and inflammatory background [HE 200×]

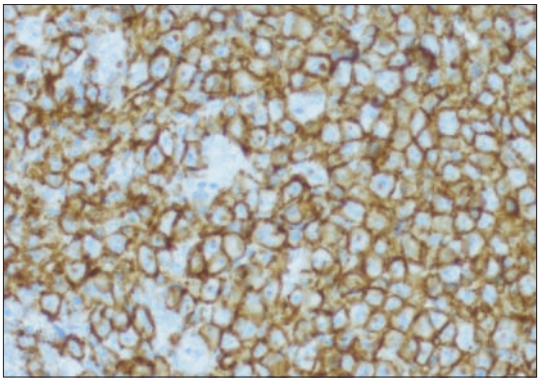

Fig. 2. Case 1. CD20 is strongly positive in the neoplastic cells [Magn. 200×]

Case 2

The patient, W.S., 27 years old, was diagnosed in October 2007 due to dry cough, effort dyspnea with lymphadenopathy in the supraclavicular area. Clinically: superior vena cava syndrome and both supraclavicular lymph nodes enlarged to 20 mm were revealed. CT of the anterior mediastinum revealed: large heterogeneous pathological mass 136 × 85 mm, extending in its anterior part the mediastinum and penetrating the wall of the chest involving interior pectoral muscle. General symptoms were present – night sweats. Laboratory tests revealed: ESR – 109/115 mm/h, LDH – not assayed. Uric acid and blood picture within normal range. Histopathological examination was performed on small specimens of the mediastinal tumor. Morphological characteristics were in line with CHL, nodular sclerosis NSII or LD. Pleomorfic, "sacomatous" H/RS cells were present, forming foci on fibrotic stroma. They were accompanied by small lymphocytes and a small number of neutrophil granulocytes. In some specimens there were thick collagen strands. Immunohistochemical characteristics were surprising – large cells showed strong positive reactions to CD20+, weak to CD30+ and weak to CD15+ in rare cells. On the basis of the morphological and phenotypic characteris-

tics (CD30+, CD15+), the mediastinal tumor was recognized as Hodgkin lymphoma, nodular sclerosis G2 with an expression of CD20+. From November 11, 2007 to April 4, 2008, the patient received 4 × ABVD, and due to the disease progression, from July 7 to July 31, 2008, chemotherapy according to the 2 × ICE scheme. From the onset of the treatment, the disease was resistant to the administered chemotherapy. The patient was qualified for non-standard procedure of CD34 cells transplantation from a related donor. The patient died during the preparation for the transplantation procedure due to disease progression 15 months from its diagnosis in February 2009.

In additional IHC tests, neoplastic cells showed a strong expression of PAX5 and Oct2 (like reactive B-lymphocytes) and in some cells a weak expression of BOB1. The majority of neoplastic cells were Bcl2+, Bcl6+, Fascin+. All cells were MUM1+. Mitotic activity was high – Ki67 in about 75% of the cells. Negative reactions were revealed to anti-CD10 and CD23 antibodies. Additionally, we performed a test with Epstein-Barr virus antibody (Epstein-Barr virus – latent membrane protein, EBV LMP), and the reaction was negative. Additional immunohistochemical tests, with Oct2+, BOB1+, Bcl6+, may suggest PMBL or MGZL (Fig. 3, 4).

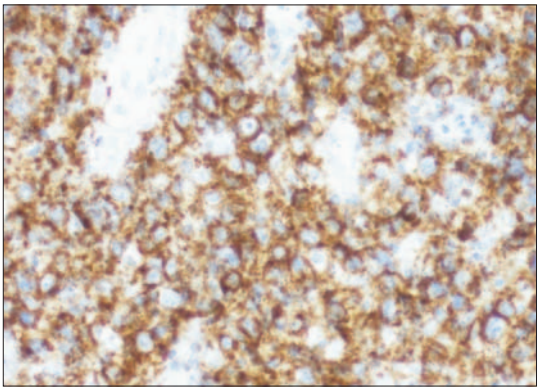

Fig. 3. Case 2. CD20 is strongly positive in the neoplastic cells [Magn. 200×]

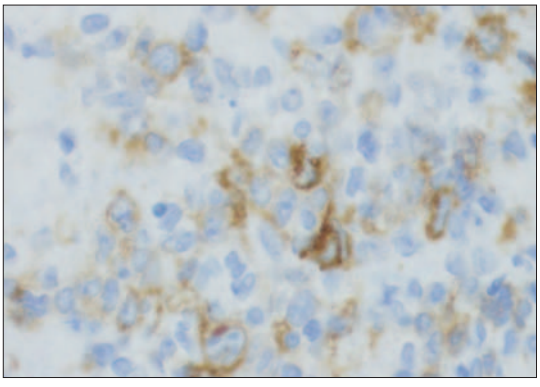

Fig. 4. Case 2. CD30 is strongly positive in some neoplastic cells [Magn. 200×]

Case 3

A 31-year-old patient, J. P., was diagnosed in January 2005 due to effort dyspnea**,** cough, periodic hemoptysis. The patient manifested general symptoms such as: night sweats and fever. Physical examination revealed: both supraclavicular lymph nodes enlarged to 15 mm, left axillary lymph node to 30 mm, and CT revealed: mediastinal tumor of 104×11×130 mm. Laboratory tests: raised ESR level to 80 mm/h, LDH 1280 (N; to 450). Bronchoscopy revealed: tumor occluding the aperture of the right upper and intermediate bronchus from which specimens were taken for histopathology testing. The morphological and phenotypic characteristics were in line with PMBL. In fibrotic stroma there were large cells showing a strong expression of CD20+, CD30+ (in a small number of cells), CD15– and a strong mitotic activity Ki67+++. The specimens also presented necrotic tissue and numerous *Aspergillus fumigatus* colonies.

In the mediastinal specimen primary mediastinal large B-cell lymphoma was diagnosed. From February 9, 2005 to April 14, 2005, the patient received chemoimmunotherapy according to the 4×R-CHOP scheme, 21-days rhythm. Simultaneously, she received antifungals (Fluconazole). In control CT after 4 courses of chemotherapy, disease stabilization was manifested. After 4 months, during chemotherapy of the 1st stage a specimen was taken for histopathology analysis: left axillary lymph node. The morphological characteristics were in line with the syncytial variant of NSCHL. Neoplastic cells showed a strong expression of CD30+ (membrane and perinuclear activity), expression of CD20+, alike in all cells, but weaker than in the surrounding reactive B-lymphocytes. Large cells were LCA– and CD15–. In the node it was recognized: CHL, nodular sclerosis, G2. Because of no reaction to chemotherapy of the 1st stage, the patient was qualified for ASCT+HDT – high dosage chemotherapy supported with transplantation of autologous hematopoietic cells. From May 6, 2006 to August 8, 2006, the patient received chemotherapy of the 2nd stage according to the 4×ICE scheme, 21-days rhythm. Imaging examinations showed only disease stabilization. Following apheresis of CD34+ cells while waiting for HDT+ASCT procedure, the patient received maintenance treatment according to the 5×CN3OP scheme, 21-days rhythm. Due to the activation of *Aspergillus fumigatus* infection, the patient received antifungal medication (voriconazole) until fungal infection was eradicated. At that time the neoplasm progressed. The patient received 4×ESHAP, 21-days rhythm. From October 13 to 17, 2006, the patient received chemotherapy according to the BEAM scheme, supported by the transplantation of autologous hematopoietic cells (October 20, 2006). PET showed complete remission. In January 2009, progression of the disease was found in the chest (CT and PET examinations). The patient refused consent to confirm the diagnosis via thoracotomy. From February 2009 the patient received 6×ABVD, achieving complete remission confirmed by PET. From October 19 to November 14, 2009, the patient received radiotherapy focused on the changes in the chest. Follow up PET (March 2010) is ambiguous – post-radiation changes or active pleonasm. The patient remains under observation – control ex-

amination is scheduled after 3 months. Additional ICH analysis performed in September 2009 confirmed the diagnosis of mediastinal PMBL, i.e. large cells were: LCA(CD45)+, CD20+, PAX5+, Oct2+, BOB1+, Bcl2+, MUM1+. A small number of cells showed a positive membrane expression of CD30+. Mitotic activity was high – Ki67+ in about 85% of the cells. Pleonasm cells reacted negatively to the following markers: CD15, Fascin, Bcl6, CD10 and CD23. Additional, supplementary examinations of the node also confirmed the previously established diagnosis of Hodgkin lymphoma. Transcription factors Oct2 and BOB1 were negative, PAX5 was positive, but considerably weaker in comparison to reactive B-cells. In the majority of the cells the expression of Fascin, MUM1, Bcl2 was observed and of CD23 in about 30% of the cells. Mitotic activity was high – Ki67+ in about 70% of the cells. There were negative reactions with: Bcl6, and CD10 markers. Within 4 months the patient was diagnosed with PMBL in the specimen of the tumor occluding the bronchus and NSCHL in the axillary lymph node. Thus, there were either two simultaneously progressing neoplastic processes or the case could be classified as MGZL, according to the definition provided by the new WHO classification, so NSCHL in the node should be seen as PMBL recurrence (Fig. 5–8).

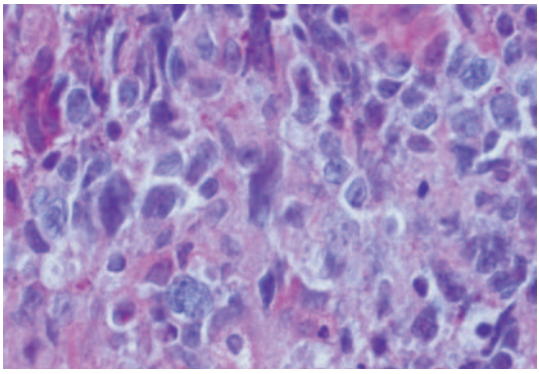

Fig. 5. Case 3. PMBL. Morphologically PMBL displays significant pleomorphism [PAS 400×]

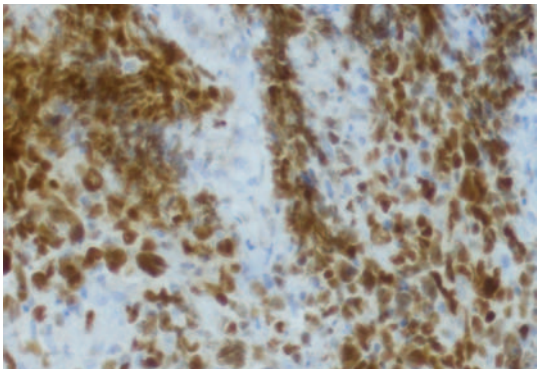

Fig. 6. Case 3. PMBL. PAX5 is strongly positive in the neoplastic cells [Magn. 200×]

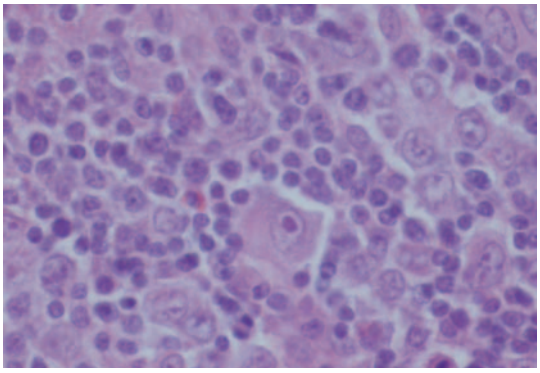

Fig. 7. Case 3. NSCHL. Lacunar cell and inflammatory background [HE 400×]

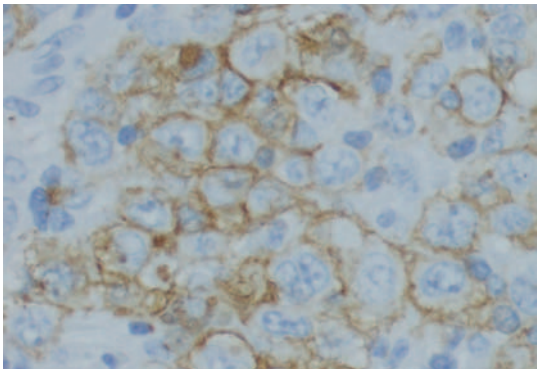

Fig. 8. Case 3. NSCHL. CD20 is positive in the neoplastic cells [Magn. 400×]

DISCUSSION

Differential diagnosis between NSCHL and PMBL is sometimes extremely difficult. In routine immunodiagnostics of CHL the following panel of antibodies is recommended: CD45, CD30, CD15, CD20, CD3 [3, 5, 11, 15]. It is, however, insufficient in diagnostically difficult cases such as the syncytial variant of NSCHL, especially when the specimen examined is small. Such a specimen may consist only of necrosis with the neoplastic cells surrounding it, in which it may be extremely difficult, if not impossible, to recognize diagnostic H/RS cells. If neoplastic cells are CD30+ and CD15+, but LCA– and CD20–, NSCHL diagnosis is obvious. However, H/RS cells show the expression of CD20+ in about 30% of all CHL cases [5, 11, 15] but the intensity of the reaction is generally weaker in comparison to reactive B-lymphocytes and it is heterogeneous. Such a picture of CD20 reaction in neoplastic cells, with a simultaneous positive membrane and perinuclear activity of CD30 and CD15 strongly indicates NSCHL. It happens, however, that the cells are CD20+ and CD30+, but CD15–, or CD20+ and

CD15+, but CD30–. Then, it is helpful to extend the IHC panel to include the following antibodies: transcription factors PAX5, Oct2, BOB1 and fascin [3–5, 10, 11, 15, 18]. PAX5 is positive in the majority of Hodgkin lymphoma cases, while BOB1, Oct2 are usually negative or, rarely, only one of them shows a weak expression. Fascin may also be helpful as it is a good marker of H/RS cells, giving a strong cytoplasmic reaction. Only 15% of non-Hodgkin lymphomas show positive staining for Fascin.

The morphological characteristics of PMBL are very diverse [6, 12–14, 16]. Specimens taken from mediastinal tumors via mediastinoscopy or surgical biopsy are often small and may be crushed. In the biopsy material all histological components of PMBCL are not always visible. Thus, if neoplastic cells look similar to H/RS cells, and fibromatosis is in the form of thick collagen strands instead of the expected thin connective tissue fibers, differential diagnosis with NSCHL is very difficult. PMBL cells have positive B-cells reactions such as CD20 and CD79a, and they are strong and identical in all cells, with a simultaneous strong expression of CD45(LCA). CD30 is present in about 80% of the cases, expression is however weak and uneven in comparison to that in Hodgkin lymphoma. A positive reaction to CD15 is present sporadically [6, 12, 16]. Tumor cells frequently display a positive reaction to MUM1 and CD23 in about 75% [1]. Reaction to Bcl2 is positive in 55–80%, and to Bcl6 in 45–100% [5, 8]; CD10 is rarely positive – in 8–32% [5, 8]. Transcription factors: PAX5,Oct2, BOB1 are positive [6, 12, 16]. It should be underlined that secondary involvement of the mediastinum in the course of DLBCL is more frequent than its primary involvement in PMBL. Consequently, differential PMBL diagnosis must encompass both NSCHL and DLBCL. Clinical data is also very important. Young age of the patient, involvement of the mediastinum, and potentially of supraclavicular nodes, without the involvement of other nodes and marrow, with a typical morphological characteristics of fibrosis indicate PMBL.

Cases described in literature as "grey zone lymphomas" or "large B-cell lymphomas with Hodgkin's features" [7] represent tumors which have both PMBL and CHL features. The new category in the latest WHO classification "B-cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL (Diffuse Large B-cell Lymphoma) and Classical Hodgkin Lymphoma" refers to such cases. They occur in the mediastinum but may also occasionally appear in other localizations. With regards to mediastinal tumors, recognizing grey zone lymphoma should be strictly limited to cases with overlapping features of PMBL and CHL, especially when there is a discordance between the morphological and immunophenotypic characteristics [2, 7–9, 17–19]. Two new subgroups have been identified in this respect:

1. Cases morphologically similar to CHL but with untypical features such as a large number of large mononuclear cells, no typical inflammatory setting and immunohistochemical reactions untypical for CHL – strong expression of CD20 and expression of CD79a;

2. Cases morphologically in line with PMBL but with phenotypic characteristics and features of CHL. The cells show weak reactions to CD20 or no reactions at all, but CD15 expression, if only focal, is noted in about 60% of the cases. Transcription factors of B-cells (PAX5, Oct2, BOB1) are usually positive, although often weak.

Complex lymphomas – NSCHL and PMBL and consecutive lymphomas, generally in the order of CHL first followed by PMBL are also classified as grey zone lymphomas, although it is not certain whether their biology is connected with lymphomas of overlapping features of CHL and PMBL. The creation of a new category – grey zone lymphoma, has taken the burden off pathologists in terms of responsibility in recognizing cases earlier impossible to diagnose unambiguously. The inclusion of a particular case to that group should be, however, careful and only after excluding all means to classify it as NSCHL or PMBL [8]. The extension of the IHC panel is absolutely vital.

CONCLUSIONS

1. Malignant B-cells lymphomas in mediastinal tumors involve cases of untypical clinical courses and untypical morphological and phenotypic characteristics.
2. It is necessary to re-examine recurrences, including other localizations than the primary ones.
3. Adequate, i.e. large enough, specimen taken during mediastinoscopy is the basis for the correct diagnosis.
4. In diagnostically difficult cases it is necessary to extend the immunohistological panel to include CD23 and transcription factors: PAX5, Oct2 and BOB1.

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CASE STUDY

DIAGNOSTIC DIFFICULTIES IN ALK+ ANAPLASTIC LARGE T-CELL LYMPHOMA IN CHILDREN

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ABSTRACT

Introduction. Lymphomas account for about 12% of malignant tumors in children, and anaplastic lymphoma for 10–20% of Hodgkin's and non-Hodgkin's lymphomas. Clinical symptoms associated with malignant tumors of the lymphatic system are not specific. Diagnosis of these tumors is particularly difficult in the absence of a visible tumor or enlarged peripheral lymph nodes, especially when the symptoms may suggest other, far more common diseases such as infections. Extensive clinical diagnostic procedures, including the exploratory laparotomy, intensive symptomatic treatment and antibiotic therapy do not explain the nature of the disease, do not improve the condition of a patient and lead to the death of sick children. In these cases only an autopsy and histopathological examinations demonstrate the presence of anaplastic large T-cell lymphoma's infiltrates of internal organs, bone marrow and lymph nodes.

Aim. The aim of this study was to demonstrate that in the diseases of children in which it is difficult to establish a definite clinical diagnosis and an intensive antibiotic therapy does not cause any improvement, a neoplastic disease should be always taken into consideration.

Materials and methods. Analysis of the histo-clinical picture of a disease of a child who died due to ALK+ anaplastic large T-cell lymphoma. Diagnostic difficulties resulted in not establishing a clinical diagnosis. Despite conservative treatment, surgical procedure and an intensive antibiotic therapy, the death occurred. The diagnosis was established post-mortem on the basis of immunohistochemical tests: LCA, CD30, CD43, Granzyme B, ALK, CD20, CD3, MPO and Ki67.

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Case study and results. A 14-year-old boy went to the doctor because of abdominal pain and fever. After week-long treatment with antibiotic (Duomox, Astellas Pharma) acute symptoms subsided, but then relapsed after a month and the boy was admitted to the surgery department. Biochemical studies showed increased levels of inflammatory process markers and aminotransferases. Physical examination revealed positive peritoneal signs. With the suspicion of acute Meckel's diverticulitis, laparotomy and appendectomy were performed. During the surgery, a significantly enlarged right lobe of liver was found. Antibiotic treatment was administered and after a few days following the surgery the symptoms subsided. On the 5th day after the surgery the patient's condition deteriorated and on the 8th day he died. The diagnosis was established on the basis of autopsy: ALK+ anaplastic large T-cell lymphoma (LCA+, CD30+, CD43+, ALK+, Granzyme B+, Ki67+ in 85% of cells).
Discussion and Conclusions. Cooperation and efficient communication between the clinician and pathologist are important and necessary in all cases when it is difficult to establish a correct and rapid diagnosis. If in an inflammatory disease the patient's condition is deteriorating despite an intensive antibiotic therapy, the neoplastic disease should be always taken into consideration and the diagnostics should focus on searching for a tumor.

Key words: anaplastic lymphoma, large T-cell, ALK+, children.

INTRODUCTION

Malignant tumors of childhood account for approximately 2% of all neoplasms; however in the 0–15 age group, tumors are the main cause of deaths, followed by accidents and poisonings [5, 9]. The most common malignancies in childhood are the non-epithelial malignant tumors derived from the hematopoietic and nervous systems and from the soft tissues. Non-Hodgkin's and Hodgkin's lymphomas account for about 12% of malignant tumors in children [13, 16–18, 23]. Anaplastic large T-cell lymphoma (ALCL) represents 10–20% of Hodgkin's and non-Hodgkin's lymphomas in childhood [7, 13]. ALCL prevails in the 10–14 age group with the male predominance (ratio M : F is as 3–6 : 1) [10, 22]. It was first described in 1985, belongs to a heterogeneous group of anaplastic lymphomas made up of cells showing the cytokine receptor CD30 expression. About 60% of ALCL [2, 3, 6] show a positive immunohistochemical reaction to the presence of anaplastic lymphoma kinase (ALK) – the product of a gene resulting from a chromosomal translocation t(2;5)(p23;q35) on chromosome 2 [4]. In 85% of ALCL cases ALK is linked to the nucleophosmin (NPM–ALK). In the WHO classification (2008) two types: ALK + ALCL, showing ALK expression (in the cytoplasm and nucleus – NPM–ALK, or in the cytoplasm solely – ALK) and ALK–ALCL**,** were isolated as two new disease units. ALK–ALCL

does not show ALK expression, but it also occurs in the 6th and 7th decade of life and is characterized by a worse prognosis as compared to ALK + ALCL [1, 8, 15, 25, 26]. ALK+ALCL is derived from the activated mature cytotoxic T-lymphocytes [11]. The most common form of tumor is characterized morphologically by the presence of large, pleomorphic cells with relatively abundant cytoplasm and eccentrically located, kidney-shaped nuclei, with distinct nucleoli.

There are also lymphohistiocytic variants, from small cells, and Hodgkin-like variants [2, 4, 19, 20]. In the case of primarily systemic ALCL, the lymph nodes as well as other organs, particularly: skin, bones, also soft tissues, lungs, liver, can be involved [5, 19, 20]. There are also known cases of primarily central nervous system ALCL in children, although they are extremely rare [14]. At the time of ALCL diagnosis most of patients (about 70%) present the III and IV stages of the disease. Peripheral lymph nodes involvement and tumor infiltrations of different tissues and organs are present [10, 12, 26]. General symptoms arising in the course of lymphoma are nonspecific and may significantly precede its clinical manifestation. High fever occurs in 75% of cases. Other symptoms include: night sweats, weight loss, itchy skin [12, 21, 22, 24].

AIM

The aim of this study is to demonstrate that in the disease of children in which it is difficult to establish a definite clinical diagnosis and an intensive antibiotic therapy does not cause any improvement, a neoplastic disease should be always taken into consideration.

MATERIALS AND METHODS

Analysis of the histo-clinical picture of the disease of a child who died due to ALK+ anaplastic large T-cell lymphoma. Diagnostic difficulties resulted in not establishing a clinical diagnosis. Despite conservative treatment, surgical procedure and an intensive antibiotic therapy, the death occurred. The diagnosis was established postmortem on the basis of immunohistochemical tests: LCA, CD30, CD43, Granzyme B, ALK, CD20, CD3, MPO and Ki67.

CASE STUDY AND RESULTS

A 14-year-old boy went to the doctor because of abdominal pain and fever. After a week--long treatment with antibiotic (Duomox) acute symptoms subsided, but then relapsed after a month and the boy was admitted to the surgery department. Biochemical studies showed increased levels of inflammatory process markers and aminotransferases.

Physical examination revealed positive peritoneal signs. With the suspicion of acute Meckel's diverticulitis, laparotomy was performed. During the surgery, a significantly enlarged right lobe of liver was found. An appendectomy was performed, antibiotic treatment was administered and after a few days following the surgery the condition of the patient slightly improved. On the 5th day after the surgery, body temperature increased above 39°C, which was accompanied by limb pain in distal parts. The patient was transferred from the surgical department to the department of pediatrics, in a medium-severe general condition. Imaging diagnostics was performed revealing a tumor-like enlargement of the right lobe of liver. Treatment implemented: intensive antibiotic therapy, plasma transfusion, symptomatic treatment. Despite the treatment the condition of the patient deteriorated. On the 8th day of stay in the department of pediatrics the patient died. Diagnosed with sepsis and a disseminated neoplastic process, the body was sent to post-mortem investigation.

Autopsy revealed: tumor-like enlargement of liver (2 kg) with clearly increased consistency, pneumonia.

Microscopically: tumor infiltrations of lungs, liver, pancreas, stomach, kidneys, spleen, abdominal and mediastinal lymph nodes and bone marrow. In the vessels: tumor embolism. Tumor cells were large, pleomorphic with abundant cytoplasm, eccentrically located nuclei and multiple mitotic figures. Moreover, pneumonia, adult hyaline membrane syndrome, and myocarditis were found.

Immunohistochemical (IHC) tests were performed: LCA, CD30, CD43, ALK, CD20, CD3, Granzyme B, MPO and Ki67. The neoplastic cells showed the expression of LCA, CD30, CD43, ALK, Granzyme B, Ki67 in 85% of the cells. Based on the morphological characteristics and immunohistochemical tests, the diagnosis was established: ALK+ anaplastic large T-cell lymphoma (Fig. 1–8).

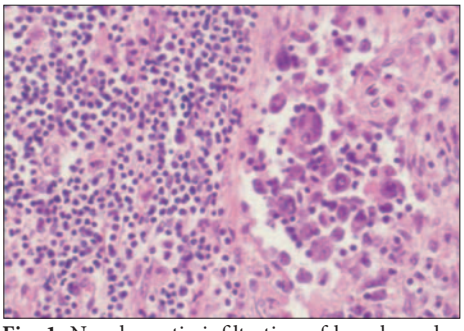

Fig. 1. Neoplasmatic infiltration of lymphonodus [HE 100×]

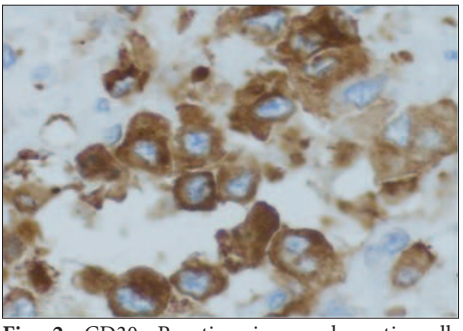

Fig. 2. CD30. Reaction in neoplasmatic cells [Magn. 200×]

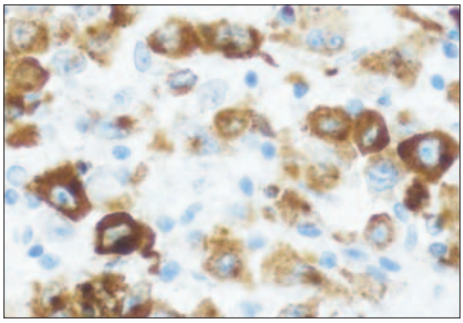

Fig. 3. Granzyme B. Reaction in neoplasmatic cells [Magn. 200×]

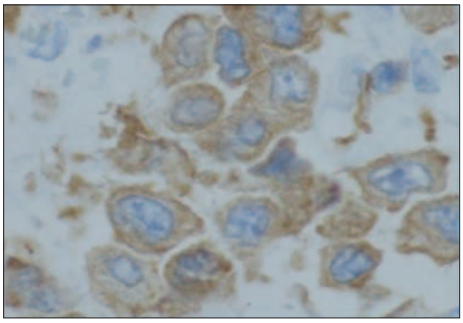

Fig. 4. ALK+. Reaction in neoplasmatic cells [Magn. 400×]

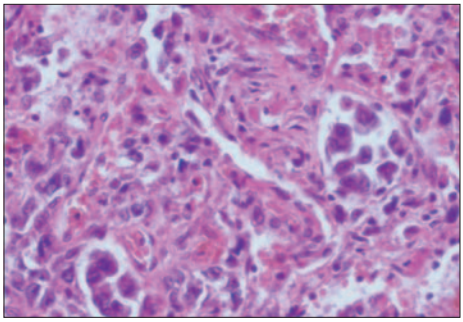

Fig. 5. Neoplasmatic infiltration of the lung [Magn. 200×]

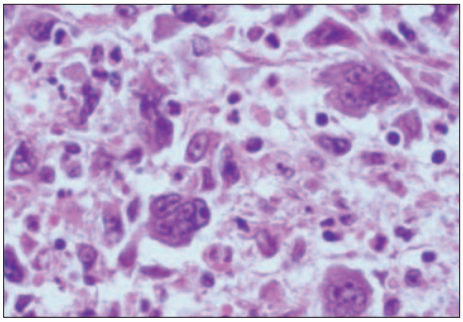

Fig. 6. Neoplasmatic infiltration of the spleen [Magn. 200×]

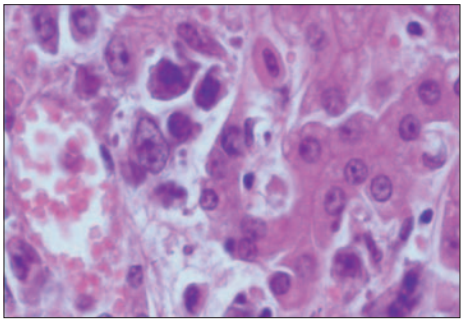

Fig. 7. Neoplasmatic infiltration of the liver [Magn. 200×]

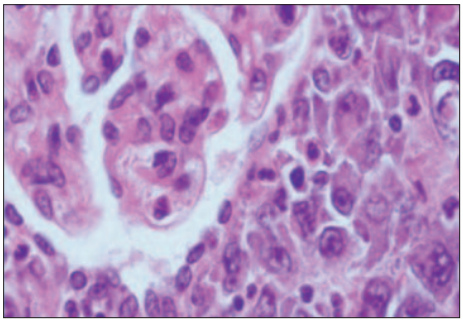

Fig. 8. Neoplasmatic infiltration of the kidney [Magn. 200×]

DISCUSSION

The observed boy was 14 years old. Therefore, he belonged to an age group in which ALCL predominates, as observed by other authors [10, 22]. Establishing a diagnosis post-mortem was possible based on the morphological characteristics and IHC tests

of specimens. The results were in line with the observations of other authors involved in the differential diagnosis of lymphomas in children, who point out diagnostic difficulties [2–4, 6]. Tumor infiltrations, observed by us, were made up of large pleomorphic cells with relatively abundant cytoplasm, eccentrically located nuclei, distinct nucleoli, and reflect the pictures described in literature [2, 4, 19, 20]. Contrary to most frequently described clinical pictures of this neoplasm, in our case there was no enlargement of peripheral lymph nodes [5, 19, 20]. But, similarly to other authors' descriptions, the general symptoms, i.e. weakness and fever, were typical of lymphatic system tumors and could have preceded clinical manifestations [10, 12, 26]. The whole clinical course could have been confusing. Therefore, establishing the correct diagnosis during the child's life was difficult.

CONCLUSIONS

1. In the diagnosis of anaplastic large T-cell lymphoma, ALK+, the immunohistochemical tests of specimens from tumor infiltrates are crucial.
2. At the time of ALCL diagnosis, III–IV stages of the disease are prognostically unfavorable.
3. If in an inflammatory disease the patient's condition is deteriorating despite an intensive antibiotic therapy, the neoplastic disease should be always taken into consideration and the diagnostics should focus on searching for tumor.
4. Cooperation and efficient communication between the clinician and pathologist are important and necessary in all cases when it is difficult to establish a correct and rapid diagnosis.

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Pol. Ann. Med., 2010; 17(1): 91–100.

CASE STUDY

HISTIOCYTIC SARCOMA IMITATING TUMOR OF THE PANCREATIC TAIL – A CASE STUDY

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ABSTRACT

Introduction. Histiocytic sarcoma (HS) is a very rare and diagnostically difficult malignant neoplasm arising from dendritic cells and histiocytes. Its microscopic image is not specific, so the diagnosis of HS requires a wide panel of immunohistochemistry tests to exclude tumors with similar morphology, but of completely different origins. While diagnosing HS, cancers, other sarcomas, lymphomas and malignant melanoma should be excluded as well.

Aim. The aim of this paper was to present a case of HS imitating tumor of the pancreatic tail in a 58-year-old woman.

Case study. Intraoperative diagnosis was as follows: solid-cystic tumor of the pancreatic tail region, penetrating into the mesocolon and occluding the colon by pressing against it. Resection of the pathologic mass and tail of the pancreas, as well as total colectomy were performed. On the basis of postoperative histopathologic evaluation of the surgical specimen and a wide immunohistochemical panel, we excluded epithelial and myogenic origins of the tumor. Gastrointestinal stromal tumor, extramedullary myeloid tumor, lymphoma, neural tumors and malignant melanoma were also excluded. Histopathologic and immnohistochemical findings, compared to other authors' findings led us to the diagnosis of histiocytic sarcoma. Complete resection of the tumor was performed, with sufficient margins of the healthy tissues.

Physical examination and imaging performed three months after the surgery revealed features of the local recurrence, infiltration of the back wall of the stomach with a major compression of the gastric lumen. Metastatic foci in regions of left ap-

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pendages and lower pole of the left kidney, multiple small hypodensic areas in the liver and enlarged paraaortal and mesenterial lymph nodes were also found.
Discussion. HS is a very rare and diagnostically difficult malignant tumor. Microscopic image is non-specific, that is why the diagnosis of HS requires a wide histochemical panel to exclude tumors with similar morphology, but of completely different origins. Analysis of negative immunohistochemical studies, results of: CD68, LCA(CD45), CD4, CD30, CD31, Fascin, CD43, CD15, CD34, and comparing them with the results obtained by other authors led us to the diagnosis of HS. Clinical prognosis is negative and the most frequent course of the disease is aggressive.
Conclusions.
1. Despite the rare prevalence of the tumor, there are numerous, well documented and immunohistochemically confirmed reports of histiocytic sarcoma and its gastrointestinal localization. That is why in a differential diagnosis of gastrointestinal tract-located tumors, sporadically occuring neoplasms should be also taken into account.
2. Diagnosis of HS requires a wide panel of immunohistochemistry tests to exclude tumors with similar morphology, but of completely different origins.
3. Recurrence of a neoplastic process in the described case confirms that, despite a surgical and microscopically total excision of the tumor, HS prognosis is negative and the course of the disease is very aggressive.

Key words: histiocytic sarcoma (HS)

INTRODUCTION

Histiocytic sarcoma (HS) belongs to the group of neoplasms derived from dendritic cells and histiocytes. The WHO classification distinguishes in this group eight types of proliferations of dendritic cells and histiocytes. These are very rare neoplasms, of which HS and interdigitating dendritic cell sarcoma have a negative prognosis and are usually characterised by a very aggressive clinical course [2, 3, 8, 13, 16]. About 10% of patients progress, in a short time, from localised, monoorgan to disseminated, multiorgan variant.

AIM

The aim of this paper was to present a case of HS imitiating tumor of the pancreatic tail in a 58-year-old woman.

CASE STUDY

A 58-year-old woman, non-smoking, denying the use of alcohol, after laparotomy at the age of 19 for a foreign body in a gastrointestinal tract lumen (swallowing of a needle),

complicated by an abscess, was admitted urgently to the Gastroenterology Department of Provincial Specialist Hospital in Olsztyn, in November 2009, for disturbing abdominal symptoms. On admission, the patient complained of constipation, lasting for 6 months, accompanied by a persistent tenesmus, feeling of an incomplete defecation and abdominal pain of a changeable nature. According to a clinical history, in 2003 the abdominal cystic tumor was performed revealing a cyst localized between the pancreatic tail and spleen. Since then, no progression in the imaging studies was observed.

Physical examination revealed paleness, post-surgical scar from the sternum to the pubic symphysis, abdominal obesity, mild systolic, mitral valve murmur, palpational tenderness and a mass of the left lumbar region.

Laboratory studies revealed: normocytic anemia (Hb 10.0 mg/dL), thrombocytosis. Tumor markers (CEA and Ca 19.9) were within normal range.

Colonoscopy findings: tumor, almost entirely occluding the intestinal lumen, 40 cm from anal sphincters (Fig. 1). Specimens for histopathological examinations were taken. Microscopic verification showed only the presence of necrotic-inflammatory masses. Abdominal sonography extended the diagnosis: a solid-cystic tumor, $14 \times 8 \times 9$ cm, near the pancreatic tail and adhering to the stomach wall was found (Fig. 2, 3). A solitary, hypogenic lymph node was revealed in the near proximity. Other organs of the abdominal cavity were normal. The physician performing USG suggested an intestinal wall origin of the tumor. Upper gastrointestinal tract endoscopy revealed features of erythematous gastropathy with a negative urease test.

Taking into account clinical signs of subileus, with endoscopically and USG suggested presence of a tumor growth, after surgical consultations the patient was qualified for surgery.

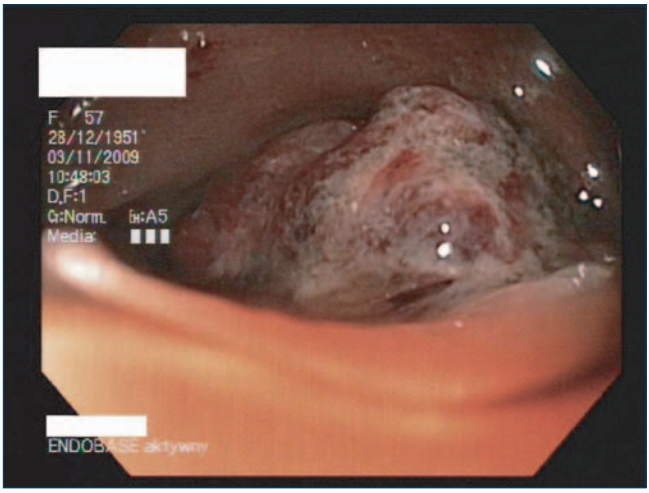

Fig. 1. Colonoscopy. Tumor mass protruding into the colon lumen

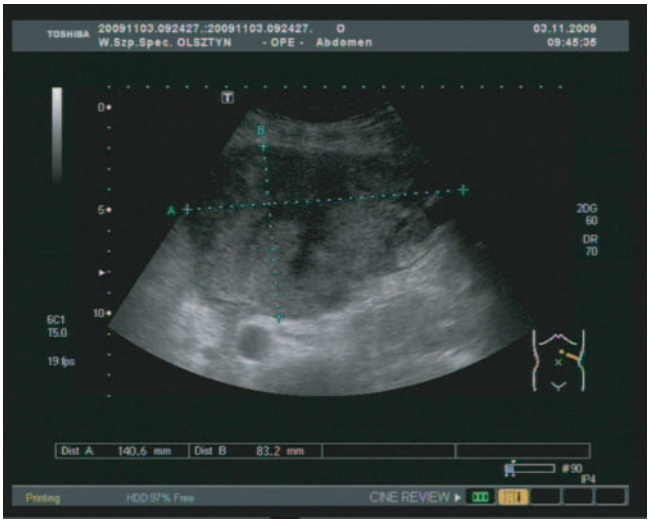

Fig. 2. Abdominal ultrasonography. Tumor-like, cyst-structured lesion in the area of the pancreatic tail

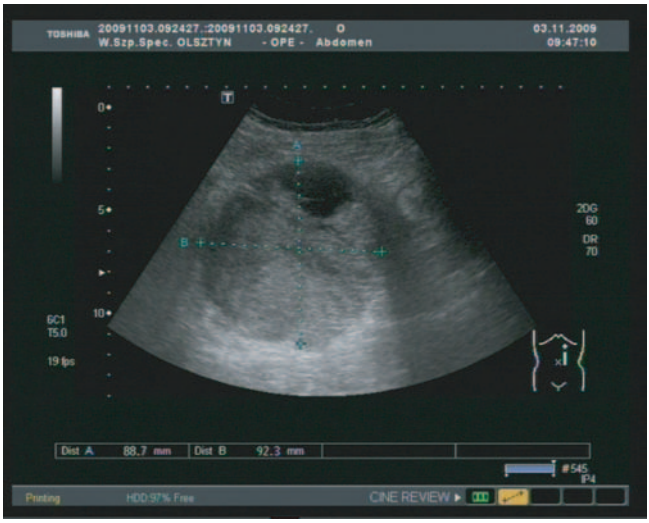

Fig. 3. Abdominal ultrasonography. Tumor-like, cyst-structured lesion in the area of the pancreatic tail

Intraoperative diagnosis was as follows: solid-cystic tumor of the pancreatic tail region, penetrating into the mesocolon and occluding the colon by pressing against it.

Resection of the pathologic mass and tail of the pancreas as well as total colectomy were performed. Morphotic elements were infused. Surgery was not followed by any complications. The patient was released from hospital on the 9th day.

Histopathological evaluation of the surgical specimen, with a wide immunohistochemical panel, led to the diagnosis of HS. Tumor was resected totally, with sufficient microscopic margins of the healthy tissues.

The patient remained under Oncology Outpatient care. A month later USG was performed revealing liquid containing an echogenic mass, 9.5 × 5 × 3 cm, in the left hypochondriac region, and a spleen enlargement.

DISCUSSION

HS is a very rare and diagnostically difficult malignant tumor. Its name was introduced in 1970 by Mathe et al. [10]. Microscopic image is non-specific, that is why the diagnosis of HS requires a wide histochemical panel to exclude tumors with similar morphology, but of completely different origins. While diagnosing HS, cancers, other sarcomas, lymphomas and malignant melanomas should be excluded.

In the described case, the surgical specimen consisted of part of an intestine 25 cm long with a mesocolonic tumor: 15 × 13 × 10 cm, cherry-brownish, infiltrating the intestinal wall. Microscopic examination revealed diffuse tumor infiltration consisting of large, epithelioid cells with acidophilic cytoplasm, with oval to irregular nuclei, often with irregularly folded surface, some of them with clearings containing distinct nucleoli; numerous multinucleated cells were also present (Fig. 4, 5). Part of the tumor showed sarcomatoid areas – spindle cells arranged in storiform pattern (Fig. 6, 7). Immunohistochemical tests excluded: epithelial (CK7–, CK20–, CDX2–), and myogenic origins of tumor (Desmin–, SMA–), gastro-intestinal stromal tumor (GIST) (CD117–), extramedullary myeloid tumors (MPO–), lymphoma (CD3–,CD20–), nervous system derived tumors and melanoma (S100–), metastasis from ovary (CA125–). Analysis of those negative immunohistochemical studies, as well as following results: CD68+, LCA(CD45)+, CD4+, CD30–, CD31+, Fascin–, CD43–, CD15±, CD34–, and comparing them with the results obtained by other authors [4–7, 9, 13, 16] led us to the diagnosis of HS.

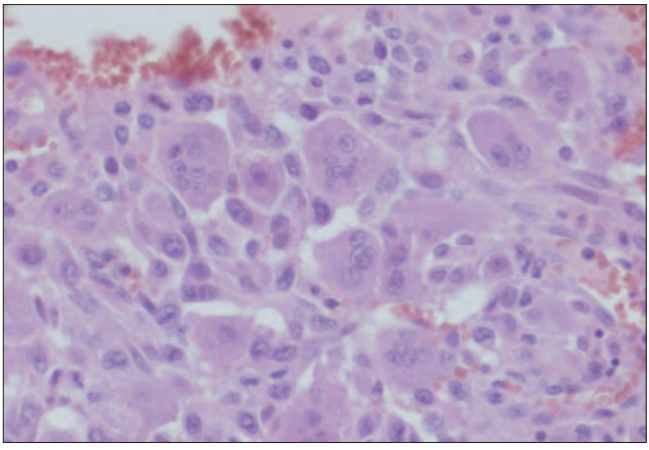

Fig. 4. HS. Multinucleated giant cells [HE 200×]

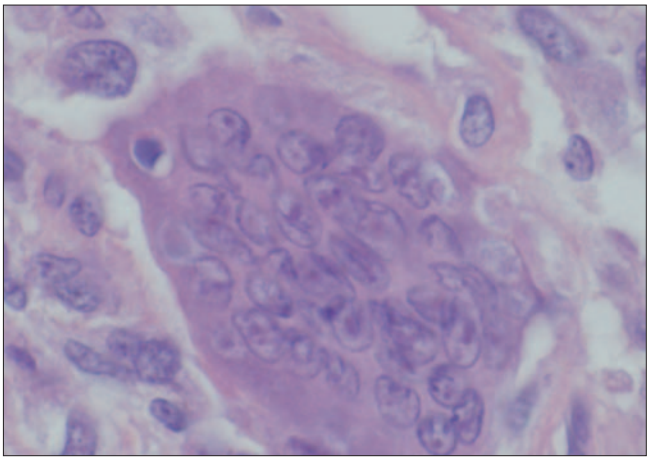

Fig. 5. HS. Multinucleated giant cell [HE 600×]

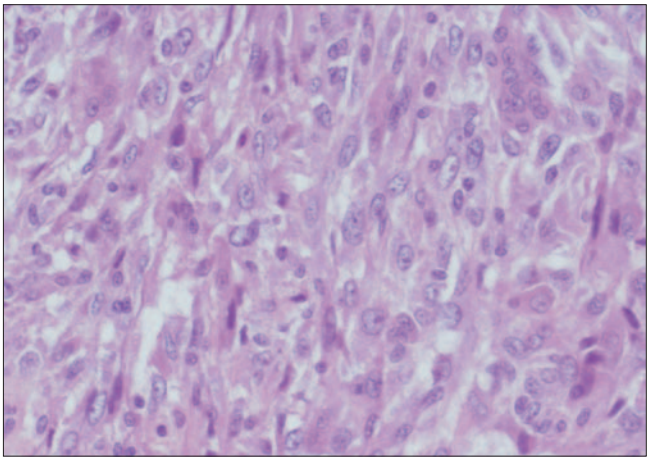

Fig. 6. HS. Sarcomatoid architecture of the tumor [HE 200×]

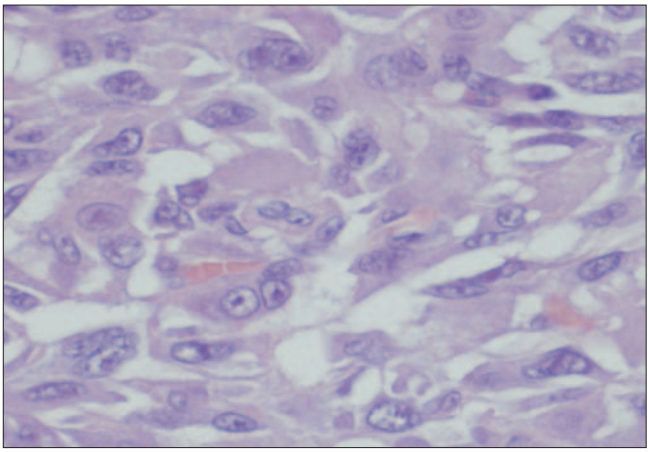

Fig. 7. HS. Sarcomatoid architecture of the tumor [HE 200×]

The patient was hospitalized again in March 2010 with symptoms of gradually increasing weakness, headache and dizziness, lack of appetite, meteorism, nausea, and dark stools present.

In laboratory tests severe anemia and increased levels of glucose were observed.

Endoscopic examination of the upper gastrointestinal tract revealed infiltration of the posterior wall of the stomach, with the presence of external pressure severly occluding gastric lumen. Mucous membrane of a changed surface was fragile and easily bleeding.

Cystic tumor imaging of abdominal cavity organs showed features of tumor recurrence with dissemination and partial occlusion of intestinal lumen – in the anatomical region of pancreas head and tail a mass, 12×14×15 cm, was found. It was pressing upon the stomach, reaching a pre-renal fascia (of a left kidney) with its focal infiltration, dislocating duodenum and jejunum loops. A similar mass, about 6×7×9 cm, was observed on the level of umbilicus, posteriorly from modelated, dislocated anteriorly jejunal loop, with the intestinal wall infiltration. Smaller foci were present in the region of left appendages on the level of lower left kidney pole (Fig. 8). Multiple hypodense foci, up to 4.5 cm, in the liver (Fig. 9) and multiple enlarged paraaortal and mesenteric lymph nodes were also found.

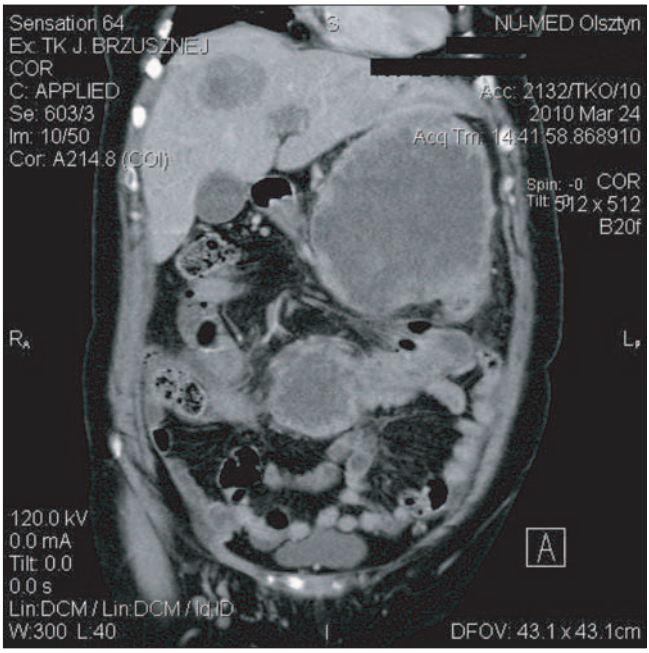

Fig. 8. Abdominal CT scan. Tumor masses in multiple localizations

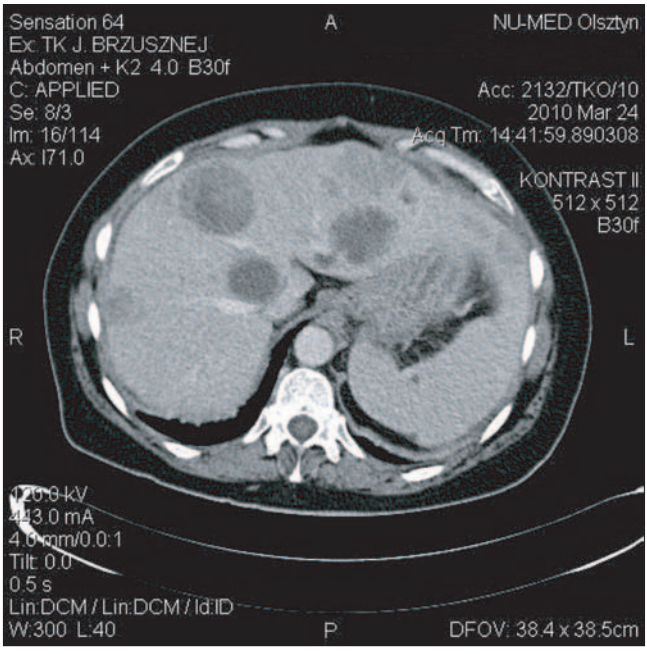

Fig. 9. Abdominal CT scan (liver). Multiple hypodensic areas

After oncology consultations, the patient was qualified for symptomatic treatment. Antalgic, spasmolytics and anti-emetic drugs were administered. After normalization of blood morphotic elements, the patient was released from hospital for further hospice, palliative treatment.

Despite the rare occurrence of histiocytic sarcoma, there are quite a few well documented and immunohistochemically confirmed cases of this tumor, including its gastrointestinal localization [1, 2, 11, 12, 15]. Clinical prognosis is negative and the most frequent course of the disease is aggressive [2, 3, 8, 13, 14, 17].

CONCLUSIONS

1. Despite the rare occurrence of histiocytic sarcoma, there are quite a few well documented and immunohistochemically confirmed cases of this tumor, including its gastrointestinal localization. That is why in a differential diagnosis of gastrointestinal tract-located tumors, sporadically occuring tumors should be also taken into consideration.
2. Diagnosis of HS requires a wide immunohistochemical panel to exclude tumors with similar morphology but of completely different origins.
3. Recurrence of a neoplastic process in the described case confirms that, despite a surgical and microscopically total excision of the tumor, HS has a negative prognosis and its course is very aggressive.

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OVERVIEW PAPER

VIRTUAL ENVIRONMENTS FOR REAL TREATMENTS

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Beit Rivka Geriatric Rehabilitation Center, Israel

ABSTRACT

Introduction. In the era of evidence-based practice, more evidence of the beneficial impact of physical therapy and rehabilitation interventions have emerged. Kwakkel and Wagenaar's meta-analysis, Carr and Shepherd's work relating to the motor learning concept, and Fiatarone's research of strength training, emphasize the influence of rehabilitation in outcome gains by demonstrating that in conjunction with the therapist's expertise, the most influencing factors are therapy frequency and intensity.
Aim. To show the problem which is the gap between this knowledge and reality.
Discusion. Recently published observational studies revealed that patients in rehabilitation facilities receive a very small amount of therapy time during rehabilitation. Virtual reality (VR) technology offers assistance, as it enables patients who have difficulties coping in the "real world" to gradually deal with their problems via the "virtual world". It provides the user with a real time interactive experience, through visual, audible, tactile or any other kind of feedback. Individuals find themselves in a pleasant, challenging, motivating and "inviting" functional environment, thus tending to forget their limitations or disability. In addition, VR encourages them to reach their goals which are difficult to achieve in any other treatment setting.
Conclusions. VR is a new, innovative technology utilizing virtual and adaptable worlds, created by sophisticated computer systems with improved graphic capability (hardware) and interactive software allowing one to interact "naturally" with the virtual environment, without the risk and cost of moving the patient into the "real world". The interactive experience is perceived by both, therapist and patient, as very positive, enabling treatment to continue over time without feelings fatigue or boredom. VR can be created through a variety of tools, simple to complex, cheap to expensive. Basic computer systems with different input and output devices, such as different

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types of monitors or expensive and sophisticated systems using helmets with small video screens head mounted display have been used.

Recently, cheap "on the shelf" video game consoles were adopted by clinicians as valuable tools in treating patients suffering from various pathologies and disabilities. Therefore, therapists are required to manoeuvre and plan treatments in systems where the delineation between therapy and fun is not always clear or controlled. The common practice has to be, as always, somewhere in between the most expensive and sophisticated systems and the "non adaptable" video game consoles. We estimate that in the near future, VR technology will be widely used. Meanwhile, today's technology allows us to take more of the VR advantages to the clinical world.

Key words: Virtual Reality, rehabilitation, physical therapy, occupational therapy.

INTRODUCTION

Virtual reality (VR) technology, a big disappointment during the late 1980s, made a big "come back" during the late 1990s, and was consequently discovered as a powerful instrument to be used in rehabilitation. This technology enables the patient to cope in the "real world" and to gradually deal with his problems via the virtual world. It provides the user with a real time interactive experience through visual, audible, tactile or any other kind of feedback. The individual finds himself in a pleasant and "inviting" functional environment, tending to forget his limitations or disability. In addition, VR encourages him to reach his goals which are difficult to achieve in any other treatment settings.

What is VR?

VR is a new, innovative technology utilizing virtual and adaptable worlds, created by sophisticated computer systems with improved graphic capability (hardware) and interactive software allowing one to interact "naturally" with the virtual environment (VE). A virtual story is constructed in the VE, which can be adjusted under laboratory conditions. VR technology creates a virtual simulation of real-time interactive environments. When using different senses and motor strategies, the patient can practice three-dimensional (depth, width, height) or two-dimensional virtual tasks. The VR experience is achieved by the user's immersion into the VE, thus facilitating the user's feelings of presence.

Technologies which create artificial worlds

VR can be created through a variety of tools, simple to complex, cheap to expensive. Basic computer systems with different input and output devices, such as different types of monitors or helmets with small video screens head-mounted dis-

play (HMD) have been used. In the HMD, video screen images are updated, using motion trackers, in accordance with the patient's head movements (Fig. 1).

Fig. 1. Head-mounted display and haptic glove

The image can also be projected on two or three walls of a room (cave). Adding sounds makes the VE much more realistic. The patient controls the VE by computer input devices, such as keyboards, joysticks, mouse, or more sophisticated devices such as speed motion detection trackers, various input–output accessories that enhance the sense of position by vibration or resistance to movement (haptic devices) and motion platforms.

Other systems use video caption technology to embed the participant's image into virtual stories, using complicated algorithms to allow the patient to control the story by body and limbs movements.

Researchers believe that the greater the immersion and sense of presence, the better the treatment results.

Clinical applications of VR systems

Hundreds of experimental and commercial systems have been used to diagnose and treat different illnesses and disabilities in almost all fields of medicine.

Many of the first VR applications were developed to treat phobias. A phobia is defined as an unrealistic fear of a situation and/or a specific object. The individual experiences irrational fear, unaware that it is not life threatening. This is the most common mental disorder, with one out of 10 individuals suffering at least one phobia during his lifetime.

Common phobias treated using VR software are: claustrophobia (fear of closed places), acrophobia (fear of heights), agoraphobia (fear of being in a public place), arachnophobia (fear of spiders), fear of flying, and more. The most common ap-

proach used in assisting phobia sufferers is through a controlled treatment situation, with gradual exposure to the phobia "generator" (desensitization). Gradual exposure is accomplished by accessing a virtual controlled world, with the patient feeling that he controls the situation. The VR software helps reduce stress and anxiety. Success rates are similar to those achieved by exposure to the real source of fear. In most cases, this treatment is more economical, safer and preferable to the patients [12, 16]. Rizzo developed a virtual classroom to help discover ADHD problems in children and to subsequently treat them [17]. The system "immersed" the child wearing an HMD into a virtual class. The child listens to the teacher conducting the class, however, simultaneously various distractions are heard, such as a car passing outside, noise of a paper aircraft flying through the room, etc. The system tracks the child's eye movements at any given moment. Therapists monitored the information to ascertain how the various events distracted the child, approximately how long it took for the child to reach a reasonable level of concentration, and then to determine if he suffered from attention deficit disorders [17].

Another VR system helped diagnose driving skills of stroke patients and determine whether they were capable of driving again. In the VR environment, the patient wore special 3D eyeglasses, an HMD or actually sat in a car and experienced a "road trip", taken with a special video camera creating a realistic scenario at 360°. When the patient "drove" on the road, the therapist evaluated the patient's decision making processes, i.e. how he reacted when a child suddenly crossed the road, if he was pressing the accelerator instead of the brakes, how he reacted in different weather situations (snow, rain), etc. [24].

VR is also used to treat post traumatic stress disorders (PTSD). The first therapeutic meaningful trial, with good results, related to soldiers returning from Vietnam suffering from PTSD [18, 19]. Weiss et al. from the University of Haifa, developed a new scenario to treat victims of terrorist attacks in Israel. The technique allowed a controlled exposure to the cause of the stress and helped the patient return to a normal life (Fig. 2).

Fig. 2. Virtual Vietnam

Hoffman et al. found that during physiotherapy treatment of patients with extensive burns, VR helped reduce pain by distraction [6]. It has also been applied in dental treatments and chemotherapy.

Applications in the rehabilitation world

During the mid to late 1990s, VR systems were developed for use in various areas of rehabilitation. In 1998, Ring suggested a potential use for VR in neurological rehabilitation [14].

One of the main goals in rehabilitation is to improve the quality and the quantitative performance of daily tasks and achieve independence in daily life [21, 22]. There are three guiding principles in rehabilitation therapy: early intervention, specific task training and multiple repetitions [10]. Rehabilitation therapy tasks are repetitive, can be "boring", distract the patient and reduce motivation [1, 15]. Treatment programs utilizing VR combine relevant experience with multi-sensory stimulation and an ecological valid environment, which is challenging, thus raising the motivation level of the patient. In recent years, technology has improved, thus facilitating the use of VR in research and clinical settings.

AIM

To show the problem which is the gap between this knowledge and reality.

DISCUSSION

Representative examples in the area of rehabilitation:

In 1998, Riva published a case report documenting a spinal cord injury patient walking on a treadmill embedded in a VR environment using a HMD [15]. Girolamo et al (1999) demonstrated that adding VR therapy is useful for treatment and assessment of vestibular problems [4]. Merians et al. showed improvement in strength, speed and movement components in the hands of three hemiparetic patients treated with the Rutgers University Cyberglove [11].

The Department of Occupational Therapy, Haifa University, tested the ability to safely cross the road. People suffering from unilateral spatial neglect after a stroke were treated using a relatively simple computer application. These results indicate the feasibility of using the system [7, 25] (Fig. 3).

Fig. 3. Safe street crossing

Weiss et al. also tested the connection between cognitive, motor ability and performance in VR in stroke patients and found that improved cognition lead to improved performance in VE. Other studies have examined hand reaching in real and VE. Viau et al. found that performance in the VE was equal or even better than in the real environment [23]. Nyberg et al. developed a system designed to evaluate the impact of attention level and unexpected obstacles on the ability of a person to control his posture and movements in VR [13]. Keshner et al. used VE to study posture and stability mechanisms by examining the impact of multiple system stimulations on balance reactions in populations with different pathologies [8].

In 1996, Vivid Group introduced an interactive video projection system called Gesture Xtreme (GX) with applications in the entertainment and education fields. The system includes a video camera recording the patient's movements in real time. The figure is digitally removed from a monochromatic background and "embedded" in real time in the VE. The system's potential for rehabilitation was identified in 1999. Cunningham et al. used this system to treat elderly people in danger of falling [3] (Fig. 4).

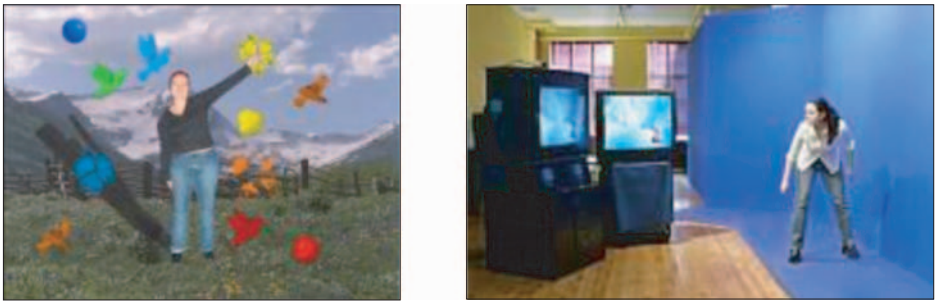

Fig. 4. Balls and birds (IREX System)

In recent years, GX has been adapted for use in rehabilitation and is now capable of changing levels of difficulty, recording a patient's performance and generating reports. The clinical application of GX is called "IREX" (Interactive Rehabilitation Exercise System) and is a product of GestureTek. Weiss et al. published clinical research papers proving the feasibility of IREX system in treating various pathologies [26].

Motek, an Israeli-Dutch Company, created a revolutionary system called CAREN (Computer Assisted Rehabilitation Environment), enhancing video projection by adding a force platform and video motion analysis working in real time, thus enabling a variety of scenarios for challenging and fully controlled experiences (Fig. 5).

Fig. 5. CAREN system

The patient stands on a computerized force platform (2.5 m in diameter) with the virtual story projected on a wide screen or in a HMD. The patient is actually immersed in the virtual scenario. Three-dimensional cameras read the markers on the patient's body and respond to his movements. The computer processes the data and moves the platform to different levels of difficulty, depending on the patient's ability. This system can treat patients in various stages of rehabilitation in addition to treating elite athlete after injuries, thus improving their skills.

The CAREN system is very expensive and requires skilled therapists, technicians, time and financial resources to operate. For these reasons, the system is used mainly for research and is less available for clinical use.

Sony has developed an interactive children's game called EyeToy on the PlayStation II platform. The EyeToy uses a video camera to capture the user's image, identifies his movement and embeds him in a virtual story in real time. The child actively controls the VE by using his body movements. The system is cheap, simple, available and does not require special rooms, monochromatic screens or external aids (Fig. 6).

Fig. 6. Sony PlayStation II with EyeToy

Sony does not develop special software for rehabilitation, but the wide range of existing applications enables clinical use, depending on the creativity of the therapists. Weiss et al. found that the IREX and the EyeToy systems obtained almost identical results in every measured variable [26].

Nintendo Company developed a new gaming console, called Wii. The user can play different sport games like bowling, golf or tennis using a wireless movement tracker, the "Wiimote" simulating a golf stick, a tennis racket, etc. Deutsch et al. reported beneficial effects of a treatment planned and executed using this system, in cases of cerebral palsy in children [4]. Sugarman et al. reported balance improvement in a geriatric stroke patient treated with a new Wii peripheral, the WiiFit [20]. The WiiFit is a wireless force plate; the subject controls the game by shifting his weight, usually without moving his feet, or stepping, while standing on the special platform. The platform detects shifts in weight bearing in the antero-posterior and lateral directions. Increasing the range of weight shifting works on limits of stability, and seems to improve balance reactions.

At present, many systems are suitable for academic research. Those designed for clinical research are very complex and demand technical expertise, expensive equipment and special physical conditions [26].

Game consoles like Sony PlayStation II with EyeToy and Nintendo's Wii are partial solutions to therapeutic needs, by allowing challenging motor and cognitive

tasks. However, it is impossible to change the difficulty level to match the patient's true ability and therefore adapt the game to his therapeutic needs. Another problem is the lack of records and reports of patients performances [26]. Therefore, therapists are required to maneuver and plan treatments in systems where the delineation between therapy and fun is not always clear or controlled [4].

Recently, a new virtual reality system, SeeMe, claimed to solve this dilemma. SeeMe uses a standard PC plus a web camera, in a double display setting with a large television screen (Fig. 7).

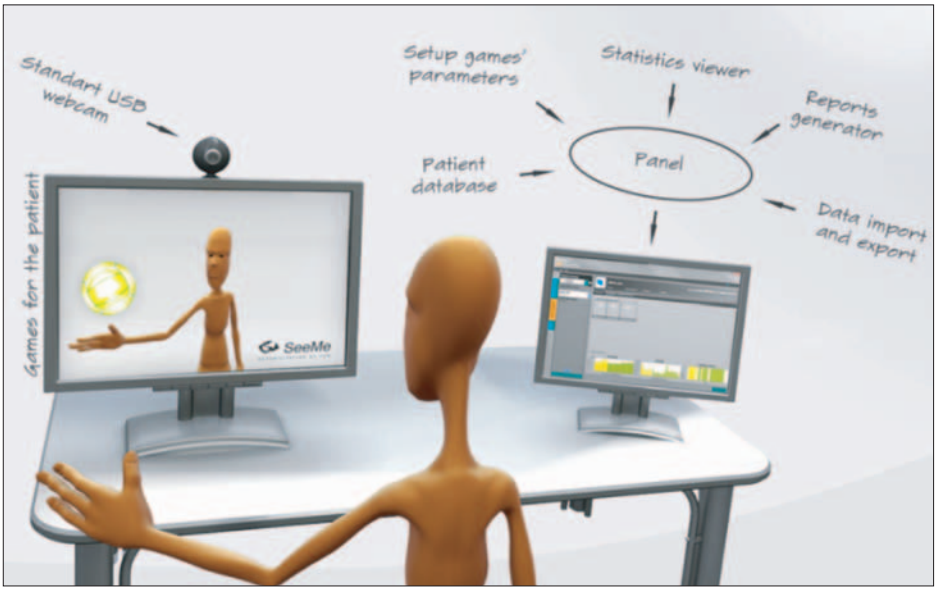

Fig. 7. SeeMe system

The therapist can make on-line changes and adaptations of the patient's ability on the PC screen. The patient sees himself on the wide screen, interacting normally, using body and limb movements within the virtual story in real time. There is no need for markers, wires or a monochromatic background. SeeMe uses novel algorithms for movement, position recognition and analysis. The system includes three "warm up" games and six challenging programs with various difficulty levels, intended to improve motor skills of patients with different cognitive and perceptual pathologies. SeeMe displays high-quality graphics (simulating three dimensional environments) for natural and interactive training. The system was successfully tested on healthy elderly individuals, who reported a high level of motivation, immersion and presence in the virtual story. In a case study describing a stroke patient with severe neglect, the system was effective in diagnosing and treating the patient [2].

The system is user friendly, intuitive, and easily tailored to the different treatment needs of patients. Demographic information and performance reports can be saved and printed, and patient progress can be monitored.

CONCLUSIONS

The interactive experience is perceived by both therapist and patient as very positive, enabling treatment to continue overtime without feeling fatigued or bored. The therapeutic intervention exists in a functional and challenging environment without the risk and cost of moving the patient into the "real world".

We estimate that in the near future, VR technology complemented by telerehabilitation will be widely used. Meanwhile, today's technology allows us to take more of the VR advantages to the clinical world.

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OVERVIEW PAPER

ENSURING REHABILITATION AND A FULL QUALITY OF LIFE FOR PATIENTS WITH CHRONIC NON-INFECTIOUS DISEASES

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ABSTRACT

Introduction. Chronic non-infectious diseases (CNID), such as heart and vascular disorders, malignant tumors, diabetes mellitus, chronic obstructive lung disease, obesity, are one of the most topical health problems for Lithuanian and Polish residents. In solving the problems of CNID three areas of medicine (prophylactics, diagnosis and treatment, rehabilitation) are important, as the diseases that begin in childhood are diagnosed most often in the mature age, and their consequences are manifested in an older age.

Aim. The aim of this article was to discuss issues concerned with providing help for patients afflicted with CNID and devising an effective rehabilitation system for them.

Discussion. Efficiency of pharmacological and surgical treatments for patients with CNID is much lower than for patients with acute disorders. They progress slowly and exert damaging effects on patients' biopsychosocial functions. When the outcomes of a disease are manifested as impaired biopsychosocial functions, a life of full quality can only be ensured with the establishment of effective rehabilitation.

Conclusions. Rehabilitation should be long-term, complex and should involve elements of prophylactics. Investment in such a system is an investment in an inevitable future for each of us, and it always pays positive dividends.

Key words: chronic non-infectious diseases (CNID), rehabilitation, biopsychosocial functions.

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INTRODUCTION

Chronic non-infectious diseases (CNID), such as heart and vascular disorders, malignant tumors, diabetes mellitus, chronic obstructive lung disease, obesity, are one of the most topical health problems for Lithuanian and Polish residents [4, 12]. Currently, they tend to be of an epidemic nature (e.g. more than 20% of Lithuanian residents have hypertension, 56% of men and 49% of women are overweight or obese). CNID have become the major cause of disability and death in Belarus, Lithuania and Poland [7, 9, 12]. There is no hope for solving this problem through medical efforts alone. Although medicine is defined as a system of scientific knowledge and practical means dedicated to maintain and improve human health and working capacity, to prolong life, to recognize and treat diseases, implementation of these means depends not just upon medical professionals, but also upon political activists and society as a whole. In solving health problems, three areas of medical care are traditionally emphasized: prophylactics, diagnosis and treatment, and rehabilitation [2, 3, 5, 6, 8].

These areas are interrelated, but their importance is not the same with respect to different diseases and people of different ages. Undoubtedly, the significance of prophylactics is emphasized in newborns, infants, children, and people of a young age; early diagnosis and treatment – at the age of maturity; and rehabilitation – for the elderly. In solving the problem of CNID, all these areas of medical care are of equal importance, as the diseases that begin in childhood are diagnosed most often in the mature age, and their consequences are manifested in an older age [1, 5, 6, 8, 9, 12].

It is well known that the incidence of CNID is determined by heredity, lifestyle, physical and social surroundings, and quality of health service. In many countries, including Lithuania and Poland, much attention is paid to health education, primary and secondary prophylactics, early diagnosis and treatment of CNID [4, 12]. All of that yields fair results: the outcomes of CNID are manifested later, the average life expectancy is prolonged (currently, in some countries it already reaches 84–85 years, whereas in Lithuania just 70 years). Yet, rehabilitation problems in Lithuania still remain rather neglected, not enough attention is paid to these issues by both, medical professionals and governmental health policy makers.

AIM

The aim of this article is to discuss issues concerning providing help for patients with CNID and devising effective rehabilitation for them.

DISCUSSION

Life expectancy is probably the most important indicator of the health condition of the inhabitants of a country. Nonetheless, the other indicator of health is currently becoming more important – healthy life expectancy. It shows the length of time a person lives without disorders and their consequences. At present, the healthy life

expectancy in developed countries reaches 55 years. Thus, a person striving to live a healthy life may avoid CNID for a long time. However, unfavorable environmental factors (unhealthy diet, stress, noise; air, water and soil pollution; unsatisfactory working conditions, etc.) result in people falling ill with some chronic disease when they are 55–60 years of age. In cases of unfavorable environmental factors or improper lifestyle, people fall ill much earlier. So, the question arises: what should be done with these people, who are late to be told about prophylactics and the timely diagnosis of diseases?

It is very misleading when chronic diseases are not manifested for a long time and do not affect the full quality of life, especially in the absence of physical or psychological stress. From the point of view of health, such a situation decreases personal awareness and creates the illusion that these people are healthy and face no dangers to their health. But with time, the diseases progress slowly and ultimately exert damaging effects on patients' biopsychosocial functions: initially on working capability, later on the sense of direction in space, sense of time, of oneself, as well as on sight, vision, personal care, sexual function, ability to be socially active and engaged in meaningful activities. The disaster often occurs unexpectedly: stroke, myocardial infarction or cancer emerge like a thunderbolt. Although it had been thought that decades of good health remained, the individual suddenly becomes disabled.

We have to admit that the efficacy of pharmacological and surgical treatments for patients with CNID is much lower than for patients with acute disorders. Generally even applying the up-to-date treatment measures, aimed at restoring the disturbed human biopsychosocial functions, is unsuccessful. Treatment most often aims at eliminating the symptoms and signs of disease (heart failure, general weakness, arrhythmias, etc.), normalization of specific physiological indicators (blood pressure, pulse rate, heart beats, glucose and cholesterol levels in blood, etc.), surgical revascularization or removal of the tumor. Consequently, the imperative to treat not just an organ or systems of organs and not just the disease but rather the individual is quite often neglected [2, 3, 5, 6, 8, 9]. Life quality of patients with CNID is limited not only by the troubles caused by the disease, but also by the abundant usage of drugs, drug intolerance and adverse reactions (allergies, digestion disorders, etc.), and frequently by the uncertainty of future possibilities. People suffering from limited physical activity, brought on by a disease, are at risk of infections of the respiratory, urinary or other systems; bedsores, faster progression of other chronic illnesses such as osteoporosis, osteochondrosis, changes in the brain, often disturbed self-esteem, isolation, the emerging feeling of shame and guilt, and depression resulting from reduced possibilities of activity. It is estimated that people with disturbed social functions 2–3 times more often use alcoholic drinks, narcotic drugs, and are more often prone to suicide. CNID become a pressing, current problem as with an aging population

the number of people with various illnesses also increases, and the fact that these diseases are manifested at an older age is no longer just a medical, social or economic issue, but also a moral one. Because of the emigration of younger people, the lack of care for the elderly patients, as well as necessary medical, social and economical assistance are becoming a pressing problem [2, 3, 5, 6, 8, 9, 12].

Often people afflicted with CNID address alternative medicine, parapsychologists or even quack doctors, as traditional medicine does not seem to meet their expectations [10]. It is admitted that the traditional medical care model is clearly insufficient for people with CNID. Because of the damage caused to their biopsychosocial functions, traditional medical care does not cover all areas of assistance required by such patients.

The WHO, with membership of 193 countries, suggested the introduction of a biopsychosocial health care model. According to this model, when assistance is delivered to the ill, assessment involves not only the causes of health disorders, but also concerns the outcomes that can be reduced through environmental adjustment for the patient, application of technical rehabilitation means and the influencing of the patient's behavior. With that purpose in mind, *The international classification of functioning, disability and health* was developed by the WHO in 2001 [10]*.

The classification aims to:

- provide a scientific basis for understanding and studying health and health-related conditions, outcomes and determinants;
- establish a common language for describing health and health-related conditions in order to improve communication between different users, such as health care workers, researchers, policy-makers and the public, including people with disabilities;
- enable comparison of data across countries, health care disciplines, services and time;
- provide a systematic coding scheme for health information systems [10].

This classification supplements *The international statistical classification of diseases and related health problems, tenth revision,* 1992–1994*),* originally in use for more than a century, in which the causes of diseases are named, but the consequences to a specific individual are not presented. *The international classification of functioning, disability and health* (known more commonly as ICF) provides a new approach for the outcomes of diseases and trauma, which are estimated by three aspects, including the factors of environment and personality (Fig. 1).

* This classification was translated into Lithuanian under the initiative of the Department for the Affairs of the Disabled at the Ministry of Social Security and Labor (the scientific editor was Professor Aleksandras Kriščiūnas).

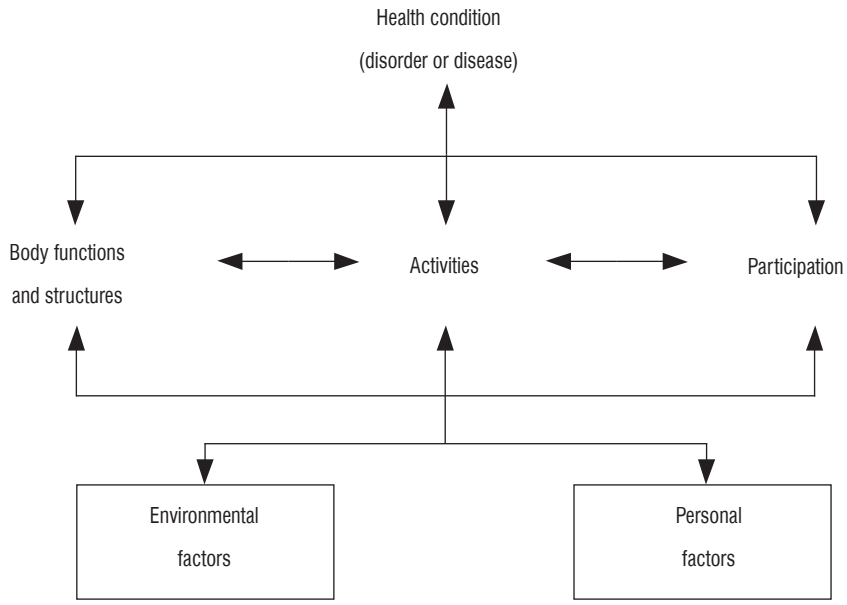

Fig. 1. Interactions between the components of ICF

It determines the following issues:
- functional and structural disorders of the body (disturbed activity of the heart, brain, etc.);
- activity disorders of the individual (not capable of walking, carrying, lifting, performing personal care activities, etc.);
- participation disorders of the individual (not capable of working, participating in social life, etc.).

This classification emphasizes the individuality of the sick person and the environment, and highlights not only the symptoms of the disease, but also the disturbed activities and social capabilities of the person [10].

It is of high importance that this classification indicates five groups of environmental factors that can aggravate or facilitate the outcomes of a disease. They are as follows:
- products and technology (any product, instrument, equipment or technical system adjusted or specially produced to improve the functioning of an ill person);
- natural environment and man-made changes to the environment (specific features of the terrain, e.g. climate, mountains, hills, dams, social infrastructure, stairs);
- support and relationships (family, friends, strangers, health care workers);
- attitudes (local customs, values, norms, attitude to the disabled);

– services, systems and policies (provided by the community, regional or national governmental and non-governmental organizations) [10].

This classification also gives recommendations for considering personal factors such as: age, sex, education, lifestyle. It emphasizes the biopsychosocial approach in assisting seriously ill patients. Implementation of a biopsychosocial approach into practice is possible only with the establishment of an effective rehabilitation system for seriously ill patients and the disabled (Fig. 2).

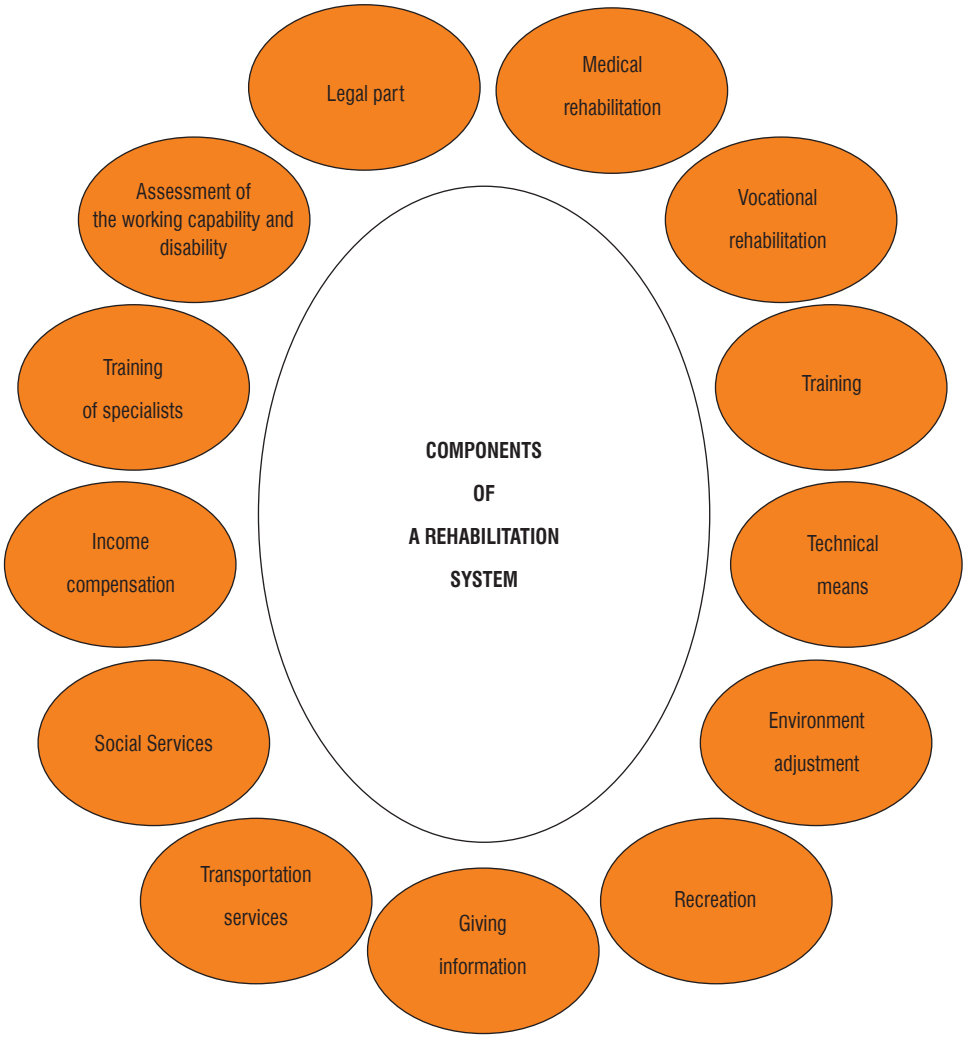

Fig. 2. Components of a rehabilitation system

Legal part (legislation regulating the work of the system). *Law on the social integration of the disabled* of the Republic of Lithuania, *National programme for social integration of the disabled into society for 2003–2012* were passed in Lithuania, but their implementation is being delayed because of the shortage of funding.

Medical rehabilitation. It is to be developed in the inpatient and outpatient institutions, health spas and home facilities. Much has been done in this field. Unfortunately, only a few patients in need of medical rehabilitation are able to access it yet. Rehabilitation institutions lack up-to-date rehabilitation equipment. A home-based Lithuanian rehabilitation system for seriously ill patients and the disabled is still lacking.

Vocational rehabilitation. It takes its first steps in Lithuania. Present vocational rehabilitation centers can provide vocational rehabilitation services (aiming at retrieving lost working skills by restoring, exercising and training) for only a few of the disabled. In comparison with the average rate in European Union countries, the employment rate of the disabled in Lithuania is 2–3 times lower.

Training. Participation in significant activities adequate to their status of health, positively influences health condition of people with CNID, improves their self-esteem and allows them to integrate into society. Their specific needs are determined not only by the nature of disability, but also by their social group (i.e. children, the elderly, women, socially supported individuals). Training (abilitation) and education of children with CNID are an important part of the rehabilitation system.

Technical rehabilitation aids. About 40% of the inhabitants in developed countries use technical rehabilitation aids (not to mention spectacles used by nearly 100% of elderly people), in comparison to only 17% of the Lithuanian population. It is necessary to increase the usage of both, individual technical rehabilitation aids (for personal care, mobility) and public technical rehabilitation means and aids (special transportation, wheelchairs, supports, props, rails and other equipment for individuals with mobility difficulties, special telephones, sound and light alarm systems). Usage of technical rehabilitation aids in Lithuania is limited by their shortage (especially of high-tech equipment), plain appearance, size, weight, short-time fitness, increased breakability, lack of a repair service for the fixing of broken items and people's lack of motivation.

Environmental adjustment. This is especially important for elderly people at risk of falling and tumbling because of disturbed cerebral circulation. Prevention involves proper street lighting, floor coating, elimination of stairs, adjusted bathroom and toilet equipment, etc.

Recreation. Recreation of the disabled, i.e. recovery of strength, health, joy of life, *raison d'être* and the conception of enjoyment in life, is an important part of the rehabilitation system. It liberates a person from stigmatization and induces his creativity. If a person is to be involved more actively in life, an environment is to

be adjusted so that the individual could rest, relax, or sometimes stay alone. This can be achieved via cultural events, sports, religion. The work of governmental and non-governmental organizations is especially important in this field. Inability of spending free time usefully, and ensuing lowered quality of life are causative for the emergence of many social problems (alcoholizm, drug addiction, suicides, crimes). Leisure activities like: watching television, playing computer games and similar free time activities are supposed to be problematic for such patients as they are connected with psychological stress, hypokinesia (diminished motor function), hypodynamia (decreased muscular strength), but nevertheless such activities are most often suggested to them [12].

Communication. As we have already mentioned, vision, hearing, attention and comprehension are often impaired in patients with CNID. Therefore, it should be accounted for while communicating with such patients. In cases of written information, sufficient illumination and size of letters are necessary, whereas when verbal information is given, accessory vocal interference is to be eliminated by turning down a radio, television, avoiding conversations at the same time with other people, etc. Elderly people often do not comprehend information communicated to them, but they try not to disclose that fact. This is why 50% of the elderly take drugs improperly. The Patient Health Literacy Investigation has revealed that a large number of Lithuanian inhabitants do not know the main risk factors for CNID [13].

Transportation system services. It is very important that transport, especially the public one, is to be adjusted to the needs of the individuals with impaired mobility and coordination (low boarding, holders and the like).

Social care and social services. Human existence is a social process. It is understood as a constant interaction with other individuals. When disease occurs, the social role of an individual and social relationships change. Ill people often find it difficult to express their wishes, as physical and intellectual problems hinder them from imagining or recognizing their possibilities. Frequently patients resign themselves to the role of dependants. Therefore, it is important to estimate special needs of daily and personal life, training, working activity and public life for the patients and provide adequate assistance for them.

Lost income compensation. Financial support must be assigned to warrant personal material conditions (social allowance, compensation for accommodation, heating, hot and cold water supply, etc.), nursing, care and aid, transportation and other expenses. This is a very important part of the rehabilitation system as it helps the person to establish a stable self-esteem. With the financial situation secured, a person becomes "the captain of his own ship".

Training of specialists. Proper adjustment of versatile rehabilitation means performed by specialists working in this field demands not only a thorough knowledge of biomedical sciences, but also of educational issues, psychology, sociology

and practical skills necessary for working with the disabled. In Lithuania, physical medicine and rehabilitation doctors, nurses (bachelors, masters), social workers (bachelors, masters), kinesitherapists (bachelors, masters), speech therapists, ergotherapists (bachelors, masters), orthotists, public health specialists (bachelors, masters) are adequately trained to work with the disabled. We have to admit with regret, however, that the number of these specialists is several times lower than in the older European countries.

Working capability and disability assessment. In disability assessment of seriously ill patients, it is extremely important not to focus on what they are not capable of doing, but rather on what they are capable of doing, to avoid stigmatization and to enhance individual self-esteem. This is done by the Working Capability and Disability Assessment Office on the basis of documentation presented by attending physicians as well as health, vocational rehabilitation and other specialists. However, frequently, individual's disability is estimated without utilizing all the possibilities for rehabilitation, with much subjectivity involved. In unclear cases there are no possibilities to perform a thorough investigation in tertiary health care institutions. In cases when disability is estimated for seriously ill patients, it is important that a personal rehabilitation program is to be arranged, with the aim to maximally enhance the functional activity of the person. Family physicians should be responsible for the implementation of such a program, and the control should be performed by the Working Capability and Disability Assessment Office.

Rehabilitation of patients with CNID will be effective, if it is complex, all the elements of the system are developed equally, rehabilitation assistance is provided by a team of professionals, which often consists of 10 or more specialists (physical medicine and rehabilitation doctor, nurse, kinesitherapist, ergotherapist, psychologist, speech therapist performing speech correction, specialist on applying technical rehabilitation aids, social worker, etc.) [1, 3, 4, 7, 9, 10, 12, 13].

Such an assistance to the patient is quite expensive, but its economic benefits are undoubted:

- seriously ill patients' hospitalization period shortens;
- severe disease complications (bedsores, contractures, thromboembolism, etc.) are avoided;
- number of used drugs decreases;
- psychological climate in the family improves;
- the extent of necessary nursing decreases;
- patient's independence and quality of life increase;
- some of the rehabilitees return to working activities;
- length of life is extended;
- exacerbations of the disease and frequency of repeated hospitalizations decrease.

It is calculated that one currency unit put into the rehabilitation system pays divi-

dends ninefold. Therefore, insurance companies of civilized countries support the establishment of such a system.

In Lithuania, only 3% of the compulsory health insurance fund means are allotted to rehabilitation (financing fund for 2009 comprised 4.48 billion litas, whereas the allotted sum for rehabilitation amounted to 148 million litas). Rehabilitation services are provided for 80 000 patients, the need being 2- or even 3-fold higher. Valuation of rehabilitation services is unreasonably low, therefore the secondary disability is not prevented. Seriously ill patients become disabled not because of disease or trauma, but because proper rehabilitation was not provided for them in time, resulting in complications which could have been avoided by applying the appropriate rehabilitation means.

Establishment of a complex rehabilitation system for seriously ill patients and the disabled is a great challenge. It is to be understood as a versatile system of legal, medical, economic, organizational, etc., means, which helps people to regain their disturbed biopsychosocial functions, compensates them and adapts them to society.

It is well known that the financing of the health system faces ethical problems as the lack of funding forces the establishment of priorities. A shortage of resources and competition in this field leads to conflicts. Patients with chronic diseases often lose in this competition as they are mostly the elderly ones, their dysfunctions being chronic, changes irreversible and lasting all life long, and prolonged time is needed for their correction [1]. Frequently rehabilitation of such patients encounters "ageism", i.e. a false attitude that treatment of the elderly is expensive, not paying dividends, unattractive, etc. [1, 2, 5, 6, 9, 12].

CONCLUSIONS

To summarize, we wish to emphasize that in providing help for patients with CNID it is important to understand that:

1. Human existence is inevitably connected both with negative and positive environmental factors affecting health;
2. By choosing a proper lifestyle, individuals can influence their health noticeably and prolong the length of healthy life. Yet, unfortunately, a time comes when they will necessarily require help from people near them and from society;
3. When the outcomes of a disease are manifested as impaired biopsychosocial functions, a life of full quality can only be ensured through the establishment of effective rehabilitation. Investment in such a system is an investment in an inevitable future of each of us, and it always pays positive dividends.

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OVERVIEW PAPER

TREATMENT PROCEDURES FOR UROLITHIASIS

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ABSTRACT

Introduction. Urolithiasis remains a great medical challenge. The last two decades of the 20th century witnessed a rapid development in minimally invasive surgery methods for urolithotomy. The beginning of the 21st century is marked with a further perfecting of these methods.

Aim. The aim of this work was to present modern methods for evacuating uroliths from kidneys, ureters, bladder and urethra. The choice of the most adequate method is discussed, taking into account location and size of concrement and a patient's condition.

Discussion. Up till the 1980s, uroliths located in kidneys and ureters could have been removed only surgically. In some cases, concrements were extracted from the inferior ureter by the Zeiss-loop procedure or with a Dormia basket. At the beginning of the 1980s, three new minimally invasive surgery methods of lithotomy were introduced: extracorporeal shock wave lithotripsy, percutaneous nephrolithotripsy and ureteroscopic lithotripsy.

Modern treatment of urolithiasis is based on the rational establishment of recommendations for one of these methods or their combination. A proper treatment of urolithiasis is ensured by performing it in a center equipped with adequate medical equipment and devices, and employing urologists with clinical experiences and technical skills. Despite technological advancement, surgical treatment is not complications free. The fewest complications definitely occur in evacuating smaller uroliths as well as in treating urolithiasis uncomplicated by infection and urine retention.

Conclusions. Early diagnosis of urolithiasis and the application of minimally invasive surgery methods to remove concrements ensure retaining a proper kidney function.

Key words: urolithiasis, treatment procedures, minimally invasive surgery methods.

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INTRODUCTION

Urolithiasis is a medical condition in the course of which concrements of chemical substances that are normal or pathological components of urine, are formed in kidneys or ureters. Its pathogenesis has not been thoroughly explained so far. It is characterized by a high degree of recurrence. It is assumed that recurrence within 5–10 years occurs in 50% of cases, and within 20 years in 75% of cases [10].

Incidence of urolithiasis used to be much greater in men. Changes concerning risk factors connected with lifestyle, mostly obesity, resulted in a change of male–female incidence ratio from 1.7 : 1 to 1.3 : 1, as observed in the U.S. between 1997 and 2002 [7]. Urolithiasis is one of the most common diseases. According to various statistical data, it is reported in 1% of Asians, 5% of Europeans and 12% of North America residents.

Renal colic is one of the most frequent reasons for seeking medical assistance. The majority of uroliths are passed out of the body spontaneously. Some, assumingly 25%, require a surgical procedure. Up till the 1980s, uroliths located in kidneys and ureters were extracted surgically almost in 100% of cases. This situation changed greatly with the introduction of extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotripsy (PCNL) and ureteroscopic lithotripsy (URSL). The development of these methods reduced the number of urolithiasis cases treated with classic surgery to 5%.

Because of various possibilities available for treating urolithiasis, it is important to choose a method most appropriate for a particular case. Clinical experiences and technical skills of the physician as well as equipment available in a given center should be taken into account.

AIM

The aim of this work is to present the reasons for selecting the most appropriate procedure for treating urolithiasis, taking into account location and size of concrement and a patient's condition, in terms of body type and structure, body mass and general health condition.

DISCUSSION

Urology is inextricably bound with nephrolithiasis. People have suffered from urolithiasis from earliest times. The oldest urological find is a bladder stone found in a mummy discovered by Elliot Smith in 1901 in a prehistoric tomb located in the village of El Amrah near Abydos. Its age is assessed to be about 7 000 years [8]. In the history of treatment of urolithiasis we may notice the development involving a change starting with medications whose purpose was to dissolve concrement, through open surgical procedures, to endoscopic procedures and ESWL. The earliest known descriptions of urolithiasis came from the Asutu of Mesopotamia. The medication to

dissolve uroliths consisted of: black saltpeter, ostrich egg shell, pine turpentine, and female donkey genitals [2].

In ancient India, transperineal cystolithctomy was practiced. In ancient Greece urolithiasis was known and described. The Hippocratic Oath forbade, unfortunately, the performing of operations to treat urolithiasis. Hippocrates believed that bladder wounds must be fatal. He stated: "I will not cut for stone, even for patients in whom the disease is manifest; I will leave this operation to be performed by practicioners, specialists in this art" (translated by M. North). Lithotomy was thus practiced by non-medicals until the Renaissance. In this period lithotomy was commonly performed, with a high mortality rate.

The introduction of evacuating uroliths via urethra with special forceps (lithotrite) by Jean Civiale in 1824 initiated the development of endoscopy. However, these procedures were also connected with high mortality. The use of aseptics and ether anesthesia reduced mortality to 2.4% [3]. In 1871, Simon performed nephrectomy because of urolithiasis. The technique of treating urolithiasis was perfected, but these methods involved major open surgeries. The requirement of repeating the procedures caused grave surgical difficulties and also impaired kidney function leading to their insufficiency.

The beginning of the 1980s revolutionized treatment of urolithiasis. This resulted from the almost simultaneous introduction of three methods: PCNL, ESWL and URSL, which was preceded by numerous discoveries. In 1955, Goodwin introduced percutaneous nephrostomy. In 1953, Mulvoney discovered that sound waves may crush stones. In 1950, Jutkin patented the use of the electrohydraulic wave, and in 1967 a device for breaking up stones URAT-1 was presented [12]. In 1968, Mulvoney and Beck described for the first time the employment of laser energy for breaking stones.

Thus, various types of energy which could break stones were known. The next step was to direct these energies to uroliths. There are three possibilities:

1. From the outside, without intruding upon the continuity of the body and causing collateral damage. This has led to the invention of ESWL. This procedure is performed via devices called lithotriptors, in which generators, different depending on the type of device, generate shock waves. Uroliths are located by real-time live X-ray or ultrasound. Stones broken up during lithotripsy into small pieces are then passed out of a patient's body spontaneously. This method was used for the first time in Munich in 1980 [4]. The first center employing this method in Poland was established in the Clinic of Urology of Teaching Hospital at the Medical Academy in Warsaw in 1988. Presently, this method has dominated treatment of urolithiasis;
2. Without intruding upon the continuity of the body via a natural opening. Cystoscopy has been performed since the end of the 19th century. Reaching the ureter and renal pyelocalyceal became possible when Perez-Castro designed in 1980 a rigid ureterorenoscope, which was a prolonged pediatric cystoscope. A probe is inserted

via a ureterorenoscope to break up stones. Pneumatic, ultrasonic, electrohydraulic and laser lithotripsy may be used. This procedure is abbreviated as URSL;

3. With a minimal intrusion upon the continuity of the body. The PCNL procedure is preceded by the insertion of a ureteral catheter into the renal pelvis. The renal pelvis is then filled in with contrast medium via the catheter. In a lithotomy position, the selected renal calyx is punctured and the access port is enlarged. A nephroscope is inserted via the port to break up the stone and remove small debris. To break up stones a sonotrode is most frequently used which enables the physician to suck small debris.

Before the application of a potential procedure, a spontaneous passing of the concrement from the body should be considered. When the stone diameter is not larger than 4 mm, spontaneous passing will occur in 80% of cases. When the diameter is larger than 7 mm, the chance of spontaneous passing is minimal [5]. A surgical procedure to evacuate concrement is recommended when the stone diameter is larger than 7 mm. As refers to smaller uroliths, therapeutic indications for surgical treatment involve the following cases: ineffective analgesic treatment, urinary outflow obstruction involving one or both kidneys, infected hydronephrosis, the risk of pyelonephritis, urinary sepsis [9].

ESWL, being the least invasive method, has dominated treatment of urolithiasis. It is most effective for stones not larger than 2 cm in diameter. At a time when ultrasound imaging is available, this type of urolithiasis is most common. The effectiveness of this method is evaluated to be 50–95%, depending on the type of the device, location and size of the concrement [9]. Renal pelvic stones of a diameter up to 2 cm are an ideal indicator for the application of this method. ESWL is also an ideal method in upper and middle calyceal calculi. In lower calyceal calculi the results are not so satisfactory due to the difficulties in passing the disintegrated stone. It requires special physiotherapy combined with tapping the kidney area. In calyceal diverticular calculi ESWL effectiveness is minimal [1].

In multiple nephrolithiasis, in selected cases multistage ESWL procedure may be performed, controlled by a double J stent catheter. In ureterolithiasis ESWL is the first choice method [9]. Only the pelvic section is excluded from the application of ESWL due to the difficulties in locating the stone. The effectiveness is estimated to be 59–100%, according to various authors. The necessity to employ multistage ESWL is assessed to involve 10% of cases. ESWL contraindications include: pregnancy, anatomical obstruction in urine outflow located below the stone, urinary tract infection, and coagulation disorders. Complications include: hematuria, renal colic, steinstrasse formed by numerous debris of the broken stone located one upon another.

URSL is very effective in treating ureterolithiasis. In the case of calculi in the lower section of the ureter it is effective in 100%. In the middle and proximal sections, the effectiveness is estimated to be approximately 75%. Effectiveness depends

on the stone size and energy used to break it up. Laser is most effective. The application of URSL in treating ureterolithiasis enables physicians to extract the concrement during a single procedure. This gives an advantage over ESWL which in some cases requires the procedure to be repeated [6].

Urinary tract infection is a contraindication for URSL. Ureteral perforation is the URSL complication. It is treated by a double J stent ureteral catheter. A delayed complication involves ureterostenosis. The most serious complication is ureteral avulsion which requires a surgical intervention. A constant development in ureterorenoscope designs increases their effectiveness and safety.

PCNL enables physicians to extract concrements from the pyelocalyceal system of the kidney and from the upper section of the ureter. PCNL is recommended for those stones which cannot be removed by ESWL. Such a situation occurs in case of: renal pelvis stones and caliceal calculi larger in diameter than 2 cm (passing a large number of debris from a large stone is rarely possible); very hard stones which are resistant to breaking up by ESWL – uric acid stones and cystic stones; calyceal diverticular calculi; kidney stones with co-occurring ureteropelvic junction stricture (during PCNL the stricture is cut); lower calyceal calculi, when the neck of a calyx is narrowed and results in calycectasis. After the extraction of the concrement, the neck is diluted and a thick drain is inserted through it to the renal pelvis for 2–3 weeks. In multiple urolithiasis, PCNL is the primary treatment by forming up to three access ports in the kidney [1, 11].

Contraindications for PCNL include: coagulation disorders, pregnancy, urinary tuberculosis, septic condition due to the retention of infected urine in the pyelocalyceal system, anatomical defects of the kidney and the skeletal system preventing a correct puncture of the kidney.

Complications include: damage to adjacent organs, hemorrhage with perirenal hematoma, extravasation of urine, septic condition and overhydration.

Cystine nephrolithiasis is the most difficult problem in treating urolithiasis. All techniques are applied: ESWL, PCNL and surgical treatment, including a partial nephrectomy. Renal parenchyma should be maximally retained. Most frequently, the major part of concrement is extracted via PCNL, whereas the remaining parts are broken up by ESWL.

In cystolithiasis transurethral lithotripsy is used. In case of very large concrements an open surgery is performed. Stones stuck in the urethral meatus may be extracted following their partial breaking up with Pean's forceps. The remaining ones are translocated to the bladder and broken up there.

Laparoscopy can also be applied in treating urolithiasis. Ureteroliths resistant to breaking up via ESWL and inaccessible via URS may be extracted by transperitoneal or extraperitoneal laparoscopic procedures. Pelvic lithiasis with ureteropelvic junction stricture is treated laparoscopically in selected centers.

CONCLUSIONS

The introduction of ultrasound as a diagnostic method and minimally invasive surgery methods as treatment procedures changed the picture of nephrolithiasis at the end of the 20th century. Modern treatment for urolithiasis enables one to avoid kidney function insufficiency in the majority of cases, which prevents patients from the necessity of undertaking renal replacement therapy.

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OVERVIEW PAPER

PSYCHOLOGICAL ASPECTS OF POST-OPERATIVE HOSPITAL INFECTIONS

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ABSTRACT

Introduction. Post-operative hospital infections (POI) are conditions whose specific courses strongly determine patients' psychological conditions, potentially leading to the exacerbation of the pathomechanism and the prevention of effective treatment.
Aim. The aim of this article was to present the specificity of psychological functioning of patients suffering from POI.

The objective is both theoretical and practical due to the possibility of utilizing theoretical assumptions to improve the cooperation with patients suffering from infections, and, consequently, to improve the global healing process.
Discussion. This analysis focuses on the correlation between the biological aspects of the infection process and those psychological aspects emerging as a result of pathological biological changes occurring in the body of an infected person. It is based on the recognition of two mutually complementing concepts concerning a human being: the holistic concept and the concept of biopsychosocial unity. The former assumes a harmonious integration of body, mind and soul. The latter recognizes the mutual connections between body, mind and social functioning.

This article attempts to extrapolate the assumptions and study results concerning the functioning of a human being dealing with a disease understood as a difficult, threatening situation, to the functioning of patients dealing with POI.
Conclusions. The mechanism explaining the biological-psychological correlations in the course of POI requires further studies involving the empirical level. Additionally, in order to achieve a comprehensive picture of psychological aspects of POI, research needs to be extended and to include medical staff.

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Key words: post-operative hospital infection (POI), behavior, emotions, cognitive processes.

INTRODUCTION

Development of medical sciences involving a constant extension of diagnostic methods of a surgical nature, as well as increasing the number and types of surgical procedures, frequently of an invasive nature, creates favorable conditions for POI. Considering the number of surgeries performed daily worldwide, the incidence of POI has become a serious challenge for contemporary medicine. Hospital infections are a direct cause of deaths of 30 000 patients globally, and an indirect cause in the case of 70 000 patients. Every day 1400 patients die from septicemia [4]. Apart from posing a direct threat to life, POI are also indirectly life threatening, contributing to complications or a worsening of the general condition of the patient.

Medical literature reports extensively on the pathogenesis (etiology) of the infection process as refers to the biological level. Risk factors, means of infection dissemination (epidemiology) and activities aimed at the prophylactics and controlling POI are discussed broadly [5, 17, 11, 2]. There is, however, a lack of data concerning the psychological aspects of POI. Collecting empirical data revealing psychological aspects of POI is very difficult to accomplish. These difficulties stem directly from the evaluation of the POI process at the biological level. Specificity of the infection process, its course and therapeutic treatment principles frequently prevent, considering the well-being and health of the patient, conducting additional psychological examinations. The necessity of treating the patient in septic conditions, without the access of people other than medical staff, some symptoms of infection (pain, high fever, breathing difficulties, psychomotor anxiety, a loss of consciousness) seriously limit or exclude the possibility of conducting any psychological examinations. Consequently, an attempt undertaken in this article to analyze the psychological functioning of patients with POI is of a theoretical nature.

AIM

The aim of this article is to present the specificity of the psychological functioning of patients suffering from POI. The objective is both theoretical and practical due to the possibility of utilizing theoretical assumptions to improve the cooperation with patients suffering from infections, and, consequently, to improve the global healing process.

DISCUSSION

This analysis focuses on the correlation between the biological aspects of the infection process and those psychological aspects emerging as a result of pathological biological changes occurring in the body of an infected person.

The analysis is based on the recognition of two mutually complementing concepts of a human being: the holistic concept [6] and the concept of biopsychosocial unity [13]. The former assumes a harmonious integration of body, mind and soul. The latter recognizes the mutual connections between body, mind and social functioning. POI process is defined as an infection directly connected with an undergone surgical procedure and hospital stay, which develops during the patient's hospitalization or after release from hospital. In the case of micro-organisms of a long or very long incubation period (*Legionella*, virus hepatitis B and C, HIV), the development of a disease may last 2 weeks (*Legionella pneumonia*), 6 months (virus hepatitis B) or many years (AIDS and virus hepatitis C) [12].

The analysis of the psychological aspects of POI is of a two-stage nature. The first stage refers to infection as a specific disease process on a general level, while the second stage takes into account a clinical picture of specific types of POI.

The assumption of the holistic concept of a human being and the biopsychosocial unity justifies the claim that infection is a process involving three levels of human functioning: biological, psychological and social. When analyzing the psychological functioning of people dealing with a disease, three coexisting processes need to be considered: cognition, emotions and behavior [19]. Infection, as any other disease, creates in the patient's mind a specific cognitive representation. A picture of one's own disease, involving an evaluation of the situation and assumptions concerning it (causes of infection, course, prognosis, treatment possibilities) is subjective, and as such is not always consistent with the actual situation and its objective, medical aspects. Patients rarely rely on knowledge received from their physicians. This stems from the fact that frequently patients do not receive sufficient information concerning their health condition, and even if they do, they prefer to rely on information from non-medical, non-professional sources (other patients, the Internet, general knowledge, life experience). The way of thinking about infection generates specific emotions and, consequently, determines the patient's behavior in this situation.

POI is a sudden event, unexpected by patients already suffering from many physical ailments, for which they are not psychologically prepared. It generally occurs at the point of hospitalization when patients, having undergone surgical procedures, expect health improvement. A sudden turn towards the worsening of the health condition or even one that is life threatening, affects patients' psychological stability [17].

In the majority of cases, patients treat infection as a signal of an actual threat to their health, values and lives. If, additionally, infections' genesis is associated with physicians' mistakes or other medical staff errors, the patient's perception of the situation leads to losing trust in the physicians or medical staff, and occasionally to the science of medicine as such. The patients loses a feeling of safety in the therapeutic situation in which he/she is involved, becomes suspicious and distrustful. This, in

turn, may generate the patient's lack of willingness to cooperate with medical staff, not observing medical recommendations, rejecting treatment suggestions (further diagnostic examinations, introducing new medication, another surgery), which may finally lead to a further worsening of the health condition.

Lack of the expected improvement, the presence of infection symptoms or their intensification at the physical level are usually sources of a strong, general anxiety. Anxiety may generate two types of reactions. On the one hand, it makes the patient more sensitive to the disease symptoms, ailments stemming from it and information concerning threats connected with it. This results in a heightened focus on one's body, visible pathological changes within it, burning sensation, swelling, pain, etc. Increased psychological tension frequently causes increased muscular tone, which heightens physiological sensations, most of all pain [7]. In effect, this may lead to falsifying the evaluation of actual sensations accompanying the infection and searching for somatic disorders where they are in fact absent. Sometimes natural physiological signs are treated as disease symptoms. On the other hand, if the anxiety level is so high that the patient in order to function in relative psychological stability must reduce it unconsciously, defense mechanisms appear: denying the symptoms, repressing or ignoring them. The patient, contrary to the first type of reaction, becomes as if insensitive to the symptoms of infection, does not register them in his/her consciousness, negates them. Even if recognized, the symptoms are treated as indicators of some other, not dangerous disease or considered as insignificant and not worthy of attention. The patient avoids contact with the physician, afraid of revealing the symptoms of the disease. Assuming a naive stand "it has come – it will go", the patient does not feel a need to inform the physician about his/her ailments. The patient then does not ask for assistance, diminishes the significance and strength of the symptoms ("it's nothing"). Moreover, this specific, unconscious perceptive defense may select and distort information provided by the physician.

In both types of reactions to anxiety, communication with the physician may involve false information from the point of view of biological evaluation. The patient may claim feeling much worse or better than he/she does in reality [8–10]. Such an attitude negatively affects the therapeutic process and is life threatening.

Further, the analysis of the psychological aspects of POI requires taking into account the specificity of the clinical picture of a given infection. Type of infection and specificity of its course affect the specificity of psychological functioning of the patient. Consecutive stages of the infection's development and specific somatic symptoms accompanying them determine particular psychological reactions. These reactions are evaluated and modified, beginning from diagnosis and including particular treatment stages.

Hospital infections of post-operative wounds are determined by the interaction between the host, the wound and the virulence of the colonizing micro-organisms. Initially, the patient complains about unpleasant physical symptoms, such as: pain,

reddening, swelling, pus, increased bodily temperature, disruption in organs' functions, diarrhea [5]. Physical sensations emanating from the organism, initially being a source of discomfort, after the diagnosis quickly change into a feeling of threat, accompanied by a general anxiety turning to fear. Moreover, if the infection is to result in further, painful, unpleasant medical procedures, or another surgery, anxiety may be connected with anger and aggression on the part of the patient directed at the entire medical situation or at particular people (attending physician, other medical staff). The patient may directly blame a particular physician or other members of the medical staff for the appearance and development of the infection. Hospital becomes a threatening institution rather than a safe place providing an assurance of recovery or at least a hope for regaining health.

Pathological changes accompanying post-operative wound infection at the bodily level (wound dehiscence, exudate) may be also evaluated negatively by the patient in terms of esthetics. Thus, they pose a threat to values professed by the patient, making up the image of one's body or person as such. In this case, with regard to the patient's emotions we may note a mood lowering of a depressive nature [14].

The second most frequent hospital infection, often diagnosed as post-operative complication (lung and abdomen procedures) is hospital-acquired pneumonia [18]. As in the case of post-operative wound infection, the most frequent psychological reactions, as reactions to the symptoms (fever, shivering, dyspnea, pain in the chest) and diagnosis involve: fear, terror and anxiety. Development of pneumonia leading to a serious clinical condition, with the necessity of using the respirator, heightens the sensation of threat experienced by the patient and his/her family.

"The course of sepsis leads to a systemic immunological reaction, manifested by a diversified clinical picture, with the most serious form being septic shock with circulatory and respiratory failure and organ dysfunctions" [16]. Very often, the patient loses touch with the surrounding environment, remaining in a pharmacological coma. Psychological weight is then transferred to the patient's family. The probability of death is high, and the loss of someone close is connected with an enormous psychological burden for the family. Perception of a life threatening situation provokes very strong fear and anxiety. Psychological reactions at the behavioral level include: crying accompanied sometimes with aggression directed at medical staff who are blamed for the infection and accused of not looking after the patient properly enough. Both crying and aggression may be rooted in unconscious defense mechanisms activated in this difficult situation. The person who reveals them despite his/her own will reacts to the disease according to the earlier stage of his/her psychological development, and behaves as if a child. Apart from regression, there appear rationalization, denial and withdrawal. Attempts at negating the actual situation may appear as well – "this can't be true" or avoidance. Members of the family are not then so interested in the patient's health condition. They assume that there is no need to be

"hysterical" about it since it is nothing serious, it is the normal course of the disease and the patient will recover soon. Family members do not come to the hospital, as they do not want to "disturb" the patient and "occupy" the physician's time who have other, more serious cases to treat.

HIV and virus hepatitis C infections may also result from surgical procedures and hospitalizations. These are infections with a prolonged incubation period (from a few months to a few years) whose results involve the entire life, leading directly to chronic and terminal diseases. As such, they result in strong disturbances of psychological stability leading to permanent personality changes [14], and sometimes to mental disorders. First, fear and anxiety appear which are caused by the very information about the infection. Patients, aware of the infection's development and specificity, feel completely hopeless [3], suffer from depression, experience suicidal thoughts [1].

The very result of the test indicating the presence of HIV or virus hepatitis C significantly affects psychological functions. It often releases coping strategies connected with avoidance. Patients are shocked, they do not believe that it is true. The second step is withdrawal from social life and refusing social support [15]. Patients, aware of further stages of the disease, lose the feeling of safety. They live on a daily basis with the awareness of the possibility of disease progression and death. They function in a permanent uncertainty as to what the next day might bring. They also face the necessity of changing life priorities and the ravages of the disease itself.

CONCLUSIONS

Post-operative infection is a difficult moment in the therapeutic process as it involves the worsening of the health condition at the point when the patient and family expect improvement. Because of its crisis-like nature, it becomes a source for disturbing psychological stability and for creating changes in a patient's functioning.

Psychological processes revealed in POI involve: cognition, emotions and behavior of the patient. At the cognitive level, the perception of infection as threatening to health, values and life itself is most frequent. The patient loses a feeling of safety. In terms of emotions, this way of thinking leads to strong anxiety and fear experienced by the patient. If the anxiety level exceeds the patient's adaptive possibilities, defense mechanisms appear, such as: regression, rationalization, denial, repression. Additionally, aggression and fury may appear, directed at the general situation connected with the disease or at particular members of the medical staff. In the case of infections involving the perspective of an entire life (HIV, virus hepatitis C) there appear depression and suicidal thoughts.

This theoretical analysis requires empirical verification, and research needs to be extended to include medical staff.

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OVERVIEW PAPER

INTERNAL AUDIT AS A MANAGEMENT IMPROVEMENT TOOL IN THE HEALTHCARE SECTOR UNITS

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ABSTRACT

Introduction. A subsequent, yet a significant amendment to the Public Finance Act, which has been effective since January 1, 2010, extends the list of sector units obliged to implement internal auditing. This Act also specifies the healthcare sector units which need to implement auditing. The function and development of internal auditing, places it in the organizational structure of the public finance sector units.

Aim. This work aims to discuss the binding internal audit regulations, instructions and standards as well as the principles of internal auditing in the healthcare sector units.

Discussion. The author discusses the legal basis binding for internal auditing in the healthcare sector and the organization of the audit committee in the Ministry of Health. The legal basis concerning qualification requirements for internal auditors is presented. The role, objectives and fundamental rules of internal auditing in the healthcare sector units are defined. The author also presents the documentation involved in internal audit.

Conclusions. Public sector internal auditing is and will continue to be constantly improved since it is introduced, i.a., by virtue of the amended Public Finance Act effective as of January 2010 as well as the new version of the International Standards for the Professional Practice of Internal Auditing put in practice in the Public Finance Act in 2009. Internal auditing becomes obligatory in more and more public finance sector units, including the healthcare sector units, thus it is necessary and efficient for the public finance sector operation.

Key words: internal audit, internal control, management, healthcare sector, public finance sector.

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INTRODUCTION

The state executes its tasks in the public sphere by means of the public finance sector units (PFSU). To ensure efficiency and stability of the public sector, its supervisory systems conduct internal audits. Internal audits in this sector are adopted as instruments to control public finance. The obligations and rules connected with internal auditing were introduced in PFSU in January 2002 by virtue of the Public Finance Act (PFA). The introduction of internal auditing to the public sector was required by the European Union. Further, it was necessary to develop mechanisms of control in state administration.

A subsequent, yet a significant amendment to the PFA, which has been effective since January 1, 2010, extends the list of sector units obliged to implement internal auditing. This Act also specifies the healthcare sector units which need to implement auditing. One of the reasons for its implementation is the fact that the healthcare reform should lead to an establishment of a modern healthcare system, which would treat patients efficiently, create favorable conditions for the sector employees, as well as manage public funds effectively. Hence, pursuant to pertinent regulations of the PFA, particular units, such as independent public healthcare centers, are obliged to establish internal audit divisions or units. The Act also specifies sector units authorized to outsource internal auditing, provided they meet the PFA-defined criteria. Internal audits in mentioned units can be conducted by superior or supervisory bodies.

Internal audits must be conducted in accordance with the provisions of the PFA, the pertinent executory orders and instructions of the Minister of Finance as well as the internal audit standards effective in PFSU. The underlying objective of the currently binding internal audit regulations and norms is to support a manager in efficient unit management. Presently, internal auditing not only analyzes the internal control efficiency, but also public finance management control. Furthermore, it is a vital tool for risk management and execution of corporate governance and public governance tasks.

AIM

This work aims to discuss the binding internal audit regulations, instructions and standards as well as the fundamental principles and scope of internal auditing in the healthcare sector units.

DISCUSSION

Legal basis of internal auditing in the healthcare sector

In 2010, in accordance with the PFA [9], internal auditing is obligatory for the following healthcare units: the Ministry of Health, the National Health Fund, independent public healthcare centers, and other state or independent corporate entities operating within the sector established pursuant to separate Acts of law to execute

public tasks, provided they receive substantial public funds or make substantial public outlays. Internal auditing in the healthcare sector is also governed by:

- the Regulation concerning the internal audit committee [6];
- the Regulation concerning internal audit execution and documentation [7];
- Announcement No. 1 concerning internal audit standards [2];
- Announcement No. 13 concerning management control standards [4];
- Announcement No. 16 concerning issuing the "Internal Auditor's Code of Ethics" and the "Internal Audit Charter" [3];
- Announcement No. 25 concerning the report outlay for internal audit task execution [5].

Additionally, for the execution of the internal auditing tasks concerning information system audits, internal auditors are recommended by the Minister of Finance to apply guidelines published by the international Information Systems Audit and Control Association (ISACA): CISA [8] – standards and guidelines for information systems auditing and COBIT [1] – guidelines for information technology management. Further, the Minister of Finance also published the list of documents that should be followed by managers and auditors in PFSU, i.a.: "Instructions for the internal audit self-assessment in PFSU".

As of January 2010, the PFA regulates the following internal audit-related matters:

- definition and rules of internal auditing;
- the obligation to establish internal audit committees at the Ministries;
- a possibility of internal audit outsourcing to a party not employed with a given unit, for instance, to an auditor. The Act specifies the units the provision applies to, provided they meet the requirements referred to therein;
- professional qualifications for internal auditors in the public finance sector units.

Under the provisions of Article 275 of the PFA, an internal audit is carried out by an internal auditor employed with a given unit or by a service provider not employed with a given unit. Internal audits in the Ministry of Health, the National Health Fund and independent public healthcare centers are conducted by internal auditors employed with said units. Independent public healthcare centers are exempted from this regulation, as they can outsource internal auditing on condition that neither their revenue nor costs exceed 100 000 000 zlotys or the unit employs fewer than 200 people. This applies also to the departments headed by the Minister of Health, which can outsource internal auditing upon his/her consent. Further, the healthcare sector units established by local governments can also outsource internal auditing, if the local government's budgetary resolution stipulates income and revenue as well as expenses and costs below 100 000 000 zlotys.

Under the provision of Article 276 of the PFA, tasks related to internal auditing in a local government are assigned to its head, i.e.: commune administrator, mayor, chairman of the local government's management board, respectively.

The head of an internal audit division obliged to conduct an internal audit, save for local government units, presents all the internal auditing-related information and documents at the request of the Minister of Finance. Therefore, as of 2010 the heads of independent public healthcare centers, which were not established by local government units, are obliged to notify the Minister of Finance in writing about the commencement of an internal audit, if their revenues or costs recorded in the financial plan exceed 40 000 000 zlotys. This also pertains to other healthcare sector units specified in the PFA, such as:

- state budgetary units, if revenues or expenses recorded in the budgetary unit's financial plan exceed 40 000 000 zlotys;
- local government units, if a budgetary resolution of a local government stipulates that revenues and incomes or expenses and costs exceed 40 000 000 zlotys;
- in other public finance sector units, internal audits are conducted at the head's discretion.

Organization and tasks of the audit committee in the Ministry of Health

In 2010 the audit committee will be established in the Ministry of Health as well as in other Ministries. The audit committee's main task is to counsel the Minister in adequate, effective and efficient management control as well as effective internal auditing in the state administration divisions headed by the Minister. The committee's counseling also pertains to management control and internal auditing in all units subordinate to and supervised by the Minister. The objectives of the audit committee were defined in the amended Public Finance Act, Article 289, and they define in particular:

- specifying significant risks and weaknesses in management control and presenting facilitating proposals;
- setting out priorities for annual and strategic internal audit plans;
- reviewing significant audit results and recommendations and monitoring their implementation;
- reviewing reports involving the internal audit plan execution together with management control evaluation;
- monitoring the effectiveness of internal auditing, inclusive of reviewing the results of internal and external audit estimations;
- approving terminations and modifications of employment contracts of the heads of internal audit divisions.

On the basis of a delegation of powers of the PFA in December 2009, the Minister of Finance issued a Regulation concerning the audit committee. This Regulation defines, among others, the required qualifications for independent audit committee members, their remuneration as well as the requirements to be met by the rules and regulations of the audit committee. As stipulated in this Regulation, an independent member of the audit committee must be a university graduate and have at least five

years of professional experience, inclusive of two years in a managerial function. Further, an independent member of the committee should have proper qualifications, i.e., have adequate knowledge or documented experience in: internal auditing or management control or risk management or financial economy in PFSU or objectives, tasks and specificity of a division of state administration, for which an internal committee is established.

The rules and regulations of an internal audit committee must be approved by the Minister of Health. The regulations should outline in detail the scope of activities of an audit committee and the rules of access to documents, information and other materials related to the healthcare sector units with the observance of protected confidentiality. The rules and regulations should also define the organization and operation of an audit committee, including, for instance: the manner and frequency of meetings, mode of meetings, resolution adoption, meeting documentation and task execution, rules of meeting attendance by third parties.

Qualification requirements for internal auditors

As already mentioned, an internal audit is carried out by an internal auditor employed with a given unit or by a service provider not employed with a given unit. The currently binding amendment to the PFA features Article No. 286, which stipulates that an internal auditor in PFSU, i.e. including the healthcare sector units, can be a person, who:

- is a EU citizen or a citizen of any other country, the citizens of which, pursuant to international agreements or the European Community legislation, are entitled to be employed in the Republic of Poland;
- is capable of performing legal activities, executing all public rights;
- was not punished for any intentional crimes or any intentional fiscal crimes;
- is a university graduate;
- has the qualifications defined in the PFA to conduct an internal audit:
  - holds one of the following international certificates: Certified Internal Auditor (CIA), Certified Government Auditing Professional (CGAP), Certified Information Systems Auditor (CISA), Association of Chartered Certified Accountants (ACCA), Certified Fraud Examiner (CFE), Certification in Control Self Assessment (CCSA), Certified Financial Services Auditor (CFSA), Chartered Financial Analyst (CFA) or
  - in the years 2003–2006 passed the internal audit examination before the Examination Board appointed by the Minister of Finance, or
  - holds external auditor's qualifications, or
  - has a two-year internal audit practice and graduated from post-graduate studies in internal audit organized by a unit, which, upon the diploma issue, was authorized to award Ph.D. degrees in economics or law.

Moreover, internal auditing practice means at least part-time employment documented by the head of a unit from the public finance sector which is involved with:

- conducting audits under the supervision of an internal auditor;
- certifying and issuing EU financial assistance discontinuation declarations, which are referred to in the Fiscal Supervision Act, by fiscal inspectors and meets following criteria:
  - is exclusively a Polish citizen and can fully execute civil and civic rights;
  - enjoys an impeccable opinion and was not punished for any intentional crimes;
  - holds a university degree in law, economics or any other specialization useful for fiscal inspection;
  - is employed in a fiscal inspection organizational unit and has been employed in tax administration for at least five years or has three years of practice in fiscal inspection organizational units;
  - passed a qualification examination in order to function as an inspector before a board appointed by the General Fiscal Inspector,
- supervision or controlling by a controller from the Supreme Chamber of Control, referred to in the Supreme Chamber of Control Act, who, pursuant thereto, meets the following criteria:
  - is a Polish citizen;
  - is capable of performing legal activities, executing all public rights;
  - was not punished for any intentional crimes;
  - holds a university degree;
  - is healthy enough to be employed for this function;
  - completed controller's training and passed the controller's examination before the Examination Board appointed by the President of the Supreme Chamber of Control.

Any agreement executed between a unit and an outsourced service provider should feature provisions guaranteeing an internal audit will be conducted in accordance with the Act and relevant executory orders. Such an agreement, under the provisions of the relevant Article of the PFA, should specify how to handle documents. In particular, it should indicate how to manage electronic documents, prepared for internal auditing so as to make them accessible, while protected against unauthorized dissemination, mutilation or destruction.

The role, objectives and principles of internal auditing in the healthcare sector units

As previously mentioned, internal audits must be conducted in accordance with the provisions of the PFA, pertinent Regulations and instructions of the Minister of Finance as well as the International Standards for the Professional Practice of Internal Auditing, which were adopted as internal audit standards for PFSU.

Consequently, the aim of internal auditing is to identify and comprehend potential risks faced by a hospital and to examine and evaluate the effectiveness of the

internal control system, which was implemented to control risks and financial safety. The underlying objective of an internal audit is to support a unit's management in attaining their goals and in the execution of their tasks by regular management control and evaluation of public spending. It must be stressed that the amended PFA features a new definition of an audit. In accordance with Article 272 of the Public Finance Act, internal auditing means independent and objective activities, which support the Minister or a manager heading a given division or unit in attaining their goals and executing their tasks by regular evaluation of management control as well as counseling. In particular, it is evaluated whether management control in the government administration or a given unit is adequate, effective and efficient. In accordance with the Standards of auditing in PFSU, the fundamental goal of an audit is to add value and facilitate a unit's operation. Internal audits should provide the manager of a given unit with an unbiased and independent evaluation of whether the management and internal control mechanisms, inclusive of financial control procedures, are in place and operate adequately, effectively and efficiently. An internal audit involves the examination and evaluation of risk management and task execution quality.

Internal audits include assurance activities (evaluation) and counseling. Assurance activities constitute a fundamental task of an internal audit. An independent and unbiased management evaluation, inclusive of evaluation of risk management and control as well as a unit's operation areas and systems, should assure a manager that the systems operate properly. Audit by counseling should also lead to the facilitation of a unit's operation. An internal auditor can submit requests to the manager of a division or audited units, which should result in the facilitation of the operation of a division or its units. Nevertheless, auditor's requests, recommendations and opinions are not binding for management.

An internal audit should cover all areas of a unit's operation. Through internal auditing the manager of a unit is assured that:

- the objectives and tasks of a given unit are executed;
- procedures specified by acts of law or adopted by the manager of a unit are implemented and observed;
- the mechanisms and procedures constituting an internal control system are adequate and effective for a proper unit's operation.

Internal audits should include in particular:

- a review of internal control mechanisms as well as reliability and credibility of operational, management and financial information;
- an identification and analysis of risks related to hospital operation, including evaluation of the effectiveness of risk management and internal control;
- an opinion as to whether the control mechanisms put in place in the audited systems by unit management are adequate and efficient;
- an opinion about procedures and practices of financial information development, classification and presentation;

- an opinion as to whether acts of law, internal unit regulations as well as programs, strategies and standards introduced by pertinent bodies are observed;
- an opinion as to unit property security, an evaluation of the effectiveness and economy of unit resources use and public funds management;
- an evaluation as to whether a unit's operation is adjusted to previously presented recommendations of an internal audit or a control.

Further, it must be stressed that the Regulation concerning internal audit procedures and documentation of 2010, defines in detail the rules of internal auditing in PFSU. It features both regulations, which were modified, and numerous new provisions, including: provisions concerning internal audit documentation and procedures, internal audit report preparation and report components, counseling and conditions of an outsourced internal audit.

The internal audit standards, published in a new version in 2009, which should be observed by auditors in PFSU, i.e. including the healthcare sector units, are divided into: Attribute Standards (Series 1000), which pertain to the organization of an internal audit unit and the procedures for internal auditors, and Performance Standards (Series 2000), which characterize activities undertaken during internal audit, among others: planning, examination, reporting, as well as quality criteria for their evaluation (Tab. 1).

Tab. 1. Structure of internal audit standards in PFSU in 2010

Attribute Standards	Performance Standards
1000. Purpose, Authority, and Responsibility	2000. Managing the Internal Audit Activity
1010. Recognition of the Definition of Internal Auditing, the Code of Ethics, and the Standards in the Internal Audit Charter	2010. Planning
1100. Independence and Objectivity	2020. Communication and Approval
1110. Organizational Independence	2030. Resource Management
1111. Direct Interaction with the Board	2040. Policies and Procedures
1120. Individual Objectivity	2050. Coordination
1130. Impairment to Independence or Objectivity	2060. Reporting to Senior Management and the Board
1200. Proficiency and Due Professional Care	2100. Nature of Work
1210. Proficiency	2110. Governance
1220. Due Professional Care	2120. Risk Management
1230. Continuing Professional Development	2130. Control
1300. Quality Assurance and Improvement Program	2200. Engagement Planning
1310. Requirements of the Quality Assurance and Improvement Program	2201. Planning Considerations
1311. Internal Assessments	2210. Engagement Objectives

1312. External Assessments	2220. Engagement Scope
1320. Reporting on the Quality Assurance and Improvement Program	2230. Engagement Resource Allocation
1321. Use of *Conforms with the International Standards for the Professional Practice of Internal Auditing*	2240. Engagement Work Program
1322. Disclosure of Nonconformance	2300. Performing the Engagement
	2310. Identifying Information
	2320. Analysis and Evaluation
	2330. Documenting Information
	2340. Engagement Supervision
	2400. Communicating Results
	2410. Criteria for Communicating
	2420. Quality of Communications
	2421. Errors and Omissions
	2430. Use of *Conducted in Conformance with the International Standards for the Professional Practice of Internal Auditing*
	2431. Engagement Disclosure of Noncompliance
	2440. Disseminating Results
	2500. Monitoring Progress
	2600. Resolution of Management's Acceptance of Risks

Source: Own work based on *The International Standards for the Professional Practice of Internal Auditing* [10]

As intended by legislators, internal auditors in PFSU should be trusted. Internal auditors are trusted if they are ethical. The currently binding Code of Ethic for internal auditors in PFSU was published in 2006. The Code supplements the internal audit standards and provides instructions for internal auditors in the public finance sector units. In the light of the Code of Ethics, an internal auditor is obliged to work in an honest, reliable and decent manner. The Code presents rules of internal audit practice and standard procedures expected from an internal auditor. The rules are helpful in practice and are to promote ethical behavior among auditors. The rules pertaining to the internal audit practice in PFSU involve: honesty, objectivity, confidentiality, professionalism, internal auditor's bahavior and relations between internal auditors and conflicts of interest (Tab. 2).

Tab. 2. The rules pertaining to the internal audit practice in PFSU

1. Honesty	If an internal auditor is honest, his/her work is trusted and his/her evaluation relied on.
2. Objectivity	An internal auditor is highly objective during an internal audit, in particular when collecting, examining and forwarding information about the audited activities or processes. An internal auditor makes balanced judgments taking into consideration all significant circumstances connected with the audit task. In opinions he/she disregards his/her own interest and does not allow other persons influence his/her judgments.
3. Confidentiality	An internal auditor respects the value of and ownership rights to information, which he/she receives and does not disseminate it when unauthorized, unless he/she is legally or professionally obliged to do that.
4. Professionalism	An internal auditor uses his/her knowledge, skills and experience to conduct an internal audit.
5. Auditor's behavior	An internal auditor acts in a manner which reinforces professional cooperation and good relations with other auditors.
6. Conflict of interest	An internal auditor does not participate in an audit task, if it could result in a conflict of interest.

Source: Own work based on Announcement No. 16 concerning issuing the "Internal Auditor's Code of Ethics" and the "Internal Audit Charter" [3]

Each of the above rules was described in detail in the procedures for internal auditors in PFSU. The Minister of Finance recommends the managers of PFSU to implement the Code in the internal regulations of PFSU or to oblige internal auditors in any other manner to observe the Code.

Internal audit documentation

In accordance with acts of law and internal audit standards, a person in charge of internal auditing should establish rules and procedures to be observed during the audit. The form and content of the rules and procedures depend on the scope and structure of an internal audit as well as its complexity. The internal audit charter as well as the description of the internal audit procedures, which are frequently referred to as Internal Audit Book of Procedures, constitute fundamental internal documents regulating internal audit performance. The internal audit charter specifies the chief objectives and rules of an internal audit. Further, it should define the basic rights, obligations and responsibilities of an internal auditor and specify his/her status in a unit. Additionally, it should specify the relations with other control institutions such as, e.g. The Supreme Chamber of Control, inspectors from Tax Offices and Social Insurance Company.

The Internal Audit Book of Procedures specifies the general provisions of the charter and describes the detailed planning procedures, audit task execution and reporting. The Book of Procedures constitutes the basic source of information for au-

thorities and organizational units, as it describes not only audit organization but also internal audit procedures. The Book of Procedures is to provide the management of an organization, managers of audited units and an auditor with rules and instructions for current operation. The Book is most frequently composed of several parts and describes the organizational and operating audit objectives, audit method, audit files and evaluation of the internal auditor's work quality. It can also be used by other interested parties, both inside the sector, for example the supervisory bodies or audit committee, and outside the sector, for example, internal auditors examining internal audit's independence or reviewing procedures and other external controllers [8].

The Book of Procedures specifies the rules and methods of internal auditing in order to ensure the audit division operates smoothly and that audit activities are consolidated and properly documented. Furthermore, it defines obligations and deadlines for internal auditors to submit authorized unit plans, reports and other information connected with audit division operations and audit procedural modifications. The Book of Procedures features a collection of internal audit procedures. Because the procedures are in writing, the internal audit tasks are executed in a standard manner, as the outlay of forms and reports is uniform. The form outlay of the working documents makes the procedures more uniform and the document types and their graphics more alike. The procedures also help to define requirements concerning the internal audit activities. It also refers to the post-audit and counseling activities as well as the rules of drawing up audit documents. It should describe the criteria for increasing audit quality in a unit.

An internal auditor documents all activities and events, which are significant for internal auditing. An internal auditor keeps permanent internal audit files to collect information about risk areas, which can possibly constitute the subject of an internal audit and current internal audit files in order to document the internal audit and its results.
Permanent files include in particular:

- a list of fundamental standards and other acts of law connected with a unit where an internal audit is conducted and which regulate its operation;
- a list of documents describing management and control systems, inclusive of the financial control procedures;
- annual audit plans and reports from annual audit plan execution;
- other information significant for the audit, inclusive of the analysis of risk areas.

Current files include in particular:

- documents collected prior to the commencement of the audit task, inclusive of the materials which constitute the basis for the task commencement (for instance, system description) and personal authorization to conduct the audit;
- documents collected and drawn up at the audit schedule planning and preparation stage, inter alia, audit schedule, all potential schedule amendments, risk analysis documentation for a given audit task, minutes from an opening meeting, selected audit methods;

- materials drawn up by an auditor or received from any 3rd parties and statements of the audited unit's employees made during the audit, which influence the assessment of management and control systems (minutes from meetings, certified document copies, copies or excerpts from documents, statements and calculations, written and oral – in the form of a memo – information and explanations made to an auditor and statements concerning the audit subject, filled in questionnaires, minutes from talks and discussions, memos, test results, etc.);
- reports, inclusive of a draft report, any reservations and approved final reports, inclusive of a memo with initial conclusions (draft report), minutes from a closing meeting, additional explanations or reservations expressed by a manger of the audited division to the audit report together with a copy of the auditor's opinion, audit report, recommendation and requested execution plan, documents certifying the report was submitted to the unit's manager;
- documents concerning verification stage, inclusive of the verification memo, in particular the information from the audited unit's manager about the recommendation implementation;
- other documents significant for the audit task.

The head of a unit, the head of the audited unit, in which an audit is performed as well as all authorized persons can gain access to current audit files. The internal audit documents are marked and stored in accordance with the general rules concerning the files left behind in a unit.

CONCLUSIONS

Internal auditing was introduced to PFSU in January 2002. Internal auditing is a managerial instrument employed by unit managers to gain rational assurance that the objectives and tasks of a given unit are being attained, procedures stemming from acts of law or adopted by a unit manager are being implemented and observed, while internal auditing mechanisms and procedures adequately and correctly support a unit's operation.

It must be emphasized that the idea of professional and independent internal auditing dates back to the first half of the 20th century. In the United States in 1941 the Institute of Internal Auditors (IIA) was established. The IIA branch was also set up in Poland in 2001. In 1977 the European Court of Auditors was established in Luxemburg. The IIA standards are recognized worldwide as international standards. They were adopted by the EU institutions and by many other countries. In many countries they are perceived as models for developing national regulations. Also in Poland they served as a basis for the first national internal auditing standards for PFSU in 2003.

The function and development of internal auditing in PFSU places it in the organizational structure of the public finance sector units. Internal auditing in the sector is constantly facilitated by the regulations and instructions of the Minister of

Finance but also by the *International Standards for the Professional Practice of Internal Auditing*, which were adopted in July 2006, the ISACA standards as well as the financial control standards and the management control standards, which are based on international standards and concepts.

Public sector internal auditing is and will continue to be constantly improved as it is introduced, inter alia, by virtue of the amended Public Finance Act effective as of January 2010, as well as the new version of the *International Standards for the Professional Practice of Internal Auditing* put in practice in PFSU in 2009. Internal auditing becomes obligatory in more and more public finance sector units, including the healthcare sector units. It is necessary to and efficient for the public sector operation. The healthcare reform should lead to an establishment of a modern healthcare system, which will treat patients efficiently, create favorable conditions for the sector employees as well as manage public funds effectively. It is common knowledge that in the wake of the current bad situation of the Polish healthcare system and the poor financial situation of numerous units of the sector, among others, independent public healthcare centers, the sector is ineffectively managed. Thus, in light of the effective regulations and adopted standards, an internal audit should support the manager of a unit in effective unit management, evaluation of the efficiency of internal control, public finance economy, risk management and execution of corporate and public governance tasks.

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OVERVIEW PAPER

PROBLEMS IN QUALIFYING HEALTH SERVICES PROVIDED BY PHYSICIANS AND INFORMED CONSENT TO TREATMENT

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ABSTRACT

Introduction. Under the provisions of the Act on Patients' Rights and Patients' Rights Ombudsman of November 6, 2008, the patient has the right to receive health services adequate to current medical knowledge. The patient has the full right to give consent to medical procedures performed on him/her or to refuse such consent. By this consent, the patient legitimizes in a legal sense the physician's interference with a patient's fundamental rights and freedoms. Acting without consent is usually illegal, thus the physician risks disciplinary action, civil and criminal liabilities.
Aim. The aim of this work was to provide guidelines to assist in distinguishing between concepts concerning health services provided by physicians.
Discussion. In practice, the most significant difficulties arise from fluid boundaries between two legal terms "surgical procedure or therapeutic method posing an increased risk to life and health" and these same activities "posing the risk of causing loss of life, grievous bodily harm and grievous health disorder". In the former case, the physician must obtain informed consent to treatment, whereas in the latter case the consent is not required for providing health services.

On the basis of legal literature overview, legal acts and Polish courts judicature, the article presents a comparative legal classification stemming from the provisions

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of the Criminal Code of 1997, which contains the notion of causing "health disorder", along with the recent judicature of the Supreme Court. This is an attempt to make up for the lack of statutory definitions of particular elements that contribute collectively to the concept of health services.

Conclusions. The classification discussed poses interpretative problems, although the knowledge of the statutory division of health services and correct differentiation between terminological concepts are essential for physicians because they enable a correct assessment with regards to the informed consent required in a particular situation and determining those individuals authorized to providing such consent.

Physicians are legally obliged to qualify their actions according to the abovementioned classification each time they provide health services, which is difficult for them to cope with. Medical law has not kept pace with constant developments in medicine; however, a complex regulation addressing this matter seems to be impossible to arrive at presently.

Key words: informed consent, health services, criminal liability of physicians.

INTRODUCTION

General comments

Under the provisions of the currently binding Act on Patients' Rights and Patients' Rights Ombudsman of November 6, 2008 [7], the patient has the right to receive health services adequate to current medical knowledge, and when the availability of providing proper health services is limited, the patient has the right to a transparent, objective procedure based on medical criteria, indicating the order of availability for these services.

The patient also has a full right to give consent to medical procedures performed on him/her or to refuse such consent. It may be claimed that one of the most important rights of a patient is the opportunity to give or refuse consent for health services to be performed.

The obligation to obtain a patient's consent to medical procedures is a means of empowering the patient concerning the therapeutic and diagnostic processes [1]. It is to the patient's benefit, but also to that of the physician, that said consent should not be treated instrumentally and purely formally. Informed consent legitimizes in a legal sense the physician's interference with a patient's fundamental rights and freedoms. Acting without consent is usually illegal, thus the physician risks disciplinary (professional) action, civil and criminal liabilities.

When discussing the subject-matter of a patient's consent to offered health services, it should be first determined which procedures the patient may give consent to.

Analyzing Article 3 of the Act on Health Care Institutions of August 30, 1991 [8], it may be stated that health services are understood as all activities aimed at maintaining, saving, restoring and improving health.

The Medical Profession and Stomatologist Profession Act of December 5, 1996 [6] allows for classifying health services – as regards the obligation of obtaining informed consent to treatment – into:

- examination;
- surgical procedure and therapeutic or diagnostic method posing an increased risk, but not necessarily the risk of loss of life, grievous health disorder, grievous bodily harm;
- surgical procedure and therapeutic or diagnostic method, posing the risk of loss of life, grievous health disorder, grievous bodily harm;
- medical experiment;
- other medical procedures.

It should be noted that the aforementioned classification poses interpretative problems, although the knowledge of the statutory division of health services and the correct differentiation between terminological concepts are essential for physicians because they enable a correct assessment in terms of the consent required in a particular situation and in determining those individuals authorized to providing such consent.

Physicians are thus legally obliged to qualify their actions according to the aforementioned classification each time they provide health services, which is difficult for them to cope with.

Notion, subject-matter and legal nature of informed consent

Informed consent may be defined as an act of a patient's or his/her statutory representative's volition, freely undertaken and expressed according to the rules of communication and meaning understandable by other parties in the medical process, on the basis of thorough information provided by the physician with regards to all stages of medical treatment [5]. Informed consent must be specific and detailed. It refers fully to the consent to a surgical procedure [4].

As a rule, a patient specifies his/her will as regards every medical procedure performed on him/her, in the form of consent or refusal. The exception to this rule involves situations in which a patient's autonomy is limited. In particular, it refers to compulsory medical procedure and patients who because of their ages or health conditions are unable to independently make decisions concerning the therapeutic process [15].

Consent given by the patient for undertaking therapeutic activities may be subclassified as regards:

- type of consent, i.e. entity authorized to giving consent for providing health services;
- form of consent in which it must be expressed [15].

There are three types of consent that may be given for performing medical procedures. Legal doctrine divides the discussed consent into: consent proper (personal), parallel consent (cumulative) and substitute consent [1, 6, 15].

Generally, the patient expresses consent to suggested health services personally – in this case it is regarded as consent proper. This form of consent concerns:

- an adult person, enjoying full legal capacity;
- a woman who, by consent of the Guardianship Court, got married at the age of 16;
- a person who is partially legally incapacitated as regards medical procedures not posing an increased risk.

Parallel consent (consent given by two authorized entities) is required in the case of:

- patient between 16 and 18 years of age and this patient's statutory representative;
- fully legally incapacitated person who understands the situation and this person's statutory representative;
- legally partially incapacitated person and this person's statutory representative (court appointed guardian), with regards to diagnostic procedures posing an increased risk and surgical procedures.

Finally, substitute consent is given by a statutory representative of a patient less than 16 years of age, or a fully incapacitated person who does not understand the situation or by the Guardianship Court.

As regards the form of consent, it should be noted that the general rule provisioned by Article 32, §7 of the Medical Profession Act is that – unless the Act specifies otherwise – a patient's consent to treatment may be expressed orally or implicitly (*per facta concludenta*), that is by any conduct which unambiguously indicates the patient's will to undergo a particular medical procedure. Moreover, when there is no patient's refusal, it allows the physician to perform other medical procedures which do not pose risk and which are necessary for disease diagnosis [1].

There are, however, exceptions to this rule. The requirement of the written form – according to the aforementioned classification of health services – is compulsory in two cases, namely: a surgical procedure and therapeutic or diagnostic methods posing an increased risk for the patient and a medical experiment.

On the other hand, when a delay in providing medical assistance by a physician might result in the risk of loss of life, grievous bodily harm or grievous health disorder, according to Article 30 and Article 34 §7 of The Medical Profession and Stomatologist Profession Act, a physician may provide health services such as a surgical procedure or therapeutic or diagnostic method posing an increased risk for the patient without obtaining the consent of the patient's statutory representative or proper Guardianship Court.

It is worthwhile reviewing at this point the judgment in the case of the Supreme Court – Civil Chamber, case reference number 396/2006, which indicated that "health services referred to in […] Article 30 of the Medical Profession and Stomatologist

Profession Act of December 5, 1996, involve, generally, emergency and unexpected conditions which cannot be predicted (e.g. patients with stroke, myocardial infarction, road accident casualties). These services do not involve life-saving procedures which are performed on chronically treated patients and which require undergoing medical procedures systematically" [14].

The physician's activity described above is formally conditioned by obtaining an opinion of a second physician, preferably of the same specialization. Next, the physician should make an adequate note in the patient's medical documentation.

AIM

The aim of this work is to provide guidelines to assist in distinguishing between concepts concerning health services provided by physicians.

DISCUSSION

Qualification of health services provided by a physician with regards to informed consent

According to the authors of this article, in practice, the most significant difficulties arise from fluid boundaries between "surgical procedure or therapeutic method posing an increased risk to life and health" and these same activities "posing the risk of causing loss of life, grievous bodily harm and grievous health disorder". In the former case, the physician must obtain informed consent to treatment, whereas in the latter case – under conditions specified before in this article – consent is not required for providing health services.

It is obvious that physicians would prefer to have clear legal guidelines referring directly to procedures that they perform, which would allow them to easily qualify particular health services and define the required form of a patient's consent to treatment. However, due to constant progress in medicine, such a law would always lag behind, and a complex regulation concerning this issue would require creating a list of health services in a volume greater than a multi-volume universal encyclopedia.

In practice, when distinguishing between the described concepts of medical procedures, it is helpful to follow the classification devised in the Criminal Code of 1997, which contains the notion of causing "health disorder" and an unambiguous notion of a medical experiment, whose legal interpretation was provided by the legislators. This is an attempt to make up for the lack of statutory definitions of those particular elements that contribute collectively to the concept of health services.

In the Criminal Code, the concept of "health disorder and bodily harm" is used alternatively with the uniform term "injury". According to the Criminal Code, a severe bodily injury means:

- causing loss of sight, hearing, speech, and reproductive ability;
- other serious disability, serious incurable disease or long-lasting disease;

– truly life threatening disease;
– permanent mental disease;
– complete or significant permanent occupational incapacity;
– permanent, significant bodily disfigurement or marring.

On the basis of the principle of non-contradiction of law it must be assumed that remaining threats (effects) – other threats of increased or decreased significance – connected with a surgical procedure or therapeutic or diagnostic method performed by a physician lie within the scope of an increased risk rather than a risk of loss of life, grievous health disorder and grievous bodily harm.

It seems useful to review at this point specific judgments of the Supreme Court which indicated specific premises enabling the differentiation between particular notions making up the term of "serious injury".

According to the judgment of the Court of Appeal in Krakow of May 27, 1997, serious disability as defined in Article 156 §1 item 2 of the Criminal Code, does not refer to any bodily injury of permanent effect, but to disability comparable to the loss sight, hearing, speech, etc, thus leading to "serious" limitations in the functions of a human body [3].

Serious disability as understood in Article 156 items 1 and 2 of the Criminal Code should be understood as a complete discontinuation or a very significant limitation in the function of an important organ. For instance, a discontinuation of the function of one testicle, even with retained functional activity of the reproductive organ as such, should be considered a serious disability because it is an important organ in human life, of an independent, highly specialized function. If nature provided a human being with a number of parallel organs significant for life, the loss of one of these organs means the failure, to a large degree, in the functional activity in terms of the purpose of this important organ [11, 14].

It should be noted that the Criminal Code does not define the notion of disease. Still, if the term "disease" generally means "a pathological process, resulting in abnormal functioning of the organism or its part" [3], it must be assumed that the Criminal Code employs the notion of "long-lasting disease" according to this concept.

On the other hand, "serious incurable disease or long-lasting disease", another effect of the crime referred to in Article 156 §1 of the Criminal Code, in fact refers to two distinct concepts: "serious incurable disease" and "serious long-lasting disease", whereas in some situations a particular disease may simultaneously fulfill both premises, being "a serious disease" both "incurable" and "long-lasting".

Consequently, causing a serious long-lasting disease does not have to be, according to Article 156 §1 item 2 of the Criminal Code, connected with a serious "incurable" disease or truly "life threatening" disease, as this regulation defines these types of disease as alternative effects of the crime [12].

"Incurable disease" refers to a disease which cannot be cured according to current medical knowledge because of the lack of effective medication or the impossibility

of performing an effective surgical treatment (e.g. paralysis of lower limbs caused by spinal cord injury) or other medical procedure. This concept refers directly to current medical knowledge because only a specialist in a given section of medicine may specify a prognosis concerning the possibility of curing a particular patient. According to Article 156 §1 item 2 of the Criminal Code, such a disease must be not only "incurable" but also "serious", and such an evaluative premise of the effect of the crime may mean that it refers both to diseases of a sudden course (as in acute diseases) and of a long-lasting, devastating course, as in chronic diseases, but also diseases which are accompanied by significant functional disturbances.

"Serious long-lasting disease" is a disease which should fulfill both of these premises simultaneously. Its course, symptoms and the patient's ailments, etc., must support terming the disease as "serious".

With regards to the notion of an "truly life threatening disease", this is of a more subjective nature. Adopting such a qualification is conditioned by determining whether the disease is truly life threatening, rather than posing a theoretical threat. In other words, it must involve a real threat to a specific patient's life. Consequently, it does not have to be a disease whose features suggest that "it usually is life threatening" in an abstract way, but a disease which may not be characterized by such features but in a specific case it poses an actual (real) threat to a specific patient's life. "Truly life threatening disease" does not have to be either serious or long-lasting, it may be, however, "incurable" [2].

Consequently, in medical practice it is possible that a disease which from a theoretical point of view does not pose a threat to a patient's life, may in specific circumstances, e.g. at a lowered individual immunity, another disease existing earlier, etc., create a real threat for the person of such qualities.

Generally, however, a truly life threatening disease should be understood as a condition in which a serious disturbance of basic functions of systems of organs is observed, e.g. central nervous system, respiratory or circulatory systems, because of which the insufficiency and failure of their function may occur, leading to a patient's death [11].

The notion of a "permanent mental disease" referred to in Article 156 §1 item 2 of the Criminal Code may involve some problems in medical practice because in psychiatry, the etiology of the majority of mental diseases has not been in fact unambiguously explained. Thus, it is highly doubtful to attribute such an effect to the offender. In practice, such a possibility refers only to a small number of mental diseases, e.g. post-traumatic epilepsy.

The qualification of the patient's condition as "complete or significant permanent occupational incapacity" may be connected with some other effect referred to in Article 157 of the Criminal Code, e.g. "serious disability" (such as causing the loss of sight to a professional driver simultaneously results in complete permanent work

incapacity in this profession). Professional incapacity should be understood as an inability to perform work for which a given person is qualified professionally, even if he/she is able to perform other jobs.

Serious injury refers also to "permanent, significant bodily disfigurement or marring" listed in Article 156 §1 item 2 of the Criminal Code. Marring generally refers to causing significant, visible changes to the skin, but this category may involve also the loss of some parts of the body, e.g. auricle, nose. When determining the significance of this effect, the location of damages to the skin may be important. Changes involving the skin on the face should be treated differently from those in other, covered parts of the body. In practice, when performing the evaluation, it is more important whether the effect is "permanent" and also "significant".

Bodily disfigurement refers to causing such changes to the body which are visibly different from anatomical norms, i.e. kyphosis following the spinal fracture.

Permanent, significant bodily disfigurement or marring, is a notion which refers to esthetic criteria. This effect may be qualified only together with some other effects listed in Article 156 §1 items 1 and 2 of the Criminal Code, e.g. serious disability.

The described attempt to review and explain judgments of the Supreme Court as regards discussed definitions of medical procedures is definitely not fully satisfactory. However, due to the absence of judicature made on the basis of the provisions of the Medical Profession and Stomatologist Profession Act, the aforementioned judgments should be treated as specific guidelines in distinguishing between "surgical procedure or therapeutic method posing an increased risk to life and health" and these same activities "posing the risk of causing loss of life, grievous bodily harm and grievous health disorder".

CONCLUSIONS

The classification discussed poses interpretative problems, although the knowledge of the statutory division of health services and correct differentiation between terminological concepts are essential for physicians because they enable a correct assessment with regards to the informed consent required in a particular situation and determining those individuals authorized to providing such consent.

Physicians are legally obliged to qualify their actions according to the abovementioned classification each time they provide health services, which is difficult for them to cope with. Medical law has not kept pace with constant developments in medicine; however, a complex regulation addressing this matter seems to be impossible to arrive at presently.

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