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*ORIGINAL PAPER*

# STUDYING THE LEVEL OF ANXIETY AND DEPRESSION IN PATIENTS WITH CHRONIC SOMATIC PATHOLOGIES

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## ABSTRACT

**Introduction.** Among numerous emotional conditions found in somatic patients are, first of all, emotional pressure, depression, aggression, frustration, and emotional stress described as anxiety. Many authors analyze the role of negative emotional conditions with respect to the development of psychosomatic diseases.

**Aim.** The aim of this paper was to study the level of anxiety and depression in patients with ischemic heart disease (IHD), chronic obstructive pulmonary diseases (COPD), and asthma.

**Materials and methods.** By means of the Hospital Anxiety and Depression Scale (HADS) (Zigmond A., Snaith R., 1983) we investigated 68 IHD patients, 52 COPD patients and 57 asthma patients. The control group consisted of 30 healthy people comparable with respect to sex and age with the patients studied.

**Results and discussion.** The analysis of particular indicators taken from the HADS shows that patients with IHD, asthma, and COPD exhibit clinical levels of anxiety significantly exceeding the respective indicator in the control group ($\chi^2 = 7.9$, $p < 0.05$). However, these levels are higher in IHD, than in asthma and COPD ($\chi^2 = 14.7$, $p < 0.001$). According to the test, in COPD there is a tendency towards an increased clinical level of depression in comparison with IHD ($> 0.1$), whereas this indicator shows normal and subclinical values in asthma.

**Conclusions.** Thus, we have established that disturbing and depressive frustrations occur more frequently in patients with chronic somatic pathologies than among healthy subjects. It is obvious that the analyzed emotional frustrations negatively affect the formation of an internal picture of the disease and, also, patients' reactions to treatment.

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Timely diagnostics and targeted corrections of anxiety and depression in patients with somatic pathologies will allow physicians to improve both treatment results and a patient's quality of life.

**Key words:** ischemic heart disease (IHD), chronic obstructive pulmonary diseases (COPD), asthma, anxiety, depression

## INTRODUCTION

Among numerous emotional conditions found in somatic patients are, first of all, emotional pressure, depression, aggression, frustration, and emotional stress described as anxiety [1, 10, 16, 20]. Many authors analyze the role of negative emotional conditions with respect to the development of psychosomatic diseases [1, 2, 13, 17, 19]. It can be assumed that the most significant consequences of such diseases as ischemic heart disease (IHD), asthma, and chronic obstructive pulmonary diseases (COPD) involve the impossibility of carrying out social interactions in conformity with patients' ages as well as social and economic positions [4, 5, 12, 14, 15, 18]. However, the entire spectrum of emotional disturbances exhibited by these patients is still insufficiently studied [3, 9, 12, 15, 19]. Thus, frustration, its structure and degree of expressiveness are hardly studied in depth. The issues referring to the presence of mental frustrations and their features observed in the given category of patients are insufficiently examined. There are no accurate data about emotional disturbances, mental frustrations, and indicators of social activity in patients with IHD, asthma, and COPD. It is obvious that the received data will help towards designing programs of social adaptation for patients suffering from these diseases, since it is expedient to recognise the social adaptations of patients as the major problem to be addressed by public health services [4, 7, 8, 10, 11, 13, 15, 16, 20].

## AIM

The aim of this research was to study the level of anxiety and depression in patients with IHD, COPD, and asthma.

## MATERIALS AND METHODS

By means of the Hospital Anxiety and Depression Scale (HADS) [20] we investigated 68 IHD patients, 52 COPD patients, and 57 asthma patients. The control group consisted of 30 healthy people comparable with respect to sex and age with the patients studied.

## RESULTS AND DISCUSSION

The results obtained by the application of the HADS revealed that among IHD patients a normal level of anxiety was exhibited by 39.7% of such patients, a subclinical level of anxiety by 10.3% of such patients, and a clinical level of anxiety by 50.0% of such patients. A normal level of depression was revealed in 72.6%, a subclinical level in 21.0%, and a clinical level of depression was revealed in 6.4% of those patients with IHD. The respective data are presented in Tab. 1.

**Tab. 1.** Indicators of anxiety and depression in IHD patients according to the HADS

| Levels | IHD patients | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|
| | anxiety | | depression | | anxiety | | depression | |
| | abs. | % | abs. | % | abs. | % | abs. | % |
| Normal level | 27 | 39.7 | 45 | 72.6 | 19 | 63.3 | 27 | 90.0 |
| Subclinical level | 7 | 10.3 | 13 | 21.0 | 9 | 30.0 | 3 | 32.4 |
| Clinical level | 34 | 50.0 | 4 | 6.4 | 2 | 6.7 | 0 | 0 |

When analyzing these indicators, one may observe that clinical levels of anxiety and depression are significantly higher in patients with IHD in comparison with the control group ($\chi^2 = 24.2$, $p < 0.001$). However, anxiety indicators (both at subclinical and clinical levels) exceed the level of indicators of depression.

Among patients with asthma, 59.6% of the respondents had normal levels of anxiety, 22.8% expressed subclinical levels of anxiety, and 17.7% of the respondents showed clinically expressed anxiety.

The clinical level of depression was absent among these patients; the subclinical level was light in 38.8% of the cases, and 61.4% of patients with asthma revealed a level of depression corresponding to the norm according to the applied test (Tab. 2).

On the basis of the presented data it can be observed that in asthma patients, due to the absence of a clinical level of depression according to the applied test, their clinical level of anxiety significantly exceeds this indicator in the control group ($\chi^2 = 6.2$, $p < 0.05$).

**Tab. 2.** Indicators of anxiety and depression in asthma patients according to the HADS

| Levels | Asthma patients | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|
| | anxiety | | depression | | anxiety | | depression | |
| | abs. | % | abs. | % | abs. | % | abs. | % |
| Normal level | 34 | 59.6 | 35 | 61.4 | 19 | 63.3 | 27 | 90.0 |
| Subclinical level | 13 | 22.8 | 22 | 38.8 | 9 | 30.0 | 3 | 32.4 |
| Clinical level | 10 | 17.7 | 0 | 0 | 2 | 6.7 | 0 | 0 |

The analysis of anxiety and depression indicators in COPD patients reveals that a normal level of anxiety is exhibited by 51.9% of patients, a subclinical level of anxiety by 27.0%, and a clinical level of anxiety by 21.1% of such patients. A normal level of depression was revealed in 36.5% of such patients, a subclinical level in 46.2%, and a clinical level of depression was revealed in 17.3% of those patients with COPD (Tab. 3).

**Tab. 3.** Indicators of anxiety and depression in COPD patients according to the HADS

| Levels | COPD patients | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|
| | anxiety | | depression | | anxiety | | depression | |
| | abs. | % | abs. | % | abs. | % | abs. | % |
| Normal level | 27 | 51.9 | 19 | 36.5 | 19 | 63.3 | 27 | 90.0 |
| Subclinical level | 14 | 27.0 | 24 | 46.2 | 9 | 30.0 | 3 | 32.4 |
| Clinical level | 11 | 21.1 | 9 | 17.3 | 2 | 6.7 | 0 | 0 |

The results obtained by the application of the HADS allow us to notice that in patients with IHD, asthma and COPD, clinical levels of anxiety significantly exceed this indicator in the control group ($\chi^2 = 7.9$, $p < 0.05$). However, these levels are higher in IHD, than in asthma and COPD ($\chi^2 = 14.7$, $p < 0.001$). According to the test, in COPD there is a tendency towards an increased clinical level of depression in comparison with IHD ($> 0.1$), whereas this indicator shows normal and subclinical values in asthma.

## CONCLUSIONS

Thus, we have established that disturbing and depressive frustrations occur more frequently in patients with chronic somatic pathologies than among healthy subjects. It is obvious that the analyzed emotional frustrations negatively affect the formation of an internal picture of the disease and, also, patients' reactions to treatment.

Timely diagnostics and targeted corrections of anxiety and depression in patients with somatic pathologies will allow physicians to improve both treatment results and a patient's quality of life.

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Pol. Ann. Med., 2011; 18 (1): 12–19.
*ORIGINAL PAPER*

# EXPRESSION OF KI-67 AS A PROLIFERATION MARKER IN PROSTATE CANCER

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## ABSTRACT

**Introduction.** Prostate carcinoma (PCa) is the most common male cancer found in industrialized societies and represents a serious public health problem. Delineation of gene expression patterns in early PCa that correlate with an aggressive phenotype is a priority and may allow for radical treatment to be offered on a more selective basis to those patients with a clinically localized, yet aggressive disease. Ki-67 was recognized as associated with carcinogenesis in PCa.

**Aim.** The aim of this study was the immunohistochemical evaluation of Ki-67 and its expression in PCa following radical prostatectomy, and analysis of its relationship to chosen clinical and morphological parameters of such tumors.

**Materials and methods.** A total number of 56 randomly selected patients undergoing radical prostatectomy were investigated. The tumors, after fixation with 10% neutral buffered formalin, were completely embedded in paraffin. The sections were cut into hematoxylin-eosin staining for histological examination. The sections were also immunostained, with monoclonal antibodies against Ki-67. Immunolocalization of Ki-67 was performed using the LSAB method. Serum PSA levels were obtained from clinical information. These obtained results were statistically analyzed using the Fisher's exact test and $\chi^2$ test.

**Results and Discussion.** No statistically significant correlation was found between the expression of Ki-67 and the preoperative PSA level, lymph node metastases, capsular penetration, seminal vesicle invasion, and positive or negative surgical resection margins. However, a strong statistically significant correlation between Ki-67 positive and the T stage was found. We also found a relationship between the Gleason score of 7 or above and a high expression of Ki-67 in PCa ($p < 0.004$, $p < 0.02$ respectively).

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**Conclusions.** It is noteworthy that a significant correlation exists between the Gleason score and the expression of Ki-67 in this present study. We observed a high expression of Ki-67 for a Gleason score of 7 or above. Our results suggest that Ki-67 may be useful to serve as a tumor marker in PCa.

**Key words:** prostate cancer (PCa), Ki-67, immunohistochemistry

## INTRODUCTION

Prostate cancer (PCa) is the most common malignant tumor found in men. Identification of patients with aggressive rather than indolent PCa is a major challenge for optimal management purposes and is only partially met by currently available prognostic parameters. Delineation of gene expression patterns in early PCa that correlate with an aggressive phenotype is a priority and may allow for radical treatment to be offered on a more selective basis to those patients with a clinically localized, yet aggressive disease. Various indices of cellular proliferative activity have been investigated. Mitotic counts only detect cells in the M phase, are dependent on the period of time between surgical removal and fixation of the specimen, and suffer from heterogeneous distribution and confusion between mitoses and nuclear pyknosis and karyorrhexis. Ki-67 recognizes a proliferation specific nuclear antigen. It is expressed by proliferating cells in late $G_1$, S, $G_2$, and M phases, but not in resting cells in $G_0$. Staining is commonly nucleolar or perinucleolar. Ki-67 gives a higher labeling index than other antibodies, with good inter-reading reproducibility. It is therefore important to identify the antibody used in each study [12].

Therefore Ki-67, the most frequently used cell proliferation marker, recognized nuclear antigens as associated with all phases of the cell-cycle, except $G_0$ [7]. Ki-67 was recognized as associated with carcinogenesis in PCa [5, 6, 10].

In this study we evaluated the immunohistochemical profile of Ki-67 and correlated the results with chosen clinicopathological parameters in resected specimens of PCa.

## AIM

The aim of this study was the immunohistochemical evaluation of Ki-67 and its expression in PCa following radical prostatectomy, and the analysis of its relationship to chosen clinical and morphological parameters of the tumors.

## MATERIALS AND METHODS

All patients in this study were diagnosed and treated for PCa. A total of 56 randomly selected patients undergoing radical prostatectomy were investigated in the present study. The tumors, after fixation with 10% neutral buffered formalin, were complete-

ly embedded in paraffin. Up to three blocks from each case were obtained to provide representative material from the major foci of cancer within each prostate. The sections were cut to hematoxylin-eosin (HE) staining (Fig. 1), to AMACR examination (Fig. 2, 3), to Cytokeratin 34βE12 (Fig. 4) for pathological examination according to the TNM classification and according to the Gleason grading system. Tumors were classified as high grade when the combined Gleason score was 7 or above and as low grade when the combined score was 6 or below. Serum PSA levels were obtained from clinical information.

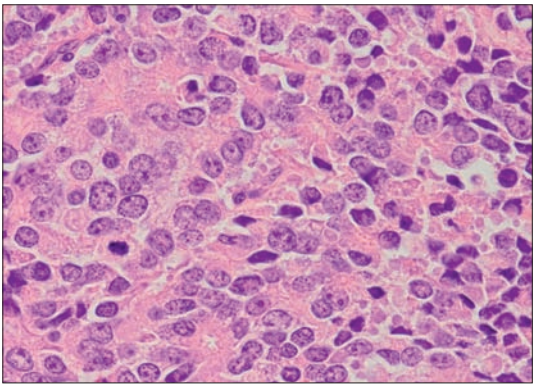

**Fig. 1.** Adenocarcinoma of the prostate after radical prostatectomy – Gleason score 9 [HE, magn. 400×]

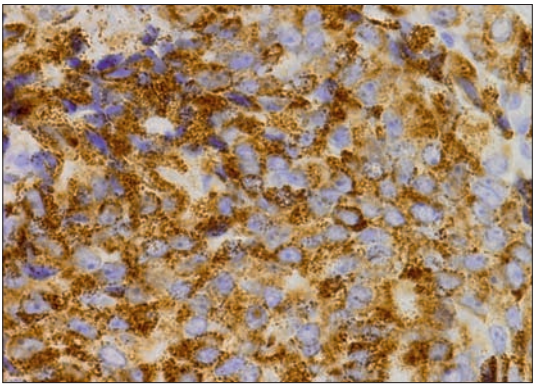

**Fig. 2.** Adenocarcinoma of the prostate after radical prostatectomy – Gleason score 7 [AMACR, magn. 400×]

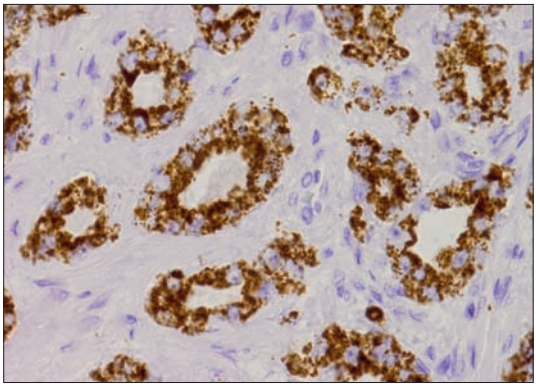

**Fig. 3.** Adenocarcinoma of the prostate after radical prostatectomy – Gleason score 9 [AMACR, magn. 400×]

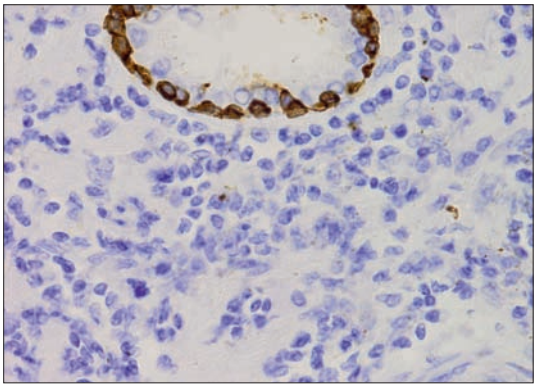

**Fig. 4.** Adenocarcinoma of the prostate after radical prostatectomy – Gleason score 9 [Cytokeratin 34βE12, magn. 400×]

The sections were deparaffinized in xylene and rehydrated in decreasing concentrations of ethanol. The sections were treated with 2% $H_2O_2$ for 10 minutes at room temperature to inactivate endogenous peroxidase activity. The deparaffinized tissue sections were incubated in 10 mM citrate buffer, pH 6.0, and heated at 95°C for 15 minutes. The sections were stained immunohistochemically with the anti-human Ki-67, PCNA monoclonal (Dako/Ki-67, No N1574 and Dako/PCA, No M0879). The immunolocalization of Ki-67 was performed using the Labeled Streptavidin Biotin (LSAB) method. The Ki-67 expression was semiquantitatively assessed in neoplastic cells and defined as follows: Ki-67 negative (lack of reaction), Ki-67 low (reaction present in less than 10% of cells) (Fig. 5), and Ki-67 high (reaction present in more than 10% of cells) (Fig. 6).

The obtained results were statistically analyzed using the Fisher's exact test and $\chi^2$ test.

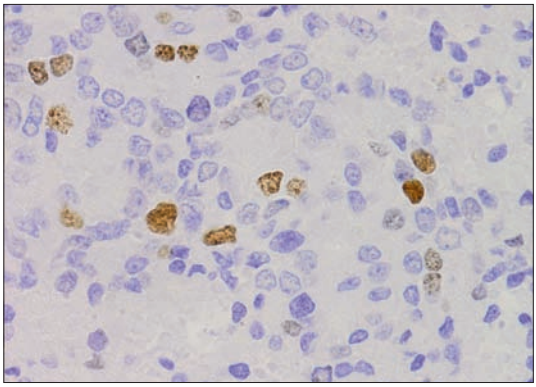

**Fig. 5.** Adenocarcinoma of the prostate after radical prostatectomy – Gleason score 7 [Expression of Ki-67, magn. 400×]

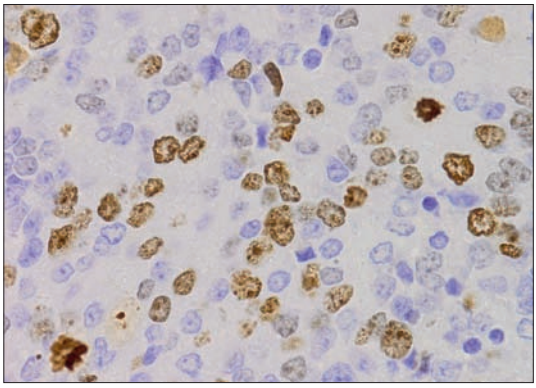

**Fig. 6.** Adenocarcinoma of the prostate after radical prostatectomy – Gleason score 9 [Expression of Ki-67, magn. 400×]

## RESULTS

The overall results of immunohistochemical examinations have been presented in Tab. 1. The average age of the patients was 62 years. Depending on the preoperative serum PSA concentrations, we distinguished three groups: first (6 cases) when the PSA concentration was 0–4 ng/mL, second (18 cases) when the PSA concentration was 4–10 ng/mL, and third (32 cases) when the preoperative serum PSA level was 10 ng/mL or above. In the present study, following pelvic lymph node dissection and radical prostatectomy, tumor specimens were classified as pT2 (38 patients, 67.9%) and pT3 (18 patients, 32.1%). The statistically significant correlation was found between pT and Ki-67, where 16 (88.9%) out of 18 patients with a pT3 stage were Ki-67 positive and only 2 of them were Ki-67 negative. Also, no correlation was found

between the Ki-67 expression in PCa and anatomoclinical parameters such as lymph node metastases, capsular penetration, seminal vesicle invasion, surgical resection margin, and between the preoperative serum PSA levels. However, a strong association between the expression of Ki-67 in a high Gleason score is noteworthy. 24 out of 26 cases with a Gleason score of 7 or above were immunopositive for Ki-67 (Fig. 6), ($p < 0.004$, $p < 0.02$).

**Tab. 1.** Expression of Ki-67 and clinicopathological findings

| Variable | | No. of cases | Ki-67 Negative | | Ki-67 High | | P value |
|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | |
| PSA | 0–4 | 6 | 2 | 33.3 | 4 | 66.7 | NS |
| | 4–10 | 18 | 12 | 66.7 | 6 | 33.3 | |
| | 10 | 32 | 6 | 18.8 | 26 | 81.3 | |
| pT | pT2 | 38 | 18 | 47.4 | 20 | 52.6 | 0.06 |
| | pT3 | 18 | 2 | 11.1 | 16 | 88.9 | |
| pN | Negative | 48 | 18 | 37.5 | 30 | 62.5 | NS |
| | Positive | 8 | 2 | 25.0 | 6 | 75.0 | |
| GS | <7 | 30 | 18 | 60.0 | 12 | 40.0 | 0.004 |
| | ≥7 | 26 | 2 | 7.7 | 24 | 92.3 | |
| CP | Negative | 24 | 12 | 50.0 | 12 | 50.0 | NS |
| | Positive | 32 | 8 | 25.0 | 24 | 75.0 | |
| SVI | Negative | 28 | 10 | 35.7 | 18 | 64.3 | NS |
| | Positive | 28 | 10 | 35.7 | 18 | 64.3 | |
| SRM | Negative | 38 | 16 | 42.1 | 22 | 57.9 | NS |
| | Positive | 18 | 4 | 22.2 | 14 | 77.8 | |

Comments: GS – Gleason score, CP – capsular penetration, SVI – seminal vesicles invasion, SRM – surgical resection margins, NS – not specified.

## DISCUSSION

PCa is the most common solid tumor found in the Polish male population and is the second leading cause of cancer specific mortality. Neoplastic diseases, as proliferative disorders, are characterized by uncoordinated cell growth. Activation of protooncogenes and inactivation of tumor suppressor genes are the main adverse genetic and epigenetic events that are responsible for neoplastic transformation [2, 4].

Over the last few years, the proliferation rate of cancer has been assessed by means of immunohistochemical markers and exploited as a potential prognostic marker [3, 5, 6, 13]. The Ki-67 nuclear antigen, present in the $G_1$ through M phase of the cell cycle but not at rest, correlates well with the traditional assessment of proliferation such as bromodeoxyuridine uptake and thymidine labeling [8, 14]. In our study, Ki-67

defined as positive in more than 10% of tumor cells was found in 36 (64%) of 56 resected PCas. In this study, no statistically significant correlation was found between the expression of Ki-67 and preoperative PSA levels, lymph node metastases, capsular penetration, seminal vesicle invasion and positive or negative surgical resection margins. However, a strong statistically significant correlation between Ki-67 positive (more than 10% of neoplasmatic cells) and the T stage was found. It is similar to that shown in numerous studies, where a significant correlation between nuclear proliferation antigens, such as Ki-67, and the tumor grade in PCa was observed [9, 16]. Although Kallarury et al. [11] show a correlation between Ki-67 expression and tumor grade; that correlation did not demonstrated a significant predictive value for disease recurrence. These results are consistent with previously reported observations [1, 15], in which Ki-67 was not an independent predictor for poor survival in patients with PCa.

## CONCLUSIONS

1. Significant correlation exists between the Gleason score and the expression of Ki-67.
2. A high expression of Ki-67 for a Gleason score of 7 or above was observed.
3. Ki-67 may be useful to serve as a tumor marker in PCa.

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*ORIGINAL PAPER*

# THE DEVELOPMENT OF THE AORTA IN PRENATAL HUMAN LIFE

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## ABSTRACT

**Introduction.** The anatomy and role of the aorta in prenatal life differ from those in postnatal life.

**Aim.** We aimed at investigating the development of the aorta during a period between the 4th and 8th months of fetal life. We also analyzed the influence of sex on the values of the parameters examined.

**Materials and methods.** We examined the diameters of aortas in 223 human fetuses, including 108 males and 115 females, aged between 4 and 8 months of prenatal life. The entire material was obtained from the Department of Histology and Embryology at the Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. All fetal specimens had been conserved in a 9% formaldehyde solution for a period of more than 3 months. Only spontaneously aborted fetuses of a normal morphology and a normal karyotype were used in this research. We measured the diameter of the proximal and distal ascending aorta, of the aortic arch, and of the proximal thoracic aorta. The measurements were taken in the following locations: the diameter of the proximal ascending aorta was taken at the level of the aortic valve; the diameter of the distal ascending aorta was taken at the ostium of the brachiocephalic trunk; the diameter of the aortic arch was taken between the ostium of the left common carotid artery and the left subclavian artery; the diameter of the proximal thoracic aorta was measured just beneath the arterial duct.

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**Results, Discussion and Conclusions.** All analyzed diameters grew linearly in time. We found no significant differences in the anatomy of the aorta with respect to sex. The ascending aorta is broader than the descending, thoracic aorta.

**Key words**: aorta, human fetus, prenatal life

## INTRODUCTION

The circulation of blood differs between the fetal and postnatal life. These differences involve the changing pressure load of the proximal aorta. In prenatal life, the ascending aorta and the aortic arch carry half of the blood volume that flows through the distal, i.e., thoracic aorta. The initial segment of the aorta also carries less blood in the prenatal period than in the postpartum period. Blood from the ascending aorta and the aortic arch is directed to the upper part of the body, primarily to the head and the central nervous system. This is possible due to vascular structures specific for prenatal life, i.e., the arterial duct and the aortic isthmus. The unique anatomy and functioning of prenatal circulation call for a meticulous monitoring of the growth of particular segments of the aorta as a means of evaluating the development of the entire circulatory system [3, 18, 19, 23, 25, 31, 34].

## AIM

We aimed at investigating the development of the aorta during that period between the 4$^{th}$ and 8$^{th}$ months of fetal life. We analyzed the proximal and distal part of the ascending aorta, the aortic arch, and the initial segment of the thoracic aorta. We assessed how the anatomy of this vessel varies depending on sex. We also analyzed the relationship between the diameters of the ascending and descending aortas.

## MATERIALS AND METHODS

Research material consisted of 223 human fetuses, including 108 males and 115 females, aged between 4–8 months of prenatal life. The entire material for this project was obtained from the Department of Histology and Embryology of the Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. This study was approved by the Research Bioethics Committee of the Nicolaus Copernicus University (resolution KB/433/2004). All fetuses had been conserved in a 9% formaldehyde solution for a period of at least 3 months. Only spontaneously aborted fetuses with a normal morphology and a normal karyotype were included in this study. None of the analyzed specimens demonstrated any visible malformations, or developmental abnormalities upon close inspection. The morphological age of each fetus was estimated according to the crown-rump length (vertex-tuberale). To this end we used a regression function initially proposed by Iffy et al. [17] in a paper evaluating a pop-

ulation of white U.S. fetuses. All specimens were categorized into monthly subgroups according to the determined morphological age. Different numbers of fetuses were allocated to particular age groups.

The vessel beds were filled with latex LBS 3060, without distorting the dimensions of the vessels, at an amount of approximately 15–30 mL, through a catheter, which was inserted by dorsal access into the thoracic aorta. All measurements of the parameters related to the aorta were taken by two independent investigators. With the aid of binocular magnifying glasses (MBS-9, Russia, magnification 0.6–7 × 14), they used digital calipers (INCO, Poland, resolution 0.01 mm) to collect all measurements, with an accuracy range of 0.01 mm. All measurements were taken twice by each investigator for consistency and verification purposes. The mean value of the two obtained values was considered for further quantitative analysis.

The diameters of the proximal and the distal ascending aorta, the aortic arch, and the proximal thoracic aorta were measured. The measurements were taken in the following locations: the diameter of the proximal ascending aorta was taken at the level of the aortic valve (1); the diameter of the distal ascending aorta (2) was taken at the ostium of the brachiocephalic trunk (BCT); the diameter of the aortic arch (3) was taken between the ostium of the left common carotid artery (LCCA) and the left subclavian artery (LSA); the diameter of the proximal thoracic aorta was taken just beneath the arterial duct (AD) (4) (Fig. 1).

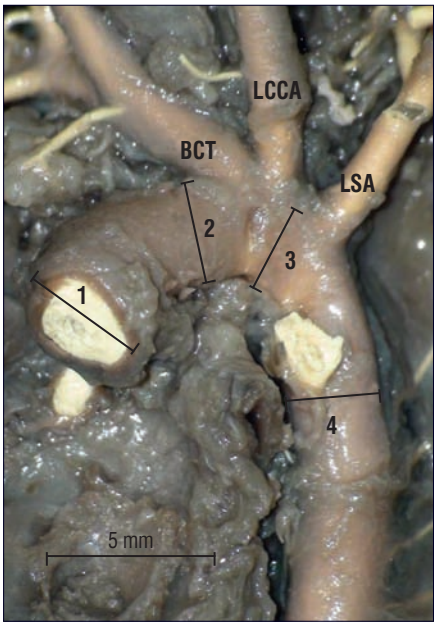


**Fig. 1.** Ascending aorta, aortic arch, thoracic aorta and branches of aorta in a 24-weeks old female fetus. Comments: BCT – brachiocephalic trunk, LCCA – left common carotid artery, LSA – left subclavian artery, AD – arterial duct. Points of measurements: 1 – the diameter of the proximal ascending aorta, 2 – the distal ascending aorta, 3 – the aortic arch, 4 – the proximal thoracic aorta

Statistica 8.0 software (StatSoft Polska) was used for statistical analysis of the obtained data. We calculated mean values and standard deviations for each age group with respect to sex. In order to compare the means from particular groups, we applied univariate (age) and bivariate (age and sex) analyses of variances (ANOVA) for independent variables and Tukey's HSD post hoc test for non-equal populations. Statistical significance was defined as $p \leq 0.05$.

## RESULTS

All analyzed diameters: of the proximal and the distal ascending aorta, the aortic arch, and the proximal thoracic aorta, increased with age according to a linear regression curve. All diameters had a high regression coefficient (r) with respect to age – above 0.92, which was statistically significant – $p < 0.001$ (Fig. 2–5).

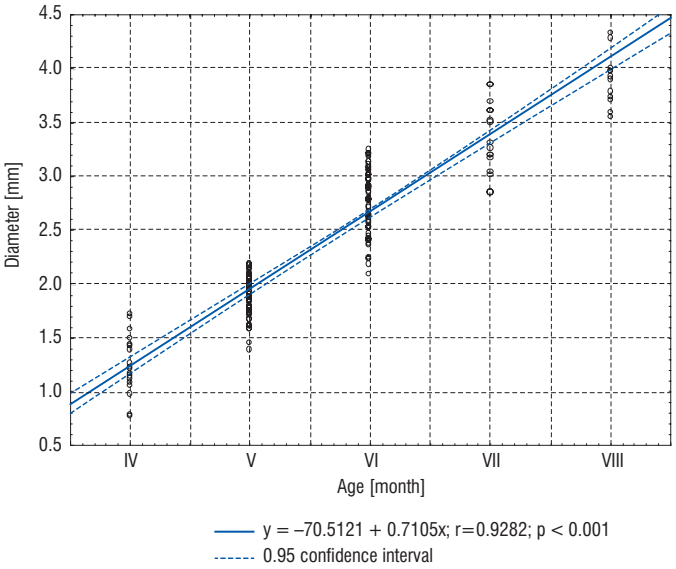


**Fig. 2.** Regression curve for the diameter of the proximal ascending aorta versus fetal age (x)

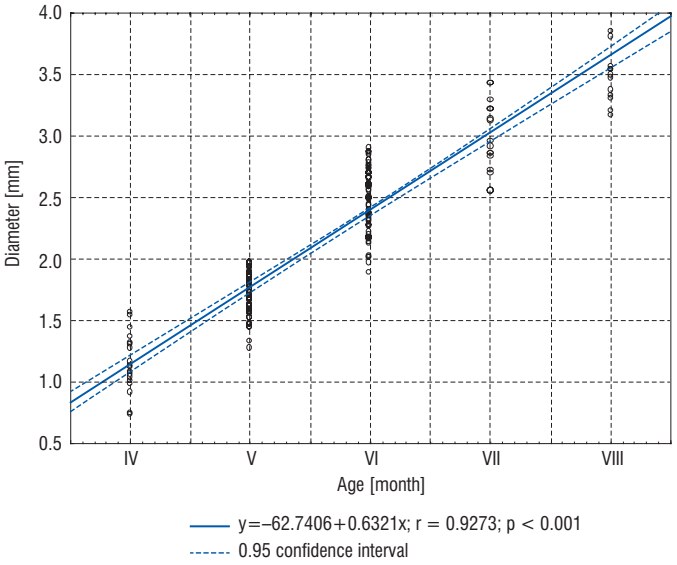


**Fig. 3.** Regression curve for the diameter of the distal ascending aorta versus fetal age (x)

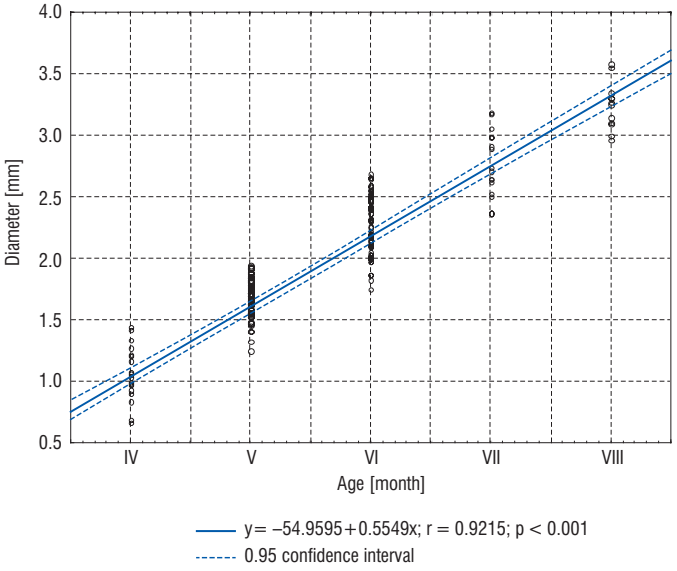


**Fig. 4.** Regression curve for the diameter of the aortic arch versus fetal age (x)

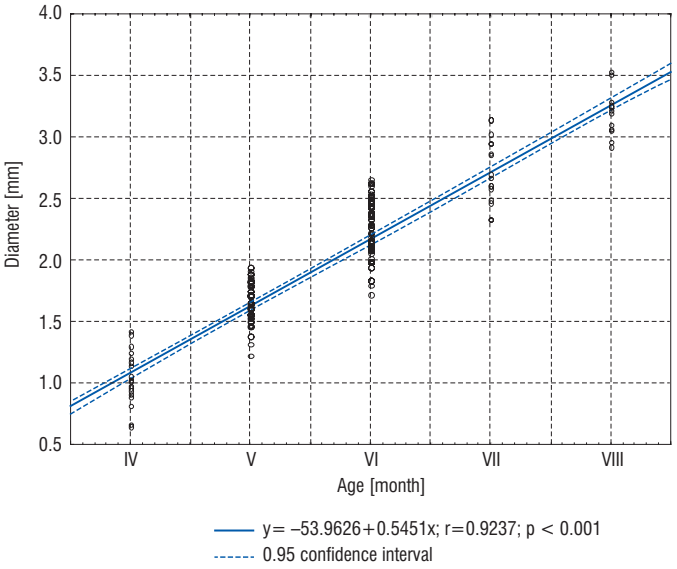


**Fig. 5.** Regression curve for the diameter of the thoracic aorta versus fetal age (x)

The diameter of the proximal ascending aorta in the 4$^{th}$ month was 1.25±0.27 mm, and it reached 3.89±0.24 mm in the 8$^{th}$ month. The mean diameter was 2.46±0.71 mm and it did not differ significantly between sexes ($p = 0.2598$). It was 2.52±0.73 mm in males and 2.41±0.69 mm in females. This difference did not reach the level of significance for any month of fetal life ($p > 0.05$) (Tab. 1). The diameter of the distal ascending aorta in the entire group was 2.19±0.63 mm, and it was similar in both sexes ($p = 0.2645$). Also, in particular age subgroups there were no differences between the sexes ($p > 0.05$) (Tab. 2). The diameter of the aortic arch was 2.08±0.58 mm in females and 2.00±0.53 mm in males. Within the entire group, the average aortic arch diameter was 2.04±0.55 mm. Both in the entire group ($p = 0.3304$) and in monthly subgroups there were no sex related differences ($p > 0.05$) (Tab. 3). The last analyzed parameter was the diameter of the proximal segment of the thoracic aorta. The mean value of this parameter was 2.03±0.55 mm for the entire group and it did not statistically differ in males (2.06±0.57 mm) and females (1.99±0.52 mm) ($p = 0.3937$). The diameter of the thoracic aorta was not different with regard to sex in any of the monthly age subgroups ($p > 0.05$). In the 4$^{th}$ month the diameter of the thoracic aorta was 1.01±0.22 mm and in the 8$^{th}$ month it was 3.16±0.19 mm (Tab. 4). The increase of all analyzed diameters of the aorta for the entire group in consecutive months (i.e., the 5$^{th}$ and the 4$^{th}$, the 6$^{th}$ and the 5$^{th}$, the 7$^{th}$ and the 6$^{th}$, the 8$^{th}$ and the 7$^{th}$ months) was statistically significant ($p < 0.05$). This also holds true for both sexes analyzed separately.

**Tab. 1.** Mean diameter of the proximal ascending aorta in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 1.25±0.27 | 1.24±0.29 | 1.26±0.28 | 0.8439 |
| 5 | 70 | 32 | 38 | 1.87±0.18* | 1.88±0.19* | 1.87±0.17* | 0.9304 |
| 6 | 105 | 50 | 55 | 2.75±0.27* | 2.76±0.27* | 2.74±0.28* | 0.5467 |
| 7 | 18 | 12 | 6 | 3.33±0.33* | 3.31±0.32* | 3.33±0.38* | 0.9855 |
| 8 | 12 | 6 | 6 | 3.89±0.24* | 3.95±0.32* | 3.85±0.12* | 0.4659 |
| Total | 223 | 108 | 115 | 2.46±0.71 | 2.52±0.73 | 2.41±0.69 | 0.2598 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

**Tab. 2.** Mean diameter of the distal ascending aorta in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 1.11±0.24 | 1.10±0.26 | 1.12±0.25 | 0.8448 |
| 5 | 70 | 32 | 38 | 1.66±0.16* | 1.67±0.17* | 1.66±0.15* | 0.8774 |
| 6 | 105 | 50 | 55 | 2.44±0.24* | 2.46±0.24* | 2.43±0.25* | 0.6091 |
| 7 | 18 | 12 | 6 | 2.96±0.29* | 2.96±0.29* | 2.96±0.34* | 0.9957 |
| 8 | 12 | 6 | 6 | 3.47±0.21* | 3.51±0.29* | 3.42±0.11* | 0.4659 |
| Total | 223 | 108 | 115 | 2.19±0.63 | 2.24±0.64 | 2.14±0.61 | 0.2645 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

**Tab. 3.** Mean diameter of the aortic arch in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 1.02±0.22 | 1.01±0.23 | 1.03±0.23 | 0.8392 |
| 5 | 70 | 32 | 38 | 1.63±0.16* | 1.65±0.15* | 1.61±0.16* | 0.3782 |
| 6 | 105 | 50 | 55 | 2.24±0.22* | 2.25±0.22* | 2.23±0.23* | 0.5551 |
| 7 | 18 | 12 | 6 | 2.72±0.27* | 2.71±0.26* | 2.72±0.31* | 0.9928 |
| 8 | 12 | 6 | 6 | 3.19±0.19* | 3.24±0.27* | 3.16±0.09* | 0.4659 |
| Total | 223 | 108 | 115 | 2.04±0.55 | 2.08±0.58 | 2.00±0.53 | 0.3304 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

**Tab. 4.** Mean diameter of the proximal thoracic aorta in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 1.01±0.22 | 1.00±0.23 | 1.02±0.23 | 0.8523 |
| 5 | 70 | 32 | 38 | 1.63±0.16* | 1.60±0.16* | 1.66±0.15* | 0.1169 |
| 6 | 105 | 50 | 55 | 2.22±0.22* | 2.23±0.22* | 2.21±0.23* | 0.5767 |
| 7 | 18 | 12 | 6 | 2.69±0.27* | 2.69±0.26* | 2.69±0.31* | 0.9902 |
| 8 | 12 | 6 | 6 | 3.16±0.19* | 3.21±0.26* | 3.12±0.31* | 0.4796 |
| Total | 223 | 108 | 115 | 2.03±0.55 | 2.06±0.57 | 1.99±0.52 | 0.3937 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

**Tab. 5.** The ratio of the diameter of the proximal ascending aorta and the diameter of the thoracic aorta (x)

| Age [month] | N | X | P value |
|---|---|---|---|
| 4 | 18 | 1.32 | 0.7659 |
| 5 | 70 | 1.15 | 0.6512 |
| 6 | 105 | 1.24 | 0.5690 |
| 7 | 18 | 1.24 | 0.4532 |
| 8 | 12 | 1.18 | 0.2591 |
| Total | 223 | 1.21 | 0.4892 |

Comments: SD – standard deviation. There is no difference between consecutive age groups ($p > 0.05$), P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

The ratio of the diameters of the proximal ascending aorta to proximal thoracic aorta in the entire group and in particular age subgroups ranged between 1.15 ($5^{th}$ month) and 1.32 ($4^{th}$ month). For the entire group this ratio was 1.21 (Tab. 5). It was similar in both sexes.

## DISCUSSION

Several published papers point to a greater diameter of the aorta in the male sex [21, 22, 24]. However, no differences were found when the size of the aorta was correlated with the total body area. Gielecki et al. [13, 14] and Szpinda [28, 29, 30] also found the aorta diameters to be similar in both male and female fetuses. Our results lead to a similar conclusion.

The linear growth of the aorta in time, as assessed by the analysis of diameter changes in selected vessel segments (the ascending aorta, aortic arch, and the thoracic aorta), that we discovered was also reported by other authors. Ursell et al. [32] in a group of 274 human fetuses, aged between 3 and 7 months of intrauterinal life,

demonstrated a linear growth pattern of the exterior diameters of the aorta (at the level of the aortic valve and of thoracic aorta). Also Hornberger et al. [15] in their study concerning 92 fetuses, aged between 5 and 10 months, proved that the diameters of 5 segments of the aorta grew linearly in time. Firpo et al. [11] who investigated the prenatal growth of the main arteries of the thorax, reached a similar conclusion. According to Hyett et al. [16], the diameter of the aorta between the 3rd and the 5th months increased linearly. Also Gembruch et al. [12] in a study group of 136 fetuses and Achiron et al. [1, 2] in a similar group, both demonstrated a linear growth pattern of the aorta with respect to fetus age. According to Zalel et al. [35], who investigated a very large group of 338 fetuses, aged between 4 and 7 months, the diameter of the initial segment of the aorta grew linearly in time. This observation was confirmed on the basis of the proximal segment of the ascending aorta by Chaoui et al. [9]. Szpinda [28, 29, 30] demonstrated that the linear model best described the mode of growth of the aorta. Also, Gielecki et al. [13, 14] found that in fetuses aged between 4 to 8 months, the diameter of the aortic arch grew linearly. Similar conclusions can be found in many other papers [4–8, 10, 20, 27].

Castillo et al. [8] in their study concerning the development of the aorta between 4 and 6 months of fetal life discovered that the diameter of the ascending aorta ranged between 2.1 mm and 4.2 mm. According to these authors [8], the external diameter of the aortic arch ranged between 1.92 mm and 3.8 mm as compared with 1.75–3.35 mm found in the proximal thoracic aorta. These results are very similar to the data obtained by Szpinda [29, 30]. According to Szpinda [29], the diameter of the proximal ascending aorta changed from 2.02±0.26 mm in the 5th month to 6.84±0.63 mm in the 9th month. At the same time, the diameter of the distal ascending aorta changed from 1.73±0.2 mm to 6.29±0.52 mm. According to this author [30], the diameter of the proximal thoracic aorta during the same time period changed from 1.25±0.28 mm to 5.65±0.48 mm. Our data confirm these findings. Similar results were reported by Gielecki et al. [13]. In their study the diameter of the aortic arch increased from 1.77 mm to 4.09 mm [13]. Also Ursell et al. [32] analyzed the dimensions of the proximal ascending and the proximal thoracic aorta. These were 0.9 mm and 0.7 mm respectively in the youngest group (the 3rd month of prenatal life) versus 3.1 mm and 2.3 mm respectively in the oldest group (the 7th month).

Most investigators found the diameter of the ascending aorta to be larger than that of the thoracic aorta [8, 32, 33]. Rosenberg et al. [25] found the ascending aorta to be broader than the thoracic aorta. They found the ratio of these diameters to be 1.13. Van Meurs-van Woezik and Krediet [20] determined this ratio to be 1.25. Hornberger et al. [15] and Angellini et al. [5] confirmed this ratio in their echocardiography studies. According to Szpinda [28], the diameters (proximal and distal) of the thoracic aorta were smaller than the diameters (proximal and distal) of the ascending aorta. Our data confirm this relation; the calculated mean value of the ratio in question is 1.2.

## CONCLUSIONS

1. In the period between the 4th and 8th months of fetal life, aorta growth is linear in all analyzed vessel segments.
2. There are no sex related differences with regard to dimensions of this vessel.
3. The proximal ascending aorta is broader than the proximal thoracic aorta.

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*ORIGINAL PAPER*

# THE DEVELOPMENT OF THE PULMONARY TRUNK AND THE PULMONARY ARTERIES IN THE HUMAN FETUS

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## ABSTRACT

**Introduction.** Up to date studies dealing with embryogenesis of the pulmonary trunk and arteries seldom analyze the anatomical variations between sexes and proportions of the pulmonary arteries dimensions. A large number of investigated subjects in our study enabled a detailed description of the growth of the pulmonary trunk and pulmonary arteries. Other studies involved fewer subjects.

**Aim.** We aimed at investigating the development of the pulmonary trunk and its branches, i.e., the left and the right pulmonary arteries, during a period between the 4th and 8th months of fetal life.

**Materials and methods.** We investigated 223 human fetuses, including 108 males and 115 females, aged between 4 and 8 months of prenatal life. All fetuses had been conserved for a minimum period of 3 months in a 9% formaldehyde solution. All fetuses of a normal karyotype were obtained from spontaneous abortions and none of them revealed any external signs of malformations. We measured the diameters of the initial part of the pulmonary trunk and of the two main arteries: right and left pulmonary arteries. We determined the mean value of each assessed parameter for every age group, the rate of growth of particular vessels, the variations in these parameters with relation to sex, and the ratio between the left and the right pulmonary artery dimensions. For statistical analysis ANOVA, regression analysis, and Tukey's HSD post hoc test were used.

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**Results, Discussion and Conclusions**. The growth of the diameters of pulmonary vessels (pulmonary trunk, left and right pulmonary arteries) is linear in time. The vessel dimensions do not differ with regard to sex. Only in the 5$^{th}$ month was the pulmonary trunk statistically significantly wider in female fetuses. The left pulmonary artery is smaller than the right one.

**Key words:** pulmonary artery, prenatal development, human fetus

## INTRODUCTION

Autopsy serves as an important and relevant source of information concerning the development of the human circulatory system in prenatal life. Other methods, such as radiographic imaging, cannot be widely employed being deleterious to the growing organism. Echocardiography is a useful, complimentary method as it employs harmless radiation. It is not free from limitations however; not all cardiac structures and large vessels, such as the pulmonary trunk and its divisions, can be visualized in detail [3]. The importance of investigating the embryogenesis of pulmonary arterial vessels arises from discrepancies in cardiovascular anatomy between fetal and postnatal life. The assessment of diameters of these vessels is valuable in diagnosing and monitoring congenital heart defects. Frequently, heart defects show up as, or co-occur with, abnormalities of the major arteries – including the pulmonary trunk and its branches [2, 3, 5, 7, 8, 12, 14, 17, 21, 28, 34, 36, 38].

## AIM

We aimed at investigating the development of the pulmonary trunk and its branches, i.e., the left and the right pulmonary arteries, during that period between the 4$^{th}$ and 8$^{th}$ months of fetal life. We also investigated sex related differences concerning the diameters of these vessels. Also, we assessed the relationship between the dimensions of the left and the right pulmonary arteries.

## MATERIALS AND METHODS

Research material consisted of 223 human fetuses, including 108 males and 115 females, aged between 4–8 months of prenatal life. The entire material for this project was obtained from the Department of Histology and Embryology of the Collegium Medicum of Nicolaus Copernicus University in Bydgoszcz, Poland. The fetuses had been conserved for a minimum period of 3 months in a 9% formaldehyde solution. All fetuses of a normal karyotype had been aborted spontaneously. None of them demonstrated any external signs of malformations or developmental abnormalities. The morphological age of each fetus was determined according to the crown-rump length (vertex-tuberale) using a polynomial initially proposed by Iffy et al. [19]. All

specimens were categorized into monthly subgroups according to the determined morphological age. Different numbers of fetuses were allocated to particular age groups.

The vessel beds were filled with latex LBS 3060, without distorting the dimensions of the vessels, at an amount of approximately 15–30 mL, through a catheter, which was inserted by dorsal access into the thoracic aorta. During specimen preparation we used binocular magnifying glasses (MBS-9, Russia, magnification 0.6–7 × 14). The measurements were taken using digital calipers (INCO, Poland, resolution 0.01mm) with an accuracy range of 0.01 mm. We measured the diameter of the initial segment of the pulmonary trunk (PT) and the diameters of the right (RPA) and the left (LPA) pulmonary arteries – also in their initial segments (Fig. 1, 2). All measurements were taken by two independent investigators. Each investigator took the measurements twice. For further analyses the arithmetical means of the obtained values were used.

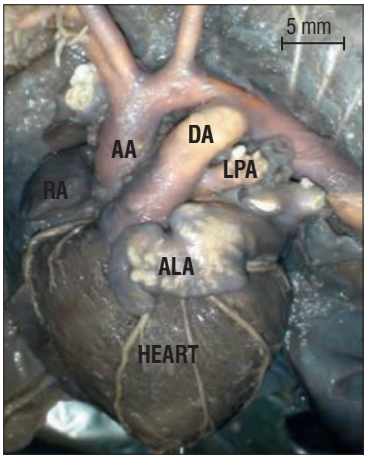


**Fig. 1.** Heart and the great arteries of a 28-weeks old female fetus, anterior surface. Comments: AA – ascending aorta, PT – pulmonary trunk, LPA – left pulmonary artery, DA – ductus arteriosus, ARA – auricle right atrium, ALA – auricle left atrium

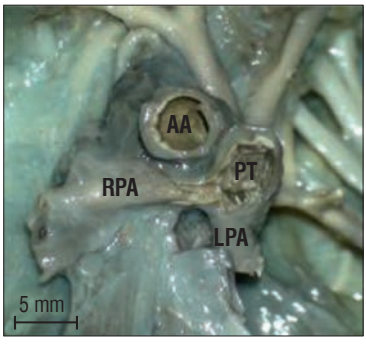


**Fig. 2.** The great arteries of a 24-weeks old male fetus, view from the diaphragmatic surface, the heart was removed. Comments: AA – ascending aorta, PT – pulmonary trunk, LPA – left pulmonary artery, DA – ductus arteriosus, ARA – auricle right atrium, ALA – auricle left atrium

Statistica 8.0 software (StatSoft Polska) was used for statistical analysis of the obtained data. We calculated mean values and standard deviations for each age group with respect to sex. The results obtained were analyzed by the one-way ANOVA test for unpaired data (age) and two-way ANOVA test for unpaired data (age and sex), and Tukey's HSD post hoc test for non-equal populations. The differences between pulmonary artery dimensions were analyzed using a two-way (side of the body and age) analysis of variances (ANOVA) for dependent variables and Tukey's HSD post hoc test for non-equal populations. Statistical significance was defined as $p \leq 0.05$.

## RESULTS

The diameter of the pulmonary trunk increases according to the linear regression curve $y = -86.8853 + 0.8744x$. Initially, in the 4th month, the diameter of the pulmonary trunk was 1.51±0.24 mm, and it grew to 4.85±0.31 mm by the 8th month (Tab. 1). The pulmonary trunk diameter correlation coefficient for age was $r = 0.9364$, and it was highly statistically significant ($p < 0.001$) (Fig. 3). We found no significant sex differences in the pulmonary trunk diameter within each group ($p = 0.2945$). Only in the 5th month was that diameter larger in females ($p = 0.0084$) (Tab. 1). The diameter of the right pulmonary artery also increases according to the linear regression curve $y = -48.9848 + 0.4925x$. The correlation coefficient for age was $r = 0.8873$, with a high level of significance $p < 0.001$ (Fig. 4). In the 4th month the right pulmonary artery diameter was 0.69±0.18 mm, and it grew to 2.74±0.31 mm by the 8th month (Tab. 2). The diameter of the right pulmonary artery within the entire group was 1.59±0.51 mm. There were no sex related differences with regard to that vessel's diameter ($p > 0.05$), neither in the whole study group ($p = 0.2603$) nor within particular age groups (Tab. 2).

**Tab. 1.** Mean pulmonary trunk diameter in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 1.51±0.24 | 1.44±0.28 | 1.57±0.2 | 0.3162 |
| 5 | 70 | 32 | 38 | 2.34±0.24* | 2.22±0.22* | 2.44±0.22* | 0.0084 |
| 6 | 105 | 50 | 55 | 3.26±0.32* | 3.27±0.32* | 3.24±0.33* | 0.6091 |
| 7 | 18 | 12 | 6 | 3.95±0.39* | 3.95±0.39* | 3.94±0.45* | 0.9957 |
| 8 | 12 | 6 | 6 | 4.85±0.31* | 4.86±0.24* | 4.83±0.39* | 0.8639 |
| Total | 223 | 108 | 115 | 2.93±0.86 | 2.99±0.88 | 2.87±0.84 | 0.2945 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

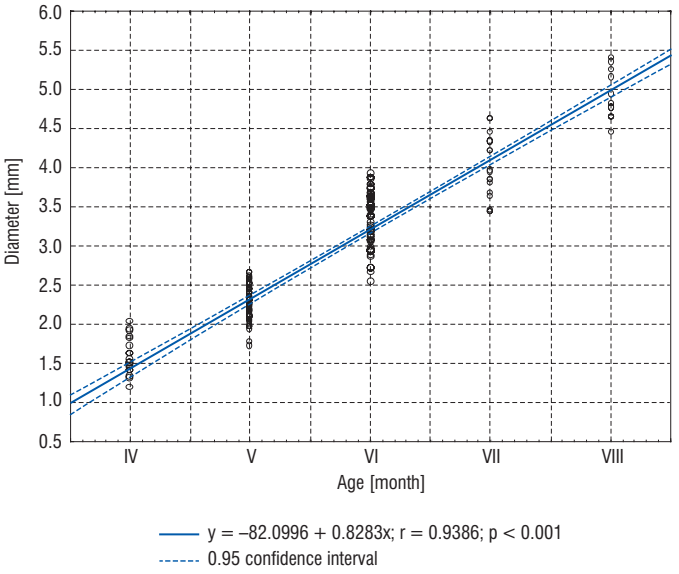


**Fig. 3.** Regression curve for the pulmonary trunk diameter versus fetal age (x)

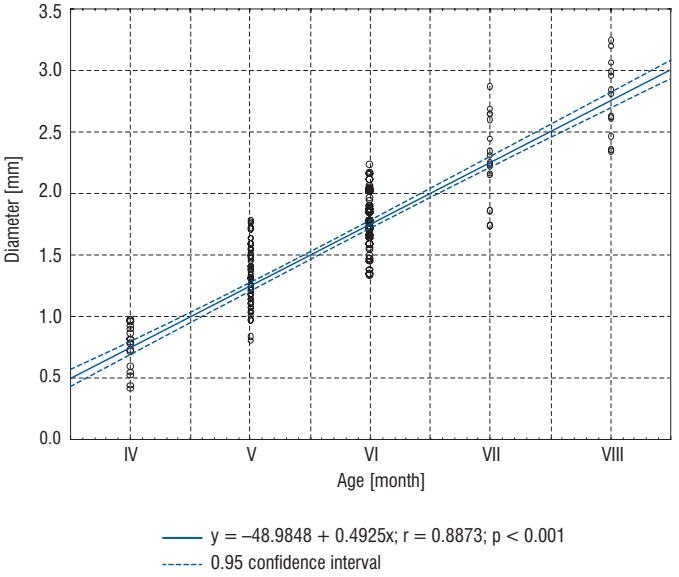


**Fig. 4.** Regression curve for the right pulmonary artery diameter versus fetal age (x)

**Tab. 2.** Mean right pulmonary artery diameter in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 0.69±0.18 | 0.70±0.18 | 0.69±0.19 | 0.9540 |
| 5 | 70 | 32 | 38 | 1.27±0.23* | 1.26±0.24* | 1.28±0.22* | 0.7361 |
| 6 | 105 | 50 | 55 | 1.74±0.22* | 1.75±0.22* | 1.73±0.21* | 0.6508 |
| 7 | 18 | 12 | 6 | 2.19±0.36* | 2.23±0.38* | 2.11±0.33* | 0.5279 |
| 8 | 12 | 6 | 6 | 2.74±0.31* | 2.80±0.33* | 2.69±0.32* | 0.5717 |
| Total | 223 | 108 | 115 | 1.59±0.51 | 1.64±0.54 | 1.56±0.48 | 0.2603 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

The average diameter of the left pulmonary artery within the entire group was 1.33±0.40 mm. It ranged from 0.78±0.22 mm in the 4$^{th}$ month to 2.2±0.18 mm by the 8$^{th}$ month of prenatal life (Tab. 3). The growth of the diameter of the left pulmonary artery was reflected in a linear regression curve $y = -35.0635 + 0.3544x$. The correlation coefficient was $r = 0.8128$, which was highly statistically significant ($p < 0.001$) (Fig. 5). There were no significant sex differences with regard to that parameter within the entire study group ($p = 0.2465$), nor within particular age groups ($p > 0.05$) (Tab. 3).

**Tab. 3.** Mean left pulmonary artery diameter in particular monthly age groups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 10 | 8 | 0.78±0.22 | 0.86±0.17 | 0.72±0.25 | 0.2036 |
| 5 | 70 | 32 | 38 | 1.12±0.21* | 1.12±0.20* | 1.13±0.21* | 0.7585 |
| 6 | 105 | 50 | 55 | 1.36±0.22* | 1.36±0.25* | 1.36±0.19* | 0.9811 |
| 7 | 18 | 12 | 6 | 1.98±0.3* | 2.03±0.32* | 1.9±0.26* | 0.4277 |
| 8 | 12 | 6 | 6 | 2.2±0.18* | 2.14±0.19* | 2.27±0.17* | 0.2501 |
| Total | 223 | 108 | 115 | 1.33±0.40 | 1.37±0.42 | 1.31±0.39 | 0.2465 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter value, SD – standard deviation, P value – the differences between mean values in the female and male fetuses in particular age groups ($p < 0.05$).

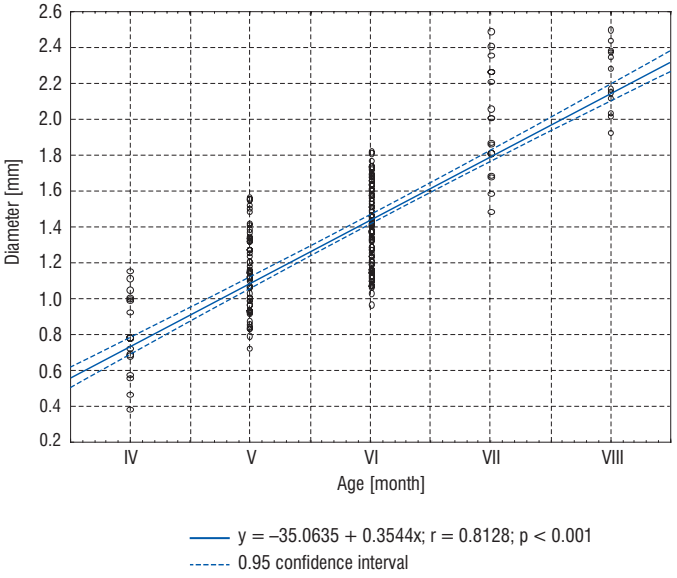


**Fig. 4.** Regression curve for the left pulmonary artery diameter versus fetal age (x)

The development of the pulmonary trunk and of the left and the right pulmonary arteries in consecutive months showed significant dimension changes when compared to preceding months. These differences were notable in the entire group between the 5th and the 6th, the 6th and the 5th, the 7th and the 6th, the 8th and the 7th months. As far as the sex of fetuses was concerned, these differences were marked between the 5th and the 4th, the 6th and the 5th, the 7th and the 6th, and the 8th and the 7th months, both in females and males (Tab. 1–3).

We found a significant difference between the dimensions of the two main pulmonary arteries ($p=0.0031$). The right pulmonary artery was consistently larger. The ratio of the two diameters calculated for the entire group was 1.21±0.27 and it changed in time only slightly and insignificantly ($p \geq 0.05$) within a range from 1.08 to 1.25 (Tab. 4). Also, this ratio did not differ statistically significantly between sexes ($p > 0.05$).

**Tab. 4.** The ratio of the right to left pulmonary artery diameters (x)

| Age [months] | N | X | SD |
|---|---|---|---|
| 4 | 18 | 1.08 | 0.09 |
| 5 | 70 | 1.16 | 0.26 |
| 6 | 105 | 1.21 | 0.27 |
| 7 | 18 | 1.12 | 0.21 |
| 8 | 12 | 1.25 | 0.15 |
| Total | 223 | 1.21 | 0.27 |

Comments: SD – standard deviation. There is no difference between consecutive age groups ($p>0.05$).

## DISCUSSION

In this study we found that the pulmonary trunk and arteries growth rates have a linear pattern. Similar results were found in other studies where echocardiography [28, 38, 39] or autopsy [4, 6, 24] were used. Also, Szpinda et al. [31, 32] found that the growth of the pulmonary trunk was proportional to fetal age and followed a linear regression. This was found at the correlation coefficient for age $r = 0.86$ ($p < 0.001$). Alvarez et al. [4], who also described a linear growth pattern concerning the pulmonary trunk, pointed to a highly statistically significant correlation coefficient ($r = 0.852$; $p < 0.0001$). Hyett et al. [18] in their study concerning 61 fetuses aged between 3 and 5 months, plotted a linear regression curve showing the relationship between the diameter of the pulmonary trunk and age ($r = 0.889$, $p < 0.0001$). These autopsy findings confirm echocardiographic observations. Studies of Chaoui et al. [10] and Gembruch et al. [15] demonstrated a linear pattern of the pulmonary trunk growth. Also Achiron et al. [1] in their study concerning 139 fetuses, aged between 4 and 7 months, and Firpo et al. [13] in their study concerning 181 fetuses, aged between 4 and 9 months, proved that the diameter of the pulmonary trunk grew linearly in time. The correlation coefficient was very high in both studies: $r = 0.94$ ($p<0.0001$) according to Achiron et al. [1], and $r = 0.9081$ ($p < 0.01$) according to Firpo et al. [13]. Similar findings were reported for the pulmonary arteries diameters. A linear growth rate of the fetal pulmonary arteries was confirmed both in anatomical [4, 18, 33, 37] and echocardiographic studies [13, 17]. We found the diameter of the right pulmonary artery to be consistently larger than the left one ($p < 0.001$). This is in accordance with other authors' findings [6, 9, 11, 16, 20, 27, 30, 31, 33]. Only Tan et al. [35] in their study concerning fetuses aged between 6 and 9 months did not find any difference between the diameters of the two main pulmonary arteries ($p = 0.254$).

The diameters of the pulmonary trunk, the left and the right pulmonary arteries that we found in our material are similar to data presented in available literature. Ursell et al. [37] discovered that the diameter of the pulmonary trunk was 1.1 mm before the 3$^{rd}$ month, 2.0 mm in the 4$^{th}$ month, 2.5 mm in the 5$^{th}$ month, and 3.5 mm following the 6$^{th}$ month of fetal life. Castillo et al. [9] in their material consisting of 103 fetuses, aged between 4 and 9 months, found that the pulmonary trunk diameter ranged from 2.1 mm to 4.2 mm. The diameter of the right pulmonary artery was 1.2–2.5 mm, and the left one 0.9–2.18 mm [9]. Szpinda [32] found the diameter of the pulmonary trunk in the 4$^{th}$ month to be 1.51 mm, and in consecutive months: the 5$^{th}$ – 2.44 mm, the 6$^{th}$ – 3.79 mm, the 7$^{th}$ – 4.16 mm, the 8$^{th}$ – 5.15 mm. Also according to Szpinda [33], the left pulmonary artery diameter in the 4$^{th}$ month was 0.88 mm, in the 5$^{th}$ – 1.09 mm, the 6$^{th}$ – 1.87 mm, the 7$^{th}$ – 2.1 mm, and the 8$^{th}$ – 2.35 mm. According to Szpinda [33], the right pulmonary artery diameter in the 4$^{th}$ month was 0.93 mm, in the 5$^{th}$ – 1.19 mm, the 6$^{th}$ – 2.05 mm, the 7$^{th}$ – 2.32 mm, and the 8$^{th}$ – 2.62 mm.

Within the entire study group, we did not find any sex related differences with respect to the dimensions of the analyzed pulmonary vessels. Also, no differences with regard to sex were reported by Firpo et al. [13], Szpinda et al. [31], and Szpinda [32, 33]. Similar conclusions were reached by Schulz and Giordano [29] in their study concerning fetuses and newborns (526 subjects). Other studies on cardiovascular embryology also failed to show any sex related differences [22, 23, 25, 26]. However, Malinowski et al. [22, 23] found female fetuses to have slightly larger vessel diameters, which he then explained to be as a result of accelerated organogenesis in females. Such an explanation would justify the larger pulmonary trunk and the left pulmonary artery diameters found in females in the 5$^{th}$ and 6$^{th}$ months of prenatal life respectively (Tab. 1, 3).

## CONCLUSIONS

1. Growth with respect to the diameters of the pulmonary trunk and arteries is linear in time.
2. These dimensions do not differ between the sexes.
3. The left pulmonary artery is smaller than the right pulmonary artery.

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*ORIGINAL PAPER*

# THE DEVELOPMENT OF THE AORTIC ISTHMUS IN HUMAN FETAL LIFE

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## ABSTRACT

**Introduction**. The aortic isthmus is a specific feature of fetal circulation. It undergoes regression by becoming wider postpartum. Developmental abnormalities of an isthmus may lead to congenital defects.

**Aim**. The aim of this work was a morphometric study of the aortic isthmus in human fetuses aged between 4 and 8 months of fetal life.

**Materials and methods**. We investigated 223 human fetuses, including 108 males and 115 females, aged between 4 and 8 months of fetal life. The entire material was obtained from the Department of Histology and Embryology at the Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. All fetal specimens had been conserved in a 9% formaldehyde solution for a period of more than 3 months. Only spontaneously aborted fetuses with a normal morphology and a normal karyotype were used in this study. We investigated the diameter of the aortic isthmus in human fetuses at different stages of prenatal life. We also analyzed the ratio of that diameter with regard to the diameters of other segments of the aorta and ductus arteriosus. We considered how these measurements varied depending on sex.

**Results, Discussion and Conclusions**. We found the growth of the aortic isthmus diameter to be linear in time. The measured diameters were similar in males and females. No significant differences with regard to sex were found between the ratios of that vessel's diameter to the diameters of the ascending and descending aorta

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and the ductus arteriosus. The relative ratio of the aortic isthmus diameter to the diameters of the ascending and thoracic aorta decreased with time. On the contrary, the ratio of the aortic isthmus diameter to the ductus arteriosus diameter increased over time.

**Key words:** aortic isthmus, prenatal development, human fetus

## INTRODUCTION

The isthmus is a natural feature of the fetal aorta. Its embryogenesis is connected with the development of the aortic arch. It consists of three parts with different origins: the 4$^{th}$ left aortic arch, the 6$^{th}$ left aortic arch, and the left dorsal aorta. About 10% of fetal cardiac combined output (CCO) flows through the isthmus. As a result, oxygenated blood from the ascending aorta is primarily directed to the upper part of the body and, in particular, to the head and the central nervous system. The isthmus prevents excessive mixing of that blood with the desaturated blood from the distal aortic arch and the thoracic aorta [27]. The latter flows into the distal aorta through the ductus arteriosus and provides blood for the lower part of the body of the fetus [17, 23]. The complex organogenesis of the aortic isthmus leads to frequent developmental abnormalities. Among these, coarctation of the aorta above the ductus arteriosus is the most prevalent. According to Bonnet's classification (1903) this type of coarctation is called "infantile". Coarctation of the aorta accounts for 5–8% of all congenital heart defects, with the variant above ductus arteriosus being most prevalent. The defect is more often seen in boys than in girls [19]. Another, less frequently observed defect is the interrupted aortic arch (IAA). This accounts for about 1.5% of all defects. In 40–45% of cases a "type A" defect, directly correlated with isthmus abnormalities, is seen. It seldom occurs as an isolated defect. In 90–95% of cases it co-occurs with the interventricular septal defect. Also, concomitant patent ductus arteriosus (PDA) and defects obstructing the left ventricular outflow, such as bicuspid aortic valve, are frequently observed [15]. It is also worth noting that according to Hoffman et al.[11, 12], the incidence of an interrupted aortic arch is on the increase. Such plentitude of congenital defects arising from impaired embryogenesis of the aortic isthmus calls for intensive research concerning the changes this structure undergoes in fetal life [6, 18, 28].

## AIM

The aim of this work was to determine the diameter of the aortic isthmus in human fetuses aged between 4 and 8 months of prenatal life. We calculated the ratios of the aortic isthmus diameter with respect to the diameters of the ascending and descending (thoracic) aorta and the ductus arteriosus. We also analyzed the differences of

obtained measurements and ratios with regard to the sex of the fetus.

## MATERIALS AND METHODS

Research material consisted of 223 human fetuses, including 108 males and 115 females, aged between 4 and 8 months of prenatal life. Only spontaneously aborted fetuses with a normal karyotype were included in this study. None of the analyzed specimens demonstrated any visible malformations or developmental abnormalities upon close inspection. The entire material was homogenous in terms of race and skin color. All fetuses were obtained from the Department of Histology and Embryology at the Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. This study was approved by the Bioethics Committee at the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland (resolution KB/433/2004). All fetuses had been conserved in a 9% formaldehyde solution for a period of at least 3 months. The morphological age of each fetus was estimated according to the crown-rump length (vertex--tubulare). To this end, we used a polynomial proposed by Iffy et al. [16]. All specimens were categorized into monthly subgroups according to the determined morphological age. Different numbers of fetuses were allocated to particular age groups. Random numbers were assigned to each fetus of each age group in the project.

The vessel beds were filled with latex LBS 3060, without distorting the dimensions of the vessels, at an amount of approximately 15–30 mL, through a catheter, which was inserted by dorsal access into the thoracic aorta. All measurements were performed by two investigators who, with the aid of binocular magnifying glasses (MBS-9, Russia, magnification 0.6–7 × 14), used digital calipers (INCO, Poland, resolution 0.01 mm) to collect all measurements required with an accuracy range of 0.01 mm. All measurements were taken twice by each investigator for consistency and verification purposes. The mean value of the two obtained values was used for further quantitative analysis.

Statistica 8.0 software (StatSoft Polska) was used for statistical analysis of the obtained data. The results obtained were analyzed by the two-way ANOVA test for unpaired data and Tukey's HSD post hoc test for non-equal populations. Statistical significance was defined as $p \leq 0.05$.

## RESULTS

The mean diameter of the aortic isthmus for the entire group was 1.75±0.47 mm. In male fetuses it was 1.78±0.49 mm, and in females 1.72±0.46 mm. The differences in diameter values between males and females were not significant, either in the entire group ($p = 0.2658$) or in any monthly age groups investigated ($p > 0.05$) (Tab. 1). The aortic isthmus diameter increased through the investigated time period in a linear pattern ($y = -47.494 + 0.4794x$), with a correlation coefficient ($r = 0.9276$) and a high level of statistical significance ($p < 0.001$) (Fig. 2). The aortic isthmus diameter grew significantly in consecutive months for both sexes and for the entire group ($p < 0.05$) (Tab. 1).

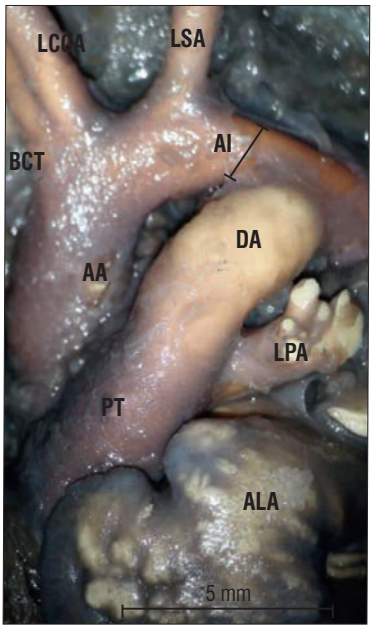


**Fig. 1.** The great arteries of the fetal heart in a 28-weeks old female fetus. Comments: AA – ascending aorta, AI – aortic isthmus, TA – thoracic aorta, BCT – brachiocephalic trunk, LCCA – left common carotid artery, LSA – left subclavian artery, DA – ductus arteriosus, PT – pulmonary trunk, LPA – left pulmonary artery, ALA – auricle left atrium

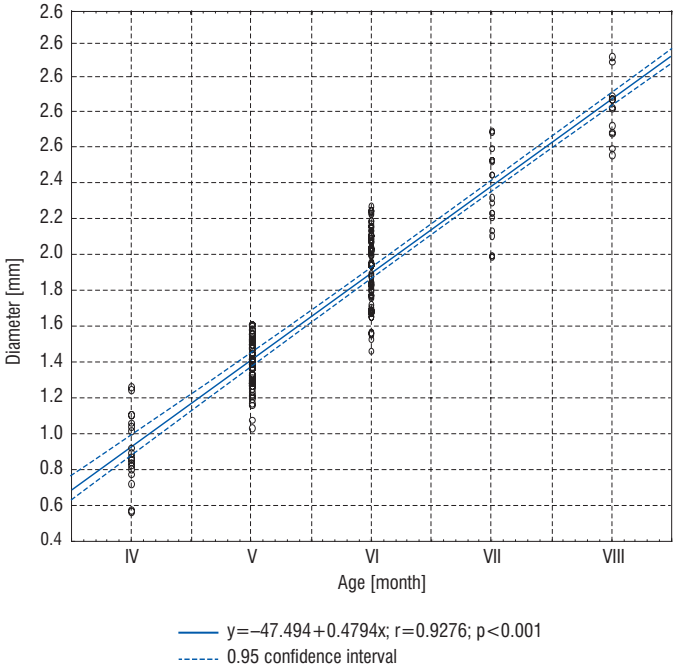


**Fig. 2.** Regression curve for the diameter of the isthmus of the aorta versus fetal age (x)

**Tab. 1.** Mean aortic isthmus diameter in monthly age subgroups shown for the entire group and with regard to sex

| Age [month] | N | | | X±SD [mm] | | | P value |
|---|---|---|---|---|---|---|---|
| | total | male | female | total | male | female | |
| 4 | 18 | 8 | 10 | 0.91±0.19 | 0.91±0.21 | 0.92±0.2 | 0.9154 |
| 5 | 70 | 32 | 38 | 1.39±0.13* | 1.38±0.14* | 1.39±0.12* | 0.7473 |
| 6 | 105 | 50 | 55 | 1.92±0.19* | 1.93±0.19* | 1.90±0.19* | 0.4754 |
| 7 | 18 | 12 | 6 | 2.32±0.23* | 2.33±0.23* | 2.32±0.27* | 0.9328 |
| 8 | 12 | 6 | 6 | 2.8±0.17* | 2.84±0.23* | 2.76±0.09* | 0.4659 |
| Total | 223 | 108 | 115 | 1.75±0.47 | 1.78±0.49 | 1.72±0.46 | 0.2658 |

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter dimension, SD – standard deviation, P value – the differences between the mean values in the male and female fetuses within particular age groups ($p < 0.05$).

The mean ratio of the aortic isthmus diameter to the ascending aorta diameter in the entire group was 0.73±0.09 (Tab. 2). When analyzed within particular monthly subgroups, it ranged between 0.74±0.03 in the 5$^{th}$ month to 0.69±0.05 in the 8$^{th}$ month. These values were similar for both sexes ($p > 0.05$). The mean ratio values for particular subgroups did not differ significantly from the ratios calculated for the consecutive younger subgroups (Tab. 2). The ratio of the aortic isthmus diameter to the thoracic aorta diameter for the entire group was 0.79±0.11. When analyzed within particular monthly age subgroups, it ranged between 0.8±0.03 in the 4$^{th}$ month to 0.78±0.05 in the 8$^{th}$ month. This ratio was not different between sexes, nor for particular monthly age subgroups ($p > 0.05$) (Tab. 3).

**Tab. 2.** The ratio of aortic isthmus diameter to the ascending aorta diameter (x)

| Age [month] | N | X | SD | P value |
|---|---|---|---|---|
| 4 | 18 | 0.73 | 0.04 | 0.3751 |
| 5 | 70 | 0.74 | 0.03 | 0.4859 |
| 6 | 105 | 0.72 | 0.06 | 0.8321 |
| 7 | 18 | 0.69 | 0.07 | 0.7395 |
| 8 | 12 | 0.69 | 0.05 | 0.0813 |
| Total | 223 | 0.73 | 0.09 | 0.2819 |

Comments: SD – standard deviation. Lack of significant difference between the immediately, younger monthly age subgroups, P value – sex related differences, level of significance ($p < 0.05$).

**Tab. 3.** The ratio of the aortic isthmus diameter and the thoracic aorta diameter (x)

| Age [month] | N | X | SD | P value |
|---|---|---|---|---|
| 4 | 18 | 0.80 | 0.03 | 0.0685 |
| 5 | 70 | 0.79 | 0.07 | 0.1298 |
| 6 | 105 | 0.79 | 0.06 | 0.4219 |
| 7 | 18 | 0.78 | 0.03 | 0.7617 |
| 8 | 12 | 0.78 | 0.05 | 0.0939 |
| Total | 223 | 0.79 | 0.11 | 0.4138 |

Comments: SD – standard deviation. Lack of significant difference between the immediately, younger monthly age subgroups, P value – sex related differences.

The mean ratio of the aortic isthmus diameter to the diameter of the ductus arteriosus was 0.85±0.13. This value grew gradually for consecutive age subgroups from 0.85±0.06 in the 4$^{th}$ month to 0.9±0.07 in the 8$^{th}$ month. However, the differences between the consecutive months did not reach a level of statistical significance ($p > 0.05$). Also, there were no significant differences between sexes ($p > 0.05$) (Tab. 4).

**Tab. 4.** The ratio of the aortic isthmus diameter and the diameter of the ductus arteriosus (x)

| Age [month] | N | X | SD | P value |
|---|---|---|---|---|
| 4 | 18 | 0.85 | 0.06 | 0.1989 |
| 5 | 70 | 0.86 | 0.04 | 0.7320 |
| 6 | 105 | 0.86 | 0.05 | 0.4183 |
| 7 | 18 | 0.88 | 0.04 | 0.6734 |
| 8 | 12 | 0.90 | 0.07 | 0.4290 |
| Total | 223 | 0.85 | 0.13 | 0.6432 |

Comments: SD – standard deviation. Lack of significant difference between the immediately, younger monthly age subgroups, *P* value – sex related differences.

## DISCUSSION

In our research material we found no sex related differences of the aortic isthmus diameter ($p > 0.05$) (Tab. 1). Similar conclusions were reached by Szpinda [24, 25], Ursell et al. [26], and also Gielecki et al. [9, 10].

Our data revealed that the growth of the aortic isthmus diameter was linear in time (Fig. 2). This is confirmed by Hyett et al. [14, 15] who found that diameter, in the period between the 9$^{th}$ and 18$^{th}$ week of gestation, to be growing according to a linear regression curve. Also Achiron et al. [1, 2] and Nomiyama et al. [21] described the increase of the aortic isthmus diameter as linear in time. Alvarez et al. [3] discovered that the circumference of the aortic isthmus in the fetus with relation to the body mass also grew linearly. Szpinda [25] found that the growth of the aortic isthmus diameter with regard to time followed a linear regression curve. A similar

relation concerning isthmus growth with regard to body length was observed by van Meurs-vanWoezik and Krediet [20].

Castillo et al. [5] noted that in fetuses aged between 4 to 7 months, the aortic isthmus diameter ranged between 1.45 mm to 3.0 mm. These data correspond with our results. Other research also supports these conclusions. According to Ursell et al. [26], the diameter was 0.5 mm in the 3rd month, 1.1 mm in the 5th month, 1.5 mm in the 6th month, and 1.8 mm in the 7th month. Szpinda [25] found that diameter to, be 0.92 mm in the 4th month, 1.71 mm in the 5th month, 2.84 mm in the 6th month, 3.26 mm in the 7th month, and 4.39 mm in the 8th month. On the other hand, Hornberger et al. [13] found the aortic isthmus diameter to be independent of age and equal to 3.6 mm.

Two contradictory trends with respect to the changing ratio of the aortic isthmus to other aortic diameters are to be found in available literature. One trend shows the relative growth of the aortic isthmus diameter. This trend is confirmed in the research conducted by Hyett et al. [14], where the relative isthmus diameter was found to be growing from 0.6 mm to 0.8 mm in the time period between 3rd and 5th months of fetal life. Similar findings were reported by Szpinda [25], who found the relative isthmus diameter (in relation to the diameter of the proximal ascending aorta) to be growing from 0.45±0.1 mm in the 4th month to 0.72±0.07 mm in the 6th month of fetal life. He found this to be also true in terms of the ratio of the isthmus diameter to the proximal thoracic aorta diameter; by the 9th month that ratio increased from 0.73±0.1 to 0.88±0.09 [25].

On the contrary, our research supports the opposite trend – the ratio of the aortic isthmus diameter to the proximal and thoracic aorta decreased with time (Tab. 2, 3). Similar conclusions were also drawn by other authors. Ursell et al. [26], Nomiyama [21], and Gielecki et al. [10] concluded that the ratio of the aortic isthmus diameter to the diameters of the ascending and thoracic aorta decreased over time. According to Ursell et al. [26], in fetuses aged between 4 and 6 months, the ratio of the isthmus diameter to the diameter of the ascending aorta ranged between 0.61 and 0.65 and decreased to 0.58 by the 7th month. Also, the mean ratio of the isthmus diameter to the diameter of the thoracic aorta ranged between 0.71 and 0.78. Nomiyama et al. [21] found that in fetuses aged between 7 and 10 months, the ratio of the aortic isthmus diameter to the proximal thoracic aorta diameter decreased over time. According to Gielecki et al. [10], the ratio of the isthmus diameter to the ascending aorta diameter decreased from 0.64 in fetuses aged 5 months to 0.45 in fetuses aged 6–7 months. These authors also found that the ratio of the aortic isthmus diameter to the thoracic aorta diameter decreased from 0.8 to 0.76.

According to some investigators [5], in fetuses aged between 5 and 7 months, the ratio of the aortic isthmus diameter to the diameters of the ascending and thoracic aorta is highly variable and falls within a range of 0.66 and 0.99. On the other hand,

Angelini et al. [4] calculated that the relative diameter of the aortic isthmus exceeded 0.6. They did not, however, consider the variability associated with age.

Ursell et al. [26] believe that the relative decrease of the aortic isthmus diameter implies that the majority of left ventricle stroke volume is forwarded to the encephalon. Szpinda [25], who found the relative dimensions of the aortic arch ramifications to be growing, concurs with this reasoning. On the basis of our results, we also agree with Ursell et al. [26]. Nevertheless, we do not fully agree with the reasoning presented by Ursell et al. [26] in their work. It is true that the ratio of the dimensions of the aortic isthmus to the ascending aorta decreases, but at the same time a similar phenomenon is to be observed with regard to the ratio of the aortic isthmus to the thoracic aorta. This may indicate that the isthmus limits excessive blood flow between the ascending and thoracic aorta, thus preventing the oxygenated and desaturated blood from mixing; consequently, this results in a privileged flow of oxygenated blood to the upper part of the body. When evaluating the function of the isthmus it is important to correctly asses the direction of the blood flow. Physiologically the blood flows from the ascending aorta into the thoracic aorta. However, in the case of a defect this flow may be bidirectional [7, 8].

Hyett et al. [14] analyzed the ratio of the aortic isthmus diameter with respect to the diameter of the distal ductus arteriosus. Their data corresponded with our findings. They found this ratio to be growing linearly in time. This may indicate the capacity of the ductus to obliterate postpartum. This is also reflected by the decrease of CCO from 40% to 30% through the ductus arteriosus in the period between the $20^{th}$–$30^{th}$ weeks of prenatal life [22]. These data may reveal the role of the isthmus as a restrictive structure creating a pressure gradient between the ascending and the thoracic aorta, thus regulating fetal circulation. Our results are in strict concordance with those observations made by Ursell et al. [26] and Gielecki et al. [10]. In certain areas our data support the results demonstrated by Hyett et al. [14] and Szpinda [25].

## CONCLUSIONS

1. The diameter of the aortic isthmus in a fetus aged between 4 and 8 months grows linearly in time.
2. No differences with regard to dimensions of this vessel were found in both males and females.
3. The ratio of the aortic isthmus diameter with respect to the diameters of the ascending and thoracic aorta decreases in time, whereas the ratio of the aortic isthmus diameter to the diameter of the ductus arteriosus increases.

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*ORIGINAL PAPER*

# PERIOPERATIVE DISORDERS OF COAGULATION AND FIBRINOLYSIS IN PATIENTS SUBJECTED TO COLORECTAL CANCER RESECTION

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## ABSTRACT

**Introduction.** Venous thromboembolism and disseminated intravascular coagulation are frequent complications of malignant neoplasia. Abnormally high coagulation activity and fibrinolytic inhibition induced by surgery are suggested to be responsible for frequent occurrences of coagulative disorders.

**Aim.** The aim of this work was to assess the influence of surgery on coagulation and fibrinolitic systems during the early postoperative period in the high risk thromboembolism population, receiving heparin prophylaxis.

**Materials and methods.** This study was carried out in a group of 19 patients (12 males and 7 females), ages from 51 to 82 (mean 66.1), all with colorectal adenocarcinoma, who underwent scheduled elective total tumor resection.

**Results and Discussion.** Following surgical procedures the initially elevated D-dimer plasma level increased significantly. Activated partial thromboplastin time and the prothrombin time were prolonged significantly until the end of the observation period. Substantial reduction of initially normal fibrinogen concentration was revealed 6 hours after surgery, with significant increases at the 24$^{th}$ hour and then after 48 hours. The platelet count decreased linearly between 6 and 48 hours. The same pattern with nadir values after 48 hours was observed for antithrombin, protein C and the plasminogen plasma levels.

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**Conclusions.** Colorectal cancer and surgery significantly activate the coagulation and fibrinolytic systems, despite prophylaxis with low molecular weight heparin. Elective cancer resection is accompanied by a process resembling consumptive coagulopathy with an impairment of standard coagulation markers as well as significant reduction in natural plasma anticoagulants. Further studies are required to determine whether substitutional administration of natural anticoagulants added to routine heparin treatment in case of prophylaxis failure should be considered.

**Key words:** colorectal neoplasms, venous thrombosis, blood coagulation disorders

## INTRODUCTION

Venous thromboembolism (VT) and disseminated intravascular coagulation (DIC) are both frequent complications of ongoing neoplasmatic growth and also serve as early indicators of malignant proliferation [3, 15]. The risk of clinically significant VT in patients diagnosed with malignant disease is estimated to be increased up to 4- to 7-fold in comparison to the healthy population [1, 18]. Pathogenesis of developing a hypercoagulative state is multifactorial. Neoplasmatic cells may directly impact on the coagulation system by platelet activation, increased expression of tissue factor (TF) on cell's surface, release of cancer procoagulant, mucin and factor V receptor, and generation of thrombin [9, 21]. Indirect impact by the stimulation of vascular endothelial growth factor (VEGF) dependent angiogenesis, release of cytokines (e.g., TNF, IL-1) activating monocytes, macrophages and endothelial cells is also considered [9]. This process increases expression of coagulation activators and may suppress fibrinolysis, decreasing the activation of natural anticoagulants. However, their precise roles in this case is unclear. It has been indicated that plasma protein C (PC) levels vary in the course of malignant diseases and do not predict thromboembolic events [9].

Surgery is the next commonly recognized risk factor in developing VT that increases the risk of this complication over 20-fold [17, 18]. It has been proved that cancer patients compared to those without malignancy run a 2- to 3-fold higher perioperative risk of VT [2, 34]. The main reason for coagulation activation is related to direct surgical trauma to the vessels, secondary exposure of subendothelial TF, and release of cytokines. Limited postoperative mobility of patients favors the venous stasis and also results in further damage of the endothelium [9, 16]. Additionally, surgery is associated with hemodilution, which can be recognized as another cause of hypercoagulability [6, 29, 35].

Furthermore, fibrinolytic activity suppression impacts adversely on the pathogenesis of VT. In cancer patients, fibrinolytic inhibition during surgery has been found to be more enhanced in comparison with those patients having nonmalignant tumors [25].

A particularly high activation of coagulation as well as inhibition of the fibrinolytic system have been observed in patients after open colorectal cancer resection [12].

Van Duijnhoven et al. [42] have found that those patients with untreated colon carcinoma show increased activation of coagulation and fibrinolysis. The high tendency for thromboembolic complications results from the abnormal balance between both these processes.

It is estimated that despite introducing heparin prophylaxis in the perioperative period, a significant proportion of up to 41% of the colorectal cancer patients in the metastatic stage, suffer from thromboembolism [20]. Therefore, the standards of deep vein thrombosis prophylaxis are not always effective during this vulnerable period. Recently it has been found that despite prophylaxis with low molecular weight heparin, the frequency rate of pulmonary embolism is the highest during the first 3 postoperative days [37].

However, the question arises as to whether after wide implementation of low molecular weight heparin prophylaxis during the early perioperative period in patients undergoing colon cancer surgery, abnormalities in routine coagulation and fibrinolytic tests indicative of hypercoagulative stage are still present.

## AIM

The aim of this study was to assess the influence of surgery on coagulation and fibrinolitic systems during the early postoperative period in the high risk thromboembolism population, receiving heparin prophylaxis.

## MATERIALS AND METHODS

The study was conducted in conformance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Edinburgh, 2000). All patients signed a written informed consent and agreed to participate in the study. The study was approved by the local Ethics Committee.

The prospective open study was carried out with a group of 19 patients (7 females and 12 males), aged from 51 to 82 (mean 66.1 years), with histologically confirmed colorectal adenocarcinoma and scheduled for elective total tumor resection. Till the end of the study none of them received chemotherapy. The average time of surgery was 2.5 (±0.5) hours. Patients with a history of diabetes, coagulopathy, previous thromboembolic disorders, liver or renal dysfunction and those receiving blood transfusions within 48 hours were excluded from the study. For thromboprophylaxis all patients received Enoxaparin in doses of 40 mg subcutaneously 2 hours before surgery and 40 mg daily thereafter for 4 weeks [19]. Thromboprophylaxis was the only indication for administering low molecular weight heparin and it was not given before the perioperative period. Each patient was premedicated with 7.5–15 mg of Midazolam. The induction of anesthesia included intravenous (IV) bo-

lus consisting of 100 μg of fentanyl, 0.1 mg $kg^{-1}$ of norcuron, 1.5 mg $kg^{-1}$ of propofol, and 0.5–1 mg $kg^{-1}$ of chlorsuccillin. During general anesthesia norcuron 60 μg $kg^{-1}$ per hour, fentanyl 20–60 μg $kg^{-1}$ per hour, propofol 3–6 mg $kg^{-1}$ per hour were administered together with ventilation with oxygen and nitrous oxide mixture in a ratio of 1:2. The blood samples were taken immediately before surgery (T1) – these served as control values for assessing surgery's impact on the coagulation system. Next, samples were taken 6 (T2), 24 (T3) and 48 (T4) hours after surgery completion. Three different peripheral blood samples were obtained. One was collected into 3.8% trisodium citrate in 9:1 volume, centrifuged at 2 500 g for 15 minutes at 4°C. Separated plasma samples were stored at –70°C until used for the analytical tests. These included antithrombin (AT), PC and plasminogen (PG), which were determined by chromogenic substrate tests (Diagnostica Stago). From the second sample plasma fibrinogen (FG) levels were assessed by the Clauss method. D-dimer (DD) plasma levels were determined by STA Liatest DDI optical density method, activated partial thromboplastin time (APTT), and prothrombin time (PT) estimated as international normalized ratio (INR) were determined using standard kits manufactured by Diagnostica Stago. Additionally, platelet count, hemoglobin concentration, and hematocrit values were measured from the third sample.

The hypothesis of normal distribution of analyzed variables was verified and confirmed by the Kolmogorov–Smirnov test. Statistical analysis was performed using a SPSS software (V6.0 SPSS PC, Inc. Chicago, USA). Statistical significances of differences between means for continuous parameters of normal distribution were tested with Student's t-test.

## RESULTS

Before surgery the plasma DD level exceeded the upper limit of reference value (0.5 mg/dL) more than 2-fold and increased significantly 6 hours following surgery. Maximal values were found after 24 hours with an insignificant decrease on the next day (Fig. 1).

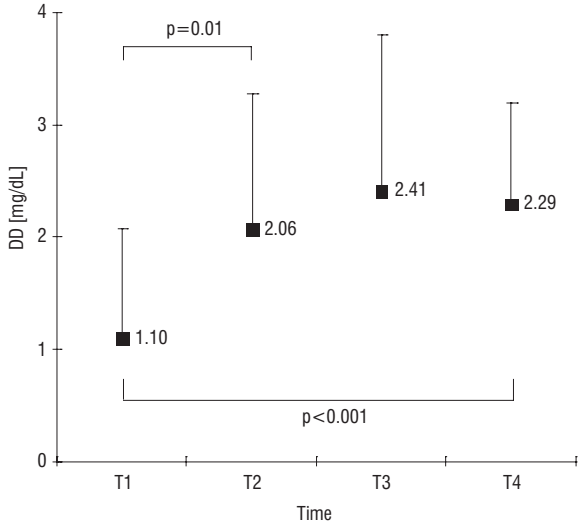


**Fig. 1.** DD plasma levels after colorectal cancer resection. Comments: $p < 0.01$ for T2 value compared to T1 (control sample). Values expressed as mean ±SD

APTT results, presented in Fig. 2, did not change during the initial 6 hours after surgery, but then lengthened significantly after 24 and 48 hours.

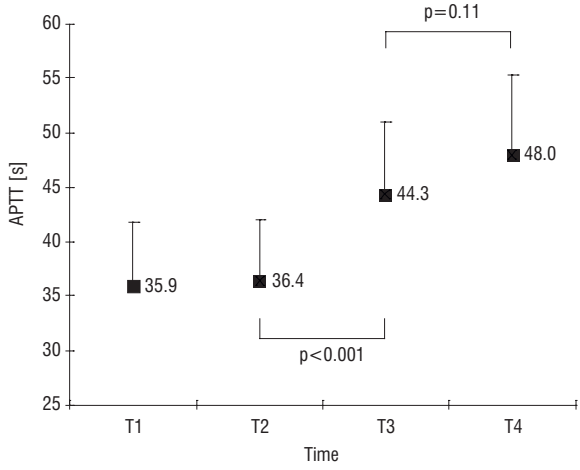


**Fig. 2.** APTT after colorectal cancer resection. Comments: $p < 0.001$ for T3 and T4 values compared to T1 and for T2 compared to T3 and T4 values. Values expressed as mean ±SD

PT defined as INR increased significantly 6 hours after surgery, reaching maximal value after 24 hours, with subsequent insignificant diminishing after 48 hours (Fig. 3).

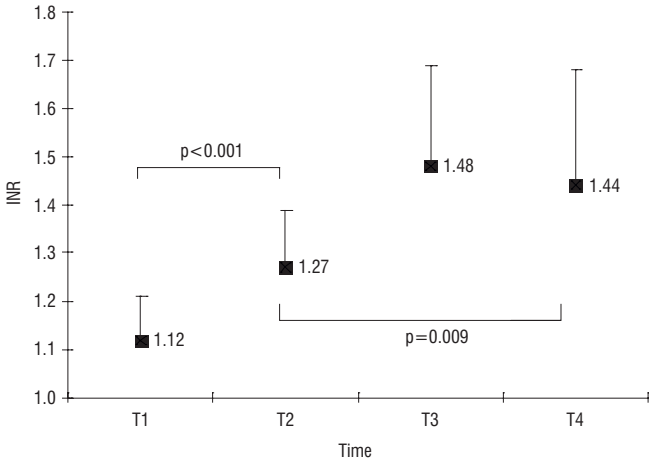


**Fig. 3.** INR levels after colorectal cancer resection. Comments: $p < 0.001$ for T2, T3, T4 values compared to T1; $p < 0.001$ for T2 compared to T3 value and $p = 0.009$ for T2 compared to T4 value. Values expressed as mean ±SD

FG plasma levels in perioperative period are summarized in Fig. 4.

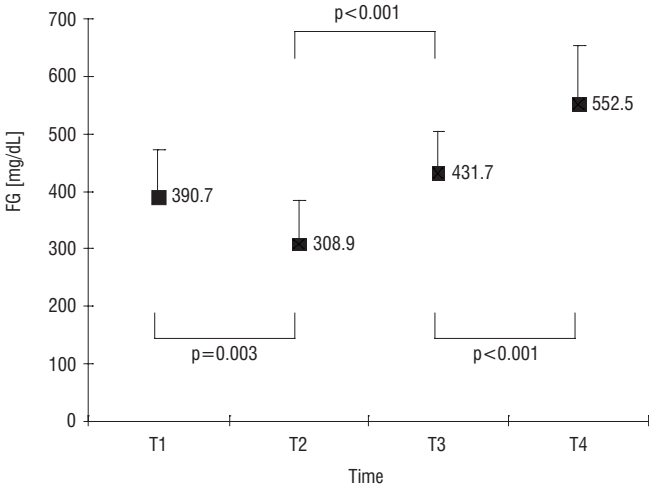


**Fig. 4.** FG levels after colorectal cancer resection. Comments: $p < 0.001$ for T2 value compared to T1. Linear increase of T3 and T4 values ($p < 0.001$) compared to T2 value. Values expressed as mean ±SD

A substantial reduction of initially normal FG concentration was revealed 6 hours after surgery. However, FG plasma level significantly increased after 24 hours compared to the lowest detected value and exceeded the upper reference limit. On the next day, the FG concentration plasma level showed a further significant increase.

Platelet count diminished significantly after 6 hours, showing a further linear decline up to 48 hours. At that time the mean value was the lowest one. Results are presented in Fig. 5.

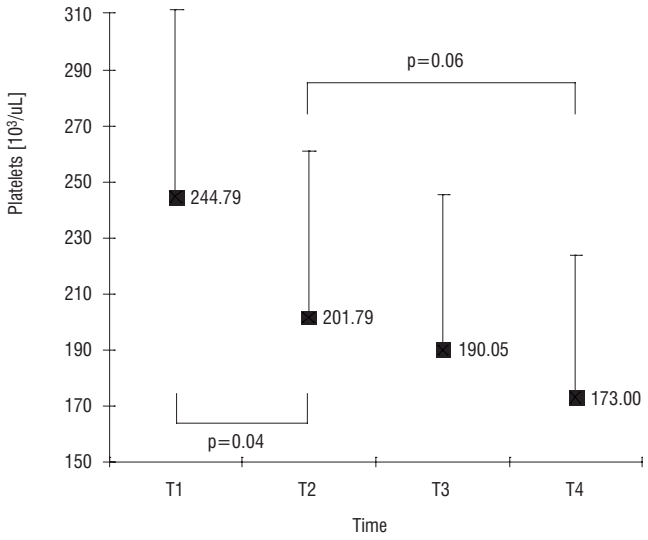


**Fig. 5.** Platelets count after colorectal cancer resection. Comments: p = 0.04 for T2 value compared to T1. Linear decrease of all subsequent values (T3, T4); p = 0.009 for T1 compared to T3 value and p < 0.001 for T1 compared to T4 value. Values expressed as mean ±SD

The mean AT plasma level before surgery was within normal limits. At 6 hours after surgery a significant drop was noted and lasted up to 48 hours (Fig. 6).

PC plasma level before surgery reached a level of 110.79%. All the subsequent mean postoperative values were significantly and progressively decreased. The lowest value was observed 48 hours after surgery. PG plasma level before surgery amounted to 97.67% and a substantial decrease was detected up to 48 hours (Fig. 6).

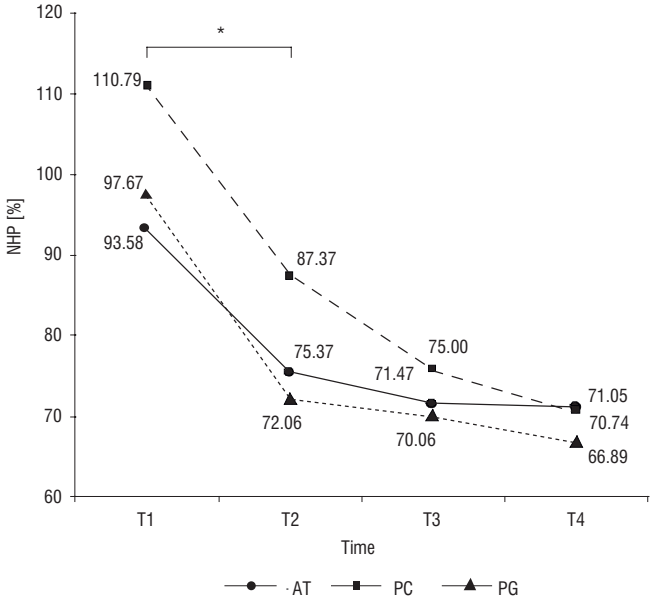


**Fig. 6.** AT, PC and PG levels expressed as the percentage of normal human plasma (NHP) after colorectal cancer resection.

Comments: * $p < 0.001$ for T1 value compared to all subsequent values for PC and PG; $p = 0.002$ for T2 value compared to T1 for AT. Values expressed as mean ±SD

Significant decreases in the hemoglobin (Fig. 7) and hematocrit levels (Fig. 8) were detected after 6 hours with further significant reductions 48 hours following surgery.

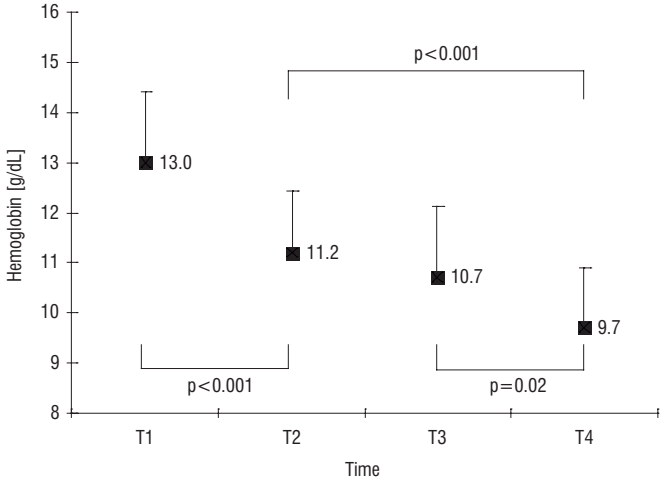


**Fig. 7.** Hemoglobin levels after colorectal cancer resection. Comments: $p < 0.001$ for T2, T3, T4 values compared to T1 and for T2 value compared to T4; $p = 0.02$ for T3 compared to T4 value. Values expressed as mean ±SD

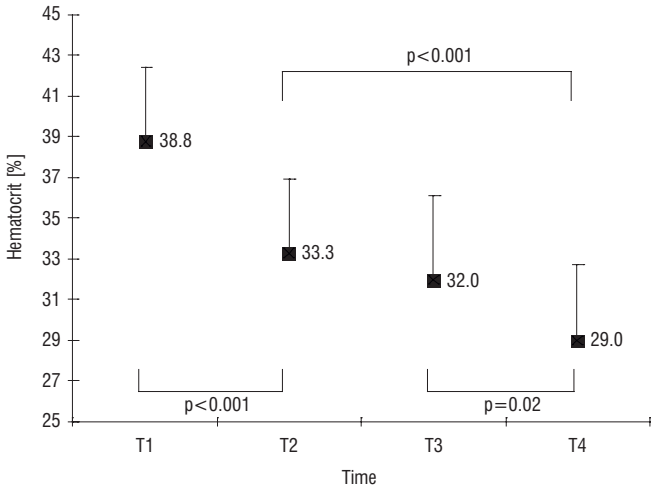


**Fig. 8.** Hematocrit levels after colorectal cancer resection. Comments: $p < 0.001$ for T2, T3, T4 values compared to T1 and for T2 value compared to T4; $p = 0.02$ for T3 compared to T4 value. Values expressed as mean ±SD

## DISCUSSION

In the studied group of patients, DD plasma levels before surgery increased over 2-fold compared to the upper reference value. DD value is considered to be an indicator of coagulation activation, secondary clot proteolysis and correlates with colorectal cancer progression [5, 12, 19, 20, 38]. A high plasma DD level before surgery confirms numerous, already published, conclusions concerning preoperative activation of coagulation and fibrinolytic systems in patients with colorectal cancer [12, 13, 19, 42].

It seems that increased DD plasma concentration in the studied group of patients with the highest level at 24 hours after surgery was caused mostly by the compensatory fibrinolysis process. Galster et al. [12] have found that in the patients who underwent gastrointestinal cancer resection in comparison to these operated on due to non-malignant disease, fibrinolysis assessed by DD plasma level was more intense, and lasted longer, until the 14$^{th}$ day of the postoperative follow-up. The mean values of the DD increased up to 48 hours, and were similar to those in the study group. However, these authors observed a decrease of fibrinolytic processes known as fibrinolytic shutdown assessed after 24 hours, which was not observed in our study.

Postoperative fibrinolysis is crucial for fibrin degradation rate and protects against the new thrombotic incidents. Its activity depends on t-PA activity and PAI-1 activity. Neudecker et al. [28] have found that patients who have undergone colorectal cancer resections regardless of the operation type – conventional or laparoscopic, have had increased t-PA activity without an increase in PAI-1 activity during per-

formed procedures. A significant decrease of t-PA activity was observed 8 hours after surgery, and a moderate increase was found again after subsequent 16 hours. PAI-1 activity was increasing since the 8th hour to the end of the 24-hour observation period [28]. Fibrinolytic shutdown was found in over 60% of patients in whom elected abdominal surgery was performed and is considered to be an important reason for developing perioperative VT complications [8, 24]. Persistently elevated DD level indicates that this process has not occurred in our study despite an accompanying hemodilution process.

In addition, from the 24th hour till the end of the observation period, APTT statistically prolonged and reached therapeutic values. INR was significantly increased since the 6th hour, with its maximal value after 24 hours, whereas platelet count was significantly decreased until the end of the study period.

Boldt et al. [7] have noticed a non-significant prolongation of APTT in the 1st day after abdominal surgery. Usuba et al. [41] have observed a significant prolongation of APTT accompanied by decreased platelet count in patients operated on due to esophageal cancer. Similar coagulative disturbances in patients have been reported also by Samama et al. [36]

Detected impairment of coagulative activity in the study group probably resulted from consumption of coagulation factors and significant hemodilution, which were manifested by decreased hemoglobin and hematocrit values. Increasing DD plasma level, accompanied by the prolongation of APTT, increased INR and decreased platelet counts 48 hours after surgery may be interpreted as a surgery triggered activation of consumptive coagulopathy despite prophylaxis with low molecular weight heparin. Results from other studies concerning a similar population confirm such interpretation [23, 32]. Galster et al. [12] have noted that differences in the activation of coagulation depend on the operated cancer type, which suggests that this process is mainly related to procoagulants released from the neoplasmatic cells [22].

AT and PC activities were decreasing beginning with the 6th hour after surgery and reached nadir values after 48 hours. The decreased AT activity observed immediately after surgery is considered to be a consumption effect [39]. Effectiveness of heparin treatment depends on AT activity, which inhibits activated factors IX, X, XI, XII, FVII-TF complex, and thrombin [40]. The more so, because the compensation of decreased AT activity proceeds faster and is more augmented in patients below 60 years of age [7]. In the studied patient group the average age was more advanced, which can be regarded as the next factor contributing to a reduced AT activity measured until the end of the observation period.

PC is an important natural anticoagulant with an inhibitory effect on coagulation. In its activated form (APC), it decreases thrombin generation by factor V and VIII inhibition [27]. It is believed that APC deficiency results in thrombosis of capillary vessels, leukocytes adhesion, and generation of cytokines [10]. Gouin-Thibault et al.

[15] explain that decreased AT, PC and protein S (PS) activities in cancer patients result from diminished hepatic synthesis and overconsumption. Nguyen et al. [30] found laparoscopic and open gastric bypass surgery to result in a gradual postoperative decrease of initially normal PC and AT plasma levels as we detected in our group of patients [38]. Garcia-Avello et al. [13] found a decreased PC plasma level only in samples taken from the tumor draining vein after colorectal cancer resection. In the study group both the consumption of coagulation factors and postoperative hemodilution can be regarded as contributing to decreased plasma levels of natural anticoagulants. In a large prospective study Folsom et al. [11] concluded that in a population without cancer, a low PC level rather than AT deficiency is responsible for new onsets of thrombotic complications. When comparing patients with thrombosis and cancer to those without malignancy, PC concentration is found to be significantly decreased in the former group [14]. These observations suggest a clinical significance of low PC plasma levels in the development of thromboembolic complications.

Decreased PG values 6 hours after surgery in the study group was accompanied by a rapid increase in FG plasma level. Low PG level may lead to deterioration in plasma fibrinolytic potential. However, isolated congenital PG deficiency was not recognized as a risk factor for VT [31].

Nguyen et al. [30] suggested that a decrease in PG level and a concomitant increased FG concentration may facilitate fibrin generation. This process shifts the coagulation-fibrinolysis balance towards a hypercoagulable state [42].

Before heparin prophylaxis era, it was found that general anesthesia was associated with a statistically significant increase in postoperative thromboembolic complications [33]. Despite the introduction of low molecular weight heparin prophylaxis, it was proved that general anesthetics may still produce more VT complications [26]. There is no doubt that heparin prophylaxis by impairing the coagulation system reduces the risk of thromboembolic complications in patients subjected to open surgery. Nevertheless, the activation of the coagulation system occurs as a result of processes described above, and leads to impairment of intrinsic and extrinsic coagulation pathways, decreased platelet count as well as the lowering of natural anticoagulants. Thus, a question arises: What is the significance of both these processes in pathogenesis of thromboembolic complications? It seems that decreased levels of anticoagulants may be of the greatest importance.

The limitation of this study is the fact that the prothrombotic effect of applied general anesthetics in this research cannot be excluded. Due to the safety reasons, we did not compare our patients with a control group without heparin prophylaxis. It is therefore impossible to establish whether the observed hemostatic disarrangements are related to the applied standard general anesthesia or to what extent they were prevented by the use of prophylaxis with low molecular weight heparin.

## CONCLUSIONS

Colorectal cancer induces a significant activation of coagulation and fibrinolytic systems. Despite prophylaxis with low molecular weight heparin, colorectal cancer resection interferes with hemostasis by induction of a process resembling consumptive coagulopathy with an impairment of standard coagulation laboratory tests and triggers reactions leading to a decreased level of natural anticoagulants. Further studies are required to determine whether substitutional administration of natural anticoagulants added to routine heparin treatment in case of prophylaxis failure should be considered.

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*ORIGINAL PAPER*

# PULMONARY REHABILITATION WITHIN INTENSIVE CARE UNITS EXEMPLIFIED BY TRAFFIC COLLISIONS CASUALTIES

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## ABSTRACT

**Introduction.** The early introduction of a rehabilitation procedure is of vital importance in the process of acting upon the respiratory system. In comprehensive therapy, pulmonary rehabilitation is perceived as an integral part of treatment for mechanically ventilated patients.

**Aim.** The aim of this work was to conduct a comparative analysis of pulmonary rehabilitation concerning patients who had sustained an injury as the result of traffic collisions, and were subsequently treated in an intensive care unit (ICU).

**Materials and methods.** Research material consisted of information contained in the medical documentation of 43 patients, ranging in ages from 15 to 57 years, treated in the ICU for injuries sustained during traffic collisions. This analysis involved the values of the parameters recorded first on admission of the patient to the unit, and then every 7 days thereafter, and finally upon discharge from the ICU, and included: arterial blood gasometry, pulsoxymetry, capnometry, body temperature, arterial blood pressure, and pulse rate.

**Results and Discussion.** Pneumonia occurred most frequently in patients ventilated mechanically during the period from the $15^{th}$ to the $28^{th}$ day of hospitalization and constituted 60% of the total occurring pneumonias. Deaths were observed more often in patients with acidosis and hypercapnia. Values of arterial oxygen saturation of hemoglobin ($SaO_2$) below 94% were recorded in that group of patients for whom therapeutic procedures ended in failure (40%). For the remaining patients, $SaO_2$

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values exceeded 94%. The analysis of our material showed divergences concerning the values of partial pressure of end-tidal carbon dioxide ($PetCO_2$) and partial pressure of carbon dioxide in the arterial blood ($PaCO_2$). The mean values of $SaO_2$ and percutaneous monitoring of hemoglobin oxygen saturation ($SpO_2$) were similar.
**Conclusions.** The length of stay within the ICU is significant with respect to the occurrence of complications in the form of pneumonia. Patients whose parameter values were within the norm during pulmonary rehabilitation attained spontaneous respiration at discharge. $SpO_2$ and $PetCO_2$ are of vital importance in the pulmonary rehabilitation process, complemented by regularly taken arterial blood gasometry measurements.

**Key words:** pulmonary rehabilitation, mechanical ventilation, gasometry

## INTRODUCTION

The present work focuses on pulmonary rehabilitation concerning traffic collision casualties treated in the Intensive Care Unit (ICU). The specificity of pulmonary rehabilitation in intensive care involves the ability to adapt it to a constantly changing clinical condition of the patient, the type of injury sustained, and those therapeutic procedures administered [15, 23, 37, 38]. The lack of activities undertaken to rehabilitate the respiratory system may contribute to complications and result in death. Available data suggest that pulmonary rehabilitation is regarded as an integral part of the therapeutic process for mechanically ventilated patients [5, 6, 22, 32].

The reports of numerous authors allow us to conclude that the early introduction of an adequate rehabilitation procedure is of vital importance in the process of acting upon the respiratory system [3, 5, 9, 16, 17].

## AIM

The aim of this work was to conduct a comparative analysis of pulmonary rehabilitation concerning patients who had sustained an injury as the result of traffic collisions, expressed in parameters depending upon the patient's condition at discharge and the type of participation in a traffic collision.

## MATERIALS AND METHODS

Research material was obtained by comparing information contained in the medical documentation of 43 patients, ranging in ages from 15 to 57 years, treated in the Provincial Specialist Hospital in Olsztyn for injuries sustained during traffic collisions. These injured patients amounted to 17.84% of all patients treated from January 1, 2008 to December 31, 2008 in the ICU. The majority of hospitalized patients were male (30), i.e., 69.8% (Fig. 1).

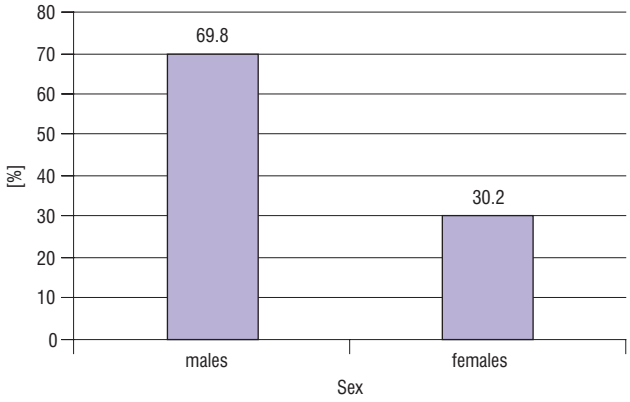


**Fig. 1.** Percentage of male and female patients in the study group

To achieve the aim of this study, the values of the parameters recorded on admission of the patient to the unit, and then every 7 days thereafter, and finally upon discharge from the unit were collected. These parameters included: arterial blood gasometry, pulsoxymetry, capnometry, body temperature, arterial blood pressure, and pulse rate. Mean values of each parameter for each patient were calculated from the obtained data. The study group was divided according to the participation in the traffic collision. The variables adopted were: driver, passenger, pedestrian. The group was differentiated according to the method of respiration upon discharge from the ICU, which determined the patient's condition. The following cases were considered: physiological breathing, i.e., via natural respiratory tract; tracheostomy, i.e., physiological breathing supported with a tracheostomy tube; mechanical ventilation, i.e., patients requiring mechanical ventilation following discharge from the unit; and death. The collected data were parameterized, and following their input into the data base, were statistically analyzed, and then correlations were determined.

## RESULTS

Mean time spent in the ICU unit amounted to 16.88 days, 17.7 days for men, 10.38 days for women.

Statistical analysis conducted revealed that the type of participation in the traffic collision was not statistically significant for the hospitalization period in the ICU, the condition of the patient upon discharge, and the respiratory therapy period. An attempt was made to determine the correlation between the length of hospitalization in the ICU and the condition of the patient upon discharge. The study revealed no such correlation. The hypothesis of the correlation between systolic and diastolic pressure and pulse rate on the method of respiration at discharge was also dismissed.

The length of hospitalization within the ICU and its influence with respect to the occurrence of pneumonia were analyzed, assuming time intervals of up to 14 days, 15–28 days, and more than 28 days. As Fig. 2 indicates, pneumonia was much more frequent in patients during the time interval of 15–28 days, constituting 60% of the total occurring pneumonias. In the time interval of up to 14 days the incidence was much smaller and amounted to 25% of the total occurring pneumonias.

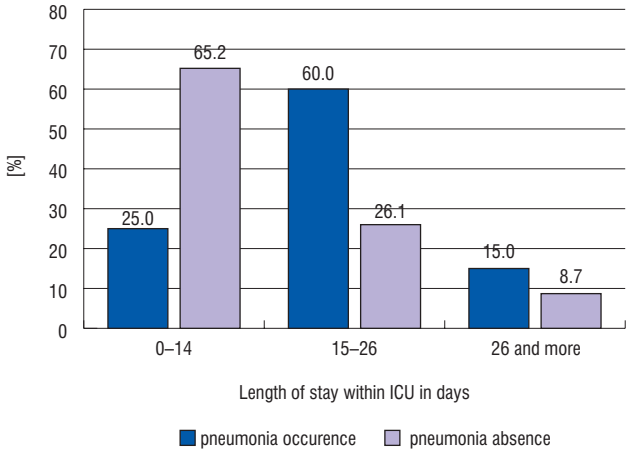


**Fig. 2.** Pneumonia in time intervals

The analysis of arterial pH values and their correlations with the condition of patients upon discharge from the ICU revealed that deaths were more frequent in patients with acidosis (80%). Patients who breathed spontaneously via a tracheostomy tube (75%) and physiologically (86.7%), generally had arterial pH values within the norm. As Fig. 3 indicates, patients who were not diagnosed with acidosis left the unit in better condition.

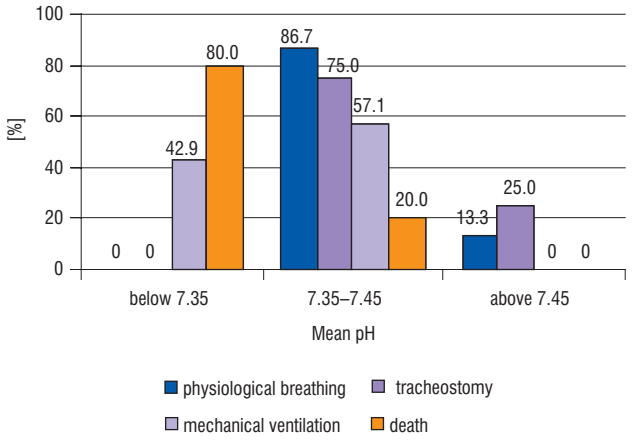


**Fig. 3.** Percentage of studied patients concerning arterial pH ranges

The analysis of specific data collected in Tab. 1 reveals that patients breathing spontaneously via a tracheostomy tube (93.8%) and physiologically (86.7%) most often exhibited partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) values within the norm, i.e., 35–45 mmHg. Deaths were most frequently observed among patients with hypercapnia (60%). In 71.4% of patients transferred to other units who required mechanical ventilation, normocapnia was recognized.

**Tab. 1.** Correlation between $PaCO_2$ mean value and the method of respiration upon discharge from the ICU

| Mean $PaCO_2$ | Condition upon discharge from ICU | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | physiological breathing | | tracheostomy | | mechanical ventilation | | death | | total | |
| | n | % | n | % | n | % | n | % | n | % |
| Below 35 | 1 | 6.7 | 1 | 6.3 | 0 | 0.0 | 0 | 0.0 | 2 | 4.7 |
| 35–45 | 13 | 86.7 | 15 | 93.8 | 5 | 71.4 | 2 | 40.0 | 35 | 81.4 |
| Above 45 | 1 | 6.7 | 0 | 0.0 | 2 | 28.6 | 3 | 60.0 | 6 | 14.0 |
| Total | 15 | 100.0 | 16 | 100.0 | 7 | 100.0 | 5 | 100.0 | 43 | 100.0 |

Arterial oxygen saturation of hemoglobin ($SaO_2$) below 94% was noted in that group of patients for whom therapeutic procedures ended in failure (40%). For the remaining patients, $SaO_2$ values exceeded 94%. The results are presented in Tab. 2.

**Tab. 2.** Correlation between mean $SaO_2$ and the method of respiration upon discharge from the ICU

| Mean $SaO_2$ | Condition upon discharge from ICU | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | physiological breathing | | tracheostomy | | mechanical ventilation | | death | | total | |
| | n | % | n | % | n | % | n | % | n | % |
| Below 94 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 40.0 | 2 | 4.7 |
| 94–98 | 9 | 60.0 | 8 | 50.0 | 3 | 42.9 | 1 | 20.0 | 21 | 48.8 |
| Above 98 | 6 | 40.0 | 8 | 50.0 | 4 | 57.1 | 2 | 40.0 | 20 | 46.5 |
| Total | 15 | 100.0 | 16 | 100.0 | 7 | 100.0 | 5 | 100.0 | 43 | 100.0 |

Data analysis showed divergences concerning the values of partial pressure of end-tidal carbon dioxide ($PetCO_2$) and $PaCO_2$. The mean values of $SaO_2$ and percutaneous monitoring of hemoglobin oxygen saturation ($SpO_2$) were similar.

Mean values of gasometry parameters over time were compared in order to illustrate the changes. Fig. 4 shows the comparison of $PaCO_2$ mean values. A decrease in this parameter values was observed, indicating the improvement of health conditions, in those patients requiring further ventilation. In the group breathing physiologically and via a tracheostomy tube, $PaCO_2$ values were within the norm. In patients who subsequently died, this parameter values were extremely unstable.

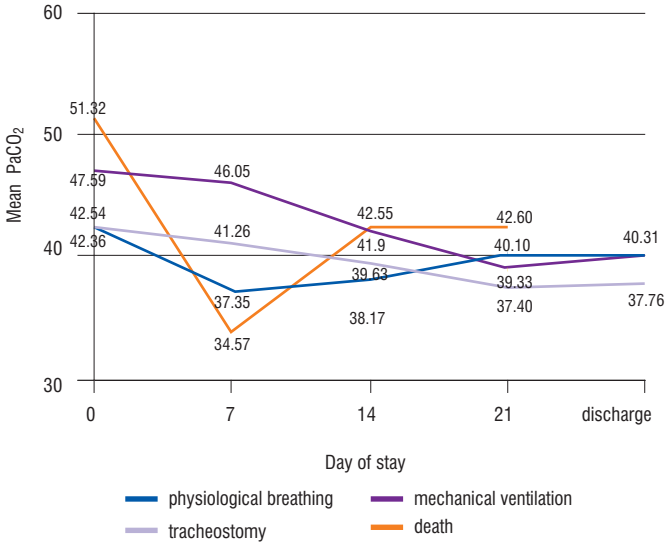


**Fig. 4.** $PaCO_2$ mean values within 24 hours from admission, on the 7th, 14th, 21st day, and on the day of discharge, in groups according to the method of respiration upon discharge

## DISCUSSION

Until recently pulmonary rehabilitation has been believed to be within the scope of pulmonology, which may have resulted from the fact that numerous authors discuss its applicability in chronic obturative pulmonary diseases [8, 18, 28, 29]. Presently, reports and scientific papers examine the issues of pulmonary rehabilitation with reference to many specialties [12, 22, 35, 37].

Therapeutic processes in ICU often require the application of mechanical ventilation, which necessitates intubation or tracheostomy [19]. The activities performed upon the patient involve comprehensive therapy, in which pulmonary rehabilitation has been considered to be an integral part of treatment for mechanically ventilated patients [5, 6, 32]. Pulmonary rehabilitation is defined as a multidisciplinary program of care that is individually devised for a given patient and aims at stabilizing and reversing adverse changes in the respiratory system [15, 18, 24, 30]. According to the definition, the activities performed upon the patient are individually tailored and designed, both in terms of their range and intensity [12]. Many authors claim that rehabilitation activities should be constantly supervised, with the use of a 24-hour non-invasive monitoring system of life functions, and periodical invasive control tests, in order to follow the changes in recorded parameters, detect disorders early, and react appropriately in time [3, 4, 13, 32, 33].

A standard monitoring parameter in ICU is end-tidal concentration or pressure of $CO_2$ [9]. In physiological conditions, the values of the partial pressure of $CO_2$ in arterial blood and in exhaled air are similar, and the difference is only that of a few mmHg [34]. Clinical test results point to the need for complementing the monitoring process with invasive $PaCO_2$ measurements due to vast divergences between the values [9, 10, 22].

Available subject literature does not discuss patients divided into groups on the basis of the method of respiration upon discharge. However, some correlations with the adopted variables have been noticed. Values within the norm have been more often observed in patients who breathed spontaneously in a physiological way or via a tracheostomy tube.

The application of artificial ventilation often contributes to complications in the form of pneumonia [19, 25]. Available data also indicate the more frequent occurrence of this complication in mechanically ventilated patients [3, 21, 22, 31]. The treatment aims at prevention of complications and pulmonary rehabilitation. In comprehensive therapy, the issue of pneumonia should not be overlooked because it may become a significant epidemiological factor. The effect of pneumonia as regards prognosis is the subject of numerous discussions [21].

In the analyzed research material, it has been observed that the length of hospitalization within the ICU influenced negatively the occurrence of pneumonia. Similarly, other authors emphasize the correlation between pneumonia and the length of stay in the ICU, which is sometimes connected with intubation or mechanical ventilation period [3, 22, 36]. Berlly et al. [3] have shown that pneumonia risk increases from 1% to 3% per each day of intubation. Preventing pneumonia via the introduction of pulmonary rehabilitation is the subject of numerous studies [1, 25, 26]. Ahrens et al. [1] conducted a prospective, randomized study involving 234 patients from Intensive Care Units in various centers. They proved that the risk of developing pneumonia was less in patients who underwent pulmonary rehabilitation than in the control group, whereas the lenght of stay in the ICU did not differ between the groups. Ntoumenopoulos et al. are of a different opinion [25]. The study they conducted concerning 46 patients suggested that physiotherapy did not decrease the incidence of pneumonia in mechanically ventilated patients in an ICU.

Numerous authors also discuss the cost-effectiveness of treatment via shortening the stay in an ICU and reducing complications [7, 15, 20]. When analyzing our research material concerning the influence of the type of participation in traffic collisions with respect to the length of respiratory therapy and that time spent in the ICU, we have shown no significant correlations.

The overview of available subject literature indicates that over the centuries the effectiveness of pulmonary rehabilitation was based solely on the length of its application and experience [22]. In the era of scientific development, pulmonary rehabilitation is regarded as a set of activities based on scientific evidence [24]. Various authors

are, however, not uniform concerning its effectiveness. Many researches emphasize the need of further research as quite necessary in order to evaluate clinical benefits [2, 5, 32, 39].

## CONCLUSIONS

1. The length of stay within the ICU is significant with respect to the occurrence of complications in the form of pneumonia.
2. The types of participation in traffic collisions (driver, passenger, pedestrian) do not influence the course of rehabilitation or the method of respiration upon discharge from the ICU.
3. Patients whose parameter values were within the norm during the pulmonary rehabilitation process attained spontaneous respiration at discharge.
4. Percutaneous monitoring of $SpO_2$ and $PetCO_2$ are of vital importance in the pule monary rehabilitation process, complemented by regularly taken arterial blood gasometry measurements.

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*ORIGINAL PAPER*

# CHANGES IN BODY POSTURE IN CHILDREN BETWEEN THE 10TH AND 13TH YEARS OF AGE

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## ABSTRACT

**Introduction.** The possibility of detecting postural defects early, a significant development with respect to available therapeutic methods, and an awareness of the necessity for continuous and individually adjusted treatment, are regarded as an important progression in the modern conservative treatment of faulty postures.

**Aim.** This work aimed at determining changes in body postures in 10- and 13-year old children within a 3-year period.

**Materials and methods.** This research was conducted in Mława in two primary schools and involved 10-year old children, who were reexamined after a 3-year period, at the age of 13. The final group included in this research consisted of 76 subjects.

**Results and Discussion.** Changes in body posture observed in the study group over the 3-year period are as follows: 34.29% of children manifested excellent and good posture during examination I; whereas during examination II 45.71% of children had good posture.

The adopted methodology did not allow us to determine physiological changes concerning body silhouette. However, it allowed us to detect posture abnormalities, and to diagnose postural defects.

**Conclusions.** The results confirmed the occurrence of changes in body postures in children between the 10th and 13th years of age. These changes, defined as detected body posture abnormalities, showed both improving and worsening tendencies with respect to the analyzed elements of body posture. A general percentage analysis showed an improvement in the body posture of children within a 3-year period.

**Key words:** body posture, children, changes in body silhouette

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## INTRODUCTION

Postural defects are defined as changes observed in an unrestrained, erect position, which significantly differ from postures typical of a particular age, sex, race, and constitution. They result from pathological changes, may occur in all planes and are manifested as changes in the spinal curvature and body sections directly connected to the spine [4, 14, 16, 17]. It is extremely important to conduct examinations in the period critical for postural development. The second growth spurt occurs between the 10th and 12th years of age. After the age of 10, developmental changes intensify. Maintaining a proper body posture often requires a more concentrated effort due to physiological weakness in the muscles. During this period, there may occur spontaneous corrections of postural defects, as well as their worsening [10]. The possibility of detecting postural defects early, a significant development with respect to available therapeutic methods, and an awareness of the necessity for continuous and individually adjusted treatment, are regarded as an important progression in the modern conservative treatment of faulty postures. Therapeutic procedures should be holistic and involve not only a psychic sphere, but also environmental factors [11]. Discontinuing corrective therapy during the period of physiological development, results in disturbances with respect to efficiency as well as the economy and esthetics of movement. This, in adult life, leads to an early overstraining of joints and to both degenerative and deformative diseases [15].

## AIM

This work aimed at determining the changes in the body postures in children during the period of the second growth spurt – between the 10th and 13th years of age (health check) and an anthropometric analysis of the changes occurring within this developmental period.

## MATERIALS AND METHODS

This research was conducted in Mława in two primary schools and involved a group of 10-year old children, who were reexamined after 3 years. The examination of 10-year old children (92 subjects) was termed as examination I, and that of 13-year olds – as examination II. Because the parents of 16 children did not consent to the examination II, the analysis of the results excluded these children. The final study group consisted of 76 subjects. The examination record form was adjusted for the purpose of this study. Examinations were conducted according to a visual assessment of selected elements of body build and posture on the basis of the modified point-based method [7], the New York posture test, and the detailed posture evaluation test [17, 18].

On the basis of an obtained number of points, during the final analysis, each child's posture was graded as being excellent, good, poor or bad.

STATISTICA 7.1 for Windows by Statsoft® was used for a statistical analysis of the obtained data. Statistical significance was defined as $p \leq 0.05$.

## RESULTS

Changes in body posture observed in the study group over the 3-year period are as follows: 34.29% of children manifested excellent and good posture during examination I; whereas during examination II 45.71% of children had good posture (Fig. 1).

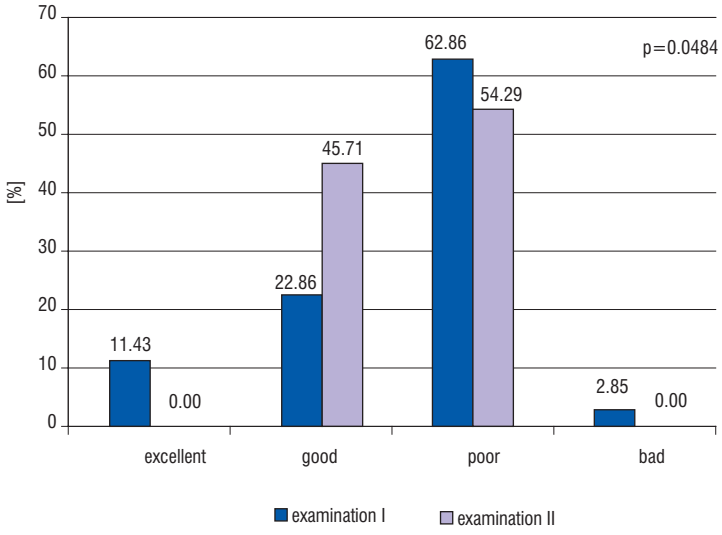


**Fig. 1.** Changes in body postures of children between the 10th and 13th years of age

13-year old children generally manifested improved postures, with an increased number of postures graded as good (by 14.58% in boys and by 23.1% in girls). A significant improvement was observed with respect to hollow back (by 37.5% in boys). A decrease in the incidence and intensity of changes also occurred in the case of: protuberant abdomen (by 10.53% in girls), protruding head – sagittal plane (by 5.27% in girls), asymmetric shoulders (by 6.25% in boys and by 5.27% in girls), asymmetric shoulder-blades – frontal plane (by 31.58% in girls), abnormal spinal curvatures (by 12.5% in girls and by 10.53% in boys), waist asymmetry (by 12.5% in boys), slanting pelvis (by 6.25% in boys), and improper calcaneus positions (by 6.25% in boys and by 5.27% in girls).

Within the age bracket of 10–13, the worsening with respect to the frequency of occurrence and intensity of changes was observed for the following defects: protruding head – sagittal plane (by 18.75% in boys and by 36.85% in girls), forward protrusion of the shoulders – sagittal plane (by 31.25% in boys and by 26.31% in girls),

winged scapula (by 6.25% in boys and by 16.13% in girls), abnormal chest shape (by 18.75% in boys and by 36.84% in girls), rounded back (by 21.05% in girls), hollow back (by 5.26% in girls), asymmetric shoulder-blades – frontal plane (by 6.25% in boys), asymmetry of the back in the forward bending position (by 10.53% in girls). Three 13-year old children manifested varus knee; this deformity was not observed when they were 10 years old.

Statistically significant differences were obtained concerning the following defects:

- hollow back in boys: $p = 0.0019$,
- abnormal chest shape – sagittal plane in girls: $p = 0.0443$,
- asymmetric shoulder-blades – frontal plane in girls: $p = 0.0422$.

## DISCUSSION

The term "changes in body posture" appearing in the title of this paper refers, in its basic meaning, to physiological changes in the human body silhouette, which can be observed both during the overall development of a given individual and during a single day, e.g., due to physical fatigue or the psychological condition of a given individual [4, 7, 12, 13]. The methodology adopted in this work did not enable us to determine physiological changes in the body silhouette. It allowed us, however, to detect posture abnormalities and to diagnose postural defects. With an increase in age, posture generally improved. Examination II revealed an increase in the number of postures graded as good (by 14.58% in boys and by 23.1% in girls). Nevertheless, these results are not satisfactory, because 68.75% of boys and 42.11% of girls still manifested poor postures, and no child's posture could be graded as excellent. The frequency of occurence of abnormal lateral curvature of the spine is consistent with the findings of other authors [3, 5, 6, 8]. Research conducted by Górniak in 2003 concerning a group of rural children [5], revealed a progression of this defect in 31.2% of cases. In the town of Rzeszów [6], abnormal spinal curvatures were detected in 40.9% of examined children, whereas in Kłobuck County [8] in 57% of girls and 35% of boys. When comparing the obtained results with the results of children examined in Konstancin [3], in Rzeszów [6], and in Bydgoszcz [1], one may draw the same conclusion: abnormal spinal curvatures in older children (13–14 years old) are more frequent in girls than in boys (the research showed that this defect was twice as frequent in girls); varus knee occurs rarely, whereas valgity tends to increase with age (irrespective of sex). A slight decrease in the number of defects concerning the heels is observed with advancing age. In both age groups, varus deformities were not observed, whereas valgus heel wedges were detected in few cases, and the intensity of this deformity was low. Between the ages of 10 and 13, a general improvement of body posture was observed: 34.29% of 10-year old children manifested postures graded as excellent and good, whereas after a 3-year period, posture graded as good

was detected in 45.71% of children. Consequently, discordance appeared with respect to the findings of other authors, who detected an increasing tendency with regard to the frequency of occurrence of postural defects in children [1, 2, 9]. After a thorough analysis of the results, along with an accounting for particular types of defects, we are not able to conclude that the improvement involved all the postural defects examined in children within the age bracket of 10–13 years of age. The frequency of occurrence of protruding head – sagittal plane increased twice as much in 13-year old girls and boys. The difference in the frequency of occurrence and intensity of a defect occurred also for: forward protrusion of the shoulders – sagittal plane, winged scapula, abnormal chest shape, rounded back (increased number of girls), valgus knee (the same level of incidence, but increased intensity), and asymmetry of the back in the forward bending position. Three 13-year old children manifested varus knee which was not diagnosed earlier. A general percentage analysis of the remaining 9 elements of examined body elements, considered when assessing body postures, exceeded the percentage of the worsening of the enumerated defects, which accounts for the obtained discrepancy in our results with respect to the findings of other authors.

## CONCLUSIONS

1. Our research results confirmed the occurrence of changes in body postures in children between the $10^{th}$ and $13^{th}$ years of age. These changes are understood as detected abnormalities showing both improving and worsening tendencies with respect to the analyzed elements of body posture.
2. A general percentage analysis showed an improvement of body posture in children examined after 3 years.

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*ORIGINAL PAPER*

# THE EFFECTIVENESS OF REHABILITATION PROCEDURE AFTER THE RECONSTRUCTION OF THE ANTERIOR CRUCIATE LIGAMENT ACCORDING TO THE NORWEGIAN PROTOCOL

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**ABSTRACT**

**Introduction.** In the 1970s and 1980s, the rehabilitation program after anterior cruciate ligament (ACL) reconstruction recommended that patients' limbs should be immobilized from 2 to 4 weeks. After such a period, the patient would be wearing a stabilizer until the end of the 3rd or 4th month. The limb could not be strained for 6 weeks.

**Aim.** The aim of this paper was to present a Norwegian rehabilitation protocol after ACL injury and to show its effectiveness through examining the muscle strength on the Biodex system 3 Pro after periods of 3 and 6 months following the reconstruction.

**Materials and methods.** The rehabilitation protocol described in *Physical Therapy* No. 6 Vol. 87 was employed. 18 patients (5 women and 13 men) were rehabilitated after reconstruction with semitendinosus and gracilis tendon grafts. All patients were rehabilitated from 2008 to 2009 in the Stefan Bołoczko Motor Rehabilitation Center, located in the Olsztyn Higher Education Institution. After periods of 3 and 6 months, these patients underwent isokinetic muscle strength test. The Biodex system 3 Pro was used.

**Results and Discussion.** Patients rehabilitated according to the described protocol reached an average value of muscle strength between an operated limb and a healthy one amounting to 16.8% for extensors and 11.3% for flexors after 3 months following ACL reconstruction. This result allowed them to start a running program. After

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6 months, the average value of muscle strength for extensors was 6.15% and 4.45% for flexors. This also allowed these patients to practice appropriate sport disciplines. **Conclusions.** The rehabilitation performed according to the Norwegian protocol speeds up regeneration of muscle strength after periods of 3 and 6 months, which enhances the patients' quicker recoveries with respect to their daily functioning and physical activities. The aforementioned rehabilitation procedure does not have any negative effects, provided that patient, physician and physiotherapist cooperate closely with each other.

**Key words**: anterior cruciate ligament (ACL), rehabilitation protocol, proprioception

## INTRODUCTION

The anterior cruciate ligament (ACL) is an intra-articular, but extrasynovial structure, from 3.7 cm to 4.2 cm long and 5 mm thick on average. The ACL attaches in a fan-like form to the posteriomedial wall of the lateral femoral condyle. Next, it runs down, anterially and posteriomedially. Turning by 90°, it attaches to a tibial plateau in the tuberculum mediale area. The sizes of this ligament are varied depending on a type of build, shape, head of the femur, bone thickness, and shape of the tibial plateau [10].

The ACL consists of bundles: the anteromedial bundle, a bigger, posterolateral bundle and the smallest intermediate bundle [4]. Arthroscopy for ACL reconstruction has been in use since the 1980s. Currently, the following autografts are used in this kind of treatment: a free autologous central one-third bone-patellar-tendon-bone (BPTB) graft, semitendinosus (ST) and gracilis (GR) muscle tendons, rectus femoris tendon and iliotibial band (ITB). Allografts are also used, including: Achilles tendon with fragments of heel bone, pattelar ligament, flexor ligament (tibialis anterior muscle) or synthetic grafts [1, 6, 7].

In the 1970s and 1980s, the rehabilitation program after ACL reconstruction recommended that the involved limb should be immobilized from 2 to 4 weeks. After such a period, the patient would be wearing a stabilizer until the end of the 3$^{rd}$ or 4$^{th}$ month. The limb could not be strained for 6 weeks. The first muscle strength test was carried out 6 months following the reconstruction, the next one after 12 months. If the difference between the operated upon and the healthy limb was less than 20%, then a patient was allowed to do unlimited physical activities. In 1986 a protocol was introduced which allowed patients to perform the passive motion immediately after treatment. It was possible thanks to a continuous passive motion (CPM) device (Fig. 1), which helped to avoid long-lasting immobilization [2]. Today, the employment of a CPM device is a controversial issue. With the earlier introduction of motion and strain on an operated limb into the rehabilitation program, the advantages of this device are becoming less significant. Few current research programs show crucial, long-term benefits as a result of using the aforementioned device [3].

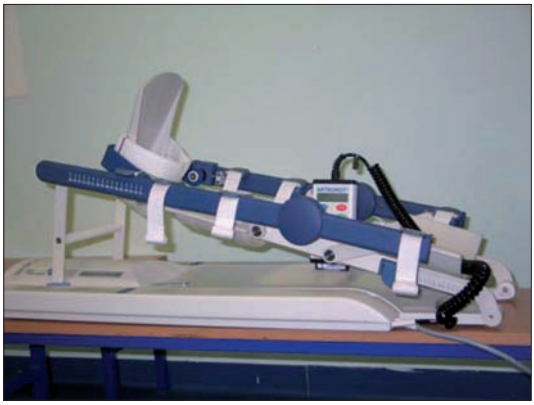

**Fig. 1.** CPM (Continuous passive motion)

In 1998, Tyler et al. proved that the immediate strain after ACL reconstruction lessens the restraining of muscle functions of a knee joint area usually observed in an early postoperative period. This is also proved by the enhanced myoelectrical activity of the vastus medialis oblique (VMO) muscle two weeks following the operation. They also observed that anterior knee pain lessened in patients who were treated with limb strain just after the operation. No differences with respect to knee flexibility, range of motion or functional assessment were noted between patients treated with limb strain and those without it. Possible complications may appear in patients who were treated by autogen BPTB graft [3].

The advantages of the earlier strain are as follows:

- better cartilage nutrition,
- minimizing bone mass loss,
- minimizing arthrofibrosis risk,
- faster recovery of quadriceps femoris muscle function [3].

The modern rehabilitation process is comprehensive and should involve the entire organism of the patient, including cardiovascular system training, proprioception and muscle coordination training, by the appropriate activity selection. The activities should be safe, adjusted to the patients' abilities and interests, but also should contain the elements of a sport discipline a patient would like to return to [3]. The major aim of the modern rehabilitation program is to enable a patient to recover as quickly as possible with respect to daily functioning, work, and sport activity. Such a recovery brings about both mental and economic benefits [2].

## MATERIALS AND METHODS

The research group consisted of 18 people (5 women and 13 men, aged from 17 to 46, average age of 24) after ACL reconstruction with ST and GR tendon grafts. All patients were rehabilitated from 2008 to 2009 in the Stefan Bołoczko Motor Rehabili-

tation Center, located in the Olsztyn Higher Education Institution. The rehabilitation protocol described in *Physical Therapy* No. 6, Vol. 87 was employed [8]. After periods of 3 and 6 months, patients underwent isokinetic muscle strength test. The Biodex system 3 Pro was used. The test involved both healthy limbs and those after ACL reconstruction.

After 3 months following reconstruction, the examination was performed at 90––40° for both limbs with speeds of 180°/s and 300°/s. In the 6th month the examination was carried out from 90° to the maximum extension established for each lower limb separately with speeds of 90°/s and 240°/s. If the difference of muscle strength after 3 months for extensor and flexor was within a range of equal to or less than 30%, then the running program was started. After 6 months the repeated test with respect to full motion range was performed. If the difference of muscle strength between the operated and the healthy limb was equal to or less than 15%, the patient was allowed to begin an appropriate sport activity.

The rehabilitation program began in the 1st week following reconstruction. It was divided into 6 stages. Rehabilitation sessions took place 3–5 times a week for 6 months. Activities were adjusted with respect to the patient's needs and abilities [8].

**Phase 0: Early Postoperative Phase**

*Weeks 1–2*

Goal: Restoring full passive knee extension and diminishing joint swelling.

Patients are hospitalized from 1 to 3 days. In the period between discharge from hospital and the beginning of the rehabilitation program at the outpatient clinic, patients should follow a home program with the main focus on restoring a full range of motion and diminishing joint swelling. To diminish swelling, the patient is advised to keep the limb elevated and to perform ankle plantarflexion-dorsiflexion exercises (Fig. 2), quadriceps isometric setting and hamstring stretches (cocontraction) (Fig. 3). Crutches can be used to improve gait and to reduce swelling. Full passive knee extension is the most important goal in the 1st week. Gravity is used to restore full knee extension by using two chairs, with the leg elevated on a hard pillow under the heel when sitting or with the leg elevated on the edge of the bed in the supine position (Fig. 2).

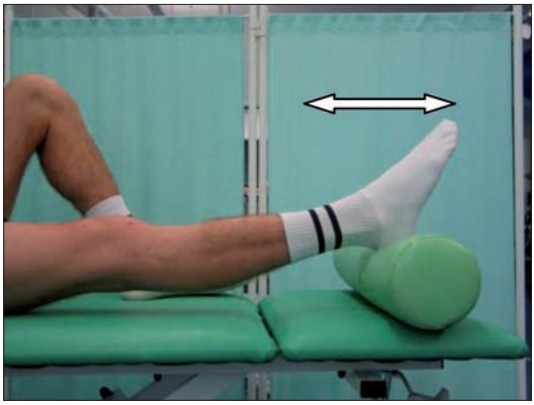

**Fig. 2.** Passive extension with dorsal and plantar foot flexion

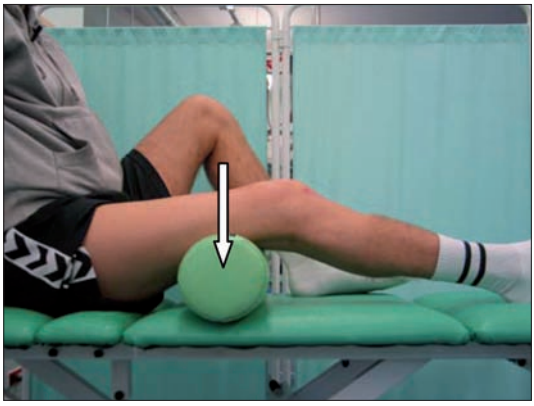

**Fig. 3.** Cocontraction

**Phase 1: Walking Phase**

*Weeks 2–4*

Goals: Achieving normal walking pattern without crutches; controlling balance with both-limb support; controlling balance with single-limb support; controlling dynamic stability of the uninvolved leg. Crutches are used for 2 weeks following reconstruction until the patient's weight is gradually tolerated. The criterion for discontinuing the use of crutches is evidence of no limping. Weight shift exercises are started as early as possible. If full body weight is not tolerated during squatting exercises, counterweights are used to avoid swelling or pain. Cold therapy (glacier packs) is applied for 15 minutes every 3–4 hours and immediately following exercises until swelling diminishes (Fig. 4).

Exercises:

- stationary bicycle to improve range of motion and diminish swelling,
- walking exercises on even surface,
- walking exercises on treadmill to improve gait patterns after discontinuing crutches,
- squats: if the patient has persistent swelling or pain, squatting exercises are performed employing a pulley apparatus with the use of counterweights (Fig. 5),
- gastroc exercises: heel lift exercises,
- single leg stance, starting on uninvolved leg,
- single leg stance, involved leg,
- balance exercises, starting on uninvolved leg,
- lunges: front, front/side, side, rear/side, and rear lunges on uninvolved leg,
- step-up exercises: front, side, rear, starting with uninvolved leg.

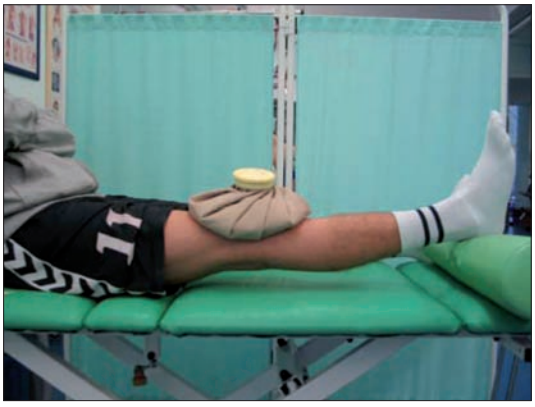

**Fig. 4.** Cold therapy

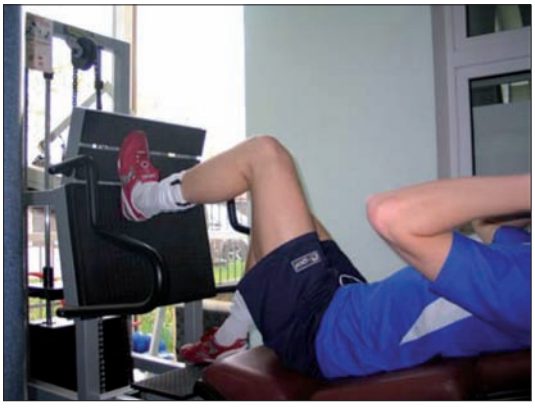

**Fig. 5.** Leg press

**Phase 2: Balance and Dynamic Joint Stability Phase**

*Weeks 5–8*

Goals: Controlling balance initially with both-limbs support, then with single-limb support, on uneven surface; controlling dynamic stability, both-limbs support; controlling dynamic stability, involved leg; step-up and step-down; squatting, both legs; sideways and backwards walking.

Week 5

Exercises:

- single leg stance, eyes closed,
- single leg standing on balance mat, appropriate knee and hip positions,
- rocker board, Wobble board, both legs (Fig. 6, 7),
- leg balance reach, involved leg,
- arm balance reach, involved leg,
- step-up, both legs.

**Fig. 6.** Rocker board

**Fig. 7.** Wobble board

Week 6
Exercises:
- backwards and sideways walking on treadmill,
- wobble board, both legs with weights,
- wobble board, both legs, ball throws,
- wobble board, single leg,
- step-down, uninvolved leg (Fig. 8).

**Fig. 8.** Step-down on uninvolved leg (steps from the left side: 18 cm, 10 cm and 5 cm high)

Week 7
Exercises:
– single leg stance on trampoline, ball throws,
– step-up and step-down, involved leg, different directions,
– balance exercises on balance mat and wobble board.

Week 8
Exercises:
– lunges with bars/weights,
– single leg stance on trampoline, ball throws, different directions (front, back, and sideways),
– single leg stance on balance mat, ball throws,
– step-up on wobble board.

**Phase 3: Muscle Strength Phase**
*Weeks 9–12*
Goal: Increasing muscle strength.
Exercises:
– single leg stance with weights, eyes closed,
– single leg stance on wobble board, eyes closed,
– squats on wobble board,
– squats with weights, improving knee flexion (Fig. 9),
– lunges with weights, enhancing knee flexion,
– step-up with weights, increasing heights and weights.

**Fig. 9.** Squat with weight

**Phase 4: Running Phase**

*Weeks 13–16*

Goals: Starting a running program following positive testing results on Biodex system; controlling jumps, both legs; controlling jumps with turns on trampoline, both legs.

Exercises:

- running on treadmill,
- running or jogging outdoors,
- jump training: both legs, trampoline, increasing knee flexion (Fig.10).


**Fig. 10.** Two-legged jumps on trampoline

**Phase 5: Jumping and hopping Phase**

*Weeks 17–19*

Goals: Running sideways and backwards; controlling two-legged jumps on flat and even surface; controlling hops for distance; controlling jumps on steps.

Exercises:

- running backwards,
- hop for distance,
- jumps: two-legged, 180-degree turns, flat, even surface,
- jumps: stair jumping,
- running: figure-of-eight, stop-turn-run,
- agility drills, slow speed.

**Phase 6: Plyometric and Agility Training Phase**

*Weeks 20–24*

Goals: Controlling single leg jumps; controlling vertical jumps; controlling sport-specific activities.

Exercises:

- single leg jumps, trampoline,
- single leg jumps, balance mat,
- single leg jumps (forward, backward, sideways on flat and even surface),
- vertical jumps,
- scissors jumps,
- series of jumps: 6–8 2-legged jumps (Fig. 11); 2-legged jumps down a step, then vertical jump,

Sport-specific tasks are introduced during the agility training depending on the kind of sport the patients may return to.

**Fig. 11.** Series of jumps

**Final testing**

About 24 weeks after the beginning of the rehabilitation program, patients underwent final testing to evaluate their capacity to begin sport activities.

The criteria the patients had to accomplish were as follows:

- range of motion equal to that in uninvolved leg,
- completed progressive running program,
- the difference in the muscle strength is equal to or less than 15% (Biodex testing),
- positive results of functional tests:
  - single leg speed jumps (10 m distance),
  - single leg hop for distance,

- squat with 50 kg on Smith machine (number of repetitions),
- single leg speed bench jumps,
- single leg jump on dynamometric platform.

## RESULTS

Negative results signify that the operated limb is stronger than the uninvolved one. In the muscle strength test carried out after 3 months, 5 people exhibited a large deficit in extensor strength. It exceeded 30% and resulted in the running program delay and rehabilitation process extension. After 6 months, the difference in extensor muscle strength exceeding 15% was noted in 3 people. After 6 months, 1 person manifested the difference in flexor muscle strength exceeding 15% with a speed of 90°/s and 6 patients with a speed of 240°/s. Average results indicate that muscle strength for all muscle groups was reduced by 10% between the 3rd and the 6th month (Tab. 1).

**Tab. 1.** Difference in muscle strength after 3 and 6 months following ACL reconstruction [%]

| No | Sex | Difference in muscle strength after 3 months (180°/s) | | Difference in muscle strength after 3 months (300°/s) | | Difference in muscle strength after 6 months (90°/s) | | Difference in muscle strength after 6 months (240°/s) | |
|---|---|---|---|---|---|---|---|---|---|
| | | extensors | flexors | extensors | flexors | extensors | flexors | extensors | flexors |
| 1. | M | 31.3 | 1.6 | 44.1 | 9.2 | 14.3 | -9.2 | 19.5 | 5.4 |
| 2. | M | 11.5 | 1.2 | 13.8 | 15.2 | 16.9 | -9.3 | 12.8 | 8.4 |
| 3. | W | 25.3 | 10.5 | 1.5 | 10.9 | 10.9 | 16.8 | 17.6 | 16.7 |
| 4. | W | 17.9 | 7.4 | 35.7 | 17.9 | 4.4 | 6.1 | 3.8 | -0.1 |
| 5. | W | 17.3 | 16.0 | 7.0 | -5.5 | 2.7 | -5.7 | -0.2 | -2.4 |
| 6. | M | 13.6 | 4.8 | 16.6 | 20.4 | 3.0 | 1.1 | 3.3 | 4.2 |
| 7. | M | 13.9 | 2.4 | 9.0 | 14.3 | 11.0 | 3.4 | 13.3 | 12.1 |
| 8. | M | 7.1 | 8.7 | 13.5 | 22.9 | 4.1 | 2.5 | -2.3 | 9.3 |
| 9. | M | 1.6 | 8.1 | 15.3 | 11.0 | 2.1 | 6.0 | 3.2 | -4.7 |
| 10. | W | 11.3 | 11.6 | 14.5 | 7.8 | 1.6 | -2.5 | 7.3 | 6.4 |
| 11. | M | 7.5 | 0.1 | 14.2 | 15.5 | 13.7 | -10.4 | 5.3 | 22.5 |
| 12. | M | 11.1 | 22.6 | 4.2 | 16.9 | -9.9 | 6.3 | -7.6 | 0.6 |
| 13. | M | 18.9 | 6.0 | 38.8 | 15.5 | -2.5 | 6.5 | 4.6 | -13.7 |
| 14. | W | 16.6 | 25.8 | 27.1 | 14.3 | 5.1 | 1.5 | 3.1 | 20.8 |
| 15. | M | 34.4 | 19.6 | 22.2 | 12.0 | 22.8 | 12.5 | 24.7 | 18.3 |
| 16. | M | 2.5 | 22.7 | 8.5 | 16.0 | -6.3 | 15.0 | 7.6 | 16.1 |
| 17. | M | 6.9 | 0.8 | 6.2 | 12.7 | 2.0 | -1.6 | -4.5 | 23.1 |
| 18. | M | 27.2 | 10.9 | 37.6 | 0.0 | 3.5 | -11.7 | 11.7 | -9.9 |
| 19. | Average | 15.3 | 10.0 | 18.3 | 12.6 | 5.5 | 1.5 | 6.8 | 7.4 |
| 20. | SD | 9.4 | 8.2 | 13.0 | 6.8 | 8.2 | 8.6 | 8.5 | 11.0 |

## DISCUSSION

On the basis of conducted research concerning muscle strength on Biodex after 3- and 6-month periods following ACL reconstruction, it can be concluded that early, as well as physician and physiotherapist controlled rehabilitation consisting of the quickest beginning of mobility and gradual straining of the operated limb, does not have a negative influence on ACL graft and does not lead to its weakness. Acting according to the aforementioned protocol eliminates the negative results of immobilization such as: stiffness of the graft, muscle atrophy (especially of the quadriceps femoris muscle) and anterior knee pain, occurring as complications [2]. The possibility of starting the running program after only 3 months, thanks to muscle strength testing performed on Biodex, speeds up patients' recoveries with respect to their daily functioning and physical activities without the risk of graft damage. However, it should be also mentioned that the proposed treatment can be carried out only when a given patient has been properly prepared before ACL reconstruction. Such a preparation usually lasts a few weeks, but following reconstruction it then speeds up a patient's recovery in the first rehabilitation stage and positively affects a patient's psyche. In addition, muscle strength should be used as indicator rather than muscle mass measurement, because thigh sizes of many patients following ACL reconstruction do not become comparable in both legs, even after a year of treatment, whereas muscle strength is comparable to a healthy leg. The strength measurement allows for a more accurate evaluation of a patient's current condition [9].

## CONCLUSIONS

1. An early implementation of the Norwegian rehabilitation program speeds up a patient's recovery with respect to normal functioning. It may be achieved by enhancing muscle strength reconstruction.
2. Patients rehabilitated according to the abovementioned program were able to begin a suitable physical activity as early as 6 months following ACL reconstruction.
3. The straining stage began early makes a patient's full recovery quicker and, according to the conducted research, decreases the difference in muscle strength between an operated upon and healthy limb.
4. Rehabilitation based on early and gradual straining diminishes the artrofibrosis risk, as well as bone mass and muscle strength loss.

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*CASE STUDY*

# EPIDERMOID CYST OF THE CRANIOVERTEBRAL JUNCTION – A CASE REPORT

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## ABSTRACT

**Introduction.** An epidermoid cyst (EC) is a congenital, benign, and nonifiltrating tumor which originates from the central nervous system (CNS) as a result of neural tube defects (NTD). The presence of lesion may cause CNS symptoms by means of mass-effect, when compressing the adjacent structures, or rupture and secondary aseptic inflammatory process. Within the CNS, EC is most frequently located in: pontocerebellar angle, suprasellar region, posterior cranial cavity, and spinal canal. The clinical symptoms can be general, like headache or dependent on the lesion location: dizziness, nystagmus, damage to the cranial nerves within the pontocerebellar angle and brain stem, disturbed fields of vision, and epileptic seizures. Magnetic resonance imaging (MRI) allows for visualizing the lesion which is shown as a heterogenic iso- or hypointense mass in relation to the cerebrospinal fluid. Using diffusion weighted images (DWI) is a helpful tool in differentiating tumor mass from cerebrospinal fluid. In computed tomography (CT) scans, EC has the same or almost the same density as the cerebrospinal fluid which makes the image difficult to differentiate from an arachnoid cyst. Treatment of choice is to remove the lesion in a possibly complete spectrum. In asymptomatic patients or patients exhibiting a mild intensity of symptoms, it is possible to wait and observe which solution could be chosen.

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**Aim.** The aim of this paper was to present a case report concerning treatment of an EC located in the craniovertebral junction.
**Materials and methods.** A clinical management concerning a patient diagnosed and treated both in an outpatient clinic and in hospital at the departments of neurology and neurosurgery has been described.
**Case study.** A 69-year old female patient came to the Neurology Outpatient Clinic complaining of headaches, pain in her neck, and balance disturbances. These symptoms had intensified for 2 years. An MRI scan of the cervical spine revealed a large lesion in the posterior cranial cavity. An MRI scan of the head showed a multicystic tumor located in the posterior fossa in the projection of cerebellomedullary cistern, which did not undergo contrast intensification. The patient was treated surgically. Following surgery, headaches, pain in the neck as well as neurological symptoms subsided.
**Results and discussion.** Microsurgical removal of the lesion is the treatment of choice for EC. A total removal should be strived for, preferably en block, although leaving part of the cyst is not a mistake. Postoperative mortality may reach 8.9%, whereas recurrences amount to 4.5% during an 8-year long observation period. EC untreated surgically can, through dermal fistulas, cause bacterial meningitis. Thus, treatment limited to the observation of the lesions may pose a threat, and surgical treatment should be decided upon quickly.
**Conclusions.** Surgical treatment with the use of microscopic technique aided with neuromonitoring allows for removing tumors of the cholesteatoma type safely and radically.

**Key words:** epidermoid cyst (EC), brain tumor, craniovertebral junction

## INTRODUCTION

An epidermoid cyst (EC) was first reported in 1807, when Pinson, an artist in the School of Medicine in Paris, made a wax model of a small lesion located in the cerebellopontine angle. In 1829, Cruveilheir, a French pathologist, first recognized EC as a specific entity and called it "cholesteatoma" [3].

EC is a result of ectodermal structures being misplaced and appearing within the neural tube when it is being formed in the 3$^{rd}$–5$^{th}$ week of fetal development [10]. This lesion accounts for 0.2–1.8% of all intracranial tumors and less than 1% of intracanal tumors, with the incidence being similar in both sexes [10]. The first symptoms most often occur in the 4$^{th}$ decade of life. Frequently, however, such tumors are found during routine autopsies carried out due to other reasons [6].

Symptoms depend on tumor location, and involve: dizziness, nystagmus, features of damage to the cranial nerves (facial and vestibulocochlear), disturbed fields of vision, and epileptic seizures [2, 8, 9]. The symptoms usually progress slowly, but sudden and intermittent courses have been also reported [6]. Spontaneous, iatrogenic, or post-

traumatic damage to the cyst can lead to lymphocytic cerebrospinal meningitis, as a result of the cyst content penetrating into the subarachnoid space and inducing aseptic inflammatory reaction [8]. Imaging diagnostics involves computed tomography (CT) and magnetic resonance imaging (MRI). In a CT scan, EC is shown as isodense lesions in relation to the cerebrospinal fluid, which do not undergo contrast intensification. Consequently, the image is difficult to differentiate from that of an arachnoid cyst. MRI is recommended because of its being more significant in differential diagnosis of arachnoid cyst [2, 3]. MRI shows EC as a heterogenic hypointense lesion (similar to the intensity of the cerebrospinal fluid) on a T1-weighted image, which does not undergo contrast intensification, and is usually of a hyperintense signal on a T2-weighted image. Diffusion weighted imaging sequence in which EC is hyperintense can be helpful in differentiating the tumor from the cerebrospinal fluid surrounding it and from nonspecific CNS lesions [1, 9]. In rare cases metrizamide cisternography is also used since it allows for differentiating a tumor capsule [3, 5].

Treatment of choice involves surgical removal of the lesion. It must be performed very carefully so that the content of the cyst does not penetrate into the subarachnoid space and brain tissue [3]. In asymptomatic patients or patients with single, stable symptoms, observation is recommended in order to detect the appearance or development of clinical symptoms, and their possible intensification, before deciding on surgical treatment [4]. This paper describes the rare location of a tumor in the craniovertebral junction, which is pressing against the brain stem and cerebellum.

## AIM

The aim of this paper is to present a case report concerning treatment of an EC located in the craniovertebral junction.

## MATERIALS AND METHODS

A clinical management concerning a patient diagnosed and treated both in an outpatient clinic and in hospital at the departments of neurology and neurosurgery has been described.

## CASE STUDY

A 69-year old female patient came to the Neurology Outpatient Clinic complaining of headaches, pain in her neck, and balance disturbances. X-ray of the cervical spine revealed degenerative changes. Neurological examination confirmed a stiff neck, disturbances in alternating movement, upper limbs dysmetria, positive Romberg's sign with closed eyes.

An MRI scan of the cervical spine revealed a large lesion in the posterior cranial cavity (Fig. 1, 2), whereas an MRI scan of the head showed a multicystic tumor, measuring $39 \times 30 \times 24$ mm, located in the posterior fossa in the projection of cerebellomedullary cistern. Its signal was similar to that of the cerebrospinal fluid and did not undergo contrast intensification. The tumor compressed the medulla and the initial section of the

cervical spinal cord, and pressed them against the dens of the epistropheus. From the bottom, it also pressed against cerebellar hemispheres, especially the left one. Features of infiltration and brainstem or medulla oblongata edema were not detected (Fig. 3, 4).

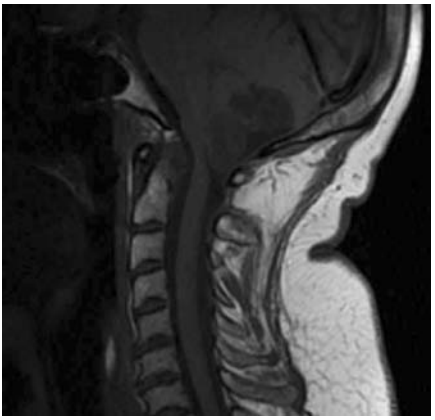

**Fig. 1.** Sagittal T1-weighted MRI scan of the cervical spine showing a cyst at the craniovertebral junction

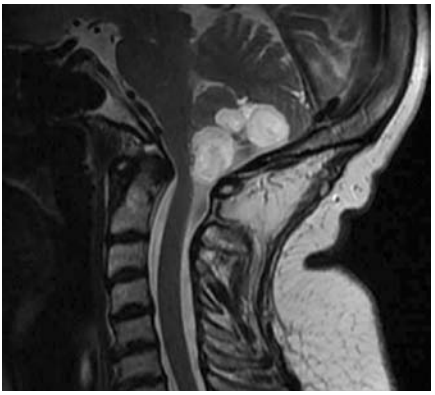

**Fig. 2.** Sagittal T2-weighted MRI scan of the cervical spine showing a cyst at the craniovertebral junction

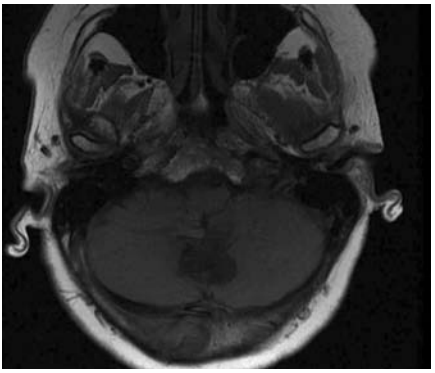

**Fig. 3.** Axial T1-weighted MRI scan of the head showing a cyst

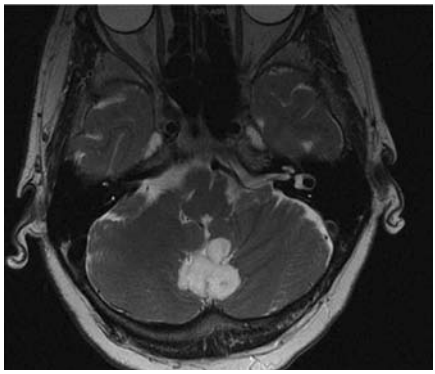

**Fig. 4.** Axial T2-weighted MRI scan of the head showing a cyst

The patient was qualified for surgical treatment. Suboccipital craniectomy was performed in the sitting position, with the use of neuronavigation and with the aid of intraoperative monitoring of: somatosensory evoked potentials and motor evoked potentials of the pyramidal tracts, cranial nerve nuclei, and auditory evoked potentials. No complications were observed postoperatively. In a follow-up CT scan of the head no features of the tumor were detected (Fig. 5). The histopathological test detected *cholesteatoma* (Fig. 6). The patient was discharged on the 7$^{th}$ day following surgery, in an improved condition. During a control examination performed 1 month following surgery, regression of all the previous symptoms: headaches, pain in the neck and neurological symptoms, was observed.

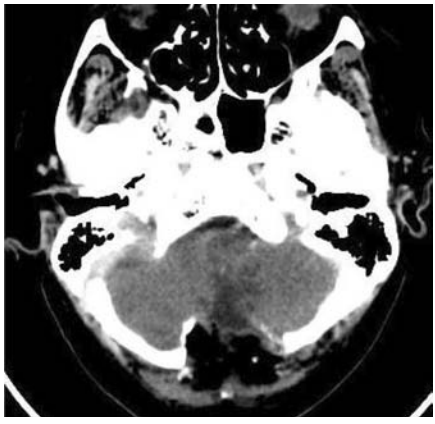

**Fig. 5.** CT scan of the head after the operation, 1$^{st}$ day, showing no features of a cyst

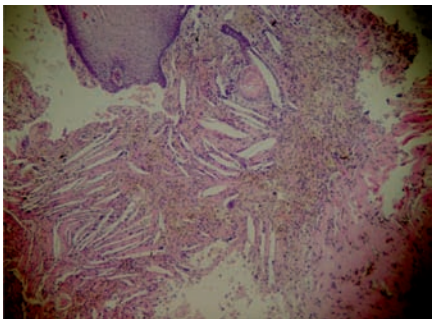

**Fig. 6.** Microscopic image of *cholesteatoma* (EC) – wall lined with keratinized stratified squamous epithelium, in the center keratinized mass, cholesterol crystals and elements of granulation tissue [HE, magn. 40×]

## RESULTS AND DISCUSSION

EC are generally found extracerebrally and show a strong tendency toward a cranial base location [1]. They are most frequently observed in the regions of the craniovertebral junction and hypophysis [1, 2, 4, 6–8, 10]. The cyst's wall is lined with stratified squamous epithelium embedded in collagen, whereas the content consists of desquamated epithelium rich in cholesterol crystals, and macroscopically looking like a pearl mass (hence EC is called *cholesteatoma*) [1, 3]. In 10% of intracranial epidermal cysts, calcifications are observed resulting from the saponification of the cyst content [1].

Tumors show a tendency for focal hyperplasia and require surgical treatment. Microsurgical removal of the lesion is the treatment of choice for EC. A total removal should be strived for, preferably en block, although leaving part of the cyst is not a mistake [3, 5, 7]. Postoperative mortality may reach 8.9%, whereas recurrences amount to 4.5% during an 8-year long observation period [3]. Aseptic meningitis is detected in approximately 20% of patients. EC untreated surgically can, through dermal fistulas, cause bacterial meningitis. Thus, treatment limited to the observation of the lesions may pose a threat, and surgical treatment should be decided upon quickly [4, 7, 10].

## CONCLUSIONS

With respect to EC, modern neurosurgical techniques, such as microsurgical techniques aided with a surgical microscope and intraoperative neuromonitoring, enable physicians to remove large lesions of adverse locations safely, irrespective of the patient's age.

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*CASE STUDY*

# NEW SYMPTOMS IN A PATIENT WITH DIAGNOSED PORPHYRIA – UNTYPICAL CLINICAL COURSE OR ANOTHER DISEASE? EXTENDED DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS

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**ABSTRACT**

**Introduction.** Acute liver porphyrias are caused by mutations of genes encoding the heme biosynthesis enzymes. A lack of any of these enzymes leads to a decrease in the heme level, which in each case is manifested by identical clinical symptoms. Nervous tissue is particularly susceptible to a depletion of heme levels. Three classical symptoms of a porphyria attack include: abdominal pain (as a manifestation of autonomic neuropathy), peripheral neuropathy, and psychic disturbances. Apart from the main symptoms, porphyria attacks may be manifested as various neurological disturbances, such as: bulbar palsy, epileptic seizures, psychic disturbances and focal symptoms of CNS damage. The intensity of individual symptoms can vary. Although neurological symptoms usually disappear after the attack, they may cause permanent deficits. Through involving CNS, porphyria can mimic other neurological disorders. Damage to the nervous system can be confirmed by additional examinations. Thus far, disseminated focal changes during the attack, which disappear after the regression of clinical symptoms, have been described in magnetic resonance imaging (MRI) scans of the brain. Spinal cord abnormalities in MRI scans have not been described yet, despite the fact that damage to the anterior horn associated with porphyria has been confirmed in literature. While examining cerebrospinal fluid during the attack, an elevated protein level has been noticed, so far without the presence of oligoclonal bands.

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**Aim.** This paper aimed to demonstrate that porphyria should be considered in differential diagnosis of clinically isolated syndrome (CIS) and multiple sclerosis (MS).
**Materials and methods.** This paper is based on the case of a symptomatic patient who carried a mutation in one of the genes for porphyria, and who developed a clinical manifestation of focal damage to CNS. A differential diagnosis of porphyria and CIS, with a subsequent conversion to a clinically defined MS, was carried out. The results of additional examinations performed routinely in both disorders, the clinical picture and data from medical literature have been used in the analysis of this case.
**Case study.** The authors present the case of a patient with confirmed genetic porphyria, who was hospitalized for purposes of establishing a diagnosis due to weakened lower extremities. The patient manifested spastic lower extremity paresis, sensation disorders and urinary incontinence, which indicated spinal cord damages. An MRI scan of the thoracic spine revealed disseminated foci with contrast enhancement. A high level of proteins and oligoclonal bands were detected in the cerebrospinal fluid. On the basis of a new clinical picture (differing from the previous attack symptoms), prolonged symptoms, spinal cord lesions in MRI, and the presence of oligoclonal bands, CIS was diagnosed. Quick and complete recovery was obtained due to the administering of a steroid therapy. After several months, the patient reported a similar, passing episode, which, according to the authors, confirmed the diagnosis and an expected conversion to a clinically defined MS.
**Results and discussion.** Taking into consideration the clinical manifestation of spinal cord involvement untypical of porphyria, the detection of spinal lesions in an MRI scan, the presence of oligoclonal bands in the cerebrospinal fluid and the positive effect of steroid therapy, the authors believe that this described patient, who was a symptomatic carrier of a mutation in a gene for porphyria, developed CIS.
**Conclusions.** This reported case, supported by data from medical literature, shows that porphyria should be taken into consideration in any differential diagnosis of CIS and MS.

**Key words**: porphyria, clinically isolated syndrome (CIS), multiple sclerosis (MS)

## INTRODUCTION

Acute liver porphyrias are a group of genetically conditioned congenital diseases involving disturbances in the heme biosynthesis pathway. Mutations of the encoding genes lead to a decreased activity of the heme synthesis enzymes. The biosynthesis occurs in several stages, yet a decrease in the activity of any of these enzymes leads to, through elevated levels of substrates (delta-aminolevulinic acid, porphyrobilinogen, porphyrins) and a depletion of heme levels, identical clinical manifestations [11]. Three classical symptoms of

a porphyria attack include: abdominal pain (as a manifestation of autonomic neuropathy), peripheral neuropathy, and psychic disturbances. Apart from the main symptoms, porphyria attacks may be manifested as various CNS-induced neurological syndromes, such as: bulbar palsy, epileptic seizures, posterior reversible encephalopathy syndrome (PRES). This multiplicity of neurological symptoms stems from the fact that nervous tissue is particularly susceptible to a depletion of heme levels [15]. The intensity of individual symptoms is variable, which frequently delays a correct diagnosis. Because porphyria involves the central and peripheral nervous systems, it can mimic other neurological disorders, including multiple sclerosis (MS) [14]. Damage to CNS can be confirmed by the abnormal results of additional examinations. Disseminated demyelinating lesions detected in a magnetic resonance imaginig (MRI) scan during an attack, which disappeared after the regression of clinical symptoms [1, 3, 9, 12], or resulted in permanent deficits [7] have been described. Demyelinating foci are found in patients between their porphyrias attacks, as well as in asymptomatic carriers of a mutated gene [10]. Abnormalities are also detected in cerebrospinal fluid examinations [2, 4, 10].

## AIM

This paper aimed to demonstrate that porphyria should be considered in differential diagnosis of clinically isolated syndrome (CIS) and multiple sclerosis (MS).

## MATERIALS AND METHODS

This paper is based on the case of a symptomatic patient who carried a mutation in one of the genes for porphyria, and who developed a clinical manifestation of focal damage to CNS. Differential diagnosis of porphyria and CIS, with a subsequent conversion to a clinically defined MS, was carried out. The results of additional examinations performed routinely in both types of disorders, and the clinical picture and data from medical literature have been used in the analysis of this case.

## CASE STUDY

A 29-year old patient was admitted to the Department of Neurology for purposes of establishing a diagnosis of strength weakness and lower limbs disability that had been present for 2 months, as well as urinary incontinence and sexual function disturbances. According to the patient, these symptoms appeared suddenly, and exacerbated rapidly within 2 days. Thus, he reported to the Outpatient Clinic of Neurology. When lower extremity paresis was detected during the neurological examination, the patient was referred to undergo MRI of the cervical and thoracic spine. These performed scans showed numerous foci in both sections of the spinal cord, which where hyperintense on T2-weighted images and isointense on T1-weighted images, and intensified after contrast medium administration. In the opinion of the radiologist describing the MRI scans, the images were not definite.

In his childhood, the patient was diagnosed with hereditary coporphyria, confirmed by DNA tests involving both him and the members of his family. He then manifested elevated levels of coporphyrin, uroporphyrin, 5,6,7-COOH porphyrin, and delta-aminolevulinic acid in the urine as well as a high level of coporphyrin I in the feces. Following an advised diet and avoidance of banned substances allowed the patient to achieve long-lasting intervals between porphyria attacks, which appeared every few years. The last episode had occurred a year before. Attacks were manifested typically as abdominal pain and a general weakness. Before the aforementioned problems appeared, the patient had not experienced any symptoms which might have suggested damage to CNS.

During the neurological examination performed on admittance to the Department, the following symptoms were detected: spastic lower extremity paresis, more intense in the right one, with exaggerated knee-jerk and ankle-jerk reflexes, and Babinski's sign on the right side, gait assisted with elbow crutches, lack of abdominal reflexes, left-sided hypesthesia beginning at the Th 8 level of the spinal cord downwards, and urinary incontinence.

Lumbar puncture was performed in the department. A high protein level – 126 mg% (norm ranges from 20–40 mg%) and the presence of oligoclonal bands type III were detected in the cerebrospinal fluid. This, according to the standards of the Charcot Foundation, confirmed intrathecal IgG synthesis. Other parameters of the cerebrospinal fluid were normal. The levels of anti-*Borrelia burgdorferi* and tick-borne encephalitis antibodies were low. An EMG examination excluded polyneuropathy. Visual evoked potentials (VEP) were normal. Due to technical reasons, an MRI scan of the head was not performed.

Considering the medical history, neurological symptoms and results of additional examinations, CIS was diagnosed. The patient received oral corticosteroids (Encorton) 60 mg/ 24 hours – unlike Solumedrol, this medication is allowed in porphyria. Physical rehabilitation was introduced. A significant improvement of gait efficiency and sphincter muscles function was achieved. The patient was discharged after 2 weeks of hospitalization, walking independently, without objective features of paraparesis. He was advised to continue therapy with Encorton, 60 mg/ 24 hours, reduced by 5 mg each day, and Ditropan, 3 × 5 mg. The patient returned to work abroad. 9 months later he informed medical personnel via a telephone call about the recurrence of the symptoms, of a lower intensity, which regressed without treatment after 2 weeks. The patient did not manifest symptoms typical of a porphyria attack, at this time. According to the attending physicians, this situation confirmed the correctness of the initial diagnosis, and the conversion of CIS to a clinically defined MS.

## RESULTS AND DISCUSSION

The case described therein served as a starting point for the attending physicians to consider the original cause of the symptoms and problems, and any abnormalities

detected in the performed additional examinations. The presence of porphyria, a disorder which can potentially involve CNS, necessitated a careful differential diagnosis and cautiousness when diagnosing a new disease.

The clinical picture was not typical of a porphyria attack. The most frequent symptoms of such an attack involve abdominal pain (in more than 95% of patients), tachycardia (80%), dark urine (about 75%) [2]. Symptoms of CNS being involved are observed in about 10% of patients [2, 16]. Such an attack can develop even over a few days and manifest new symptoms in time. Gurses et al. [7] have discussed the case of a patient who, after abdominal pain and dysuria lasting a week, developed symptoms of encephalopathy along with cortical blindness and quadriparesis. In this case, an attack resulted in permanent residual symptoms. Features of PRES are more frequently observed, when after the regression of a porphyria attack no abnormalities in the neurological examination have been found [1, 3, 9, 12]. Thus far, no symptoms of damage to the spinal cord have been reported. In the case described herein, these symptoms progressed, yet without changing their form. Stereotypical abdominal pain and weakness experienced previously were absent, whereas the symptoms of spastic paraparesis, due to their location, indicated damage to the spinal cord.

A performed MRI scan does not allow for establishment of a definite diagnosis. Many studies, already referred to, describe the presence of T2-weighted hyperintense disseminated foci. Such lesions have been detected both during porphyria attacks, and in interval periods. Aggarwal [1] has described the case of a woman who developed consciousness disturbance, and features of damage to her brain stem during an attack. An MRI scan showed disseminated foci which were hyperintense on T2-weighted images, and intensified after contrast medium administration. They were located along the gyrus both in the white and gray matter. After the administered treatment, a complete regression of the described abnormalities was observed in the follow-up MRI. However, most frequently, a porphyria attack is associated with reversible lesions typical of PRES with respect to their locations [3, 9, 12]. Bylesjö [4], when examining a group of 16 carriers of a mutation in a gene for acute intermittent porphyria, who were in an interval period between attacks, or in whom the disease had not yet revealed itself, detected in 2 persons hyperintense lesions on T2-weighted images, which were disseminated in the subcortical and periventricular white matter. One of these patients, with numerous documented attacks, had been treated for arterial hypertension for many years, which complicated the interpretation of the scan result. The other patient, apart from porphyria, did not have other comorbidities. Although changes involving loss of neurons with nuclear chromatolysis in anterior horn cells of the spinal cord have been documented in histopathological tests [6, 8], thus far lesions detectable in the spinal cord MRI scan during or between attacks have not been reported.

Both in the case of MS, and during porphyria attacks, abnormalities in the cerebrospinal fluid are observed. However, it is generally believed that in porphyria levels

of protein are usually normal or slightly elevated. Latorre and Munoz [13] analyzed 37 patients during porphyria attacks. Elevated levels of protein in the fluid were assayed in 21 patients (67%). Such a tendency is not observed between the attacks. Bylesjö detected only 1 case with a slightly elevated protein level in 16 carriers of the mutated gene. In the disease entity discussed herein, cases of significantly elevated levels of proteins in the cerebrospinal fluid have not been reported thus far. The presence of oligoclonal bands has been described only in patients with synchronous MS and porphyria [4].

## CONCLUSIONS

Taking into consideration the clinical manifestation of spinal cord involvement untypical of porphyria, the detection of spinal lesions in an MRI scan, the presence of oligoclonal bands in the cerebrospinal fluid and the positive effect of steroid therapy, the authors believe that this described patient, who was a symptomatic carrier of a mutation in a gene for porphyria, developed CIS. The criteria for recognizing CIS were met – the first clinical episode of focal damage to CNS and lesions detected in the MRI scan. Some doubts could have arisen from a very rare likelihood of two comorbidities: genetic, and so certain confirmation of porphyria, elevated levels of protein in the cerebrospinal fluid also found in porphyria, and a variety of untypical manifestations of phorphyria reported in literature. The patient's further history, with a recurrence of the disease's symptoms indicates, in our opinion, a transformation to a clinically defined MS.

This reported case, supported by data from medical literature, shows that porphyria should be taken into consideration with respect to the differential diagnosis of CIS and MS.

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*CASE STUDY*

# PARANEOPLASTIC LIMBIC ENCEPHALITIS – A CASE REPORT

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**ABSTRACT**

**Introduction.** Paraneoplastic neurological syndromes (PNS) refer to a diverse group of nervous system disorders associated with tumors. They are not directly caused by a tumor's immediate expansion, compression resulting from it, infiltration or anti-cancer treatment. Their pathomechanism involves damage to the nervous system as a result of the organism's immune response directed against cancer antigens, and also against antigens occurring physiologically in the nervous system. Onconeural antibodies and cytotoxic T lymphocytes are responsible for the immune response. These conditions are quite rare – fewer than 1 person out of 100 patients suffering from cancer develops PNS. They often precede a direct manifestation of cancer. The best known PNS conditions include: Lambert–Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration, and polyneuropathies. PNS was identified for the first time in 1949. Nowadays, the criteria established in 2004 by Graus et al. have been followed in diagnostics. These define the conditions for arriving at a possible and definite diagnosis based on the presence of a characteristic neurological syndrome, the presence of onconeural antibodies, and detecting neoplasm before or after the manifestation of neurological symptoms. Diagnosis is difficult due to the lack of laboratory markers (onconeural antibodies are present in serum only in 50–60% of cases) or direct cancer symptoms in the first phase of the disease.

**Aim.** This paper aimed at recounting the existence of a very rare neurological syndrome, limbic encephalitis, which can develop in the course of a neoplastic disease. Awareness of PNS and detecting neoplasm before its direct clinical manifestation can contribute to a better prognosis for patients.

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**Materials and methods.** This paper is based on a case analysis concerning a patient manifesting symptoms of the limbic system involvement. The medical history has been interpreted, additional examination results have been analyzed, and the developing clinical manifestations have been investigated.
**Case study.** The presented patient is a 45-year old man in whose case limbic encephalitis exceeded detecting abdominal cancer by a year. Diagnostic difficulties were caused by a synchronous pituitary microadenoma and hormonal disturbances involving cortisol and prolactin, which suggested Cushing's syndrome. The main clinical symptoms, intensifying in time during the course of the disease lasting several months included: recent memory disturbances, allopsychic disorientation, depression, and periodical aggression.
**Results and discussion.** Conducted serum tests to screen for onconeural antibodies did not confirm their presence. However, a magnetic resonance imaginig (MRI) scan revealed bilateral hippocampal damage. On the basis of a typical clinical syndrome, and cancer identified after a year following the occurrence of the symptoms, a definite, according to Graus' criterion, diagnosis of PNS was established.
**Conclusions.** Awareness and knowledge of PNS contributes to an early diagnosis and detection of cancer. This creates an opportunity to introduce adequate treatment and improves the prognosis for the patient.

**Key words:** paraneoplastic neurological syndrome (PNS), paraneoplastic limbic encephalitis (PLE), abdominal cancer

## INTRODUCTION

The term "paraneoplastic" was first used by Guichard who analyzed cases of patients who manifested features of nervous system involvement, yet their autopsies did not detect metastases to the brain or spinal cord [10]. Reports of similar cases had appeared much earlier, and the first known publication concerning this problem dates back to 1890. Auché [2] described a patient with a neoplasm who manifested symptoms of polyneuropathy.

Pathophysiology of paraneoplastic neurological syndrome (PNS) involves immune system response to the presence of oncogenes, proteins in the tumor cells. Physiologically identical or similar proteins are also present in the nervous system, yet thanks to the blood-brain barrier, they are inaccessible for the cells of the immune system. When a neoplasm develops, due to the circulating cytokines this barrier becomes less tight for onconeural antibodies and cytotoxic T (Tc) lymphocytes circulating in the serum. It is believed at present that Tc lymphocytes are primarily responsible for nervous tissue damage. This is confirmed, among others, by a lack of onconeural antibodies in a majority of syndromes [12].

PNS is a rare clinical condition associated with a neoplastic disease, co-occurring with the neoplasm in less than 1% of cases [17]. Some neoplasms, however, more often induce neurological symptoms than others. These include: small cell lung cancer, thyroid cancer, ovarian cancer, and breast cancer; the incidence of PNS in the course of such cancers is estimated to range from 10–15% [4, 13, 15, 18, 21]. Neurological syndromes frequently precede direct manifestation of the neoplasm itself, since a small amount of neoplastic tissue is sufficient to induce an immune response.

In 2004, Graus et al. established the criteria for recognizing PNS [9]. These experts divided PNS into typical, consisting of: encephalitis, myelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus myoclonus syndrome, subacute sensory neuropathy, chronic intestinal pseudo-obstruction, Lambert–Eaton myasthenic syndrome, dermatomyositis and other, untypical ones, such as: paraneoplastic retinopathy, subacute necrotizing myopathy, motor neuron syndrome, demyelinating neuropathies, neuropathies with axonal loss, neuromyotonia, and polymyositis. A panel of the so-called well-characterized onconeural antibodies (of the highest specificity) was established. The following antibodies were included in it: anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, and anti-amphiphysin. PNS diagnosis is definite if one of the following situations occurs:

- neurological syndrome typical of PNS (classical) and neoplasm recognized within 5 years,
- untypical neurological syndrome, which regresses or improves after neoplasm treatment without concurrent immunotherapy, spontaneous remission of the tumor being excluded,
- untypical neurological syndrome with determining (or without) the presence of onconeural antibodies and diagnosing neoplasm within 5 years,
- neurological syndrome (typical or untypical) with well characterized onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, and anti-amphiphysin), but without the presence of neoplasm.

If a definite diagnosis cannot be established, but a typical neurological syndrome without the presence of the neoplastic process and onconeural antibodies, but with a high-risk of developing neoplasm is observed, or a neurological syndrome (typical or untypical) with only partially characterized onconeural antibodies and no neoplasm is detected, a diagnosis called possible is established. Such a diagnosis may be also established retrospectively, if an untypical neurological syndrome without antibodies is observed and the neoplasm is detected within 2 years.

The term "limbic encephalitis" was first used by Corsellis in 1968 [3]. This condition is rare. It is estimated that it develops in only 1 person out of 10 thousand patients with neoplasm [5]. The limbic system – the term introduced by Brock – is a set of structures that lies around the diencephalons, creating a ring (*limbus*) that

includes: the hippocampus, amygdala, perirhinal cortex, fornix, mammillary bodies, thalamus, and hypothalamus. It is responsible for the creation of emotions and for interpreting external and internal stimuli [8]. A clinical picture of paraneoplastic limbic encephalitis (PLE) is dominated by behaviors stemming from increasing mood and personality disturbances. A quick progression of dementia and the occurrence of delirium are observed, depression develops and epileptic seizures appear [11, 19, 20]. Diagnosis is usually difficult because similar symptoms can be manifested as a result of the development of a neoplasm and also in the course of other diseases – toxic and metabolic encephalopathies, viral encephalitis, Hashimoto's encephalopathy [6]. Diagnosis is also difficult due to a lack of laboratory markers concerning this disease, whereas symptoms usually precede the appearance of neoplasm. Initially, computed tomography (CT) and magnetic resonance imaging (MRI) usually show normal structures [16]. Pleocytosis may be evident in the cerebrospinal fluid [19]. The electroencephalogram (EEG) result is neither typical nor pathognomonic. In some patients EEG result is normal even when epileptic seizures occur. Slowing down the basic rhythm or slow wave clusters have been described both in patients with clinical epileptic seizures (also during inter-seizure periods), and without such seizures [7]. The frequency of occurrence of onconeural antibodies in patients with PLE has not been examined [11]. In many patients it is not possible to detect them. At present, the sensitivity of testing for onconeural antibodies in determining paraneoplastic etiology of a neurological syndrome is estimated to be 50–60% [14, 22].

## AIM

This paper aims at recounting the existence of a very rare neurological syndrome, limbic encephalitis, which can develop in the course of a neoplastic disease. Awareness of PNS and detecting neoplasm before its direct clinical manifestation can contribute to a better prognosis for patients.

## MATERIALS AND METHODS

This paper is based on a case analysis concerning a patient manifesting symptoms of the limbic system involvement. The medical history has been interpreted, additional examination results have been analyzed and the developing clinical manifestations have been investigated.

## CASE STUDY

The patient, A.K., 45-years old, higher education, employed previously as a tourist guide, unemployed preceding becoming ill (he resigned from his job a few months earlier because of a growing feeling of tiredness and lowered mood lasting half a year), was admitted in June 2009 to an Emergency Department due to a sudden loss of consciousness which happened for the first time in his life, associated with

generalized convulsions, as observed by witnesses. Laboratory tests detected glicemia within a range of 400 mg%, thus the patient was hospitalized at the Department of Diabetology with a preliminary diagnosis of a newly discovered diabetes with a symptomatic epileptic seizure. During the following diagnostic procedures, elevated levels of adrenocorticotropic hormone (ACTH) and cortisol were discovered. An MRI scan revealed pituitary microadenoma. A CT of the chest and abdominal cavity did not detect abnormalities apart from features of liver steatosis. Because of evident dejection, the patient was consulted by a psychologist. He was discharged with a diagnosis of pituitary microadenoma and suspicion of Cushing's syndrome, severe obesity, diabetes, arterial hypertension, epileptic disorders to further diagnostics, and suspicion of masked depression. Despite the ordered treatment, the patient complained of poor well-being, progressing general weakness, and lowered mood. Due to those complaints, he was admitted after a few weeks to the Clinic of Endocrinology. Because the hormonal markers assayed again were normal, a definite diagnosis of Cushing's syndrome was not established. The patient was advised to take antidepressants and report for a follow up visit after 3 months. In August 2009, the patient reported episodes of sudden stupefaction, preceded by olfactory sensations occurring every few days and loss of contact, without falling down. Due to these symptoms, he was hospitalized in the Department of Neurology. An EEG detected seizure-related lesions, especially prominent in the temples, and a slightly slower bioelectric activity. A temporal lobe epilepsy was diagnosed. Antiepileptic treatment was introduced, initially with carbamazepine, and next, because of its poor tolerance, levetiracetam, resulting in a regression of seizures. After a few weeks of staying at home, his wife noticed gradually increasing symptoms involving disorientation with regards to time and place, associated with a growing helplessness, and periodic aggressive attacks directed at family members. Because of these symptoms, in November 2009, the patient was admitted to the Department of Psychosomatics. During hospitalization, the symptoms exacerbated. The patient was transferred to the Clinic of Psychiatry, where MRI spectroscopy was performed. This examination showed bilateral hippocampal damage. This resulted in diagnosing mesial temporal sclerosis. During hospitalization one generalized tonic-clonic seizure was observed. However, other cases of loss of consciousness were not excluded. The patient was transferred to the Clinic of Neurology for purposes of further diagnostics and determining antiepileptic medication dosage. During neurological examination performed on the day of admittance, recent and remote memory disturbances and low mood were noted. Video EEG was performed which showed bilateral lesions in frontal, central, and temporal areas, visible as slow sharp wave clusters. In the obtained cerebrospinal fluid a mild cytosis was detected and a slightly elevated level of protein; the levels of anti-*Borrelia burgdorferi* antibodies were normal. Tumor markers CA125, CA15-3, CA 19-9, CEA, and PSA in blood were also normal. A USG scan of abdominal cav-

ity did not show abnormalities. Epileptic seizures were not observed; the previously administered treatment was continued. Since then, the patient stayed at home looked after by his family. He periodically reported to the Outpatient Clinic of Neurology for control examinations. He also continued antiepileptic treatment. In April 2010, blood tests revealed a high level of prolactin (PRL). The patient was consulted by a neurosurgeon who ordered Parlodel. After the administered therapy the level of PRL normalized. However, an increase in the cortisol level was detected. Hence, a CT of the abdominal cavity was performed which showed a large tumor located intra-abdominally and in the hypogastrium, of undetectable origin, with metastases to the liver and lymph nodes. The patient was hospitalized in the Department of Neurology for further diagnostic purposes. The physical examination did not detect focal symptoms involving the central nervous system. A significant exacerbation of psychiatric symptoms was observed, associated with recent memory disturbances, alternate apathy and anger attacks, touchiness, lack of interest in the family, indifference to other people and events. Epileptic seizures were not observed. Blood was obtained to screen for onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, and anti-amphiphysin), and their presence was not detected. A pelvic CT scan, chest X-ray and testicular USG were performed. None of them detected abnormalities. An MRI of the head did not show metastases; an EEG showed changes in the posterior pole of the brain, typical of damage, and epileptic changes in the right temporal lobe. The patient was consulted by a surgeon. A percutaneous biopsy was carried out, which confirmed a neoplastic process, without specifying its origin. The levels of cortisol and PRL were normal. On the basis of the medical history and physical examination, as well the results of additional examinations, limbic encephalitis was diagnosed. Three weeks later, the patient died due to cancerous cachexia.

## RESULTS AND DISCUSSION

In the case described herein, epileptic seizure was the first detected symptom. Medical history indicates earlier emotional disturbances – job quitting, complaints of low mood. Seizures rarely precede other neurological symptoms, yet they can appear within 3 years before detecting the tumor [7]. The clinical picture was further complicated by the suspicions of Cushing's syndrome due to the detected pituitary microadenoma. Analyzing this case retrospectively, the authors believe that disturbances in the cortisol levels were symptomatic of PNS [17]. The leading clinical manifestations during the entire clinical course of the disease involved behavior and psychic disturbances. Imaging scans revealed mesial temporal sclerosis (hippocampus). Such lesions, unilateral or bilateral, have been reported in the course of PLE in some patients [1].

However, it was the detection of an infiltrating abdominal tumor, with suspicions of metastases to the lymph nodes and liver, which allowed for a connecting of all

previous neurological symptoms and the diagnosis of PLE. In the blood, the presence of antineuronal antibodies was not detected – tests were targeted at detecting anti-Ri, anti-Hu, anti-Yo, anti-amphiphysin, anti-CV2.1, and anti-PNMA2/Ta antibodies – although all of them can appear in this disease entity [7]. The lack of these antibodies does not undermine the diagnosis, however, since the clinical picture and the medical history meet Graus' criteria.

The following features support our diagnosis:

- quickly progressing loss of memory, epileptic seizures, psychic degradation indicating the limbic system involvement,
- meeting Graus' criteria – typical neurological syndrome preceded the appearance of the neoplasm by a year,
- excluding other reasons: metastases, infection, encephalopathy, original endocrinological disorders.

## CONCLUSIONS

Early diagnosis of PNS allows physicians to introduce targeted and precise diagnostics, frequently leading to detecting neoplasm in its early stages. This creates an opportunity for beginning treatment and increases the likelihood of surviving. Awareness and knowledge of PNS and their varieties can contribute significantly to a better prognosis for patients.

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*CASE STUDY*

# RECURRENT RESIDUAL CHOLEDOCHOLITHIASIS AFTER CHOLECYSTECTOMY – ENDOSCOPIC EXPLORATION OF BILE DUCTS PERFORMED 6 TIMES

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## ABSTRACT

**Introduction.** Recurrent residual choledocholithiasis refers to the presence of concretions in the bile ducts found in patients who have undergone cholecystectomy. The incidence of recurrent cholithiasis is estimated to be 2–10%, whereas the incidence of recurrent cholithiasis after endoscopic retrograde cholangiopancreatography (ERCP) amounts to 4–24%.

**Aim.** The aim of this paper was to analyze the case of a patient with recurrent choledocholithiasis after laparoscopic cholecystectomy, who underwent endoscopic exploration of the bile ducts performed 6 times, including endoscopic sphincterotomy (ES) and biliary prostheses.

**Case study.** A 49-year old patient was admitted to the Teaching Hospital showing symptoms of extrahepatic cholestasis. On admittance, she reported nausea lasting for a few days, meteorism and strong pain typical of biliary colic, located in her right epigastric region and irradiating to her spine. Additionally, she complained of a bitter taste in her mouth and bitter belching. The patient had been operated on 9 years before for acute cholecystitis.

**Results and discussion.** This presented case poses a question for a clinician concerning the risk factors for recurrent choledocholithiasis. In the majority of cases, i.e., as many as 80%, recurrent cholithiasis is detected within 3 years following ERCP with sphincterotomy. The risk of choledocholithiasis recurrence after endoscopic evacuation of the stones is within the range of 4–24%. The identification of factors causing

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this disease will contribute to its prevention, early diagnosis and treatment of any further recurrences and complications from choledocholithiasis. Data from published literature prove that damage to the sphincter causes chronic cholangitis, which then contributes to the formation of concretions. Other risk factors include dilated bile ducts and performed cholecystectomy. All these factors occurred and were observed in the analyzed patient.

**Conclusions.** The basic treatment for this recurrent disease is ES performed during an ERCP procedure. This case emphasizes those problems associated with the prevention and treatment of recurrent choledocholithiasis.

**Key words:** recurrent residual choledocholithiasis, cholecystectomy, endoscopic retrograde cholangiopancreatography, endoscopic biliary sphincterotomy

## INTRODUCTION

Choledocholithiasis is defined as the presence of concretions in the extrahepatic (choledocholithiasis), or intrahepatic bile ducts (cholangiolithiasis). Primary choledocholithiasis is rarely observed. Most frequently, the stones originate in the gallbladder, and this condition is referred to as a secondary choledocholithiasis. A separate problem is posed by choledocholithiasis in patients who have undergone cholecystectomy, with the incidence being estimated to be 2–10%. Stones in the bile ducts may be residual, and so overlooked during the therapeutic procedure; less frequently they form anew during various periods of time following cholecystectomy. Thus, it is vital to perform thorough diagnostics in order to detect symptoms which might suggest recurrent cholithiasis in patients qualified for cholecystectomy. Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) are standard procedures in the management of recurrent residual choledocholithiasis. Despite the high level of efficiency of such treatment, we observe the recurrence of the disease in some patients – this condition is then referred to as the so-called recurrent residual choledocholithiasis [1–10].

## AIM

The aim of this work is to analyze an untypical case concerning a patient with recurrent choledocholithiasis after laparoscopic cholecystectomy, who underwent endoscopic exploration of the bile ducts performed 6 times, including ES and biliary prostheses.

## CASE STUDY

A 49-year old patient was admitted to the Teaching Hospital showing symptoms of extrahepatic cholestasis. On admittance, she reported nausea lasting for a few days,

meteorism and strong pain typical of biliary colic, located in her right epigastric region and irradiating to her spine. Additionally, she complained of a bitter taste in her mouth and bitter belching. She negated the existence of any comorbidities and long-term use of medication. The patient had been operated on 9 years before for acute cholecystitis. Classic cholecystectomy had been performed at that time. Afterwards, this patient was frequently hospitalized for recurrent choledocholithiasis. The first hospitalization occurred 3 years after cholecystectomy. She then reported pain in her epigastric region with the co-occurring jaundice. Abdominal ultrasonography (USG) revealed a dilated common bile duct measuring 10.7 mm. Laboratory tests detected typical features of cholestasis. ERCP with sphincterotomy of the papilla of Vater was performed, resulting in a free outflow of bile. This dilated common bile duct was additionally controlled by a Dormia basket. When the symptoms subsided, the patient was discharged in a good general condition. She was advised to follow a hepatic diet. 5 years after the first endoscopic revision of her bile ducts, the patient was hospitalized, exhibiting symptoms of mechanical jaundice. She was again qualified for the ERCP examination, which then revealed the scar resulting from the previous papillotomy. An injection of dye showed dilated bile ducts measuring more than 2 cm, and two ballotting stones more than 1 cm in diameter (Fig. 1) were detected.

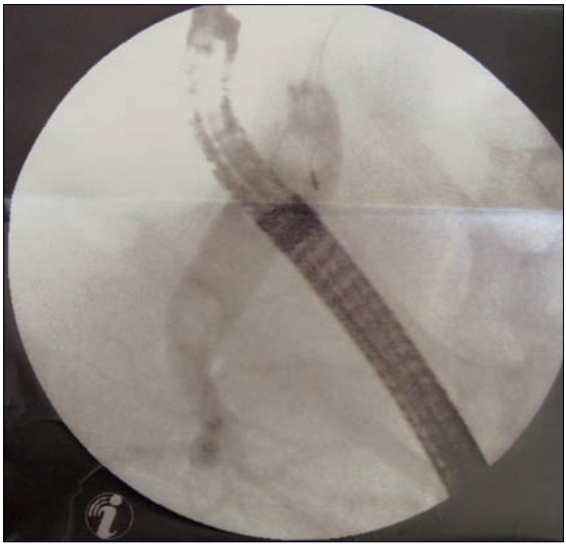

**Fig. 1.** ERCP image demonstrating choledocholithiasis before sphincterotomy

Sphincterotomy was performed again, these stones were broken up and evacuated with a Dormia basket, thus obtaining a free outflow of bile. Due to bleeding from the incised papilla, revision of the dilated bile ducts was postponed. A control examination revealed the bile ducts orifice obstructed with concretions. Extraction with a Dormia

basket was performed, which allowed an evacuation of other stones with diameters exceeding 1 cm and numerous smaller stones. In order to protect the patient from the recurrence of bile ducts obstruction, an 8.5 F Oasis prosthesis of 5 cm was placed. During hospitalization, the patient developed iatrogenic acute pancreatitis; 6 months later, the patient underwent another endoscopic revision of the bile ducts. During that procedure the prosthesis was removed, ES was performed, obtaining a free outflow of a large number of asymptomatic stones, and dilated bile ducts were controlled with a balloon. After 1.5 years, following the last ERCP examination, the patient was hospitalized once again showing symptoms of recurrent choledocholithiasis. A heightened activity of hepatic enzymes was then detected. ERCP revealed significantly dilated bile ducts (up to 3 cm), with numerous soft stones up to 2 cm in diameter (Fig. 2). The papilla of Vater was incised again and these stones were evacuated. This examination led to complications involving another iatrogenic acute pancreatitis.

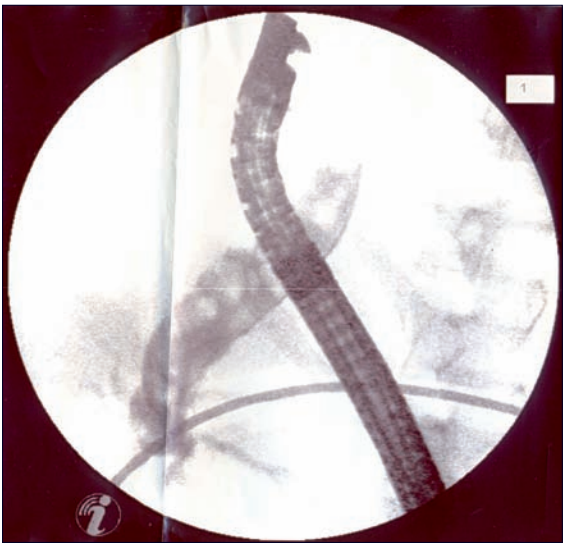

**Fig. 2.** ERCP image demonstrating recurrent choledocholithiasis

During the last hospitalization, the following departures from the normal condition were detected: yellowish discoloration of the skin and sclera, post-cholecystectomy scar, and palpable pain in the epigastrum. Laboratory tests revealed: elevated parameters of the inflammatory condition: CRP – 167.02 mg/L, WBC – $12.92 \times 10^3/\mu L$, procalcitonin (PCT) – 0.64 ng/mL; parameters indicating damage to the hepatic cells: AspAT – 422 U/L, ALAT – 598 U/L, GGTP – 440 U/L. Gastroscopy and colonoscopy did not reveal any pathology. Abdominal computed tomography (CT) showed quite numerous lymph nodes up to 10 mm in size, located along the inferior caval vein and between the vain and aorta. Additionally, in the cortex of the inferior pole of the right kidney a lump 11 mm in size and of the density of 45 HU (Hounsfield Unit)

was revealed. It was most probably angiomyolipoma. The patient was qualified again for retrograde cholangiopancreatography. A significant dilation of the bile ducts with a large stone of 3–4 cm was detected. The stone was removed, together with other numerous soft stones. Thick bile was obtained for microbiological tests. Multi-bacterial infection was discovered – a very significant increase of *Escherichia coli*, *Klebsiella oxytoca* and *Enterococcus faecalis*. Bacterial colonies were sensitive to, among others, amoxicillin with clavulanic acid, cephoperazon, ceftriaxone, ciprofloxacin and doxiciclin, and they were resistant to ampicillin and amoxicillin. The patient was treated with complex and targeted antibiotic therapy. Hospitalization led to a gradual stabilization of the laboratory parameters indicating cholestasis and inflammation. The patient was discharged in a good general condition, and advised to report for further controls to the Gastroenterology Outpatient Clinic.

## RESULTS AND DISCUSSION

This described case poses several important questions for a clinician. First of all, what are the risk factors for the recurrence of choledocholithiasis after ERCP with sphincterotomy? How does one detect and control patients with recurrent choledocholithiasis? The risk of the recurrence of choledocholithiasis after the endoscopic evacuation of the stones is estimated to be 4–24% [2]. In the majority of cases (about 85%), recurrent choledocholithiasis occurs within 3 years following ERCP. Risk factors for recurrent cholithiasis are especially important in the case of young and healthy patients, since the identification of such factors would facilitate preventing, early diagnosis and treating for further recurrences and complications resulting from choledocholithiasis. In the subject literature, it is reported that damage to the structure of the Oddi's sphincter leads to an increased susceptibility to chronic cholangitis, which then contributes to the formation of new stones. Further, the dilated common bile duct is colonized by pathogenic bacteria [6]. The longer the period of time since sphincterotomy and the larger the number of endoscopic revisions of the dilated common bile ducts, the more frequently pathogenic bacterial flora develops. Also, this pathogenic bacterial flora becomes more diversified and resistant to medication. This is confirmed by the analyzed case, since after the endoscopic exploration of the bile ducts and sphincterotomy performed 6 times, three Gram-negative bacterial strains were cultured in the bile (*E. coli*, *K. oxytoca* and *E. faecalis*).

It is worth noting, that chronic cholangitis after ES creates favorable conditions for the formation of easily broken up, soft, "clay-like" conglomerates. Such concretions were observed in the described case. Maceration of larger conglomerates, however, for instance with a Dormia basket results in releasing the bacteria contained within them. Thus, it has been concluded that sphincterotomy should be avoided in young people (20-, 30-years old), and concretions should be removed from bile ducts after balloon dilation (balloon plasty) of the Oddi's sphincter [6]. We should, however, re-

member about certain limitations of balloon dilation, which, on the one hand reduces the frequency of complications during ERCP, but, on the other hand, is a slightly more difficult procedure than ES. It is mostly applicable for evacuating small stones, whose diameters do not exceed 8 mm, and in the case of patients with duodenal diverticulum, flat papilla of Vater, cirrhosis, and portal hypertension. It is believed that in the case of stones larger than 10 mm, and such concretions repeatedly occurred in this patient, sphincterotomy should be performed. The risk of choledocholithiasis recurrence is also increased by the previously performed cholecystectomy. Removing the gallbladder increases the frequency of peripapillary diverticula being formed, as well as of large choleliths and bile duct dilation. This is most probably associated with a lack of the protective function of gallbladder motor capacity, which facilitates the clearing of the bile ducts, prevents the formation of new choleliths, and washes out the existing ones [1, 8, 10]. Another risk factor for recurrent cholithiasis is the dilation of the common bile duct above 15 mm. Hence, it is so important to constantly control and observe patients who report, in the interview, originally dilated bile ducts and cholecystectomy. It has been noted that intraductal ultrasonography (IDUS) imaging could be employed as a helpful tool in reducing the frequency of early recurrences of cholithiasis after ERCP [8]. This technique enables one to visualize even very small concretions in the bile ducts. It is believed that not removing very small fragments of concretions, invisible during cholangiography, may contribute to their early recurrence [7, 8]. It is estimated that the risk of cholelith recurrence following IDUS procedure is only 1.9%, whereas it increases to 14.7% when IDUS is not performed.

When discussing the aforementioned problem, further management of this group of patients should be considered. How to prevent further recurrences? Is chronic administration of available cholagogic and cholepoietic medication significant? What are the possibilities of invasive operative therapy? Complications of recurrent choledocholithiasis cannot be overlooked, especially secondary biliary cirrhosis, as well as the risk of enterobiliary, acute cholangitis or acute biliary pancreatitis. With respect to available literature on this subject, contradictory reports may be found. Treatments with a combination of endoprostheses and oral ursodeoxycholic acid or placebo were compared. No statistically significant difference in treating choledocholithiasis was found [4]. On the other hand, research assessing the effect of combined treatment (i.e., stenting combined with ursodeoxycholic acid and Rowachol) in managing recurrent choledocholithiasis in elderly patients, confirmed the effectiveness of such therapy [3]. It seems that we should wait for further developments with respect to the effectiveness of known pharmacological agents, or for the introduction of a new generation of medication reducing bile lithogenicity.

Operative treatment procedures for recurrent choledocholithiasis involve, among others, choledochoduodenostomy or choledochoenterostomy with Roux-en-Y reconstruction. It has been shown that the frequency of recurrent choledocholithiasis

after choledo-duodenal anastomosis in elderly patients amounts to 2.4%. Complications of side-to-side anastomosis should be paid attention to, among others, hepatic abscesses and the so-called "sump syndrome". Hence, an end-to-side anastomosis is a better solution. Naturally, the worst types of complications involve single cases of iatrogenic cholangioma, developing even many years after the performed surgical procedure [5].

It appears that in the case of recurrent choledocholithiasis, retreatment with ERCP is a reasonable and safe therapeutic procedure, especially when compared to invasive operative methods [9].

## CONCLUSIONS

1. In managing recurrent choledocholithiasis, endoscopic exploration of the bile ducts is a golden standard.
2. After ES in patients with recurrent choledocholithiasis, microbiological tests of bile should be performed.

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Pol. Ann. Med., 2011; 18 (1): 125–130.

*CASE STUDY*

# INTESTINAL OBSTRUCTION CAUSED BY SYNCHRONOUS COLORECTAL CANCER AND HEPATIC FLEXURE – A CASE REPORT

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## ABSTRACT

**Introduction.** Obstruction is an acute condition of the abdominal cavity termed "acute abdomen". This condition is managed surgically with an emergency procedure. Obstruction is not, however, a homogenous disease entity. Rather, it is a set of conditions causing similar symptoms. One of the reasons for developing obstruction may be cancer of the colon.

**Aim.** The aim of this paper was to present a case of intestinal obstruction caused by a synchronous colorectal cancer.

**Materials and methods.** This work presents a diagnostic procedure conducted in an Emergency Department and a surgical treatment carried out in the General Surgery Teaching Hospital concerning an 81-year old patient who reported symptoms of intestinal obstruction.

**Case study.** A patient with typical symptoms of intestinal obstruction reported to the Emergency Department. He manifested: retention of gases and constipation lasting for a few days, abdominal distension, abdominal pain, and general weakness. Auscultatory examination detected high-pitched tinkles, X-ray of the abdominal cavity – the presence of multiple gas-fluid levels. Rectal examination revealed rectal tumor. Obstruction was diagnosed and hospitalization and surgical treatments were advised, to which the patient consented. On the day the patient was admitted, a Miles' operation was performed. During a routine inspection of the abdominal cavity, a tumor in the hepatic flexure was also

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detected. It was decided to carry out a right hemicolectomy. No postsurgical complications occurred in the postoperative period. Parenteral nutrition was administered. The patient was discharged in a good general condition and advised to continue his therapy in the Outpatient Oncology Clinic, having received the result of the histopathological test.

**Results and discussion.** The phenomenon of the co-occurrence of neoplasms in various organs has been known for quite some time. Often, neoplasms are located far away from each other, and sometimes two or more tumors are detected within the same organ. Synchronous neoplastic tumors within the colon are well documented, and their incidence is estimated by various authors to range from 1.02% to 12.4%.

**Conclusions.** A synchronous cancer of the colon is so common that each neoplasm of this organ necessitates a thorough inspection of the entire intestine.

**Key words:** obstruction, synchronous cancer, colon cancer, rectal cancer

## INTRODUCTION

Obstruction (*ileus*) is an umbrella term for a broad set of non-homogeneous disease entities which are manifested by similar symptoms. The first group of such diseases is called paralytic ileus (*ileus paralyticus*), often termed "non-surgical intestinal obstruction".

The second group, called mechanical ileus (*ileus mechanicus*), refers to the inhibiting of the intestinal passage by an obstruction located in any section of the small or large intestine [18]. This condition usually requires surgical treatment.

There exist three basic mechanisms for mechanical ileus:

- strangulation (*strangulatio*),
- occlusion (*obturatio*),
- intussusception (*invaginatio*).

Typical features of intestinal obstruction involve: retention of gases, high-pitched tinkles, general weakness, arterial hypotension, tachycardia, disturbances of water and electrolyte equilibrium, and acidosis [18]. The most frequent cause of intestinal obstruction in the occlusion mechanism is colon cancer [18]. This type of cancer is the most frequent neoplasm found in the human population [9]. Unfortunately, it very quickly and very easily leads to metastases. Liver metastases are detected in more than 60% of patients with colon cancer upon their deaths [15]. Metastatic tumors of the colon are very common – this problem results in 1.5 million new cases worldwide annually. In the USA alone, approximately 130 thousand new cases are diagnosed annually [11, 20]. In Poland, it ranks as the second most frequent malignant cancer with respect to incidence. Each year about

10 thousand new cases are reported [9, 18]. Half of the patients with colon cancer manifest metastases to the liver, including synchronous metastases in about 35%, whereas in the remaining patients metastases develop later [2, 4, 8]. Approximately 40–50% of patients after potentially successful resections die within 5 years, most frequently due to metastases to the liver. Only a small percentage of patients with metastatic livers, who have undergone resection, benefit with respect to a long-term perspective [7].

## AIM

The aim of this paper was to present a case of mechanical ileus caused by a synchronous colorectal cancer.

## MATERIALS AND METHODS

This report is based on the case of an 81-year old patient operated on employing an emergency procedure due to symptomatic intestinal obstruction. During the procedure, the amputation of the rectum by Miles' technique was performed. A preternatural anus was formed and a right hemicolectomy was performed due to neoplastic foci detected in the rectum and hepatic flexure. This operation was performed under general anesthesia.

## CASE STUDY

A patient reported to the Emergency Department in the afternoon due to typical symptoms of intestinal obstruction – intense blunt abdominal pain lasting for 2 weeks, located mainly in the hypogastrium, intensifying with each day, intense abdominal distension, loss of weight (about 5 kg), loss of appetite, diarrhea in the last few days, retention of gases, and constipation lasting for a few days. During the physical examination, a significant distention of the abdomen above chest level, rigid abdomen, palpable pain in the hypogastrium and high-pitched tinkles were detected. X-ray of the abdominal cavity taken in the erect position indicated the presence of multiple gas-fluid levels – an image typical of intestinal obstruction (Fig. 1).

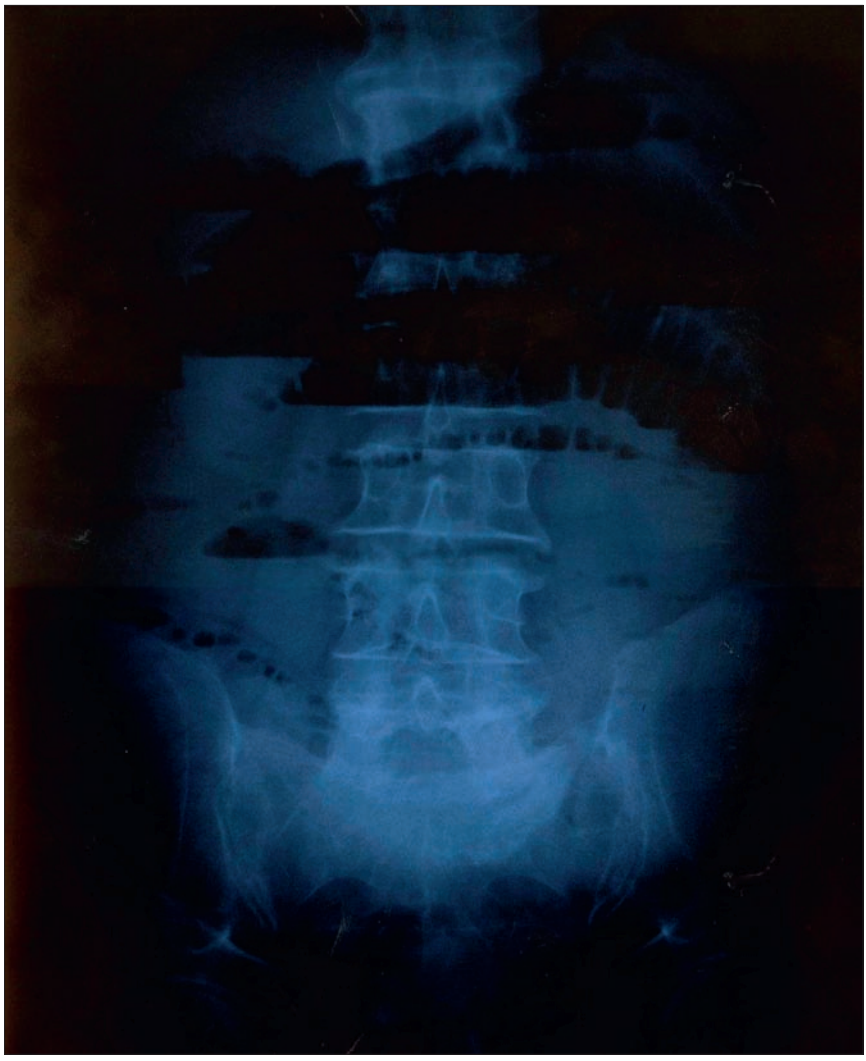

**Fig. 1.** X-ray showing the patient's abdominal cavity

Rectal examination revealed a large solid rectal tumor. Moreover, the patient's medical history involved prostate surgery and left inguinal hernia surgery, and he also reported two comorbidities: arterial hypertension and glaucoma.

The patient was informed concerning the diagnosis of mechanical ileus and offered admittance to General Surgery Teaching Hospital to undergo surgical treatment, to which he consented.

Next, the patient was informed about the rectal tumor as a most likely cause of the obstruction and about the necessity of its surgical management, with a possibility

of forming a preternatural anus. The patient provided a written informed consent to the suggested treatment.

During the operation, the rectal tumor detected earlier during rectal examination was discovered, measuring about 6.5 cm, located about 4–5 cm from the anus. Miles' technique was used to remove it. Then, during a routine inspection of the abdominal cavity, another tumor, measuring about 3 cm, was also detected in the hepatic flexure. Hence, a right hemicolectomy with side-to-side anastomosis with the use of a linear stapler was performed.

No postsurgical complications occurred in the postoperative period. During the first days after surgery, the patient was treated intensely due to circulatory and renal insufficiency. Total parenteral nutrition was administered for 18 days. On the 26$^{th}$ day after surgery, the patient was discharged in a good general condition and advised to report to the Outpatient Oncology Clinic, having received the result of the histopathological test.

Scheduled histopathological tests of both tumors revealed adenocarcinoma foci – in the rectum: *Adenocarcinoma mediocriter differentiatum G2, exulcerans* and in the colon: *Adenocarcinoma partim mucinosum mediocriter differentiatum G2, exulcerans*.

## RESULTS AND DISCUSSION

The phenomenon of synchronous neoplastic tumors found in humans has been known for quite some time and has been described frequently in medical literature. Lung cancer with synchronous gastric cancer has been already discussed [10]. In approximately 10% of cases involving synchronous head and neck cancer, their multiple presence has also been reported [12, 16]. Cases of synchronous rectal carcinoma and bilateral clear cell renal carcinoma have also been analyzed [19].

A similar situation has been described with reference to bile ducts [3], pancreas [11] and breasts [14], where the presence of two or more carcinomas has been detected within the same organ.

The presence of multiple neoplastic foci is also common within the rectum and colon [18]. The incidence of this condition is estimated by various authors to range from 1.02% to 12.4% [1, 5, 6, 13].

Many genetic syndromes have been also described, where intestinal cancer co-occurs with cancers involving other organs. This can be exemplified by Lynch syndrome II, where the colon cancer co-occurs synchronically or metachronically with cancers of: the uterine corpus, ovaries, breast, stomach, small intestine, liver, bile ducts, and urinary tract or with lymphomas. Another example of such a syndrome may be illustrated by Turcot syndrome, characterized by the synchronous presence of brain tumors and colonic polyposis. These polyps can, in turn, initiate the development of colon cancer [6, 18].

## CONCLUSIONS

A synchronous colorectal cancer is so common that in each case when a tumor is found in the colon or rectum, a thorough inspection of both entire organs is required.

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*CASE STUDY*

# UNEXPECTED POSITIVE EFFECT OF FRESH FROZEN PLASMA ON STANDARD ANTICOAGULATION IN THE CASE OF PULMONARY EMBOLISM ACCOMPANIED BY SEPSIS – A CASE REPORT

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## ABSTRACT

**Introduction.** In recent years there have been significant advances in the diagnosis and management of venous thromboembolism. This has resulted in the establishment of detailed diagnostic and therapeutic guidelines. Despite the benefits coming from their implementations, a clinical outcome of thromboembolic complications in particular patients poses a number of diagnostic difficulties. Treatment results and prognosis, despite following commonly recognized therapeutic standards, are difficult to predict.

**Aim.** This paper aimed at presenting an atypical course of high-risk pulmonary embolism (PE) and the remote outcome of its treatment in a surgical patient with an initial low risk of thrombotic complications.

**Case study.** The patient was a 58-year old female with a history of primary arterial hypertension who was electively operated on for euthyreotic polynodular goiter. On the 2nd postoperative day, she had to be resuscitated due to PE accompanied by sepsis with disseminated intravascular coagulation and shock. As shock symptoms did not subside despite the administration of typical treatment (Dextran, intravenous infusion fluids, dopamine, heparin, broad-spectrum antibiotics), and because of gastrointestinal bleeding suspicion, the patient was also administered fresh frozen plasma. Following resuscitation, lasting 2.5 hours, long-term improvement in hemodynamic parameters occurred. After respiratory therapy, lasting several hours, a gradual improvement of the patient's general condition was observed. She regained consciousness, dyspnea subsided, and features of acute right ventricular overload gradually subsided in electrocardiogram.

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**Results and discussion.** On the one hand, the effectiveness of a combined treatment employing heparin and fresh frozen plasma could have resulted from its effect on improving tissue hypoperfusion secondary to the shock; and, on the other hand, because of the coexisting intravascular coagulation process. Fresh frozen plasma, apart from its commonly known procoagulative effect, may also enhance fibrinolytic processes. The potential influence of endogenous anticoagulants contained in plasma with respect to the course of PE has been discussed. It may have contributed to the regression of PE symptoms, despite the fact that in the acute phase the patient was on heparin only.
**Conclusions.** Fresh frozen plasma, due to its endogenous anticoagulation activity, may positively influence the course of high-risk PE.

**Key words:** pulmonary embolism (PE), surgical procedure, heparin, fresh frozen plasma

## INTRODUCTION

The clinical likelihood of venous thromboembolism (VTE) is assessed individually for each patient on the basis of the presence of known risk factors [1]. Risk factors, which are most dangerous, include: age, obesity, congenital and acquired thrombophilia, neoplastic diseases, acute and chronic inflammatory diseases, paroxysmal nocturnal hemoglobinuria, long-term immobilization with venostasis, injuries, cardiac or respiratory failure, and hormonal therapy [1]. A specific risk group involves patients treated at surgical departments. It is estimated that thromboembolic complications in this population who have undergone surgical procedures account for 65% of all such complications observed in hospitalized patients [9]. It is believed that major operations, especially those involving lower extremities, pelvis and abdominal cavity, predispose one to more frequent thromboembolic complications [1, 13]. A significant advancement with respect to antithrombotic therapy has been noted within the last 30 years. A number of detailed guidelines concerning treatment have been established, and benefits stemming from implementation of particular therapeutic procedures have also been recognized. Nevertheless, a clinical course of thromboembolic complications in individual cases poses numerous diagnostic difficulties, and treatment results and prognosis despite following commonly recognized standards are difficult to assess.

## AIM

This paper aims at presenting an atypical course of high-risk pulmonary embolism (PE) and the remote outcome in a surgical patient who initially presented a low risk of thrombotic complications.

**CASE STUDY**

A 58-year old female (General Hospital Register No 5428/1991), with primary arterial hypertension lasting for several years, was admitted for elective strumectomy due to euthyreotic multinodular goiter. On admission, her general condition was stable. On physical examination her temperature was 36.4°C, pulse 72/min, BP 150/85 mmHg. Body type was normostenic (BMI 23.8). The thyroid gland was bilaterally markedly enlarged; lungs, heart and other organs and systems did not show any abnormalities. On November 12, 1991, a subtotal strumectomy was performed, removing a thyroid lump of a male fist size. On November 13, 1991, at about 9:00 in the morning, the patient fainted. Hypotonia of 60/30 mmHg was recorded. Despite the intravascular infusion of 200 mg of hydrocortisone, circulatory arrest occurred. Resuscitation procedures were undertaken, resulting in regaining cardiac function. The patient was then transferred to the Cardiac Intensive Care Unit. The patient was conscious and reported strong resting dyspnea. Tachypnoe 30–35/min, BP 70/30 mmHg, regular cardiac rhythm accelerated to 110/min were observed. The patient was pale with signs of central and peripheral cyanosis. On auscultation vesicular sounds were heard above the lungs, along with a prolonged expiratory phase, as well as single wheezes on the right side. On the left side, vesicular sound was diminished. Before the resuscitation, the electrocardiogram (ECG) showed normal axis and regular sinus rhythm of 86/min. Following the resuscitation right axis deviation, accelerated sinus rhythm to 110/min, complete right bundle bunch block were detected. Blood gases analysis revealed metabolic acidosis (pH 7.11) and hypoxemia ($pO_2$ 51.4 mmHg) with hypocapnia ($pCO_2$ 21.4 mmHg). Heparin was administered as two consecutive boluses of 5000 units intravenously (IV) within 5 minutes, and then as an IV infusion adjusted to activated partial thromboplastin time (APTT). IV infusion of dopamine and Dextran 40 000 of 500 mL were also given. Dyspnea progressed, respiratory disturbances appeared. The patient was intubated and hooked up to a respirator. An ECG monitor recorded a diminishing frequency of cardiac rhythm (30–40/min). She was given: 0.5 mg of atropine, 1 mg of adrenaline, 100 mL of Natrium bicarbonate, followed by 500 mg of hydrocortisone and 1 mg of atropine. At about 9:10 atrial fibrillation occurred, with heart rhythm about 140/min, arterial pressure on radial artery was undetectable. 0.4 mg of Lanatosid C IV and 500 mg of hydrocortisone IV were administered, and 1200 ml of fresh frozen plasma was transfused. Heart rhythm decreased to 100/min, the BP was 70/50 mmHg. Laboratory tests revealed: K 3.3 mEq/L, Na 131 mEq/L. An IV infusion of 500 mL of 0.9% NaCl with 3.0 g of KCI was given. At 11:30, the sinus rhythm of 80–100/min appeared and a BP reading was 110/70 mm Hg. Blood tests obtained in the morning revealed anemia. The hemoglobin level decreased from 14.4 g% to 9.6 g%, and the erythrocyte count decreased from $4.96 \times 10^6$/mL to $3.47 \times 10^6$/mL. At 13:00, the white blood cell count increased from $5.1 \times 10^3$/mL to $12.6 \times 10^3$/mL, showing a decreased maturation of granulocytes and shift in their image to the left

(6 rod neutrophils and 85 segments). The thrombocyte count was $7.7 \times 10^3$/mL. Since 11:30, low intensity bleeding from the postoperative wound was observed. APTT was immeasurable, prothrombin index – 69%. An infusion of heparin was stopped, 840 ml of erythrocyte concentrate and 700 ml of fresh frozen plasma were transfused. Laboratory tests revealed a gradual shortening of APTT to 60 sec. (at 20:30). Heparin infusion was reintroduced. At about 22:00, bleeding from the postoperative wound stopped. Transaminase values AlAt and AspAt were within a normal range. When the cardiovascular system was stabilized, the patient was still unconscious, her pupils were dilated with pupilloplegia; Babinski sign was positive bilaterally. Dexametasone and a wide-spectrum antibiotic therapy were administered. Since blood culture test was positive (*Acinetobacter anitratum*), consistently with the obtained antibiogram, Cefotaxim was administered in a dose of 2 g/ 24 hours. On the 2nd day the patient regained consciousness and logical contact was established. The respirator was switched off and the intubation tube was removed as well. Central cyanosis persisted, the values of pulse and BP were 86/min and 140/90 mmHg, respectively. Blood gases analysis: pH 7.42, $pCO_2$ 30.9 mmHg, $pO_2$ 92.3 mmHg. The ECG showed a disappearance of a right axis deviation alongside with signs of complete right bundle bunch block. It also showed negative T waves in leads V1–V4, which gradually normalized within the following 7 days. Chest X-ray (November 14, 1991) revealed an enlarged cardiac silhouette and features of congestion in pulmonary circulation. A neurological examination did not show neck stiffness or focal symptoms. Histopathological examination revealed *struma nodosa cum signis hyperfunctionis*. Thyroid-stimulating hormone (TSH) value was 3.2 mIU/L, and free Thyroxin (FT4) was 1.1 ng/dL – both values were within the normal limits. In the course of further antibiotic therapy the fever subsided and leukocytosis was normalized. The patient was discharged in a good general condition, with full logical contact, mobilized, and advised to follow long-term therapy with an oral anticoagulant, which she was receiving beginning with the 4th day following resuscitation. The patient discontinued use of medication 2 months following her discharge. Diagnosis: Case of surgical treatment of benign nodular goiter, complicated on the 1st day with high-risk PE and sepsis. Primary arterial hypertension.

The patient is still alive. She was hospitalized 6 times between 1994–2011. Hospitalizations were caused by: chronic gastritis, cholecystectomy due to acute gangrenous cholecystitis, and upper respiratory tract infections. Three years following the episode of PE, her chest X-ray revealed no abnormalities, the ECG was also normal. Echocardiography (ECHO) performed on June 23, 2000 showed normal morphology of cardiac valves, normal sizes of cardiac cavities and normal left ventricular systolic function, ejection fraction – 65%. The examination was repeated during 2002 and detected fibrosis on the leaflet of the mitral valve and on the cusps of the aortic valve, mitral regurgitation (+), minimal triscupid regurgitation, normal sizes of cardiac cavities and normal thickness and contractility of both ventricular walls.

## RESULTS AND DISCUSSION

It is believed that the postoperative risk of PE is highest within the first 2 weeks following the operation [13]. Embolism is more frequently found in patients who, in the perioperative period, are not administered with preventive antithrombotic therapy and is particularly dangerous when it co-occurs with asymptomatic thrombosis [2, 3]. Schizas et al., despite the implementation of heparin prophylaxis, observed that 50% of PE cases occurred up till the 3rd day following the operation [7].

In the herein described case, one of the reasons for the early occurrence of PE and its acute course may have been the lack of antithrombotic prophylaxis. Other risk factors for thromboembolism which were observed in this patient were her age and immobilization connected with the surgical procedure. Although strumectomy is not recognized as a high-risk procedure with respect to thromboembolic complications, it is, nevertheless, like the majority of surgical procedures, connected with a decreased activity of antithrombin, C protein, and plasminogen [5, 10, 11]. No recurrence of thromboembolism within a 19-year long observation period, and experiencing a surgical procedure with a higher-risk of thromboembolism, exclude hereditary thrombophilia. Another reason for PE may have been an infection, also leading to hypercoagulability. Features of infection, in the form of hyperleukocytosis and changes in blood smear, were detected during the 4th hour following the beginning of resuscitation. They do not belong to the clinical manifestations of PE. The diagnosis of PE was made on the basis of a characteristic clinical course, hypoxemia with hypocapnia, and typical ECG changes. We did not perform examinations showing the right ventricular overload due to the lack of possibility to carry out such an examination. A form of high-risk PE was suggested by the symptoms of the co-occurring shock and an enlarged cardiac silhouette seen in the chest X-ray, which later on normalized. A major and/or multiple embolism may lead to a sudden increase in the pulmonary vascular resistance to a level which the right ventricle cannot overcome [13]. Consequently, hypoperfusion may occur, accompanied with a shock, circulatory arrest and, as observed in this patient, progressive metabolic acidosis, which may have been also caused by the co-occurring sepsis. This is what we associate a decreased level of the prothrombin index and a low platelets count with. These features indicate that both these factors were used up in the course of the co-occurring disseminated intravascular coagulation syndrome. These conditions, however, do not explain changes observed in the ECG, typical of PE: right bundle bunch block, which regressed on the 2nd day following resuscitation, and negative T waves in leads V1–V4, lasting for 7 days. Such ECG changes in the course of PE have been frequently reported earlier [6, 8, 12]. Also, dominant clinical symptoms, such as dyspnea, tachypnoe, hypotonia, tachycardia, detected in the patient in the early postoperative period, were typical of PE. The chest X-ray eliminated diagnosis of pneumonia and pneumothorax. In the differentiating diagnosis, myocardial in-

farction was also considered. ECG examinations did not indicate, however, changes typical of acute myocardial ischemia. Additionally, long-term asymptomatic observation, and a lack of disturbances concerning the contractility of both ventricular walls in ECHO performed later, contribute to the fact that myocardial infarction in the acute phase of the disease was unlikely. Since symptoms of shock did not subside despite the administration of typical treatment, and because of suspicious bleedings, the patient was administered with fresh frozen plasma. Further observation did not confirm bleeding from the gastrointestinal tract, and the observed anemia may have resulted from the loss of blood during the operation.

The presence of known risk factors for PE is important in evaluating a clinical likelihood of PE. The risk increases together with the increase of their number, however, in about 30% of cases there are no predisposing factors (such as unprovoked or idiopathic PE) [13]. In order to stratify the likelihood of PE, commonly known scales are employed, such as the Wells score and modified Geneva score [13]. In the case of the patient described therein, the clinical probability of PE was moderate, respectively 6 points (range of 2–6), 7 and 8 points (range of 4–10). The patient met the criteria qualifying for the application of fibrinolytic therapy in high-risk PE, with a short-term mortality risk exceeding 15% [13], and such treatment should be currently considered. On the other hand, the implementation of this treatment before the first 24 hours following the surgical procedure is associated with a high-risk of hemorrhage complications, which is a relative contraindication for administering fibrinolytic agents [13]. Although fibrinolytic therapy was not administered, after a 2.5-hour long resuscitation, bleeding from the postoperative wound was observed. Simultaneously, long-term improvement in hemodynamic parameters occurred. It appears that these two entities should be associated with endogenous fibrinolysis, which could have been caused by the administration of fresh frozen plasma, since heparin does not produce such effects. Procoagulative activity of fresh frozen plasma was inhibited by the concurrent administration of heparin, which was documented by the prolonged APTT, and anticoagulants contained within plasma may have had a positive influence on the further course of PE. This was evidenced by an improvement in the hemodynamic status, the quick regression of dyspnea, as well as a typical evolution of ECG changes.

In the subject literature, we have not found any reports describing an anticoagulation treatment combined with administering fresh frozen plasma. Recently there have appeared reports which modify opinions concerning fibrinolysis in the course of PE. It has been reported that decreasing a standard dose of a fibrinolytic agent by 50%, or prolonging its infusion time, in comparison with current therapeutic guidelines, does not have any effect on the final outcome [14, 15]. A large study material, involving more than 2000 patients, of Polish Registry of Pulmonary Embolism (ZATPOL), indicated an association of applied fibrinolytic therapy with

increased mortality in the course of PE [4]. These data may suggest that fibrinolytic therapy alone does not always eliminate the substrate for PE, which may have an impact upon its effectiveness. In a preliminary analysis carried out during the perioperative period and involving a small group of patients with colorectal cancer, who were administered with prophylactic doses of low molecular weight heparin, and did not manifest thrombosis, coagulation times were prolonged, and the thrombocytes count decreased along with a simultaneous decrease in the levels of endogenous anticoagulants [11]. It appears that when thromboembolism develops, it results from a shift of balance towards procoagulation, which results from a simultaneous decrease in the activity of endogenous anticoagulants.

Thus far it has been believed that the major factors contributing to the ineffectiveness of managing PE are hypercoagulability or an inadequate dose of the fibrinolytic agent. Available data and everyday practice indicate that a relatively small dose of heparin controls hypercoagulability effectively, and administering fibrinolytic therapy is not always effective. Thus, a question arises as to whether endogenous fibrinolytic agents or direct substrates for a fibinolytic agent may contribute to improving the effectiveness of PE management. It should be considered whether fresh frozen plasma, via providing endogenous anticoagulants, which apart from being a simple substrate for a fibrinolytic agent may also provide anticoagulation substances acting through a different mechanism, can contribute to improving the effectiveness of treatment.

## CONCLUSIONS

Fresh frozen plasma, due to its endogenous anticoagulation activity, may positively influence the course of high-risk PE.

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*CASE STUDY*

# LIPOLEIOMYOMA OF THE UTERUS – A CASE REPORT

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## ABSTRACT

**Introduction**. Lipoleiomyoma (LL) is a rare, benign neoplasm, which most frequently occurs in postmenopausal women and is predominantly located in the uterus. However, extrauterine locations have been reported as well, e.g., in the broad ligament of the uterus, ovary, and peritoneum. Usually, LL is found in association with ordinary uterine leiomyomas.

The incidence of this neoplasm is estimated at 0.03–0.2%. Clinical manifestations of LL are identical to those of uterine myomas. Most frequently, symptoms include: palpable mass in the pelvis minor, pelvic pain, and abnormal uterine bleedings. The majority of patients do not report any symptoms. LL is an extremely rare, benign tumor of the uterus. When asymptomatic, it does not require treatment.

**Aim**. This paper aimed at presenting a very rare case of LL in a postmenopausal patient.

**Materials and methods**. This case has been described on the basis of the medical documentation concerning the patient (case record No 24285/2010), hospitalized in the Department of Oncology and Gynecologic Oncology, Health Care Institution of the Ministry of Internal Affairs and Administration (ZOZ MSWiA) with the Warmia and Mazury Oncology Center in Olsztyn.

**Case study**. The patient, 56-years old, multipara, was admitted to the Department with a preliminary diagnosis of uterine myomas, causing pain and discomfort within the region of pelvis minor. Ultrasonography (USG) showed a hyperechoic lesion, about 35 mm in diameter, well-circumscribed by a hypoechoic rim, located in an enlarged uterus. The remaining part of the uterus showed a heterogeneous echo-

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genic pattern. During hospitalization at the Department, the patient was operated on. The amputation of the uterine corpus was performed, without uterine adnexa. Histopathological test involving the postoperative uterus specimen detected LL.
**Results and discussion.** LL cases are reported as examples of neoplasms diagnosed accidentally in the postoperative specimens. Cases of complex diagnostics, with the use of USG, as well as computed tomography (CT) and magnetic resonance imaging (MRI), when LL is suspected, are extremely rare.
In postmenopausal women, suffering from hypothyroidism, diabetes or hyperlipidemia, lipomyomas in the uterus are more frequently found. It is suggested that metabolic changes occurring in postmenopausal women are a likely cause for the development of adipose tissue metamorphosis in LL.
Detection of adipose tissue in the tumor mass confirms the diagnosis of LL. Usually, LL is initially recognized as uterine myoma, and depending on the coexisting symptoms, may be treated surgically.
Diagnostic difficulties and the importance of differential diagnosis towards other tumors located in the pelvis minor are highlighted. Asymptomatic course and lack of characteristic clinical manifestations of the tumor, with a simultaneous characteristic image in USG, CT and MRI are emphasized.
**Conclusions.** When palpable mass is detected during a manual pelvic examination in postmenopausal patients, a gynecologist should consider the possibility of LL. A characteristic USG image, i.e., a hyperechoic lesion with a hypoechoic rim, detected in the uterus should be regarded as an indication for considering such diagnosis.
The final diagnosis is established on the basis of a histopathological test involving the tissue specimen.

**Key words:** lipoleiomyoma (LL), myomata uteri

## INTRODUCTION

Lipoleiomyoma (LL) is a rare, benign neoplasm, which is most frequently located in the uterus [1, 2, 5, 6]. It can be located both within the uterine corpus and in the uterine cervix. There are reports of LL extrauterine locations in the broad ligament of the uterus, ovary, and peritoneum [3, 12, 13, 19].

The incidence of this neoplasm is estimated at 0.03–0.2% [15]. It is generally found in postmenopausal women, usually as a neoplasm coexisting with uterine leiomyomas. Clinical manifestations of LL are identical to those of uterine myomas. Most frequently, symptoms include: palpable mass in the pelvis minor, pelvic pain, and abnormal uterine bleedings. The majority of patients do not report any symptoms.

Intramural locations of LL in the uterine fundus are most common, but subserosal locations have been also reported [20].

Contrary to uterine myomas, which are usually found in women at the reproductive age and regress after menopause, LL is more frequently observed in older patients. It is an extremely rare, benign tumor of the uterus. When asymptomatic, it does not require treatment [7, 8].

Imaging examinations: ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI) help to differentiate LL and uterine myomas as well as dermoid cysts – teratoma and other malignant tumors in the ovaries [4, 11, 16, 18].

Detection of an admixture of mature adipocytes and smooth muscle cells in the microscopic image is required for determining the tumor to be LL. In the subject literature there are no reports as to the amount of the adipose tissue component required for classifying the tumor as LL [9].

## AIM

A case report concerning a 56-year old woman treated surgically for diagnosed uterine myomas has been presented. In the histopathological specimen obtained from the removed uterine corpus, LL has been recognized.

## MATERIALS AND METHODS

This case has been described on the basis of the medical documentation concerning the patient (case record No 24285/2010), hospitalized in the Department of Oncology and Gynecologic Oncology, Health Care Institution of the Ministry of Internal Affairs and Administration (ZOZ MSWiA) with the Warmia and Mazury Oncology Center in Olsztyn.

## CASE STUDY

The patient, 56-years old, multipara, was admitted as scheduled to the Department of Oncology and Gynecologic Oncology, ZOZ MSWiA, with the Warmia and Mazury Oncology Center in Olsztyn with a preliminary diagnosis of uterine myomas, causing pain and discomfort within the region of pelvis minor. The interview provided the following information: first menstruation at the age of 11. She gave birth 3 times, including twins. She experienced the last menstruation at the age of 50. The patient came to a gynecologist because of discomfort and pain in the hypogastrium. She had not been operated on. Family history was irrelevant. Results of additional examinations were within the norm. Metabolic disorders, hyperlipidemia, diabetes, and hypothyroidism were not diagnosed. The patient reported allergy to penicillin and aspirin. On admission, she was in a good general condition. A physical examination did not detect any abnormalities. During gynecological examination, a bimanual examination detected a palpably enlarged uterus the size of a fist, of limited mobility, adnexal mass unchanged palpably. Uterine cervix presented no visible changes and no erosion. Cervical cytology was normal. USG showed a hyperechoic lesion, about

35 mm in diameter, well-circumscribed by a hypoechoic rim, located in an enlarged uterus. The remaining part of the uterus showed a heterogeneous echogenic pattern (Fig. 1). The patient presented the results of the biopsy of the uterine cervix, canal and cavity, performed a month earlier at this Department. In the uterine cavity scrapings, fragments of leiomyoma were detected, in the cervix canal scrapings – fragments of cervix epithelium, and no pathological changes in the specimen of the cervical disc of the vaginal portion of the cervix.

After additional preoperative examinations, the patient was qualified for the amputation of the uterine corpus, with a preliminary diagnosis of uterine myomas, as well as pain and discomfort within the region of the pelvis minor. Informed consent was obtained for performing the surgery. A typical amputation of the uterine corpus was performed, leaving the uterine cervix and adnexa intact, since the patient had not consented to their removal. The patient received prophylactic preoperative antibiotic therapy and antithrombotic therapy, as well as analgesics. In the postoperative period, on the 3$^{rd}$ day, a papular rash developed – macular, located at the back, with associated pruritus. Following dermatological consultation, it was diagnosed as an allergic drug-induced eruption (Poltram). The patient was treated with 100 mg of hydrocortisone IV and Clemastin 2 × 1 tablet. The changes regressed after 2 days. The patient was discharged on the 5$^{th}$ day following the surgery, advised to take Clemastin 2 × daily. On the basis of the histopathological test performed in the Provincial Hospital LL of the uterine corpus was diagnosed. Desmin (+/–), MIB-1 = 0% of cells; leiomyomas of the uterine corpus; atrophic endometrium; parametrium free of changes.

During a follow-up gynecological examination, 4 weeks following the operation, the patient did not report previously present pelvic pain, and felt good. The wound healed by first intention.

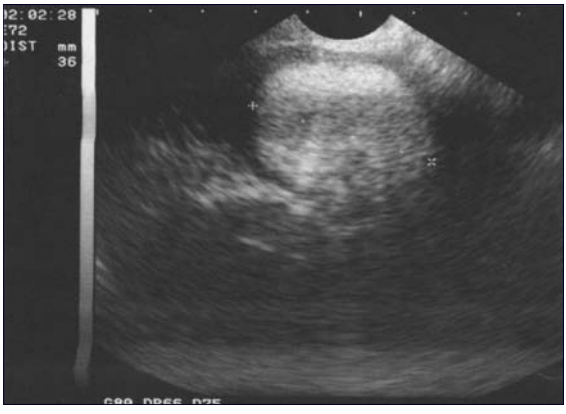


**Fig. 1.** Sonogram of the uterus showing LL – hyperechoic mass circumscribed by a hypoechoic rim

## DISCUSSION

LL cases are extremely rare in gynecological practices. They should be considered, however, in differentiating palpable lesions in the uterus, especially in postmenopausal women [9, 17, 20]. LLs are frequently reported as examples of neoplasms diagnosed accidentally in postoperative specimens [1, 2, 5, 6]. Cases of complex diagnostics, with the use of USG, as well as CT and MRI, when LL is suspected, are extremely rare [10, 16]. Detecting adipose tissue in the tumor mass confirms the diagnosis of LL. Usually, LL is initially recognized as uterine myoma, and depending on the co-occurring symptoms, may be treated surgically. USG displays features suggesting LL [14]. An image showing a hyperechoic mass circumscribed by a hypoechoic rim is characteristic for LL. Uterine myomas are the most frequent benign neoplasms found in female reproductive organs. They are associated with a hormonal activity of estrogen, and they most often occur during the reproductive period. They regress in the postmenopausal period, which is the result of a lack of hormonal activity in the ovaries. They are manifested clinically in a variety of ways: palpable mass in the pelvis minor, pain and discomfort in the hypogastrium, menstrual disorders, severe uterine bleedings leading to anemia. USG shows various images of uterine myomas. Typical uterine myomas are presented as well-demarcated hypoechoic masses, poorly suppressing and permeable for ultrasound. Myomatic uterus shows as a large, heterogeneous, circular mass, often with uneven external borders. Occasionally myomas degenerate and may show calcifications which sometimes become cystoid and undergo fatty degeneration. Differential diagnosis should also consider leiomyosarcomas, i.e., fast growing, malignant tumors formed on the basis of myomas, as well as changes involving the ovaries typical of dermatoid cysts – teratomas, whose USG image depends on the content of the cyst.

In postmenopausal women, suffering from hypothyroidism, diabetes or hyperlipidemia, more frequently LL-like changes in the uterus are found [9]. It is suggested that metabolic changes occurring in postmenopausal women are a likely cause for the development of adipose tissue metamorphosis in LL [9]. This is, however, not observed in all cases. In this described case, the patient did not exhibit any metabolic disorders.

Histogenesis of LL has not yet been precisely explained. Nevertheless, immunohistochemical studies indicate a complex histogenesis and a likelihood of LL being formed from immature mesenchymal cells, or as a result of the metamorphosis of smooth muscle cells into adipocytes [4, 5].

Detection of an admixture of mature adipocytes and smooth muscle cells in the microscopic image is required for determining the tumor to be LL (Fig. 2, 3). Adipocytes may be regularly positioned within the tumor or may exhibit a focal location [4, 5].

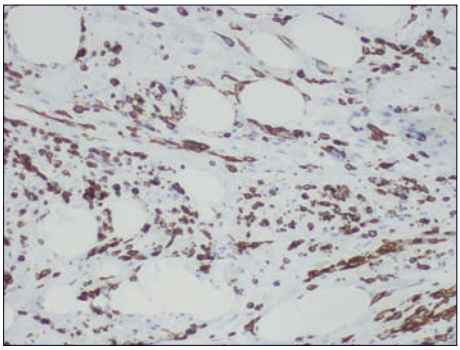

**Fig. 2.** Lipoleiomyoma [Desmina, magn. 200×]

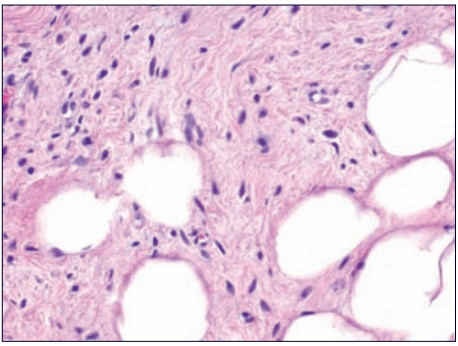

**Fig. 3.** Lipoleiomyoma [HE, magn. 400×]

In differential diagnosis of LL, imaging examinations are helpful: USG of the pelvis minor, CT and MRI [20].

In USG, LL is presented as a hyperechoic lesion circumscribed by a hypoechoic rim. The image shows a layer of myometrium surrounding the fatty central component [15]. A USG image is often interpreted by a sonography specialist as uterine myoma. In CT, the fatty component is a demarcated hypodense mass, with negative values of attenuation expressed in Hounsfield Units.

In MRI, the fatty nature of the lesion is suggested by hyperintensity on T1-weighted images. Fatty components can be also confirmed by fat suppression techniques [4, 9, 16, 18].

Imaging diagnostics play a significant role in determining the location of the intrauterous fatty nature of LL. MRI is used in differential diagnosis of LL and ovarian dermoid cysts – teratomas. Unlike LL, teratomas definitely require a surgical intervention [4].

## CONCLUSIONS

When palpable mass is detected during a manual pelvic examination in postmenopausal patients, a gynecologist should consider the possibility of LL. A characteristic USG image, i.e., a hyperechoic lesion with a hypoechoic rim, detected in the uterus should be regarded as an indication for considering such a diagnosis. CT and MRI may be helpful in preoperative diagnostics of these lesions. Such information is important for a gynecologist when qualifying a patient for a surgical procedure. The final diagnosis is established on the basis of a histopathological test involving the tissue specimen.

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*OVERVIEW PAPER*

# SELECTED BACTERIAL ZOONOSES IN MEDICAL PRACTICE

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**ABSTRACT**

**Introduction.** Zoonoses present a serious problem for medical pathology. According to epidemiologists, the occurrence of these diseases is significantly differentiated worldwide, because of dissimilar biotope structures found in particular latitudes and climatic zones.

**Aim.** The main aim of this work was to present the most important data concerning bacterial zoonoses occurring in Poland. Their etiology and epidemiology, including the methods applied to break the epidemiological chain, are discussed.

**Materials and methods.** The material used in this work consisted of available subject literature.

**Discussion.** Bacterial zoonoses are caused by microorganisms, which have adapted to human beings and specific animal species during phylogenesis. Sources of infection include sick or cured animals. Infections may be transmitted via animal products, slaughter products, as well as various elements of that environment contaminated by excrement from sick animals.

This work emphasizes the more frequent prevalence of such diseases found in rural environments as well as among representatives of specific professions. Medical procedures in the event of recognizing such a disease are presented, including the official rules of veterinary actions against these diseases occurring in animals.

**Conclusions.** 1. Prophylaxis is critical for controlling bacterial zoonoses. 2. Close cooperation of epidemiologists and specialists in epizootology is the key issue regarding efficient prophylaxis (EU directive concerning zoonoses reports from EU members). 3. Societal education with respect to zoonoses will definitely contribute to their less frequent occurrence.

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**Key words**: bacterial zoonoses, epidemiology, prophylaxis

## INTRODUCTION

Zoonoses present a serious problem for medical pathology. They occur in specific socio-economic conditions which prove favorable for infections, especially in a rural environment. They pose a serious threat to children whose immune systems are not yet fully developed. Thus, all types of infections caused by animal pathogens occur more easily and quicker in children than in adults, and the disease course is more severe. Zoonoses are defined either as diseases or infections which are transmitted naturally from animals to humans; whereas a zoonotic agent is understood to be bacteria, virus, fungi, or parasite which causes zoonoses [8].

The World Health Organization (WHO) experts committee has established a list of 134 zoonoses, but at present there are more than 200 such diseases as their numbers increase each year [16]. This results from the closer contact of man with his environment which serves as a reservoir for zoonozes, as well as containing their agents and vectors. Because of their etiology, zoonoses are divided into infectious and parasitic diseases. Infectious zoonoses are caused by pathogenic factors which have adapted to human beings and specific animal species during phylogenesis. Their etiologic factors may include some bacteria and viruses, and recently, even modified prions. Sources of infection include sick or cured animals. Infections may be transmitted via animal products, slaughter products, as well as various elements of that environment contaminated by excrement from sick animals.

## AIM

The main aim of this work is to present the most important data concerning bacterial zoonoses occurring in Poland. Their etiology and epidemiology, including the methods applied to break the epidemiological chain, are discussed. The role of zoonoses in public health, an area recognized worldwide as very important, has been emphasized.

## MATERIALS AND METHODS

This work is based on available literature concerning this subject.

## DISCUSSION

The more important zoonoses occurring in Europe include: anthrax, tuberculosis, brucellosis, salmonellosis, leptospirosis, botulism, and borreliosis [2].

**Anthrax** is an infectious, septic disease caused by the bacterium *Bacillus anthracis* which, in unfavorable conditions (in the air), produces spores extremely resistant to the outside environment. This disease primarily affects herbivores; humans are

susceptible to a lesser degree. One of the most serious epidemics of anthrax occurred in San Domingo in the 18th century. It involved cattle, horses, mules, goats, cows, cats and chickens, and killed nearly 1500 people [11]. In Europe, anthrax is found sporadically. The last time it was reported was in the year 2000 in the Danube delta in Romania. At present, it is found in some regions of Asia, South America, and Africa [16]. The disease sources include: soil, animal excrement, skin, fur fleece, infected animals and their meat.

In humans (including children) a cutaneous form most frequently occurs, manifested by painless blisters on hands or head, turning into black crusts (carbuncles). Untreated infections may occasionally lead to septicemia. Inhalation anthrax is initially manifested by fever, then the disease progresses to pneumonia and a state of shock. Intestinal anthrax is accompanied with high temperature and severe bloody diarrhea.

Mortality in humans suffering from untreated pulmonary anthrax reaches 100%, from intestinal anthrax about 50%, and in the case of cutaneous anthrax it does not exceed 20%. Anthrax is treated with antibiotics and symptomatic treatment [18].

The bacteria *B. anthracis* have a relatively low level of resistance with respect to external agents. Disinfectants kill them quickly. In gastric juice *B. anthracis* die after 15–20 minutes, at temperatures of 55–58°C within 10–15 minutes, and in a buried corpse after approximately 4 days. At a temperature of –15°C the bacteria are destroyed after about 2 weeks, whereas corning takes as long as 1.5 months to kill them. Anthrax spores are much more resistant. In dry animal material they may survive for years, just as in water, and especially in burial soil (at a depth of 1.5 m) where they were found even after 24 years had elapsed. Neither meat corning nor gastric juice affect spores, whereas at temperatures of 120–140°C (dry air) they die after 3 minutes, in steam (100°C) within 5 minutes. Spores are destroyed by formaldehyde, 5% potassium permanganate, 5% phenol, and 5% fresh calcium chloride [13].

Due to a significant pathogenicity and resilience of anthrax spores, they are classified as biological weapons posing a serious terrorist threat. The last noted usage of anthrax as a terrorist weapon, known from media, occurred in the USA in 2001, when 22 people were infected via the mail, and 5 of them died [16].

Anthrax in animals is controlled ex officio, and carcasses of infected animals are considered unfit for consumption [13].

**Tuberculosis**, according to WHO, at the beginning of the 21st century still remains a health problem of a global nature.

Approximately 30% of the world's population (about 2 billion people) is infected with tuberculosis; 7–8 million people develop this disease, and about 2–3 million die annually from it. Poland is one of those countries with a high incidence of tuberculosis, with its incidence level being twice higher than that of the Czech Republic, and 5-times higher than that of Norway and Sweden [14]. It has been shown that rural

area residents suffer from tuberculosis more frequently than urban area residents, and men twice more frequently than women. The incidence of tuberculosis in children accounted for about 1% of all registered cases in 2003. It should be added that due to diagnostic difficulties in children, they should be diagnosed by medical teams in well-equipped centers. A special board established at the Tuberculosis and Lung Diseases Institute in Warsaw has questioned the correctness of diagnoses in 30.0% of cases. Tuberculosis-related deaths account for 0.2% of all deaths and 37.4% of infectious diseases-related deaths [14].

Tuberculosis is also found in animals. They serve as reservoirs and sources of infection for humans. It can be also transmitted from humans to animals. It is caused by *Mycobacterium tuberculosis* represented by 3 pathogenic species of the genus *Mycobacterium*: *tuberculosis*, *bovis* and *avium*. *M. tuberculosis* causes tuberculosis mainly in people, rarely in animals. *M. bovis* is the main cause of tuberculosis in cattle, but may also affect people and other animal species. *M. avium* affects mainly birds, whereas humans are relatively resistant to it.

*M. tuberculosis* is very resistant to external agents. It has been discovered to have survived in the lungs of buried, deceased people after 167 days, and in the intestinal content after 178 days. It survives in the organs following 1.5-months of corning, and in cold cooked meat after a 15-minute scalding at a temperature of 85°C. *M. tuberculosis* is killed by boiling or pasteurizing milk whereas it survives up to 15 days in sour milk, in cream butter up to 4 weeks, and in salted butter (4–6%) up to 5–10 days. Effective disinfectants include: 2% phenyl solution, 1% cresol and 3% formalin, which destroy mycobacterium within 4 hours, whereas in 80% ethyl alcohol destruction occurs after 10 minutes [13].

In natural conditions, infection with *M. bovis* in cattle occurs via direct or indirect contact with contaminated objects. In 95% of cases, infections occur via the respiratory tract, in 4% via the alimentary tract and, in about 1% of cases, via the skin or mucous membrane [19]. In cattle, pathological changes generally involve lungs and bronchial and mediastinal lymph nodes, rarely other organs; whereas in pigs, changes are located mainly in the alimentary tract.

In humans, the main etiological factor is *M. tuberculosis* transmitted by infected people; less frequently it is *M. bovis* transmitted by milk or contact with an infected animal. It should be emphasized that no infections of humans caused by dogs and cats which can be infected by *M. tuberculosis* and *M. bovis* have been noted [19]. Human-to-human infections with *M. bovis* are very rare, and clinical symptoms of infected people may be the same as in *M. tuberculosis* infection [4]. Recently in Europe, due to long-term efforts to control tuberculosis in cattle, there has occurred a shift in the sources of infection due to fowl, with *M. avium* being the infectious agent. This may contribute to an increase in the incidence of infections and the development of avian tuberculosis by humans. Fish tuberculosis, especially that involving aquarium fish, cannot be overlooked. The etiological factors for these infections

include: *M. piscium, M. asinum* and *M. fortuitum* characterized by foodborne transmission, and in viviparous fish by transovarian transmission. The sources of infections include: contaminated water, sand, plants, and aquarium fish. Mycobacterium hosted by fish may cause cutaneous forms of tuberculosis in humans [16].

Tuberculosis is treated with complex anti-mycobacterial chemotherapy which usually leads to a complete cure.

Prophylaxis involves: vaccinations, isolating sputum-positive patients, improving the living conditions of the population, examining people who have come into contact with sources of infections, performing tuberculin skin tests, and chemoprophylaxis.

Tuberculosis is a disease controlled ex officio, and in people tuberculosis treatment is compulsory. Cattle infected with tuberculosis are not treated, and animals with positive tuberculin reaction are slaughtered. When tuberculosis is recognized after slaughter occurs, the entire carcass is considered unfit for consumption [13].

**Brucellosis** is a bacterial disease originally occurring in animals, but transmitted to humans. The etiological factors are bacteria of the genus *Brucella*: *melitensis*, *abortus*, *suis*, and *canis*, very common worldwide. In Central Europe the bacterium *B. abortus* is most common in cows, and in southern Europe, especially in Mediterranean countries, in goats. The main reservoirs for the bacteria include: infected fetus, fetal membranes, and amniotic fluid. Among animals the infection is transmitted after consuming contaminated fodder or water or through damaged udder and extremities skin. In the course of this disease cows excrete the bacteria with milk and excrement. The bacteria survive 8 months in an aborted fetus; up to 3–4 months in feces, urine, and liquid manure; up to 2–3 months in wet soil. At 60°C the bacteria are destroyed after 30 minutes, at 86°C after 5 minutes, and at 100°C immediately. *Brucella* bacterium survives meat pickling even in pH 4.0 environment. In corned and smoked meats it was discovered after 63 days. In frozen meat it survives up to 460 days, whereas in a 25% saline at 0°C up to 21 days [13].

In humans, high risk groups involve: people employed in barns and slaughterhouses, as well as veterinarians (in the 1970s in the Province of Gdańsk, in such a group 18.6% manifested a positive agglutination reaction) [9]. Humans are infected by infected animals, unpasteurized milk of infected animals, and cheese produced from such milk. Once transmitted to a given organism, the bacteria locate themselves in the lymph vessels of the lymph nodes where they multiply, and then penetrate into blood and other organs causing inflammation. In pregnant women, they penetrate to the fetus, leading to abortion. The incubation period lasts 7–8 weeks. Clinical symptoms include: fever, nausea, general weakness, sweating, headaches, arthralgia, and hepatosplenomegaly. After a year, the disease becomes chronic, accompanied with general weakness and arthralgia, and in women it leads to infertility [16]. In Poland, brucellosis is extremely rare, e.g., 63 cases were reported in 1997, 43 cases in 1999, and 29 in 2000 [5], whereas in 2006 no cases were reported [9].

**Salmonellosis** is an acute infectious disease (food poisoning) caused by *Salmonella* bacteria, occurring mostly in animals, but also in humans. Salmonellosis reservoirs often include: undiagnosed vectors, humans and animals excreting the bacteria into the environment in their feces, as well as animals during abortion, when the bacteria are excreted with the fetus, placenta, and amniotic fluid. *Salmonella* bacteria may survive for months and years in waste, water and soil, where they can multiply. They also congregate in animal-derived food products. The bacteria are very resistant to low temperature, e.g., in raw turkey meat stored in –18°C living bacteria were found after 3 months. *Salmonella* bacteria are sensitive to high temperatures; they die during meat cooking, and at 70°C after 10–15 minutes. They are slightly sensitive to saline, e.g., in a 20% saline at 25°C after 47 days their number is 10-times reduced [13].

Animals, especially young ones, may be infected through consuming fodder and by contact with litter. Following such an infection, bacteria penetrate into the alimentary tract, and then to blood and internal organs, where they multiply until developing clinical symptoms in the infected organism (fever, diarrhea, dehydration). In pregnant animals, they can also penetrate into the placenta and fetus leading to death [18, 19].

Infection in humans is only possible through infected food (meat, milk, eggs) or food infected during its processing. Direct infections may occur when proper hygiene is not observed. Newborns, children, and youth are most susceptible. The incubation period is short, 6–48 hours from becoming infected. Depending on the infectious dose, host sensitivity and bacterial stereotype, this disease may run various courses, from mild diarrhea to severe illness, accompanied with fever, diarrhea and vomiting. Children may manifest febrile convulsions. Frequent defecation quickly leads to dehydration, especially dangerous for children and older people, causing renal function failure. Fever and vomiting usually subside after 1–2 days, whereas diarrhea and stomach ache continue for 5–10 day. During the course of this disease, bacteria are excreted continually, and then over several weeks at intervals. Following this disease, the bacteria remain in the liver, spleen, and lymph nodes. Occasionally, as a result of stressors, the reactivation of the vector state may occur, leading to developing the disease. Immunity acquired during the disease is short-lasting and specific for the bacterial strain which caused it [2]. In 2006, 13 362 cases of salmonellosis were reported [11].

Significant activities in salmonellosis prophylaxis involve veterinary and sanitary control of animal-derived food and periodically performed tests for the vector state among meat processing workers and collective nutrition workers. Carcasses and internal organs of animals infected with salmonellosis are considered unfit for consumption [13].

**Leptospirosis** is an infectious disease which occurs worldwide, caused by spirochaetes of the genus *Leptospira*, encompassing about 200 serotypes, which were

classified as bacteria as late as 1988 [2]. In Poland, several cases of leptospirosis are reported annually [11]. The main reservoirs for the bacteria include: rodents, mice, rats, as well as domestic animals, especially dogs, cattle, and pigs. This disease is caused by infected animals and asymptomatic vectors who excrete the bacteria with their urine (occasionally up to 1 million in 1 mL), as well as with milk. Unhealed breaks in the skin and mucous membrane are the entry points for infections. Alternative modes of infection are also possible, by consuming food or water contaminated by an infected animal's urine, as well as via direct contact with an ill animal, and through insects and inhaling contaminated dust. Once the spirochaetes penetrate into an organism, leptospiremia occurs. Then, specific antibodies eliminate leptospirae from blood circulation and these are located in convoluted tubules and reproductive system cells [19]. They are very sensitive to high temperature: at 50–55°C they die within 30 minutes, and above 65°C almost immediately. The spirochaetes manifest a higher resistance to low temperatures, e.g., they survive at –4°C up to 26 days, and in frozen meat up to 15 days. *Leptospira* is especially sensitive to an acidic environment, pH 6.0 is critical for its survival. Horizontal person-to-person infection is not observed. The course of this disease in humans, as well as in animals may vary from asymptomatic to acute leading to death as a result of renal failure. Symptoms of leptospirosis include: fever, vomiting, headache, jaundice, muscle aches, poor well-being, cerebrospinal meningitis, pneumonia, and nephritics. Generally, recovery is possible. Infections caused by *L. interohaemorrhagiae* lead to developing jaundice after a few days, renal failure, cirrhosis; in such cases mortality may amount to 20%. In pregnant women, leptospirosis may lead to abortion or severe general infection of the newborn. Casual treatment involves administering antibiotics (penicillin, streptomycin) with simultaneous symptomatic treatment. People belonging to high-risk groups may be vaccinated to prevent infection [19].

Leptospirosis is not controlled ex officio, but in clinical cases carcasses and the internal organs of infected animals are considered unfit for consumption [13].

**Botulism**, also known as botulinis intoxication, is caused by anaerobe *Clostridium botulinum*. In unfavorable conditions, these bacteria produce spores which are resistant to external agents. In Poland, about 165 cases of intoxication are reported annually; in 1997, 3 cases in children aged 4 were reported and 7 cases in children aged 5–14; deaths were not reported [15]. *C. botulinum* spores survive cooking for 3–5 hours, and under pressure at 120°C they are alive for up to 5 minutes. In corpses, green fodder, and silage, they survive many months [13]. *C. botulinum* developing under anaerobic conditions can produce exotoxine which is one of the most powerful toxins for a human organism. Lethal dosage of this toxin is about 0.12 μg. It is released to the environment mainly after the bacterial autolysis. Infection is most frequently transmitted to humans via the alimentary tract, following the consumption of salted and preserved foods which were insufficiently thermally processed. In

Poland, the main source of infections (65%) is canned meat, including home-canned (20%) [15]. Infections via wounds are also possible [2]. The incubation period of this disease ranges from some to 14 days in animals; whereas in humans from some to 14 hours. In exceptional cases it is prolonged to 7 days. Botulinum toxin present in food penetrates from the alimentary tract into blood and blocks acetylcholine release, leading to the paralysis of cholinergic fibers. In the course of this disease, two sets of symptoms may be differentiated, namely, non-specific symptoms: nausea, vomiting, loose stool, stomach ache, dizziness, weakness, and specific symptoms: vision distortion, mydriasis or pupilloplegia, dry mouth and throat, drooping of both eyelids, hoarse voice, loss of voice, facial muscles paralysis, decreased peristalsis, retention of urine, and muscle weakness. In wound botulism, irrespective of the specific symptoms, increased body temperature, prolonged incubation period (up to 2 weeks) and no symptoms associated with the alimentary tract are observed. Death is caused by heart failure or respiratory muscle failure. Infant botulism is a very dangerous form of this disease. It was first described in 1976, and it refers to children up to 6 months of age [15]. The pathogenesis of this form of botulism is not entirely known. It is probably caused by *C. botulinum* spores which can, exceptionally, develop under the conditions occurring in the alimentary tract of infants, producing the toxin leading to the intoxication symptoms [15]. The major dietary reservoir is bee honey, thus in the USA an educational action has been organized concerning not adding honey to milk blends. In Europe, infant botulism associated with honey consumption accounts for 59.2% of cases [17]. Clinical symptoms of infant botulism include: decreased sucking ability, decreased muscle tone, hypotonia, lack of or decreased tendon reflexes, poor facial activity, respiratory difficulties, and constipation [2, 3, 17]. Symptomatic treatment is ordered, serum is commonly administered. However, only intravenous hyperimmune vaccine (Big-IV) used in the USA, which binds free toxin, may revolutionize infant treatment [3].

Because of producing a very powerful toxin and spores resistant to external agents, *C. botulinum* is classified as a biological weapon.

**Borreliosis**, also known as Lyme disease, is caused by the treponema *Borrelia burdgorferi* (less frequently *B. garinii*), whereas the vector is usually a tick belonging to the genus *Ixodes*, transmitting infection from human to human. A natural reservoir consists of small rodents; frequently the infection is also transmitted by deer. In Poland, borreliosis is most frequently transmitted by ticks [6, 20]. The regions which are most endangered are: Podlaskie Province, Zachodniopomorskie Province, Mazury and the region of Suwałki.

In order for the borreliosis infection to occur, a tick must remain on the skin for several hours. Then the number of transmitted bacteria is sufficient for developing the infection. The incubation period is 1–3 weeks, followed by an early stage characterized by circular skin rash called erythrema migrans. Occasionally the erythrema

involves the entire limb, is painful, and the patient feels weak and feverous. After 2–4 weeks this erythrema disappears, usually with no subsequent consequences. It happens, however, that after this period, or even after 3 months, symptoms occur, such as: arthritis, neurological and cardiac disturbances.

Arthritis develops in untreated people in the early phase: it involves large joints, exudates are observed as well as synovitis. This disease should be differentiated from rheumatoid arthritis. Proper treatment is usually effective; however, cases of recurring arthralgia are known. Cerebrospinal meningitis, peripheral neuropathy and inflammation of peripheral nerves are serious complications, leading occasionally to physical disability, and in exceptional cases to death. Another serious complication is myocarditis, which may cause complete hart block and progressive cardiomyopathy.

In diagnosing borreliosis, serological and polymerase chain reaction (PCR) tests are used. The most effective prophylaxis involves vaccines; however, devising a vaccine in Europe is complicated by the fact that three etiological factors are found here. In the USA, where only one etiological factor occurs, a vaccine (LYMErix) is administered in endemic territories [1, 7]. In Poland, the Ministry of Health recommends the guidelines devised by the Polish Society of Epidemiologists and Contagious Diseases Physicians (Societas Polona Epidemiologorum et Medicorum Contagiosorum). Some physicians also propagate the method devised by the International Lyme and Associated Disease Society.

## CONCLUSIONS

1. Prophylaxis is critical for controlling bacterial zoonoses. This is evidenced by the European Union (EU) directive concerning a requirement for annual reports on various zoonoses indentified in the EU countries, and prepared by each member state.
2. Close cooperation of epidemiologists and specialists in epizootology is the key issue regarding efficient prophylaxis.
3. Societal education with respect to zoonoses will definitely contribute to their less frequent occurrence.

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*OVERVIEW PAPER*

# CHAGAS DISEASE – AMERICAN TRYPANOSOMIASIS

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**ABSTRACT**

**Introduction.** Despite the fact that more than 100 years have passed since the discovery of Chagas disease, research carried out to date with respect to this condition and especially treatment methods concerning it, are still deemed insufficient. The World Health Organization (WHO) recognizes it as one of the Neglected Tropical Diseases (NTD), occurring primarily in the most destitute regions.

**Aim.** This work aimed at drawing the attention to the relationship between the levels of interest presented by medical and pharmaceutical circles in American trypanosomiasis and the types of social groups that this disease affects.

**Materials and Methods.** Available literature concerning this subject, as well as estimates indicating the scale of this problem have been analyzed.

**Discussion.** American trypanosomiasis is a tropical parasitic disease affecting predominantly the residents of both Americas. Chagas disease is associated mostly with the marginalized social strata, due to a special predilection of *Triatominae* vectors for residing in poor households. All insects belonging to the subfamily *Triatominae* feed on vertebrate blood and thereby transmit the parasite called *Trypanosoma cruzi*. In the disease's course, three key phases may be differentiated: acute, latent and chronic. In the majority of cases, the first two phases are asymptomatic, significantly inhibiting detection of the disease. Despite advances with respect to curtailing vector transmission, research concerning effective treatment of Chagas disease remains insufficient. There are only two types of obsolete medications to treat it. Their availability is limited and production continues unstable, whereas their administration is associated with serious side effects and their effectiveness is quite limited.

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**Conclusions.** Although vector transmission has been to a significant degree controlled, lack of effective medication which could serve to treat this disease indicates a failure with respect to health policies adopted by endemic countries. American trypanosomiasis, tropical in nature, should become an object of interest for highly developed countries in the near future, because of the increasing migrations concerning infected groups of people.

**Key words**: Chagas, *Trypanosoma cruzi*, endemic countries, Neglected Tropical Diseases (NTD)

## INTRODUCTION

Research carried out to date with respect to Chagas disease and its possible treatment methods are still insufficient, despite the fact that more than 100 years have passed since the discovery of this disease by a physician from Brazil. The World Health Organization (WHO) recognizes it as one of 17 Neglected Tropical Diseases (NTD), which have survived only in the poorest and the most marginalized societies. The majority of them could be easily eliminated. However, due to the political insignificance of those social groups affected by them, NTD are not viewed as priority threats to public health. The majority of diseases from the WHO list are found in regions stricken with extreme poverty, such as remote rural areas, urban slums, or armed conflicts zones. Thus residents of such regions frequently die before they can be diagnosed.

## AIM

This work aimed at drawing the attention to the relationship between the levels of interest presented by medical and pharmaceutical circles in American trypanosomiasis and those excluded social groups inhabiting endemic countries that this disease, until recently, has singularly affected.

## MATERIALS AND METHODS

Available literature concerning the subject has been analyzed. Official estimates provided by the WHO and Pan American Health Organization (PAHO) have been quoted, which only point to some general tendencies, since they cannot serve to describe specific situations in those endemic countries precisely.

## DISCUSSION

American trypanosomiasis is a tropical parasitic disease affecting predominately the poorest residents of both Americas. Although it has been discovered and described relatively recently, its existence is estimated for at least 4000 years. Tests performed on mummified tissues of the representatives of the pre-Columbian Chinchorro culture

revealed fragments of the parasite's DNA, which led to the conclusion that already then the disease had been endemic [14]. It is believed that Charles Darwin's death, he being the author of the famous treatise *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*, was a result of Chagas disease. Both its symptoms as well as its course in time correlate with the characteristics of American trypanosomiasis [2, 32]. Moreover, in his notes devoted to the expedition to South America, Darwin provided a description of the insect's bite, which years later was discovered to be the main vector of the disease [12].

At the beginning of the 20$^{th}$ century, a disastrous sanitary situation occurring in many countries of Latin America prevented the implementation of various infrastructure projects within the policy designed to colonize the interior of the continent. In Brazil, both private entities and governmental agencies involved in such investments were forced to undertake proper measures to eliminate epidemic diseases such as yellow fever, true smallpox and plague, which decimated workers employed in the construction of railways, roads and other public facilities [18]. In 1908, Brazilian physician Carlos Ribeiro Justiniano das Chagas was asked to undertake an antimalaria campaign in the village of Lassance, province of Minas Gerais. Chagas assumed a correlation between the health conditions of the workers and the hemipteran *Triatoma infestans* belonging to the subfamily *Triatominae*, which infested rural huts of this region [8].

Chagas dissected the insect and found in its digestive tract large numbers of single-celled parasites of the genus *Trypanosoma*. Consequently, it was important to confirm whether this insect's bite resulted in a pathogenic reaction in vertebrates. To this end, Chagas carried out an experimental inoculation of various animal species, which shortly afterwards developed disease symptoms and some of them died within a few weeks. Assuming that the final host of this microorganism, which Chagas named *Trypanosoma cruzi*, should be human, he then searched for the parasite in the blood of the people inhabiting huts colonized by the hemipterans. In one of them he found a 2-year old girl, with the symptoms of fever, hepatomegaly, splenomegaly, lymphadenopathy and a swollen face. Animals infected with the blood of this first patient died within a few days. In 1909, Carlos Chagas published a paper in which he described the clinical symptoms of American trypanosomiasis, *T. cruzi* and its life cycle as well as the main vector of the disease [22]. It is particularly remarkable that "he started, so to speak, at the wrong end: with a (possible) vector of a (possible) pathogen, causing a disease yet to be discovered and described" [18]. His discovery was immediately successful. In 1912, Chagas was presented with the Fritz Schaudinn Award, and in 1913 and 1921 he was nominated for the Nobel Prize. There appeared scientists, however, who not only questioned the significance of his discovery, but also challenged the existence of American trypanosomiasis itself. Although numerous polemical papers show that Chagas was most frequently successful in defending

his discovery, for years a false opinion predominated that the disease did not pose a serious threat to the public health in Latin America [22].

Chagas disease is mostly associated with the poorest social strata, due to a special predilection of hemipterans of the subfamily *Triatominae* (belonging to the family *Reduviidae*, order *Hemiptera*) for residing in huts with walls made of clay and palm, bamboo or thatched roofs. Crevices in such surfaces serve them as protection during the day, which they will leave after dusk to prey [6]. Some species live only in selva – tropical forest. Others, most probably because human activity has disturbed the balance of their natural environment, have adapted themselves completely to human households or their whereabouts. These species are exceptionally important in the context of epidemiology (*Triatoma infestans* in Argentina, Bolivia, Brazil, Paraguay, Uruguay, Peru and Chile; *Rhodonius prolixus* in Columbia, Mexico, Venezuela and some countries of Central America; *Triatoma dimidiata* in Ecuador, Mexico, Central America and *Rhodonius pallescens* in Panama) [10, 17, 25]. There exist many popular regional names for the vector of Chagas disease: bedbug, "kissing bug", *chinche*, *chipo*, *pito*, *bananom*, *chirimacha*, *chichâ*, *chupão*, *chupança*, *bicudo*, *fincão*, *protocó*, *chinche besucona* and *chinche gaucha*. The most common term seems to be *vinchuca*, a word which means "plots while flying" in the quechua language [6].

All insects from the subfamily *Triatominae* feed on vertebrate blood. A bite is not painful, but causes itching. Thus, through a microdamage to the skin, the host contributes to introducing *T. cruzi*, excreted by the insect, into blood vessels [28]. *T. cruzi* is haemoflagellate, which indicates this protozoan's place of inhabitation in the human host. This is within the blood and closely related tissues such as spleen and liver. Haemoflagellates may assume all four different morphologic forms during their life cycle: amastigote, promastigote, epimastigote, and trypomastigote. "While these forms appear to be successive stages, there is no specific sequential pattern of progression from one form to the next. Each form gives the parasite certain advantages and any of these forms is capable of developing into any other" [4].

**Fig. 1.** Development forms of *Trypanosoma cruzi*: amastigote, promastigote, epimastigote and trypomstigote (Kingdom: *Animalia*, Subkingdom: *Protozoa*, Phylum: *Sarcomastigophorea*, Subphylum: *Mastigophorea*, Class: *Zoomastigophorea*, Order: *Kinetoplastida*, Family: *Trypanosomatidae*, Section: *Stercoraria*, Genus: *Trypanosoma*, Species: *cruzi*).

Amastigote is an intracellular form of the *T. cruzi* parasite. It is ovoid in shape with a diameter of 1.5–5 μm, a large nucleus, and prominent kinetoplast. Promastigote occurs only in the insect vector. It is elongated with the kinetoplast at the extreme anterior end and the nucleus in the centre of the organism. Its long flagellum is free

anteriorly and serves a function of both locomotion and attachment to the insect gut wall. In epimastigote form the kinetoplast is anterior to the nucleus and the flagellum is attached to the pellicle, producing an undulating membrane. Trypomastigote is characterized by a lengthening of the body (10–20 μm long, 1–3 μm wide), elongation of the undulating membrane and flagellum, and migration of the kinetoplast to a site posterior to the nucleus. The parasite moves in the direction of the free end. The pellicle of the trypomastigote is supported by minute tubular structures which help in maintaining its shape and flexibility during movement. The flagellar membrane is closely attached to the body surface, and when the flagellum beats, this area of the pellicle is pulled up into a fold. The fold and the flagellum constitute the undulating membrane [3, 4].

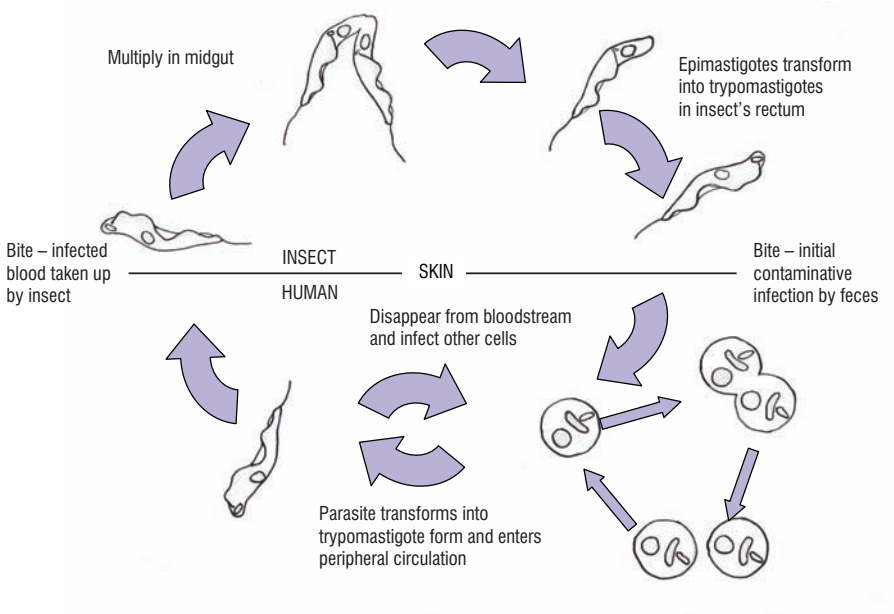


**Fig. 2.** *Trypanosoma cruzi* life cycle

The stage of *T. cruzi* infective to humans, the trypomastigote, develops in the hindgut of the *Triatominae* insect. The trypomastigote forms are passed out with the feces of the bug, usually as it is taking a blood meal from a vertebrate host. Infection occurs when infected fecal material is rubbed into the bite wound, eyes, or mucous membranes. Upon introduction into a human host, the parasites invade macrophages of the subcutaneous tissue at the site of infection, causing a local, edematous swelling called chagoma. There, the parasites rapidly transform into the amastigote (intracellular) form. The amastigotes evade the lysosome system by escaping into the cytosol of the infected cell. Following repeated longitudinal binary fissions by the

amastigotes, the infected cell ruptures and the released amastigotes enter other cells. Some of the released amastigotes revert to the trypomastigote form and enter the circulatory system. Insects become infected by ingesting blood that contains anteriorly trypomastigotes, which then undergo repeated longitudinal fission during passage through the digestive tract of the insect. By the time they reach the midgut, they have metamorphosed to the epimastigote stage. Still replicating, the epimastigotes pass into the insect hindgut where they attach themselves by their flagella to the epithelium of the rectal gland. As transformation to the trypomastigote forms occurs, the flagellar-epithelial attachment is lost. By the $10^{th}$ day after ingestion, the infective trypomastigotes appear free in the lumen of the rectum [4].

Apart from the described mode of transmission, others are also possible. Infections during blood transfusions are becoming significant, especially in those regions, where vector elimination programs are being implemented, where a large percentage of the population is infected with *T. cruzi*, and blood donors are not screened for Chagas disease [9, 13]. Vertical transmission occurs when *T. cruzi* manages to penetrate into the placenta of a seropositive mother and infects the embryo or the fetus during birth as a result of the contact between a mother's blood and the child's mucous membranes. The risk of such an infection ranges from 1% in Brazil to 12% in Argentyna, Bolivia, Chile and Paraguay [24]. It is estimated that this type of transmission will remain a serious problem for at least 30 years, until a significant reduction in the number of infected women at the reproductive age occurs [9]. Infections caused by laboratory incidents, organ transplants [13, 19] or through the digestive system, when food contaminated with vectors' feces is consumed [5, 9, 26] are relatively rare.

In the course of the disease, three key phases may be differentiated. In the first, acute phase, symptoms associated with the mode in which *T. cruzi* have penetrated into an organism occur. An inflammatory condition develops in the place of inoculation. In many cases a characteristic swelling of the eyelid, called Romaña's sign, occurs. It appears when the parasites have managed to penetrate through the membrane covering the eyeball. In his phase other symptoms, including lymphadenopathy, low grade fever, hepatomegaly, splenomegaly, diarrhea, muscular spasms, respiratory dysfunction, coma, bluish coloration of the mucous membranes, muscle and joint aches, appear after 4–10 days from inoculation indicating the incubation process. All the enumerated symptoms remain for several months and manifest that *T. cruzi* have spread within the organism via the circulatory system. It is estimated, however, that in 70–95% of cases, the acute phase of Chagas disease is asymptomatic. This significantly inhibits its detection during the first phase which is critical with respect to possible treatment [24]. In approximately 1% of such cases, if parasites violently attack cardiac tissues or the central nervous system tissues, the infection may cause sudden death (especially in children less than 1 year of age) [29].

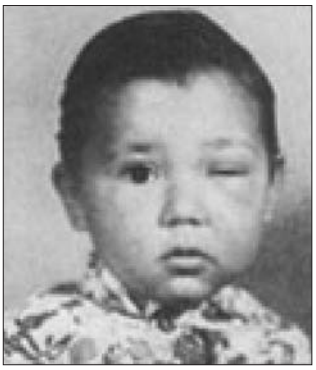

**Fig. 3.** Romaña's sign [34]

After the acute phase, an immune response of the organism appears and leads to reducing parasitemia, limiting it to some foci. This phase, called latent is characterized by a slow multiplication of parasites and lack of evident symptoms, despite serious changes within the infected tissues [27]. After about 10–35 years, 30–50% of patients enter the third phase – the chronic phase [24, 30]. A large majority of patients develop cardiomyopathy, associated with ventricular hypertrophy, caused by the activity of the parasite within the cardiac tissues. Death of the patients with chronic Chagas cardiomyopathy is provoked by *mors subita cardialis* (55–63%), progressive cardiac insufficiency (20–25%) and thromboembolic complications (10–15%) [15]. When the digestive tract tissues are affected by *T. cruzi*, a pathological dilation of the colonic lumen and enlarged esophagus (megacolon and megaesthopagus) ensue [23].

The efficacy of laboratory diagnostic methods in detecting *T. cruzi* depends on the phase of the disease advancement. The applied method should be adequate to the phase in the parasite developmental stage. In the acute phase of Chagas disease, direct microscopic observation of trypomastigote forms in the host blood is possible. This allows for detecting the disease in 85% of cases. This number increases to 95% when concentration methods are employed [20]. In the latent and chronic phases, serological tests are usually performed, most frequently enzyme-linked immunosorbent assay (ELISA) and direct immunofluorescence (IF), with 95–98% sensitivity [24].

Despite advances in curtailing vector transmission, research concerning treatment methods for Chagas disease is deemed insufficient. There exist only two obsolete medications, Nifurtimox® developed in 1965 and Beznidazol® in 1969. Their production is unstable and availability limited [21]. Slight interest in new and more effective medication is most frequently justified by a lack of adequate financial stimuli for the pharmaceutical industry. An average cost of producing a new drug is estimated at US $800 mln. Thus, it is not surprising that only 1% of newly registered medication is targeted toward controlling tropical diseases, occurring mostly in regions inhabited by

the poorest societies, whereas about 90% of the investment in research and development of this industry has been allocated for pharmaceutical products designed for 10% of the world's population with the highest incomes [33].

The administration of the aforementioned medication does not raise any doubts concerning the acute phase of the disease, as it inhibits intracellular multiplication and spreading of *T. cruzi* in various tissues. In 80% of cases, Chagas disease at this phase can be completely cured. If the medication is administered to the patient within 30 days from the appearance of the first symptoms, pharmacological therapy should last for 3–5 years. Later on, the application of both available medications is advised only for children in the early stage of the chronic phase (parasitic elimination is possible in 60% of cases within 5–10 years of continuous pharmacological therapy). In adults in the chronic phase of Chagas disease, the parasite can be eliminated only in about 20% of cases, as a result of long-term treatment lasting 20–30 years [20].

The advocates of administering available medications argue that "although they cannot eliminate parasitemia in the majority of patients, [treatment] leads to a significant reduction in pathological changes […] and less frequent exacerbations in the clinical manifestation" [33]. The opponents of prescribing Nifurtimox® and Beznidazol® prove that there is only a slender chance of being cured and it is associated with severe side effects. Complications resulting from taking available medications may last long after the completion of the therapy [21]. In 30% of cases undesirable secondary effects appear, such as: anorexia, nausea, vomiting, stomach aches, diarrhea, skin infections, insomnia, hallucinations and psychosis. Because of doubtful long-term clinical outcomes and a detrimental relation between risks and advantages stemming from the use of such medication, in the majority of cases palliative treatment is ordered [1].

## DISCUSSION

In order to assess the extent of Chagas disease, reliable data concerning the number of cases of this disease are indispensable. According to one complete statistical study carried out between 1980–1985 (before the implementation of the regional programs to eliminate the main vector) in Latin America 17.4 mln people were infected with *T. cruzi*, and about 100 mln (i.e., 25% of the inhabitants of the entire region) were directly at risk of being infected. The incidence was estimated at 300 thousand of new cases annually, and mortality at 21 thousand (especially among children) [7]. In 2005, the Pan American Health Organization evaluated the number of people infected with *T. cruzi* to be 7 694 500 [11, 31], and the number of people directly at risk of being infected to be 108 595 000 [11] (Tab. 1).

**Tab. 1.** Estimated data on Chagas disease in particular Latin American states [7, 11]

| | 1980–1985 | | | 1998–1999 | 2005 | | | |
|---|---|---|---|---|---|---|---|---|
| | Prevalence index [%] | Number of people at risk of infection | People at risk of infection [%] | Seroprevalence among blood donors [%] | Number of infected people | Prevalence index [%] | Incidence (via vector) [%] | Seroprevalence among blood donors [%[ |
| **Argentina** | 10.0 | — | 23 | 4.10 | **1 600 000** | **4.129** | 0.003 | **2.47** |
| **Belize** | — | — | — | 1.00 | 2 000 | 0.741 | 0.009 | 0.40 |
| **Bolivia** | **24.0** | 1 800 000 | 32 | — | **620 000** | **6.752** | **0.112** | **8.00** |
| **Brazil** | 4.2 | 41 054 000 | 32 | 0.73 | **1 900 000** | 1.019 | 0.000 | 0.21 |
| **Chile** | 16.9 | 11 600 000 | 63 | 0.5–2.60 | 160 200 | 0.656 | 0.000 | 0.47 |
| **Ecuador** | 10.7 | 3 823 000 | 41 | 1.00 | 230 000 | 1.739 | **0.018** | 0.36 |
| **Guatemala** | 16.6 | 4 022 000 | 54 | 8.00 | 250 000 | 1.984 | 0.017 | 0.01 |
| **Honduras** | 15.2 | 1 824 000 | 47 | 1.65 | 58 600 | **3.053** | **0.039** | 1.40 |
| **Columbia** | **30.0** | 3 000 000 | 11 | — | 436 000 | 0.956 | 0.012 | 0.80 |
| **Costa Rica** | 11.7 | 1 112 000 | 45 | 2.10 | 23 000 | 0.532 | 0.001 | 0.14 |
| **Mexico** | — | — | — | — | **1 100 000** | 1.028 | 0.007 | 0.60 |
| **Nicaragua** | — | — | — | — | 58 600 | 1.140 | 0.015 | 0.90 |
| **Panama** | 17.7 | 989 000 | 47 | — | 21 000 | 0.006 | 0.007 | 0.90 |
| **Paraguay** | **21.4** | 1 475 000 | 31 | 5.00 | 150 000 | 2.543 | 0.015 | **3.20** |
| **Peru** | 9.8 | 6 766 000 | 39 | — | 192 000 | 0.686 | 0.011 | 0.57 |
| **Salvador** | **20.0** | 2 146 000 | 45 | 7.00 | 232 000 | **3.372** | **0.036** | **2.42** |
| **Uruguay** | 3.4 | 975 000 | 33 | 0.06 | 21 700 | 0.656 | 0.000 | 0.47 |
| **Venezuela** | 3.0 | 12 500 000 | 72 | 0.78 | 310 000 | 1.159 | 0.005 | 0.78 |

Although, thanks to the efforts of the states and non-governmental organizations, the problem of vector transmission has been controlled to a large degree, the number of health programs targeted towards people from endemic zones is still insufficient. Though the majority of infected people live in Latin America, in recent decades cases of this disease have been reported also in other parts of the world, in such countries as: Canada, United States, Australia, Japan, Belgium, France, Italy, Spain, Switzerland, the United Kingdom, Austria, Croatia, Denmark, Germany, Luxemburg, Netherlands, Norway, Portugal, Romania and Sweden. The spread of American trypanosomiasis is mostly connected with the increasing tendency of people to migrate to the rich countries of the North. These destination states have not developed any preventive measures, such as screening for Chagas disease in blood banks [31].

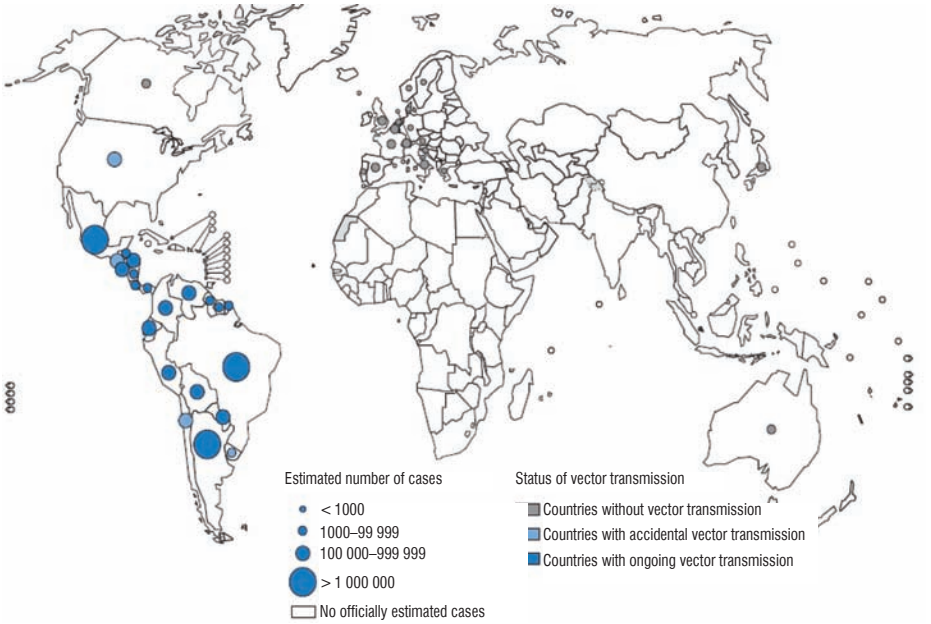


**Fig. 4.** *Trypanosoma cruzi* infections mapping in the 2006–2009 period [31]

## CONCLUSIONS

1. Although vector transmission has been to a large degree controlled, non-existence of effective medication to treat Chagas disease indicates a failure with respect to health policies currently adopted by endemic countries.
2. American trypanosomiasis, tropical in nature, should become an object of interest of highly developed countries in the near future due to the increasing migrations of infected groups of people.

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*OVERVIEW PAPER*

# IS FOOD ALLERGY A CIVILIZATION-RELATED DISEASE?

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## ABSTRACT

**Introduction.** Civilization-related diseases are defined as diseases encompassing a global range, whose appearance or spreading issues have been largely caused as a result of the advances of modern civilization. Thus, such diseases are also interchangeably termed diseases of the 21st century. Allergy, i.e., an organism's abnormal immune reaction to exposure to an allergen, due to its increasing incidence, especially in developing countries, is occasionally called "an epidemic of the 21st century". Issues concerning food allergy are significant ones with respect to allergies as such.

**Aim**. This work aimed at reviewing the most current literature concerning food allergy.

**Discussion**. The incidence of adverse reactions to food varies. Reaction depends on the allergen type, patient's age, type of evaluated mechanism, and local diet. Potentially, each food may cause sensitivity; however, in order for a reaction to occur several conditions must be fulfilled. Allergens are mainly water-soluble glycoproteins ranging in size from 10 kDa to 70 kDa. Cases of allergies caused by smaller particles (approx. 3 kDa) or larger ones (up to 100 kDa) are also known. The increased prevalence of food allergies results from an unfavorable combination of genetic and environmental factors.

**Conclusions.** The incidence of food allergies is on the increase. The symptoms are intensified and regress at more advanced ages, whereas diagnostic and treatment complexities place these diseases among civilization-related diseases of the present century.

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**Key words:** allergy, hypersensitivity, Peyer's patch, epitopes, cytokines, antibodies

## INTRODUCTION

The phenomenon of food allergy is not new. Reports of ancient historians describing the various reactions of people to food consumed are known. However, only those advances which took place in science within the last century, exhibited the full scale of this phenomenon. The term "allergy" was introduced in 1906 by an Austrian physician Clemens Johannes von Pirquet, who was a pediatrician and professor at Universities in Wrocław and Vienna. This term derives from the Greek *allos* – different and *ergos* – reaction. Reaction results from exposure to antigen (allergen). It is estimated that allergies are the 5$^{th}$ most frequently occurring diseases. The more frequent medical conditions are cancers, cardio-vascular diseases, pulmonary diseases, and AIDS [10, 19, 21].

Allergy is the abnormal reaction of an immune system that has been activated by exposure to an allergen which a given organism is sensitive to. At first contact with an allergen, the immune system of a person prone to allergies produces specific antibodies; an allergic reaction occurs only as a result of further exposure to the given allergen. Allergy is thus a specific immune response which does not occur in healthy people; whereas food allergy is an abnormal immune response leading to various, repeated clinical symptoms. These symptoms occur after having consumed food to which a given person is sensitive. In this era of technological advances and the globalization process, eating habits undergo changes in each geographical location worldwide. Vegetables, fruit, herbs, previously considered to be scarce, are currently rather commonly served throughout the world. The fact that the alimentary system is quite complex and extensive also contributes to the increase of food allergy incidence. It is estimated that the surface area of the mucous membrane of the alimentary tract amounts approximately to 300 m$^2$, which makes it the largest zone of interactions with environmental factors within the organism.

## MATERIALS AND METHODS

Available literature on the subject has been collected and grouped thematically. Describing allergy from the perspective of a civilization-related disease has been attempted.

## AIM

This work aimed at reviewing the latest literature concerning food allergy in order to characterize this disease entity, as well as to point out those dangers which may arise as a result of developments in civilization.

## DISCUSSION

Food allergy is one of the undesirable reactions which appear as a result of food consumption. Undesirable reactions to foods can be divided into toxic and non-toxic ones. The non-toxic reactions are further subdivided into food allergy and food intolerance related to non-immune mechanisms, including, e.g., congenital and acquired enzyme deficiencies within the alimentary tract. Food allergy refers to clinical symptoms caused by pathogenic immune mechanisms. Peyer's patches, located in the lymphoid tissue of the alimentary tract, are directly responsible for the allergic reaction. Exposure to an allergen leads to a disturbance in the Th (CD4) to Tc/Tc (CD8) lymphocytes ratio and IgE-mediated allergic reactions.

An allergic reaction is directly caused by substances released by mastocytes and basophils (among others, serotonin and histamine) and cytokines. Peyer's patches, located in gut associated lymphoid tissue (GALT) are constantly stimulated by antigens of various kinds, thus they are dominated by T lymphocytes of the CD8 subpopulation. Antigen presenting cells (APC) are located on the surface of Peyer's patches. Antigen presentation by APC results in a number of processes, leading to the release of cytokines by Th1 (IFN-γ, IL-2) lymphocytes and Th2 (IL-3, IL-4, IL-5, IL-10, IL-13, GM-CSF) lymphocytes. As a result of the released cytokines activity, B lymphocytes switch to producing $IgG_4$ and IgE instead of $IgG_{1,2,3}$ and IgM. Finally, the created E class antibodies connect to mast cells, leading to their sensitization.

According to the European Academy of Allergy and Clinical Immunology (EAACI), undesirable reactions to foods are classified on the basis of their pathogenesis. Abnormal reactions to foods have been divided into two groups – toxic and non-toxic. The first group includes all types of intolerance caused by the presence of toxic substances in foods, which are produced by pathogenic fungi or bacteria. The second group consists of all other types of food intolerances and allergies (Fig. 1) [3, 20].

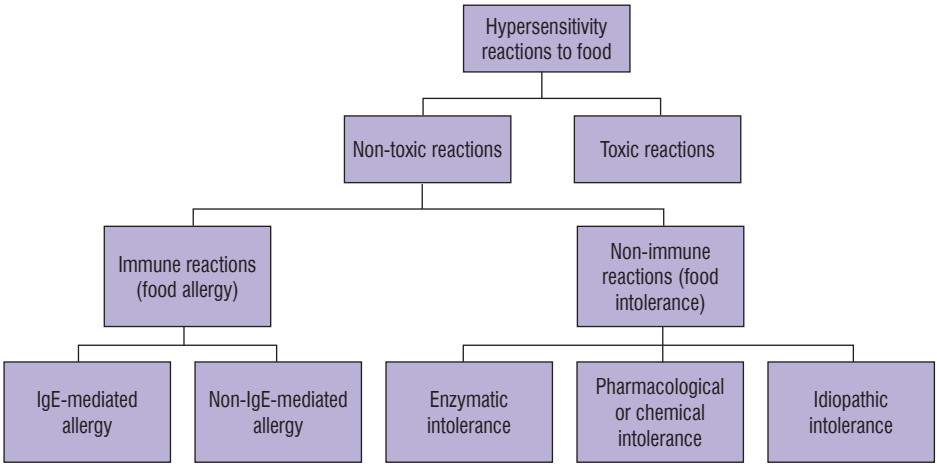


**Fig.1.** Food hypersensitivity scheme according to EAACI [7, 20]

In the 1960s Gell and Combs [4] differentiated four types of allergic reactions.

1. Type I (immediate, anaphylactic hypersensitivity) – an allergen interacts with IgE antibodies that bind with surface receptors on mast cells and basophils. As a result, histamine and cytokines are released.
2. Type II (cytotoxic hypersensitivity) – occurs as a result of IgG oraz IgM antibodies reaction to an allergen on the cell surface. In this type of hypersensitivity complement is involved, and the host cell is destroyed.
3. Type III (Arthus reaction or immune complex hypersensitivity) – as a result of the interaction of a free antigen with antibodies immune complexes are formed which then activate the complement and are deposited on tissues.
4. Type IV (cell-mediated response or delayed hypersensitivity) – the damage to the cells is caused by cytokines and a direct cytotoxic effect is mediated by macrophages and Th and Tc lymphocytes [4, 12].

Hypersensitivity is then a term applied to objectively repetitive symptoms occurring as a result of exposure to a specific stimulus; whereas, food allergy refers only to symptoms caused by IgE-mediated reactions (atopy) or non-IgE-mediated reactions which occur as a result of immune reactions. In clinical practice the terms "food hypersensitivity" and "food allergy" are used interchangeably to describe undesirable immune-mediated reactions to foods. According to the guidelines of the World Allergy Organization (WAO), these are two different diseases which are treated differently. Consequently, their differential diagnosis is extremely important. In normal circumstances, a specific antibodies class (IgE) is released as a response to a pathogen. Moreover, a properly functioning immune system guarantees the antigen tolerance, even at a very strong exposure. Foods including a potential allergen may cause various reactions in different people. Symptoms may occur immediately or may be delayed. Generally, three types of reactions are differentiated. The appearance of the symptoms shortly after food consumption is typical of IgE-mediated reaction, belonging to the first group. In the second group, patients exhibit subacute or chronic symptoms, depending on T lymphocytes. The last, third group, involves symptoms which occur immediately after food consumption and are chronic. It is believed that the reasons may be associated with abnormal humoral and cellular-mediated responses. This variety of symptoms and their durations are caused by the non-homogenous effects of allergens on patients. This means that one allergen may affect various people differently and may cause various reactions in one patient depending on the circumstances. Moreover, it is also known that one allergen may lead to various diseases in various people, and a natural history of food allergy exhibits changeable organ locations. Clinical manifestations involve skin, alimentary tract, respiratory system and, in extreme cases, anaphylaxis, including shock symptoms. Pathogenesis of an allergy is very complex. Actually, anyone, regardless of age, may develop an allergy. The appearance of this disease is largely dependent on exposure

to a specific allergen, i.e., how long and how intensely the allergen has affected the alimentary tract.

Acquiring tolerance in the course of food allergy, which underlies extinguishing an immune response to nutrition, is one of the most important mechanisms in the disease regression. It is associated with the alimentary system becoming more mature and "tighter". Earlier reports indicated that allergies regress approximately at the age of 3. At present, it is believed that it may be occurring later. It is estimated that at the age of 4, approximately 11% of children acquire tolerance to hen's egg allergens, and as many as 19% to allergic agents in cow's milk. According to contemporary estimates, about 80% of patients do not exhibit allergic symptoms at the age of 16. It has been proved, however, that acquiring tolerance is not a constant phenomenon. The re-appearance of allergic symptoms in children who earlier tolerated a specific allergen has been observed (peanuts). The recurrence manifested itself in 5 out of 20 children following a break in in-taking this allergen [8].

The intensity of an allergic reaction depends also on the type of food processing. This may be connected with changes in protein conformation, stemming from the thermal processing of food, such as the Maillard reaction. It has been shown that in Western countries where roast peanuts are eaten, the incidence of sensitivity to this allergen is significantly higher than in, e.g., China where boiled peanuts are predominantly consumed. This is closely related with non-enzymatic glycosylation (the Maillard reaction), which occurs in an increased temperature. The reaction of amino acids with reducing sugars changes protein conformation, which affects their allergic potential. A similar reaction occurs in nutrition products (peanuts) which undergo the emulgation process. It has also been proved that the application of this type of technological processing leads to increasing the allergic potential of proteins, whereas boiling diminishes it. Research carried out thus far indicates that boiling also improves digestibility [8].

Food is not a lasting product, thus the continuing attempt to improve its quality and flavor as well as to maximize its shelf life. Consequently, various substances are added to food in order to gain the expected effects. Approximately 2 900 substances of the aforementioned qualities are known at present. These additives, becoming food ingredients, may impact upon digestibility. The most frequent symptoms of allergy are rash and asthma, although cases of angioedema, rhinitis, headaches and behavioral disorders have been observed also. Numerous studies indicate that these clinical manifestations are caused by a relatively small group of additives, such as food colorings (azo dyes: tartrazine, red, sunset yellow and non-azo dyes: brilliant blue, erytrozine and indigo), monosodium glutamate, preservatives, parabens, and sulfites [9].

Allergens have specific modes of acting. By interacting with the lymphoid tissue of the alimentary system, allergens can act in a variety of ways via IgE-mediated and non-IgE-mediated mechanisms. Thus, they can cause an allergic reaction via mastocytes degranulation; they can act by complement activation; they can affect arachidonic acid cascade; or can stimulate the formation of immune complexes due to their

ability to bind antibodies. It is very significant that these mechanisms do not need to occur simultaneously. It should be noted that IgE-mediated reactions amount to almost half of all immune-mediated allergic reactions, whereas this refers mainly to people genetically predisposed to producing this specific class of immunoglobulins as a response to contact with an allergen. Usually, IgE-mediated anaphylaxis regresses after 5–30 minutes following the food in-take, but in some patients the symptoms may appear as late as several hours following exposure to the allergen [2].

Varied tolerances to allergens are connected with the adaptation of the human organism to control their activities. Over the years the organism has formed protective barriers which significantly improve digestibility of these proteins. These barriers include the acidic environment of the stomach, digestive enzymes and microflora in the alimentary tract as well as mediators released by mast cells [3].

It is believed that up to 90% of IgE-mediated food allergies are caused by eating specific types of foods, both animal-derived and plant-derived foods. The main sources of antigens are cow's milk proteins, soybean, hen's eggs, peanuts, wheat, tree-nuts, and seafood [13, 18, 21]. Apart from cow's milk, hen's eggs are the most common food allergen. This is significantly influenced by eggs being commonly eaten, and used in cakes, meats, sauces, salads and creams as additives. It is also important that egg whites improve the nutritional value of meals [5, 21].

Typical symptoms of an allergy to egg whites include: stomach ache, urticaria, pruritus, atopic skin inflammation (ASI), vomiting, and less frequently rhinitis, conjunctivitis or laryngeal edema. In extreme cases strong anaphylactic shock may occur. The intensity of degree of the symptoms may be varied. An acute allergy was diagnosed in a young woman who manifested the symptoms having used the knife which had been previously used to break an egg to spread butter on bread. Moreover, this person could not be in a room in which there were freshly broken eggs. Another strong reaction to exposure to an antigen is exemplified by a man who applied for a certificate confirming his allergy in order to present it to an army medical board. An extremely strong hypersensitivity was diagnosed; a case of an anaphylactic shock after using a not fully washed spoon which had been used by someone else to eat scrambled eggs was confirmed. Cases of milder allergy are also known. In a 6-month old boy eating an egg caused pruritus and skin inflammations. Removing the allergen from the diet improved his condition. At a later age, the boy could not eat more than two eggs at one sitting since this caused diarrhea [5, 14, 15].

Allergens from hen's eggs may be found in the milk of those mothers who included eggs in their diet. This is exemplified by a case of a boy who was exclusively breast-fed from birth. At the age of 4 months he ate an egg for the first time, which resulted in the appearance of exudative lesions and erythematous foci. After 48 hours he was diagnosed with ASI [5, 14].

Further, it is believed that antigens from hen's eggs may cause allergies in workers employed in egg processing plants. Measurements in the plant were taken which

confirmed the presence of allergens in the air, not only in primary areas but also in office rooms. The risk of dangerous allergic reaction exists also for allergic people who are administered a vaccine produced on the basis of hen eggs [5, 9].

Milk, as a diet component, has accompanied human beings since ancient times. The first reports about its adverse effects for human health appeared during those times. Hippocrates mentioned various reactions of people to eating cheese. Cow's milk harbors approximately 20 proteins of an allergic potential. The most important allergens deriving from milk include casein and whey proteins, i.e. β-lactoglobulin, α-lactoalbumin, and bovine serum albumin. Caseins from the milk of related species of mammals differ from each other to a larger degree than whey proteins. Moreover, it should be noted that thermal processing does not entirely eradicate the allergic properties of these proteins. The total disappearance of these qualities following pasteurization or boiling is only observed in bovine serum albumin. It was generally believed that cow's milk allergy is strictly a food allergy; however, recently, cases of contact and inhaled allergies have been noted in clinical practice. Typical symptoms of cow's milk allergy involve: diarrhea, vomiting, urticaria, atopic skin inflammation, and respiratory complications. Approximately 10% of patients develop anaphylactic reactions [1, 10, 11, 16, 22].

The last group of animal-derived food allergens includes those derived from fish and crustaceans. This group is exceptionally important. Owing to the examination of proteins from fish tissue, in 1921 Prausnitz and Kustner proved the existence of the factor which was years later called IgE immunoglobulin. Moreover, they examined the protein which was later to become the first sequenced allergen, officially called Gad c1 [17, 22].

Fish allergy is very often concurrent with crustacean allergy and other seafood allergies. Whereas in Poland crustaceans are not very popular as diet ingredients, in other countries shellfish allergies are a major problem. In the Unites States alone, about 30 species of shellfish are eaten (shrimps, rock lobster, lobster, crabs, and crayfish) [22].

Fish more frequently lead to allergies in children than in adults, although children less often develop cross-reactive allergies. A characteristic feature of a cross-reactive allergy is that it does not regress with age, although a clinical case of a patient is known, with a constantly detected allergy between 5 and 60 years of age, whilst at the age of 78 no allergic reaction to this type of food was observed.

Both saltwater and freshwater fish may lead to sensitivity. It depends on the availability of a particular species, climate and a cuisine tradition with respect to such foods. Allergies to this type of food are relatively easily diagnosed, since most often food allergy is observed in synergy with inhaled allergy. In Poland this medical problem is relatively rare as the consumption of this type of food is rather limited [1, 10, 16, 22].

Conducted research indicates that constant social development worldwide significantly affects the incidence of allergy. It is estimated that at present this problem

involves 2–8% of children and 1–2% of adults. It has been proved that children usually "outgrow" their allergies. An annual number of food allergy cases in children diminishes with an increase in age: from 10% (in children below 1 year of age) to 3% (in 6-year-old children) [6, 13].

Unfortunately, diagnosing food allergy remains a major problem. It is a complicated and complex process, involving an accounting of many concurrent factors. A medical interview is a very important diagnostic tool. It is necessary to regard the period which has passed between the consumption of the suspected food and the appearance of the symptoms, the amount of consumed food and the concurrence of other factors, such as effort, alcohol, medication, diet, traveling, etc. The golden mean in diagnostics is a double-blind, placebo controlled test, a food provocation. A positive result allows one to determine the harmful factor, but it does not explain the pathomechanism of food allergy. In order to detect the cause of IgE-mediated allergy, prick skin tests or allergen-specific IgE antibody tests are carried out. Negative results confirm the absence of IgE--mediated reaction in 90% of the cases; however, the positive results do not prove that a given allergen does not cause the symptoms. The assessment of the size of the skin reaction also cannot be treated as an indicator as to which allergen causes sensitivity. It has been proved that the size of skin reactions does not correlate with the symptoms' intensity. Food allergy diagnostic procedures also include atopy patch tests, especially when the outset of the disease is delayed. However, the evaluation of such tests results is at present both difficult and ambiguous [8].

It has been shown that specific groups of allergens reveal their allergic properties under favorable conditions, e.g., oral allergy syndrome is caused by cross-reactions, whereas anaphylaxis connected with effort and food consumption appears as a result of IgE--mediated mechanism (first food consumption, then effort). This mostly refers to youth and adults, and the allergens involved are, among others, wheat, seafood, and celery [8].

Similarly to the difficulties involved in diagnosing food allergy, its treatment is also complex. Avoiding food that affects a given patient remains the basic treatment procedure. Educating the patient seems to be exceptionally important. It entails enumerating those foods which contain allergens. Pharmacological treatment is adapted to the occurring symptoms. Most frequently, second generation antihistamines are administered, recommended for such medical conditions as urticaria, acute oral allergy or ASI. Patients at risk of anaphylaxis should be definitely provided with an auto-injector with adrenaline and taught how to apply the medication to themselves.

## CONCLUSIONS

1. Allergy, due to a variety of symptoms and their intensities, is a significant diagnostic and therapeutic challenge for modern societies.
2. Since allergy affects both children and adults, as well as exhibiting increasing incidence trends, it fulfils the criteria established for civilization-related diseases.

3. Since social awareness with respect to this medical condition and its outcomes is still insufficient, it is necessary to disseminate information concerning this disease.

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*OVERVIEW PAPER*

# REHABILITATION FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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**ABSTRACT**

**Introduction.** Chronic obstructive pulmonary disease (COPD) is recognized as one of the most frequent causes for hospitalization and disability, and one of the most prevalent diseases with a morbidity rate increasing worldwide. It is characterized by a not entirely reversible, usually progressive limitation of the air flow through the respiratory tract. It is associated with an abnormal inflammatory response in the lung to noxious particles or gas, most frequently triggered by tobacco smoking. Diagnosis of this disease must be objectified by accounting for the results of a lung function test (spirometry).

**Aim**. This paper aimed at emphasizing the role of rehabilitation in COPD treatment, discussing its scope, methods, program, and effects.

**Discussion.** Recently, the importance of rehabilitation in COPD management has increased significantly. It has been viewed as an integral part of the therapeutic procedure, equally important as pharmacological therapy and oxygen therapy. Pulmonary rehabilitation programs facilitate the control and subsidence of disease symptoms, enable the patient to achieve an optimal functional efficiency, limited only by the degree of disease progression, and improve the quality of life for COPD patients. It has been also noted that rehabilitation may decrease the costs of patients' social isolation, associated with respiratory dysfunction. Pulmonary rehabilitation, as a separate type of rehabilitation, was proposed in 1981 by the American College of Chest Physicians (ACCP). In the updated version of 2002, providing the guidelines devised by an international team of experts The Global Initiative for Chronic Obstructive Lung Disease (GOLD), pulmonary rehabilitation was recognized as an integral part of treatment.

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**Conclusions.** Pulmonary rehabilitation has become a valuable, important and efficient element of COPD management, equal to that of pharmacological therapy and oxygen therapy.

**Key words:** chronic obstructive pulmonary disease (COPD), rehabilitation

## INTRODUCTION

According to the statement published in 2006 by the American Thoracic Society (ATS) and European Respiratory Society (ERS), at present pulmonary rehabilitation is defined as: an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities [13]. Chronic obstructive pulmonary disease (COPD) is currently considered not only as a respiratory system disease, but also as a systemic disease which affects the function of other organs, among others, the motor organ [9, 23]. Muscle training deficiency contributes to the setting off of the anaerobic mechanism at a lower work rate than normally. COPD patients frequently develop peripheral muscle dysfunctions. Thus, a "vicious circle" appears: physical activity is limited due to dyspnea, which then weakens the muscles and results in further exertional dyspnea at a lower work rate undertaken [2]. Muscular weakness affecting skeletal muscles and body mass loss are two major manifestations with respect to the systemic impact of this disease. It has been proved that being underweight definitely worsens the prognosis in COPD patients [3, 18].

Qualification criteria for rehabilitation include symptoms and their intensities, results of functional tests, and an assessment of comorbidities. Recommended qualification criteria for pulmonary rehabilitation are as follows: poor quality of life, limited participation in physical activities, decreased ability to work in one's profession, dependence on others concerning activities of daily living, increased health service use (hospitalizations), lung dysfunction, psychosocial disturbances (anxiety, depression) [2, 8].

Planning the rehabilitation process is preceded by an initial patient assessment, involving physical examination, interview, and additional examinations. The interview provides information with respect to the following aspects: symptoms intensity, nutrition, ability to perform activities of daily living, ability to perform exercises, and psychosocial situations. Devising an individual rehabilitation program is the final stage of the qualification process [5, 22].

In pulmonary rehabilitation, special attention should be paid to evaluating the degree of dyspnea. To this end, verbal scales (e.g., the Borg scale, American Thoracic Society scale – ATS scale) or visual scales (Visual Analog Scale – VAS) are used. The Borg scale incorporates 11 possible answers – lack of exertional dyspnea (0) to maximal dyspnea (10) [2, 5].

The ATS differentiates:
- I degree – dyspnea during a quick march on flat surface or uphill, or walking upstairs on the 1st floor – normal gait,
- II degree – dyspnea when keeping pace with a healthy peer on flat surface,
- III degree – dyspnea when walking on flat surface at one's own pace,
- IV degree – resting dyspnea [5].

Other symptoms considered for qualifying a patient and then monitoring his rehabilitation course include: coughing, sputum expectoration, and cardiovascular symptoms [2, 5].

Physical examination is the next stage of the initial patient assessment. It involves measuring and assessing the basic life functions (height, weight, blood pressure, heart rate, respiratory rate), activity of peripheral respiratory muscles, chest examination, evidence of hypertrophic pulmonary osteoarthropathy, swellings and other features of cardiac dysfunction. Physical examination is a simple, non-invasive method for evaluating, monitoring and controlling a patient's progress [2, 17]. Additional initial examinations are helpful in determining the initial clinical status of each individual patient and in devising a special rehabilitation program. These examinations are performed depending on the needs and decisions of that physician qualifying a patient for rehabilitation. They include: spirometry with bronchodilatator response, gasometry, pulsoxymetry, chest X-ray, stationary ECG, exercise tolerance test using cycle ergometer or treadmill, walk tests, and blood test [2, 5]. Spirometry provides information concerning the ventilation efficiency of the respiratory system, static and dynamic lung volumes, and lung capacities. Spirometric values, which reveal lung hyperinflation are more important [19]. Before beginning the rehabilitation program, all comorbidities or dysfunctions, which can influence the rehabilitation process, should be controlled or stabilized, and the treatment of the underlying disease should be optimized [1].

## AIM

This paper aims at emphasizing the role of rehabilitation in COPD treatment, discussing its scope, methods, program, and effects.

## DISCUSSION

### Pulmonary Rehabilitation Program

Pulmonary rehabilitation is based on education and kinesitherapy. Auxiliary function is attributed to physical therapy, including aerosol therapy, and psychosocial support and modification of lifestyle [9].

**Education.** In any chronic disease, thus also in COPD, the more the patient knows about its causes, course and treatment, the easier this treatment is. A well conducted education should motivate the patient to introduce such changes into his behavior as

will lead to improving his health and allow him to participate in the treatment process actively. Depending on the patient's individual needs, preparatory courses organized within the framework of a pulmonary rehabilitation program should cover the following topics: structure and function of the respiratory system, pathophysiology of lung disease, noxious agents (including tobacco smoking), interpretation of diagnostic tests results, breathing strategies (modification of the breathing pattern), bronchial tree hygiene, proper use of medication, principles of physical exercises, activities of daily living and energy conservation, prevention and early treatment of respiratory exacerbations, nutrition, psychosocial issues, including relaxation techniques [2, 5, 12].

**Physical Training.** Before beginning physical training, each patient's exercise capacity needs to be assessed. This aims at: assessing exercise capacity before the rehabilitation program and determining the recommended exertion, determining the initial level of physical efficiency in order to evaluate treatment results, detecting hypoxemia on exertion and determining oxygen therapy requirement, recognizing extrapulmonary limitations for taking up physical exercises (e.g., associated with muscular and skeletal systems, and/or cardiovascular system), detecting exercise-induced bronchoconstriction (EIB) [2, 5, 11]. Exercise tolerance tests are relatively safe for patients with no confirmed or diagnosed cardiac dysfunctions. These tests may vary, from simple and non-invasive to more complex, invasive and technically advanced. There is no one single protocol that could apply to all patients enrolled for various programs. The most frequently used tests are the 6-minute walk test (6MWT) and the exercise tolerance test using a treadmill or cycle ergometer performed according to a specific protocol. It is important to assess exercise tolerance in the same manner before and after the rehabilitation program. The simplest test evaluating exercise capacity is the 6MWT [5, 14, 19]. As already mentioned, muscular weakness and weight loss are the two major symptoms of the systemic influence of the disease. In COPD patients, muscular weakness affecting skeletal muscles is an independent factor contributing to limiting exercise tolerance, leading to functional deficits, increasing treatment costs and mortality risk. Thus, reversing a tendency of progressive weakness of muscular strength should be an important target in therapeutic procedure. Improving muscular strength and exercise tolerance can be achieved through adequate physical exercises. They underlie any activities of a well-planned rehabilitation course [10, 20]. Muscular training is based on endurance training and resistance training. Endurance training of the lower and upper limbs contributes to increasing exercise tolerance, even when no changes in spirometric parameters are observed. It can be performed in various forms: exercises with the use of arm and leg ergometer or on treadmill, or it can involve only walking on a flat surface. Lower limb training improves exercise tolerance and significantly diminishes dyspnea during activities of daily living, as well as associated stress and anxiety [5]. Until recently, upper limb training was considered as insignificant. It has since been proved, however, that

a simple exercise such as arm elevation without weights increases ventilation and metabolism in COPD patients. Coordinating inhaling and exhaling with a raising and lowering of the arms improves ventilation and involves the respiratory muscles, including peripheral inspiratory muscles. Resistance training increases muscle strength and mass. The best results are obtained when such training consists of several short series of exercises employing a large weight and repeated several times. It is better tolerated than endurance training [2, 5]. Most rehabilitation programs include endurance trainings or a combination of endurance and strength trainings, with sessions lasting 20–30 minutes, 2–5 times a week. Patients with more advanced stages of the disease, with a significantly limited exercise tolerance, may also participate in physical trainings. Such patients follow interval trainings (3 minutes of exercises, 3 minutes of rest). When the patient is able to perform ordered exercises for 30 minutes during one session, 3–5 times a week, the intensity of such training should be gradually increased [22].

**Breathing Strategies.** Breathing strategies aim at teaching a patient a mode of breathing which will involve a reduced respiratory rate combined with a bigger tidal volume. Commonly known breathing techniques include: exercises involving slow and deep breaths (contrary to a reflexive tendency to breath quickly when experiencing dyspnea episode), pursed lip breathing (reduces respiratory rate and the level of carbon dioxide, improves tidal volume and increases partial pressure of oxygen), and diaphragmatic breathing. Breathing exercises are conducted in appropriate body positions. Due to these, inhaling or exhaling may be facilitated or made more difficult; one section of the chest may be stabilized, whereas the other mobilized. Additionally, the activity of the diaphragm or intercostals may be increased during such exercises [2, 4, 6]. Before starting breathing exercises, it is necessary to learn how to do them properly. They should begin with inspiration. The ratio of inspiration, always through the nose, to expiration through the mouth should be 1 : 2, and sometimes even 1 : 3. The target is the maximal prolongation of expiration. Inspiration through the nose clears, warms and moistens the air, whereas expiration through the mouth increases its effectiveness and facilitates controlling its length. The number of repetitions of breathing exercises should not exceed 3 or 4 in a series. Breathing exercises performed too intensively may lead to hyperventilation, which can disturb acid-alkaline balance. It is better to repeat them more often, but less intensely [6]. The length of the entire training program involving pulmonary rehabilitation may vary. However, as was emphasized during The American Lung Association meeting in 2007, it should last from 6 to 12 weeks. A shorter length of training does not lead to an optimal improvement of physiological results, whereas longer continuation brings about insignificant long-term effects [5].

**Physiotherapy – methods provoking coughing and secretion removal.** Postural drainage is the classic method of respiratory tract hygiene. It involves positioning

the patient in such a way that a bronchus draining a given lung segment is vertical to the floor, and the drained segment above the pulmonary hilus. Depending on the location of the changes, various drainage positions are used (Fig. 1). Additionally, during this procedure, manual chest and back therapy may be performed, involving percussion (clapping), vibrations or shaking. Only those lung segments which are drained in a given moment are clapped or vibrated. This should be done towards the hilus, so that the separated secretion is removed more easily. This procedure can be performed 2–3 times a day for 30–40 minutes [4].

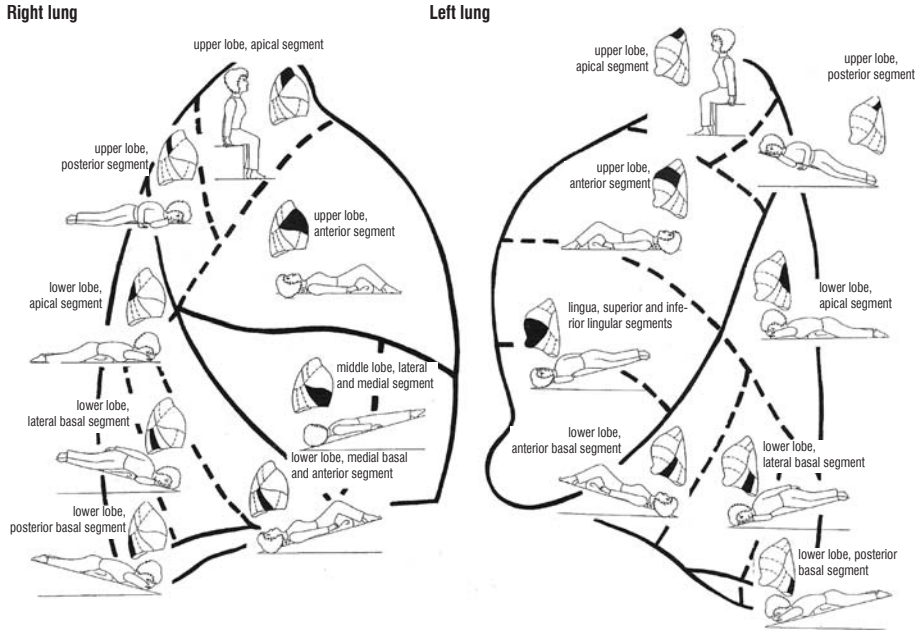


**Fig. 1.** Classic postural drainage positions [4]

**Autogenic Training**. This type of training refers to breathing with various tidal volumes, with holding the breath for a few seconds while inhaling [4].

A technique of changing end-expiratory pressure with the use of a Flutter device is based on producing a range of vibrations in the exhaled air. These vibrations are transmitted to the bronchial walls and the mucus adhering to them. This loosens mucus from the airway walls, which facilitates its being coughed up. When Flutter is placed downwards, the air resistance becomes smaller, when placed upwards – then the resistance is bigger. This device may be used in various positions assumed by the patient. The number of repetitions in a series is decided on an individual basis (from 3–4 to 8–10), depending on the respiratory capacity of the patient (Fig. 2) [4].

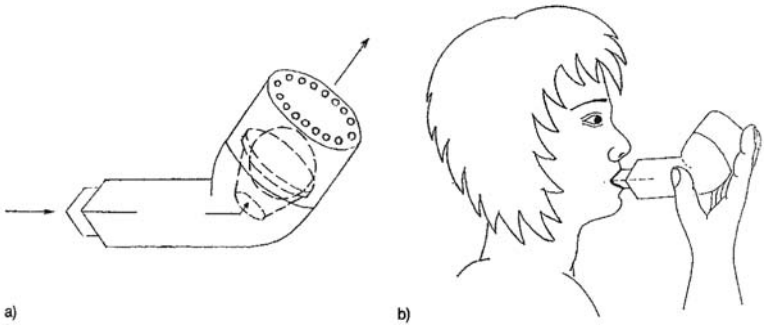


**Fig. 2.** Changing end-expiratory pressure with a Flutter device [4]

A technique of positive end-expiratory pressure requires the application of devices (Fig. 3) which enable changing expiratory pressure. Intensive air flow in the airways loosens mucus and provokes coughing which then removes it [4].

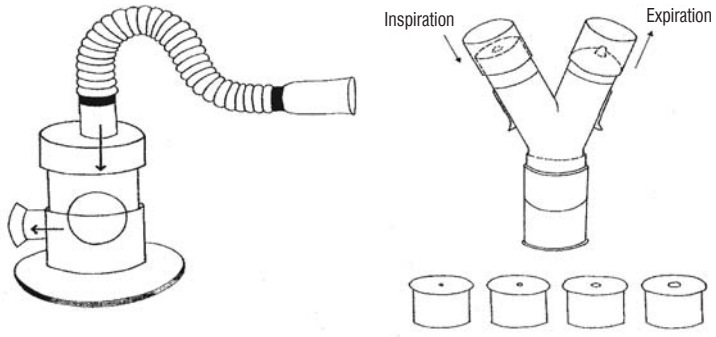


**Fig. 3.** Mediflo duo and Atemtrainer-set used in positive expiratory pressure technique [4]

Forced expiratory technique, also known as "huff coughing," consists of forced expirations with the glottis open. This intensive expiration is repeated twice or trice. While exhaling, stomach muscles may be activated, and chest muscles mobilized.

Active cycle of breathing techniques is based on controlled breathing (gentle breathing involving all respiratory muscles), thoracic expansion exercises (deep breathing with prolonged expiration, accompanied with percussion, vibrating massage and chest shaking) and forced expiratory technique (already discussed). The cycle of specific activities should be repeated for 15–30 minutes in each drainage position [4].

**Classic Massage.** Numerous authors emphasize the benefits of massage in physiotherapy performed on COPD patients. Classic massage (therapeutic, relaxing) in-

volves skin, muscles, ligaments, articular capsules, and periosteum. Local and generalized actions cause hyperemia, and as a result both skin temperature and blood flow rates increase, and the lymphatic system is activated. Consequently, tissue exchange is facilitated. Arterial blood pressure decreases, which leads to an increase in the heart rate. During massage, mucus in the airways is also loosened and coughing it up becomes easier. Vibrating massage is a form of classic massage, which involves transmitting high frequency vibrations to the patient's body by means of an electric device. It has been proved that the efficient frequency of vibrating massage, leading to the loosening up of mucus, should exceed 1100 cycles per minute [4].

**Physiotherapy.** Physiotherapy has an auxiliary function in COPD rehabilitation. The most frequently used physical therapy procedures include: inhalations (aerosol therapy), phototherapy, thermotherapy, electrotherapy, and ultrasound [5].

During aerosol therapy various types of therapeutic aerosols are introduced into the organism in order to affect the respiratory system. These aerosols may be natural or produced by medical devices. Natural methods include: inhaling sea spray, and breathing in the microclimate of salt mines or drifts. The aerosols used for inhalations can be divided into: bronchodilatation agents, expectorants, anti-inflammatory agents, antimycotic agents, and antibiotics. A proper mode of inhalation, especially proper breathing during this procedure is extremely important for its effectiveness. During inhalations, the patient should breathe slowly and deeply. A recommended respiratory rate is 5–6 breaths per minute, because the effectiveness of inhalations increases with a lowered respiratory rate. At 30 breaths per minute only 10% of inhaled aerosol is actively used, whereas at 5 breaths this usage increases to 60%. At the end of inspiration, the breath should be held for 3–5 seconds. Thus, all airflow in the airways is stopped completely and this contributes to the aerosol being deposited [17].

With respect to phototherapy, exposure to ultraviolet and infrared rays is applied (blue and red filters). These procedures aim at lowering muscle tone. They have an analgetic effect and increase tissue hyperemia. Ultrasounds and electrotherapy are used similarly. These types of therapy lower muscle tone, dilate blood vessels, block inflammations, and have an analgetic effect [2, 4].

**Psychosocial support.** Chronic lung disease may have a significant impact on a patient's quality of life and his family's life [10]. At the early stages of this disease, the patient and his family are frequently unaware of the disease or deny it and its severity. Contrary to the effects of other, well-known diseases, the debilitating effects of chronic diseases are not commonly known. Consequently, denying any relationship between respiratory symptoms and the previous or present behavior of the patient (e.g., tobacco smoking) is much easier. With disease progression, most patients experience fear and anxiety in anticipation of, and in association with, episodes of dyspnea. Moreover, heightened physiological arousal, accompanying the feeling of anxiety, can precipitate or exacerbate dyspnea. In the later stages of this disease, many

patients exhibit various psychosocial symptoms, reflecting their growing feelings of despair and inability to cope with their illness. Depression is frequently observed (51––74%), causing the following symptoms: sadness, despair, insomnia, loss of appetite, lowered willingness to act, lowered energy level, difficulties in concentration, leading to memory disturbances, and suicidal thoughts. Similar to fear and dyspnea, functional deficits may involve losing one's energy and motivation to undertake physical activity. This, consequently, leads to losing physical capacity, and a progressive disability [15, 21]. Mild to moderate neuropsychological impairments can appear both as a result of depression (as already noted) and hypoxemia. These disturbances are usually manifested as difficulties with concentration, poor memory, and cognitive dysfunction. Patients, who develop such disturbances, experience difficulties solving common problems associated with activities of daily life. They miss office or outpatient clinic appointments, and fail to adhere to the recommended therapy. That is why it is important to screen the patient for psychosocial dysfunctions. The evaluation of the patient's responses and direct observation of emotions should be complemented by the application of one of the tests specific for COPD: Saint George's Respiratory Questionnaire (SGRQ) and Chronic Respiratory Disease Questionnaire (CRQ) [5].

**Results Evaluation.** A comprehensive pulmonary rehabilitation program improves the quality of life for and the exercise capacity of COPD patients. Constant changes in health care, stressing the importance of quality, treatment costs and effectiveness, contribute to the fact that it becomes more significant to account for those indicators that reflect obtained rehabilitation results. In order to evaluate therapeutic results adequately, continuous quality control must be introduced into the pulmonary rehabilitation program. Such control facilitates the accomplishment of the targets schemed both for the individual patient and the program. Treatment results should be measured objectively so as to assess a patient's progress, as well as to evaluate the effectiveness of the rehabilitation program and medical staff activities. Patient-centered outcomes include: activities of daily living, health behavior, and participation in end-of-life decision making concerning the overall treatment strategy. Exemplary outcomes that can be monitored are as follows: change in exercise tolerance (6MWT performed before and after the program, pulmonary exercise test before and after the program, exercise diary kept for exercises performed at home, assessing muscle strength), change of symptoms (comparing dyspnea intensity, coughing frequency, sputum expectoration or wheezing, changes in body weight), other changes (activities of daily living, participant's knowledge before and after the program, frequency and length of disease exacerbations and hospitalizations, returning to professional activity) [2, 4, 9]. Pulmonary rehabilitation is a constant process aiming at changing one's life style. It begins when the patient is qualified for the program and lasts throughout the entire observation period. Follow-up examinations of patients who have completed the rehabilitation program are indispensable in order to ensure con-

stant improvement of their quality of life, up keeping their physical and functional activities. Various methods of controlling the patients and treating them after completed rehabilitation are used. These encompass: maintenance exercises programs, informing primary care physicians as to the patient's progress, support groups and educational groups, informative materials and leaflets concerning further treatment, phone controls and home visits made by a community nurse, and directing the patient to vocational rehabilitation centers [2, 7]. Continuing such activities after the completion of the program facilitates further improvement of a patient's quality of life and motivates him to constant work in achieving the aims schemed for him. A long-term support system by a multidisciplinary team of specialists inspires a patient to a maximum possible personal effort and an achievement of his own personal aims. Comprehensive pulmonary rehabilitation must take into account, also, further activities once the program is completed. This is one of the most important elements of rehabilitation [2, 4, 7, 22].

## CONCLUSIONS

Pulmonary rehabilitation has become a valuable, important and efficient part of COPD management, equal to that of pharmacological therapy and oxygen therapy. Thanks to a systematic and properly conducted physiotherapy, an improvement in physical capacity and respiratory effectiveness, an enlargement of the range of performed activities of daily living and a prolonging of the survival time are achieved.

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*OVERVIEW PAPER*

# FINANCING OF THERAPEUTIC REHABILITATION IN THE CONTEXT OF OTHER NON-INVASIVE MEDICAL TREATMENT SPECIALTIES

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**ABSTRACT**

**Introduction.** Methods of financing health care services constantly undergo changes. These changes involve both the allocated financial resources and average prices received for person-day of treating patients in hospital departments of various specialties. Thus, a constant monitoring of financing levels and service pricing in particular types of health care services is indispensable, since these issues are directly associated with the development or stagnation observed in particular branches of medicine.

**Aim.** This paper aimed at verifying the hypothesis that the pricing of person-day in the field of inpatient therapeutic rehabilitation, especially involving children, is under priced in relation to an average value of a person-day received in specialties providing non-invasive hospital treatment, and comparable as regards the costs of services.

**Materials and methods.** An analysis and comparison of costs and incomes for medical units providing health care services in selected areas of inpatient therapeutic rehabilitation for children and non-invasive hospital medical treatment have been attempted. This analysis has been carried out on the basis of data provided by the regional branches of the National Health Fund (NFZ). Generally available information concerning the terms and conditions of contracting services and agreements that NFZ has entered into with service providers has been also used.

**Results and discussion.** A comparison of the conditions for providing services that service providers should meet in order to obtain financing within the framework of NFZ, shows that personnel costs of a department of pulmonary rehabilitation and department of general rehabilitation are lower by approximately 15% than

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personnel costs of a department of pediatrics, and 9% lower than for a department of pediatric neurology. However, an average pricing of person-day received by rehabilitation departments is about 3-fold lower than that received by departments of pediatrics and pediatric neurology. Departments providing non-invasive medical treatment admit a large variety of patients. This diversification of patients only in part coincides with patients admitted to rehabilitation departments. Thus, additionally average pricings of person-day at departments providing non-invasive medical treatment and departments of general rehabilitation with respect to selected diagnosis related groups of patients who manifest diseases treated in both types of departments, have been compared. The obtained results have confirmed gross under financing of inpatient rehabilitative services.

**Conclusions.** Inpatient rehabilitative services offered for children are particularly undervalued. In this instance, service providers bear higher costs, resulting from, among other considerations, a larger average number of physiotherapists necessary to conduct rehabilitation, the requirement of assuming the full legal responsibility for children which necessitates additional educational care and 24-hours medical care, not only in the case of neurological rehabilitation, as well as providing nutrition adequate for children's ages, including five high-quality meals daily. Consequently, it is necessary to increase the pricing of inpatient rehabilitative services provided for children.

**Key words:** therapeutic rehabilitation, pricing of health care services, cost comparison, income per person-day

## INTRODUCTION

Health care is a very strongly regulated sector. Practically all organizations involved in this branch are subject to a multi-dimensional state control embracing: prices, number of provided services, quality, investments, and a possibility of entering the medical market [5]. The functioning of various spheres of health care depends on governmental policies and institutions appointed by the government to control this sector. The pricing of particular types of health care services is especially important, since this directly affects the financial standing of medical centers and the development or stagnation of specific medical specialties. It appears that recently inpatient therapeutic rehabilitation has been grossly under financed, when compared with the costs of providing such services as well as in relation to other spheres of medical practice. The price of rehabilitation services offered for children is particularly undervalued.

**Characteristics of financing health care services in Poland**

The National Health Fund (Pol. Narodowy Fundusz Zdrowia – NFZ) is responsible for carrying out the analysis of health care services costs (Act of August 27, 2004, concerning health care services financed from public resources – Article 97, paragraph 3, item 1). However, neither the principles according to which such an analysis is carried out, nor its outcomes, nor even the very fact of performing it, are announced for public opinion. With the shortage of clear and transparent principles as regards the pricing of health care services, lobbying and political interests are strongly voiced, based, among others, on a subjective selection of particular diseases deemed socially trying and thus requiring allocating more financial resources to treating them. On the other hand, it should be clearly stated that despite the availability of many methods allowing for evaluating unit costs of particular health care services [4], a comparison of cost adequacy in particular types of services is not straightforward. This difficulty is caused, among other considerations, by the fact that each type of service is financed according to a different system. Basic health care is financed within a capitated framework, specialist outpatient care – per provided consultation, hospital treatment – within the framework of the diagnosis related groups (DRG) system, and inpatient therapeutic rehabilitation – per person-day and within the DRG system.

Such a diversification of reimbursement systems is justified by a need to create separate stimuli and incentives for particular types of services. Yet, it makes it difficult to compare the financial standing regarding specific types of service providers. A fundamental principle of an effective pricing of services is that costs should be reimbursed in a way similar to the way in which they have been incurred [1]. A public payer is to create such a system of reimbursement for health care services that it would maximize social benefits stemming from the system of health care [2].

In the NFZ financial plan, therapeutic rehabilitation stands as a separate unit and about 3% of public financial resources for health care services are allocated to it. In 2009, 1.78 billion zlotys was spent on rehabilitation, and the financial plan for the year 2010 (as of July 31, 2010) allocated 1.65 billion zlotys. Therapeutic rehabilitation embraces the following types: inpatient rehabilitation (general, neurological, pulmonary, cardiac), rehabilitation in a day center/ department (general, for children with disturbances associated with developmental age, cardiac, pulmonary with the use of techniques of subterranotherapy), outpatient rehabilitation care provided by physicians (physicians' consultations), outpatient physiotherapy, home physiotherapy, speech and hearing therapy, and vision rehabilitation. Inpatient rehabilitation, except for neurological and cardiac rehabilitation, rehabilitation in a day center/ department, speech and hearing therapy, and vision rehabilitation are financed on the basis of a person-day, calculated as a product of the point value of a given service, established in the instruction of the NFZ Chairman, divided by price per point "negotiated" by a service provider with a NFZ regional branch. Since October, 2010,

neurological and cardiac rehabilitation, just like those departments included within the NFZ budget category of "hospital treatment", have been financed within the DRG system. Outpatient rehabilitation care provided by physicians is financed per consultation, whereas outpatient physiotherapy and home physiotherapy are financed according to performed procedures [9].

Each of the enumerated types of rehabilitation and hospital treatment requires specific equipment, premises, and personnel. These requirements are determined by the Regulation of the Minister of Health dated August 30, 2009, concerning guaranteed rehabilitation services and by the Instruction of the NFZ Chairman dated October 29, 2009. With respect to the professional and sanitary requirements as regards premises and equipment in a health care institution, inpatient rehabilitation departments must meet identical criteria as other departments providing non-invasive medical treatment.

**Diversification of outlays for rehabilitation provided for children and adults**

The NFZ does not differentiate between the financing of rehabilitation services as regards both children and adults. However, there are differences both with respect to diseases treated, education, number and type of personnel in particular departments, applied therapeutic methods, and conditions that services providers must create in order to ensure a proper rehabilitation process. In the case of pediatric rehabilitation departments the most frequently treated diseases include congenital defects, such as cerebral palsy or motor organ dysfunctions (e.g., spinal curvatures). In the case of, adults, post-traumatic, post-stroke and cardiac rehabilitation are most frequent.

Inpatient rehabilitation offered for children generates higher costs than for adults. Because additionally, it is necessary to:

- employ, on average, a larger number of physiotherapists required for conducting rehabilitation – due to a broader scope of individual rehabilitation procedures. Some procedures, which in the case of adults can be performed in groups, must be carried out individually with small children (it is hard to imagine an 8-person group of young children who do rehabilitative exercises effectively). Extra time is also necessary so that children can become accustomed to specific procedures and equipment, etc.;
- assume the full legal responsibility for children, which necessitates additional educational care (hospital schools financed by the Ministry of Education provide such care only partially);
- introduce 24-hours medical care on location, not only in the case of neurological rehabilitation (on-call duty is out of the question due to the fast pace of changes occurring in children's health conditions);
- provide nutrition adequate for children's ages, including five high-quality meals daily. Inpatient rehabilitation is a process lasting several weeks and frequently

requires significant physical effort. Moreover, in Poland, rehabilitation centers are located relatively far from each other, and consequently often positioned away from children's places of residence. This makes it impossible for parents to visit their children frequently and to bring meals for them.

## AIM

This paper aims at verifying the hypothesis that the pricing of person-day in the field of inpatient therapeutic rehabilitation, especially involving children, is under priced in relation to an average value of a person-day received for specialties providing non--invasive hospital treatment, and comparable as regards costs of services.

## MATERIALS AND METHODS

In order to verify the above formulated hypothesis, various sources of data have been used. The share of particular types of rehabilitation in the total budget allocated to these types of services has been established on the basis of the NFZ Financial Plan dated July 31, 2010, as well as the reference book concerning contracts entered by particular regional branches of the NFZ [3].

Data necessary for comparing the financing of inpatient therapeutic rehabilitation and selected hospital departments providing non-invasive medical treatment have been obtained from questionnaires sent to all 16 regional branches of NFZ. The questionnaires consisted of questions concerning:

- average cost of person-day of hospital treatment, specifying particular types of treatment, and covering the first half of 2010 (only completed hospitalizations, conducted within the period from January, 2010 to June 30, 2010); completed questionnaires were returned by 3 NFZ regional branches;
- contracts for the year 2010 involving inpatient rehabilitation (general, neurological, pulmonary, cardiac);
- average number of hospital treatment days in the first half of 2010 at departments providing non-invasive medical treatment with respect to patients paid for within selected groups of the DRG system, involving diseases treated both within the framework of non-invasive hospital treatment and inpatient general rehabilitation [10], where the need for applying ICD-9 procedures does not exists; completed questionnaires were returned by 5 NFZ regional branches.

Conditions required for providing health care services in particular medical specialties have been established on the basis of the requirements for particular types of services specified in appropriate instructions of the NFZ Chairman [11–17].

## RESULTS AND DISCUSSIONS

About 40% of the financial resources allocated to therapeutic rehabilitation is spent on inpatient rehabilitation (Tab. 1), the remaining amount covers the expenses incurred by rehabilitation in day centers/ departments, as well as outpatient and home rehabilitation. In inpatient rehabilitation, general and neurological rehabilitation have the biggest share – almost 90%. The pricing of services is diversified. The lowest average prices per point were received by service providers with regards to neurological rehabilitation, and the highest by those associated with cardiac and pulmonary rehabilitation. The prices range from 0.75–1.50 zlotys per point.

**Tab. 1.** NFZ budget allocation for therapeutic rehabilitation and average pricing per point in particular types of inpatient rehabilitation

| Service type | Total amount for contracted services | Share in therapeutic rehabilitation [%] | Share in inpatient rehabilitation [%] | Weighted average price per point [zlotys] | Point price min.–max. [zlotys] |
|---|---|---|---|---|---|
| Cardiac rehabilitation | 66 649 017 | 4.0 | 10.4 | 1.21 | 1.00–1.36 |
| Neurological rehabilitation | 178 036 633 | 10.8 | 27.7 | 1.09 | 0.75–1.50 |
| General rehabilitation | 378 370 796 | 22.9 | 58.8 | 1.12 | 0.90–1.40 |
| Pulmonary rehabilitation | 20 187 695 | 1.2 | 3.1 | 1.22 | 1.00–1.40 |
| **TOTAL – Inpatient rehabilitation** | **643 244 141** | **38.9** | **100.0** | **1.12** | **0.75–1.50** |
| Other types of services – outpatient | 1 011 564 859 | 61.1 | – | – | – |
| **TOTAL – Therapeutic rehabilitation** | **1 654 809 000** | **100.0** | – | – | – |

Source: NFZ financial plan dated July 31, 2010 [3].

Tab. 2 presents the NFZ requirements for the year 2011 concerning inpatient rehabilitation and selected departments providing non-invasive medical treatment for children, which treat patients with a similar intensity of diseases. Additionally, for the sake of comparison, department of internal medicine and hospitalization involving hematology-oncology therapy of children have been included. Oncology and hematology belong to cost-incurring specialties because of the applied diagnostics and pharmacotherapy. However, in the case of hospitalization involving hematology--oncology therapy, oncological diagnostics is most frequently performed earlier, and administered medication (active substances) are paid for separately [11, 19]. Thus, the intensity of therapeutic activities and resulting costs can be compared with other

**Tab. 2.** Comparison of minimal requirements specified by the NFZ for the year 2011 regarding personnel employed by health services providers in selected medical specialties

| Category | Department of Pediatric Rehabilitation | | | | Hematology-oncology hospital treatment for children[1] | Department of | | |
|---|---|---|---|---|---|---|---|---|
| | general | pulmonary | cardiac | neurological | | Pediatric | Pediatric Neurology[2] | Internal Medicine |
| Number of beds | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| Required number of full-time employees: | | | | | | | | |
| – physician – specialist | 1.5 | 1.5 | 2.75 | 2.50 | 3.0 | 3 | 2.0 | 3 |
| – nurse[3] | 14.0 | 14.0 | 14.00 | 16.00 | 18.0 | 18 | 18.0 | 14 |
| – physiotherapist | 3.5 | 3.5 | 3.50 | 5.80 | – | – | 0.5 | – |
| – child care taker | 5.0 | 5.0 | 5.00 | 5.00 | 5.0 | 5 | 5.0 | – |
| – psychologist | – | – | 1.00 | 1.75 | 0.5 | – | – | – |
| – occupational therapist | – | – | – | 1.75 | – | – | – | – |
| – dietitian | – | – | 1.00 | – | – | – | – | – |
| – speech therapist | – | – | – | 1.00 | – | – | – | – |
| Total – Personnel | 24 | 24 | 27.25 | 33.80 | 26.5 | 26 | 25.5 | 17 |
| Requirements concerning 24-hour medical care | Ensuring physician's care in the afternoon, in the evening, at night – at a nurse's request | | Ensuring 24-hour physician's care (can be combined with other hospital departments) | | Ensuring 24-hour physician's care (can be combined with other departments providing non-invasive medical treatment) | | | |
| Additional conditions | Stand for intensive medical supervision on location | | | | Beds allocated for intensive medical care – entry in the Register of Health Care Institutions: section III, column 9 | | | |

On the basis of instructions issued by the NFZ Chairman [7–9, 12–17]. Comments: [1] Conditions identical with those specified for departments of pediatric hematology and pediatric oncology. [2] Minimal number of physicians employed full-time at the department of pediatric neurology is 2: "in the case of treating children the equivalent of at least 2 FTE (full-time employment) (does not apply to physician's duty), including the equivalent of at least 1 FTE specialist in pediatric neurology, including head of hospital department (physician in charge of the department) – specialist in pediatric neurology" [7]. [3] The number of nurses is consistent with the Regulation of the Minister of Health dated December 21, 1999, concerning establishing minimal norms regarding the employment of nurses and midwives in health care institutions (Dz.U. z 1999 Nr 111, poz 1314 [Journal of Laws No 111, item 1314]).

departments providing non-invasive medical treatment. The analysis has been carried out for departments having 35 beds, since for many years the Regulation of the Minister of Health concerning the professional and sanitary requirements for premises and equipment of a health care institution included the following instruction: "A nursing section cannot exceed 35 beds". This requirement was omitted in the amendment of November 10, 2006. Nevertheless, many departments are still organized according to that original directive.

The data included in Tab. 2 show that requirements concerning the nursing personnel of rehabilitation departments are similar to those of hospital departments providing non-invasive medical treatment. They mostly concern providing 24-hour care per 7 days a week. Requirements differ with respect to the number of physicians. In rehabilitation departments this number increases as the number of beds grows, while in hospital departments this number is unchanged irrespective of the number of beds. Yet, the major differentiating factor is the necessity of employing physiotherapists in rehabilitation departments. In the case of pediatric departments, child care providers have been included as well, although they are not specified in the NFZ requirements. Their presence is, however, necessary and in practice they are employed in those departments to look after underage patients.

As regards the number of employed personnel, a department of neurological rehabilitation definitely stands out. Apart from a larger number of physiotherapists, additionally psychologists, occupational therapists and speech therapists must be employed there.

In all compared departments providing non-invasive medical treatment and departments of neurological and cardiac rehabilitation a physician on duty is required. This duty can be combined with other departments. Such a requirement has not been established for departments of general rehabilitation and departments of pulmonary rehabilitation. However, in the case of pediatric departments, the constant presence of a physician on location is necessary for safety reasons, because children are frequently unable to describe their health conditions adequately and precisely. A nurse may wrongly assess a child's condition and not provide him with adequate help.

Monthly labor costs in the departments have been calculated as a product of gross monthly salary divided by the required number of full-time employees according to the NFZ for the year 2011 (Tab. 3). In order to visualize the differences better, it has been assumed that the cost of department of pediatrics amounts to 100%. The obtained data show that the personnel costs at the department of neurological rehabilitation are higher by 23% than personnel costs at the department of pediatrics and are comparable to the costs at the department of cardiac rehabilitation. Personnel costs at departments of general rehabilitation and pulmonary rehabilitation are lower by 15% than such costs at the department of pediatrics. Among departments providing non-invasive medical treatment, the lowest personnel costs are incurred by the department of internal medicine. Since this department treats adults, it does not need to employ child care takers.

**Tab. 3.** Monthly costs of personnel gross wages, employed according to requirements specified by the NFZ (see Tab. 2), and average incomes of rehabilitation departments and selected hospital departments providing non-invasive medical treatment

| Category | Gross salary per FTE [zlotys][1] | Monthly costs of personnel gross wages at departments [zlotys] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Department of pediatric rehabilitation | | | | Hematology--Oncology Hospitalization of children | Department of | | | |
| | | General | Pulmonary | Cardiac | Neurological | | Pediatric | Pediatric neurology | Pediatric rheumatology | Internal medicine |
| Physicians – specialists | 6 000 | 9 000 | 9 000 | 16 500 | 15 000 | 18 000 | 18 000 | 12 000 | 18 000 | 18 000 |
| Nurses | 3 000 | 42 000 | 42 000 | 42 000 | 48 000 | 54 000 | 54 000 | 54 000 | 54 000 | 42 000 |
| Physiotherapists | 2 600 | 9 100 | 9 100 | 9 100 | 15 167 | – | – | 1 300 | – | – |
| Child care takers | 2 000 | 10 000 | 10 000 | 10 000 | 10 000 | 10 000 | 10 000 | 10 000 | 10 000 | – |
| Psychologists | 3 000 | – | – | 3 000 | 5 250 | 1 500 | – | – | – | – |
| Occupational therapists | 2 500 | – | – | – | 4 375 | – | – | – | – | – |
| Dietitians | 2 500 | – | – | 2 500 | – | – | – | – | – | – |
| Speech therapists | 2 800 | – | – | – | 2 800 | – | – | – | – | – |
| **Total monthly labor costs in the department** | | **70 100** | **70 100** | **83 100** | **100 592** | **83 500** | **82 000** | **77 300** | **82 000** | **60 000** |
| Comparison of monthly personnel costs (in relation to the department of pediatrics – 100%) | | 85% | 85% | 101% | 123% | 102% | 100% | 94% | 100% | 73% |
| Service value | – | 110 | 90 | 100 | 300, 240 and 220[2]<br>190, 150 and 120[3] | 15 | – | – | – | – |
| Weighted average price per point | – | 1.12 | 1.22 | 1.21 | 1.09 | 51 | – | – | – | – |
| **Average value of person-day in 2010** | **–** | **123.20** | **109.80** | **147.22[4]<br>121.00[5]** | **276.13[6]<br>167.13[7]** | **765** | **418.88** | **387.14** | **411.58** | **330.31** |
| Comparison of average costs of person-day (in relation to the department of pediatrics – 100%) | | 29% | 26% | 29% | 66%<br>43% | 183% | 100% | 92% | 98% | 79% |

Source: Author's estimates. Comments: [1] Approximate gross wages of medical personnel have been obtained on the basis of interviews with hospital directors. For the sake of analysis clarity, wages have been rounded to an accuracy of 500 zlotys. [2] Within the framework of the DRG system, in neurological rehabilitation (NR) 3 groups have been established with the following point values: RND01 – 300 points, RND02 – 240 points, RND03 – 220 points. [3] According to the requirements for year 2010, NR was priced within three different services provided: person-day in early NR – 150 points, NR in severe damage to CNS – 190 points, and secondary NR – 120 points. [4] Hypothetical price of person-day in cardiac rehabilitation, (CR), which can be obtained by service providers within the DRG system framework in 2011. The price has been calculated as a product of an arithmetical average of 3 DRG groups (RK01 – 160 points, RK02 – 115 points, RK03 – 90 points) divided by the average price per point in CR in 2010. [5] Average price of person-day in CR in 2010 (before introducing the DRG system), calculated as a product of point value divided by the average price per point. [6] Hypothetical price of person-day in NR, which can be obtained by service providers within the DRG system framework in 2011. The price has been calculated as a product of an arithmetical average of 3 DRG groups (RND01 – 300 points, RND02 – 240 points, RND03 – 220 points) divided by the average price per point in NR in 2010. [7] Average price of person-day in NR in the first half of 2010 (before introducing the DRG system), calculated on the basis of data obtained from the NFZ.

Incomes of departments of general rehabilitation and pulmonary rehabilitation have been calculated as a product of the service value determined for the years 2010 and 2011 (service value has not changed in relation to 2010) [8] divided by the weighted average of the price per point in 2010. In the case of neurological rehabilitation and cardiac rehabilitation, due to significant changes in the financing scheme introduced as of October 2010, involving a switch to the DRG system and increasing the service value, two income values per person-day have been presented:

- real income obtained in the first half of 2010: 180.81 zlotys for neurological rehabilitation (on the basis of the questionnaires from the NFZ regional branches) and 121.00 zlotys in the case of cardiac rehabilitation,
- hypothetical income possible to achieve in 2011, assuming an unchanged price per point: 276.13 zlotys in neurological rehabilitation and 147.22 zlotys in the case of cardiac rehabilitation. Point value has been calculated as an arithmetic mean of the DRG pricing for children: RND01, RND02 and RND03 [9], i.e.,

$$\frac{300+240+220}{3} \cdot 1.09 = 276.13 \text{ zlotys}$$

Income per person-day in hematology-oncology inpatient treatment of children has been calculated as a product of price per point in hospital treatment divided by service value [7]. Hospital treatment functions within the DRG reimbursement system, thus it is not possible to calculate income per person-day directly. Consequently, the average value of a person-day in the remaining analyzed departments providing non-invasive medical treatment has been calculated on the basis of the data obtained from the NFZ regional branches.

The comparison indicates that there are vast disproportions in pricing the services offered by inpatient general rehabilitation and pulmonary rehabilitation in relation to departments providing non-invasive medical treatment. On average, income per person-day in general rehabilitation (123.20 zlotys), and pulmonary rehabilitation (109.80 zlotys) is more than 3-fold lower than income per person-day obtained in departments providing non-invasive medical treatment, whereas personnel costs are lower only by 15%. The situation regarding neurological rehabilitation is equally unsatisfactory. The price of person-day estimated for 2011 (276.13 zlotys), despite a higher personnel cost (by 23%), and considering a new pricing for services within the DRG system, is still lower by 34% than an average price per person-day at the department of pediatrics (418.88 zlotys).

Departments providing non-invasive medical treatment admit a large variety of patients. This diversification of patients only in part coincides with patients admitted to rehabilitation departments. Thus, in order to make this analysis reliable, additionally average prices of person-day received at departments providing non-invasive

medical treatment and departments of general rehabilitation with respect to selected diagnosis related groups of patients who manifest diseases treated in both types of departments, have been compared. The value of person-day has been calculated as a quotient of an average hospitalization period of patients in a particular group in a particular department multiplied by the pricing for the respective group (Tab. 4). This calculation also shows that the price per person-day in inpatient general rehabilitation (123.20 zlotys) is almost 3-fold lower than an average price per person-day of treatment obtained at departments providing non-invasive medical treatment, being respectively: 340.54, 366.09, and 425.84 zlotys.

**Tab. 4.** Average hospital stay length of patients and associated average value of person-day in selected DRG groups from January to June, 2010 (only ICD-10 applicable to general rehabilitation)

| Group code | Department of | | | Point value – hospital stay | Group pricing | Department of | | |
|---|---|---|---|---|---|---|---|---|
| | Neurology (pediatric) | Internal medicine | Pediatrics | | | Neurology (pediatric) | Internal medicine | Pediatrics |
| | Average hospital stay length [days] | | | | | Average value of person-day [zlotys] | | |
| [1] | [2] | [3] | [4] | [5] | [6]=[5]×51 zlotys | [6]/[2] | [6]/[3] | [6]/[4] |
| A31 | 6.9 | 5.5 | 8.5 | 30 | 1 530 | 223 | 276 | 180 |
| A32 | 9.0 | 13.6 | 5.1 | 60 | 3 060 | 340 | 225 | 600 |
| A36 | 7.5 | – | 14.5 | 70 | 3 570 | 474 | – | 246 |
| A57 | 12.9 | 5.7 | 14.0 | 77 | 3 927 | 304 | 695 | 281 |
| A87 | 5.0 | 6.8 | 3.9 | 31 | 1 581 | 317 | 233 | 408 |
| D19 | – | 9.4 | 14.3 | 70 | 3 570 | – | 381 | 251 |
| H56 | 8.8 | 5.9 | 3.8 | 30 | 1 530 | 173 | 261 | 402 |
| H87 | 16.6 | 7.5 | 5.4 | 68 | 3 468 | 209 | 460 | 647 |
| H89 | 5.2 | 5.4 | 3.6 | 42 | 2 142 | 415 | 397 | 588 |
| P05 | – | – | 7.8 | 95 | 4 845 | – | – | 620 |
| P14 | – | – | 2.3 | 24 | 1 224 | – | – | 521 |
| P16 | 2.9 | – | 5.5 | 35 | 1 785 | 610 | – | 326 |
| P20 | – | – | 4.5 | 41 | 2 091 | – | – | 467 |
| Average length of hospital stay | 8.3 | 7.5 | 7.2 | Average price of person-day DRG for 5 NFZ regional branches[1] | | 340.54 | 366.09 | 425.84 |
| | | | | Average price of person-day for 3 NFZ regional branches[2] | | 411.58 | 330.31 | 418.88 |

Source: Average prices of person-day have been calulated as a quotient of group pricing multiplied by the average length of hospitalization of patients (Tab. 1). Group pricing has been calculated as a product of group point value – hospitalization, specified in Appendix No 1 to Instruction No 51/2010/DSOZ of the NFZ

Chairman and the point price in year 2010 – 51 zlotys. Comments: [1] Average value of person-day in selected DRG groups (alike in departments providing non-invasive medical treatment and inpatient general rehabilitation departments). [2] Average price of person-day calculated on the basis of average prices of person-day obtained by selected hospital departments in 3 NFZ regional branches which returned the questionaires. Abbreviations: A31 – peripheral nerve disorders; A32 – muscle disorders; A36 – demyelinating disorders, A57 – inflammatory diseases of the central nervous system; A87 – other diseases of the nervous system; D19 – bronchodilation; H56 – spinal pain syndromes; H87 – inflammatory diseases of joints and connective tissue; H89 – non-inflammatory diseases of bones and joints; P05 – major infections (including immune system diseases); P14 – post-traumatic injuries, except brain injuries; P16 – serious genetic diseases and other congenital disorders; P20 – skin diseases, musculoskeletal diseases and connective tissue diseases.

**How did such a drastic disproportion in the pricing of non-invasive medical services provided in hospitals and inpatient rehabilitation services come about?**

In 2005, the difference between the income per person-day between inpatient rehabilitation departments and departments providing non-invasive medical treatment was 2-fold (respectively, about 97 zlotys and about 250 zlotys). In 2006, a new Act came into force [6], which provided for a 30% increase in the financial resources allocated for salaries in medical institutions. In hospital treatment and therapeutic rehabilitation, the legislators assumed the share of labor cost in the service cost at the level of 65%, and on this basis prices per person-day were calculated (Tab. 5, line 3). In 2008, the NFZ introduced into hospital treatment a new system of reimbursement based on the DRG system. This allowed for a significant increase in the average price of hospitalization. Data provided by the NFZ indicate that in the year 2009 an average price of hospitalization in all types of hospital treatment was higher by about 40% in relation to 2007, whereas as concerns inpatient rehabilitation, the price of hospitalization increased only by about 5% (Tab. 5, line 5).

**Tab. 5.** History of changing the price of person-day for departments providing non-invasive medical treatment and rehabilitation departments

| Year | Price of person-day | | Difference in the price of person-day | Change dynamics concerning the price of person-day |
|---|---|---|---|---|
| | Departments of pediatrics and pediatric neurology | Departments of general rehabilitation and pulmonary rehabilitation | | |
| 2005 | 250 zlotys | 97 zlotys | 153 zlotys | 39% |
| 2006 | 120%[1] | 120%[1] | | |
| 2007 | 299 zlotys | 116 zlotys | 183 zlotys | 39% |
| 2008 | 140%[2] | 105%[3] | | |
| 2009 | 418 zlotys | 122 zlotys | 297 zlotys | 29% |

Source: Author's analysis. Comments: [1] Increase of the outlays resulting from the Act concerning transferring financial resources to service providers for the purpose of increasing salaries [6]. [2] Increase of the outlays resulting from the implementation of the DRG system in hospital treatment. [3] Increase of the outlays resulting from negotiating higher rates by service providers.

Apart from the low pricing of rehabilitative services already in 2005, changes in the health care financing system – adverse for this specialty – have only deepened the already existing disproportions, increasing by almost 2-fold the difference between average prices per person-day in those comparable types of services (from 155 zlotys to 297 zlotys).

## CONCLUSIONS

This presented data show that medical personnel labor costs are generally comparable in rehabilitation departments and departments providing non-invasive medical treatment. Also, the requirements concerning a physician on duty do not differ significantly. The analysis carried out clearly indicates that the pricing of inpatient general rehabilitation and pulmonary rehabilitation is grossly undervalued in relation to the pricing of services offered by departments providing non-invasive medical treatment.

Such a disproportion is particularly unfavorable for inpatient pediatric rehabilitation, where the difference between the financing level and incurred costs is the largest.

Permanent underfinancing of inpatient rehabilitation, resulting from the low pricing of services, leads to eliminating or limiting the number of beds in hospital rehabilitation departments, as is exemplified by limiting the number of beds in Children's Health Institute in Warsaw by 36% (from 70 to 45 beds). Moreover, under-waged medical personnel search for employment at other departments. This, in a long-term perspective, will lead to a permanent lowering of the quality of rehabilitative services and their availability in Poland.

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8. Załącznik nr 1n do Zarządzenia Nr 53/2010/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 2 września 2010 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju rehabilitacja lecznicza [Appendix No 1n to Instruction No 53/2010/DSOZ of the National Health Fund Chairman of September 2, 2010, concerning determining the terms and conditions of contracts and their realization as regards: therapeutic rehabilitation].
9. Załącznik nr 1r do Zarządzenia Nr 53/2010/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 2 września 2010 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju rehabilitacja lecznicza [Appendix No 1r to Instruction No 53/2010/DSOZ of the National Health Fund Chairman of September 2, 2010, concerning determining the terms and conditions of contracts and their realization as regards: therapeutic rehabilitation].
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14. Zarządzenie Nr 53/2010/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 2 września 2010 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju rehabilitacja lecznicza [Instruction No 53/2010/DSOZ of the National Health Fund Chairman of September 2, 2010, concerning determining the terms and conditions of contracts and their realization as regards: therapeutic rehabilitation].
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16. Zarządzenie Nr 69/2009/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 3 listopada 2009 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju: leczenie szpitalne [Instruction No 69/2009/DSOZ of the National Health Fund Chairman of November 3, 2009, concerning determining the terms and conditions of contracts and their realization as regards: hospital treatment].
17. Zarządzenie Nr 92/2009/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 30 grudnia 2009 r. zmieniające zarządzenie w sprawie określenia warunków zawierania i realizacji umów w rodzaju: leczenie szpitalne [Instruction No 92/2009/DSOZ of the National Health Fund Chairman of December 30, 2009, amending the instruction concerning determining the terms and conditions of contracts and their realization as regards: hospital treatment].

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*HISTORICAL PAPER*

# WŁADYSŁAW FRANCISZEK ANDRZEJ SZCZEPAŃSKI – HISTORIAN OF PHARMACY AND MEDICINE

**Zenobiusz Michał Bednarski**

*Regional Warmia and Mazury Medical Chamber in Olsztyn, Poland*

**ABSTRACT**

Władysław F. A. Szczepański was born on September 20, 1922 in Kalisz, and died on December 31, 2009 in Olsztyn, Poland. In 1947, he graduated from the University of Poznań (Faculty of Pharmacy) and was awarded the title of Master of Pharmacy. He obtained his first job at a pharmacy in Częstochowa. Next, from 1948 to 1949 he worked in the chemical plant PEMOR in Poznań. During his military service between 1949 and 1957 he served as head of a pharmacy and a laboratory. Having completed his military service, he then became a manager of a pharmacy in Częstochowa, and then the Deputy Director of the Częstochowa Department for the Katowice Board of Pharmacies. In 1972 he was appointed Director of Board of Pharmacies in Olsztyn (evolving into the Public Company of Pharmaceutical Supplies CEFARM in Olsztyn), which function he performed till 1988 when he retired. He was awarded the academic degree of Doctor of Pharmacy in 1970 and a post-doctoral degree (Assistant Professor) in pharmacy in 1998. He was most active in the field of the history of pharmacy, and also in the field of the history of medicine. He wrote many biographies concerning pharmacists. From 1972 to 1983, he served as the Vice-President of the Polish Medical Association. Between 1980 and 1992 he served as the Vice-President of the Polish Association for History of Medicine and Pharmacy, Division in Olsztyn, and remained its President since 1993. He was a member of the General Board of the Polish Historical Society. He participated in numerous congresses and conferences involving historians of pharmacy and medicine in Poland and abroad. He was honored with the Knight's Cross of the Order of Polonia Restituta, Medal of Rodło and many other regional and professional awards.

**Key words:** asst. prof. Szczepański, pharmacist, biography, history of pharmacy and medicine

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*Non omnis moriar multaque pars mei*
*vitabit Libitinam*
Horace, *Carmina* III, 30, 6–7

Władysław Franciszek Andrzej Szczepański was born on September 20, 1922 in Kalisz. In 1947, he graduated from the University of Poznań (Faculty of Pharmacy) and was awarded the title of Master of Pharmacy [3]. He obtained his first job at a pharmacy in Częstochowa. Next, from 1948 to 1949 he was employed in the chemical and pharmaceutical plant PEMOR in Poznań. In 1949 he was drafted for military service as the head of a pharmacy and a laboratory, in the rank of major. He performed this service until 1957. In 1976 he was promoted to the rank of lieutenant-colonel, and in 2001 to full colonel. After completing his military service, he became manager of a pharmacy in Częstochowa. This position allowed him to show his organizational talents. The supervising authorities noticed his efforts and skills and promoted him to the position of Deputy Director of the Częstochowa Division of the Katowice Board of Pharmacies. He remained in this position until 1972. Moreover, during this period of his life he taught pharmacology at the Medical Secondary School in Częstochowa, headed the Aseptic Laboratory of the Katowice Board of Pharmacies, Division in Częstochowa (1962–1971) and between 1957 and 1959 he was manager of the Pharmaceutical Cooperative in Częstochowa.

In 1972 he was appointed Director of Board of Pharmacies in Olsztyn, which was later transformed into the Public Company of Pharmaceutical Supplies CEFARM in Olsztyn. He performed this function until 1988 following which he retired [2, 3, 6].

He had conferred upon him the degree of Doctor of Pharmacy on January 19, 1970 by the Faculty of Pharmacy of the Medical Academy in Warsaw, on the basis of his thesis entitled *Pharmacies in Częstochowa up till the end of the 19$^{th}$ century*, supervised by prof. Stanisław Konopka, PhD. He obtained his post-doctoral degree on April 12, 1999 on the basis of the work *Pharmaceutical Agents in Old Polish Pharmacopeias (1560–1970)* at the Faculty of Pharmacy of the Karol Marcinkowski Medical Academy in Poznań (presently Poznań University of Medical Sciences), reviewed by: Jerzy Lutomski, Jerzy Masiekowski, Dionizy Edward Moska [1, 6].

Among his published works, one of the most significant is his book discussing the history of socialized pharmacies in Olsztyn (*Cefarm Olsztyn. Pięćdziesiąt lat tradycji* [*Cefarm Olsztyn. Fifty years of tradition*], Olsztyn 2001). Moreover, he authored 40 scientific papers concerning the history of pharmacy, 55 biographies of pharmacists, 2 reviews, 10 papers on social matters, and numerous reports, obituaries and chronicles [6].

In 1957 he became a member of the Polish Pharmaceutical Association, and in 1959 he was appointed President of the Częstochowa Division of this Association. Having moved to Olsztyn, he served as the President of the Olsztyn Division of the

Polish Pharmaceutical Association between 1973 and 2003, as well as the Chairman of the History of Pharmacy Section in Olsztyn, and from 1990 to 2003, the Chairman of the History of Pharmacy Section of the Polish Pharmaceutical Association.

From 1972 to 1983, he was the Vice-President of the Polish Medical Association in Olsztyn, between 1980 and 1992 the Vice-President of the Polish Association for History of Medicine and Pharmacy in Olsztyn, and since 1993 of its General Board, between 1974–1996 the Vice-Chairman of the Committee for Controlling Tuberculosis and Lung Diseases. Since 1993 he was the President of the Olsztyn Division of the Polish Association for History of Medicine and Pharmacy [7]. As he once recalled, this position, taken after the late Andrzej Skrobacki, MD, PhD, was an impulse to begin the procedure to be conferred the postdoctoral degree in pharmacy.

Between 1977–1993, he was a member of the General Board of the Polish Historical Society, and since 1995 a member of the Board of the Polish Society of War Veterans, between 1954–1972 a member of the Provincial Committee for Verifying Pharmacists in Katowice, 1965–1972 a tourist-guide and member of the Polish Tourist and Sight-seeing Society [2, 3, 6].

He was skilled at making reasonable decisions and cooperating with others in professional circles, which he did in a most natural, trustworthy manner.

He was very popular among historians both in Poland and abroad. He was especially interested in discovering and describing the history of pharmacy in Poland. Professional ethics was also one of his spheres of interest.

He participated in International Congresses of the Association for History of Pharmacy in Tübingen, Goerlitz, and Lipsk. The pharmacists' profession thanked him for the excellent way in which he organized the symposium on the history of pharmacy in Gietrzwałd and for chairing discussions during conferences in Supraśl, Suchedniów, Wenecja, Łańcut, and Iwonicz Zdrój.

For his many years of professional and social activities, as well as activities referring to the history of pharmacy and medicine he was awarded with the Knight's Cross of the Order of Polonia Restituta (1981), the Ignacy Łukasiewicz Medal (1977), medal for perfect work in healthcare service (1976), Distinguished for National Health badge (1988), Medal of Rodło (1986), Distinguished for the development of the Warmia and Mazury badge (1978), Distinguished for the Katowice Province badge (1962), Golden Cross of Merit (1974), as well as with military medals: The Armed Forces Serving to the Homeland (1955), Medal of Victory and Freedom (1976), Operation Tempest (1995), Veteran Badge of Struggle for Independence (1996) [2, 3, 6].

Associate professor Władysław F. A. Szczepański died on December 31, 2009, following a long and serious disease. He was buried on January 5, 2010 in Gietrzwałd in his family tomb after a ceremonial mass for the dead conducted in Olsztyn.

He was a kind man to and for everyone. He spoke well of those people he met in life and treated them in friendly fashion. Those who knew him, will retain fond

memories of him. His memory will be always vivid to those who will study his works concerning the history of pharmacy and medicine.

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Kowalski I. M., Protasiewicz-Fałdowska H., Jóźwiak-Grabysa D., Kiebzak W., Zarzycki D., Lewandowski R., Szarek J.: *Environmental factors predisposing to pain syndromes among adolescent girls with diagnosed idiopathic scoliosis.* J. Elementol., 2010; 15 (2) [Forthcoming].

– printed books (with author or editors name)

Świderska M.: *Zgoda pacjenta na zabieg medyczny*. Toruń 2007: 19, 37.
Albrecht G. L., Seelmann K. D., Bury M. (eds.): *Handbook of Disability Studies*. Sage Publications, Thousand Oaks 2001.

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Edgar M.: *Brace Wear Compliance* [Internet]. [Scoliosis Research Society], 2003 [accessed: 1 May 2010]. Available from: <http://www.srs.org/professionals/bracing_manuals/section3.pdf>.

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