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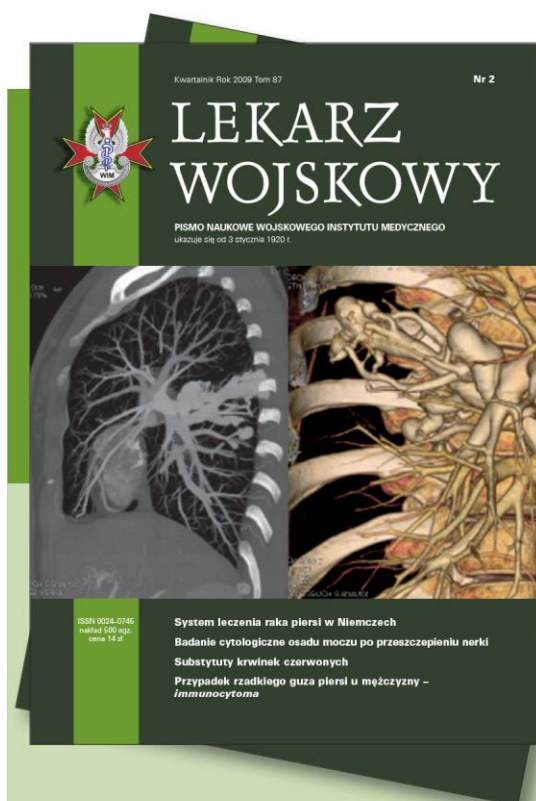
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The acceptance of disease and methods of coping with difficulties by the chronically ill

Akceptacja choroby i sposoby radzenia sobie z trudnościami przewlekle chorych

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Abstract. Health could be considered to be a variable value. When there is a threat, especially due to serious illness, people usually make a definite change in their hierarchy of values. They initiate their own personal resources, which makes it possible to re-evaluate their life goals to those that can be implemented to suit the conditions changed by the illness in order to make their life acceptable again. People cope with a chronic disease in different ways. Some cope with it in an active form, others in a contemplative form. Some plan strategically while others deal with it by prevention. Some look for informational support, others for emotional support. Last but not least, there are also those who deal with it by avoiding or postponing the activity required for such difficult circumstances. Choosing the right way to cope with the disease may be decisive not only in terms of the disease, and coping with its consequences, but also the limitations caused by the disease that determine the level of satisfaction with one's life. The aim of these studies is to answer the questions about the most frequent ways patients deal with difficulties related to going through a chronic disease, its possible variability in time, and its relation to the assessment of satisfaction with their own lives.

Key words: chronic diseases, acceptance of a difficult situation, ways of coping

Streszczenie. Zdrowie ma zmienną wartość. W sytuacji jego zagrożenia, zwłaszcza poważną chorobą, ludzie dokonują zwykle zdecydowanej zmiany swojej hierarchii wartości. Człowiek uruchamia wówczas zasoby osobiste, które pozwalają dokonać przewartościowania celów życiowych na takie, które są możliwe do realizacji w zmienionych przez chorobę warunkach i uczynią życie na powrót akceptowalnym. Style radzenia sobie z chorobą przewlekłą są różne. Jedni radzą sobie z nią w sposób aktywny, inni w sposób refleksyjny. Niektórzy planują strategicznie, inni radzą sobie przez zapobieganie. Jedni poszukują wsparcia informacyjnego, inni emocjonalnego. Wreszcie są i tacy, którzy radzą sobie przez unikanie czy odkładanie działania w trudnej sytuacji na później. Dobór stosownych sposobów radzenia sobie w sytuacji choroby może być decydujący nie tylko dla samego przeżywania choroby i radzenia sobie z jej skutkami – może także decydować o zadowoleniu z własnego życia mimo ograniczeń spowodowanych chorobą. Prezentowane badania mają za dostarczyć odpowiedzi na pytania o najczęstsze sposoby radzenia sobie z trudnościami związanymi ze stanem przeżywania choroby przewlekłej, ich ewentualną zmienność w czasie i związek z oceną zadowolenia z własnego życia.

Słowa kluczowe: choroby przewlekłe, akceptacja sytuacji trudnej, sposoby radzenia sobie

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Background

In the psychology of health the concept of "personal resources" is usually mentioned in the context of coping with stress. Personal resources involve the relatively constant presence of the personal and social factors that determine the mechanisms of dealing with both threatening and favourable life situations.

The concept of social support is similar, although more narrow, and refers to a constantly available characteristic of a relationship that enables a person to satisfy their basic interpersonal needs, associated with adjustment and health [1]. In the latter, the effect of personal traits appears to be reduced, although the same authors postulate that "social network structures (support resources) exist regardless of the presence of a difficult situation, and are formed in the course of the psychosocial development throughout a person's life" [1, 13].

Søk [2] defines resources as features potentially existing in a person and in their relationships with the environment. Therefore, resources are properties of the external world (situation) and the personal world, as well as the relationships between the two. They help us in avoiding stressors, preventing the transformation of a difficult situation into stress, especially of a chronic type, and contribute to the effective management of stress. Resources include genetic, psychological, social and spiritual factors. Most importantly, they demonstrate specific functional properties, potentially existing in a person's environment, within the person, or in the relationships between the person and their environment [2]. However, in the term "social support" the dominant factor is the interpersonal relationship ensuring that a person can rely on assistance [3]. Support results from belonging to a social network [4], and means the satisfaction of needs by significant others and reference groups [5, 1].

Many studies have attempted to offer a precise definition of social support [2, 6, 7]. They emphasise the following concepts: structural and functional support, received and perceived support, and the need and mobilisation of support. Moreover, the authors explore various sources of support.

The term "personal resources" is an important element in Antonovsky's concept of coherence [8, 9], and lies in the centre of Hobfoll's concept, referred to as "conservation of resources" [10-13]. In both cases, resources are involved in the explanation of adaptive behaviours and dealing with stressful situations, including a threat or damage to health.

Health is considered a special resource: the organism's general ability to develop and deal with the current challenges. It is a process of achieving and

maintaining balance, disturbed by the changing external and internal requirements. The resources of a person play an important role in this process [10]. People assign a great value to health. However, when they need to choose between health and other factors, they often redefine their hierarchy of values. In general, health is treated instrumentally, as a feature that enables the gaining of other values. The theory of control [14] attempts to explain the appraisal of health, by assessing health in terms of the discrepancy between a person's abilities and aspirations (goals). As a result, four models can be distinguished. In the first model, the effects of the disease may increase the discrepancy between one's abilities and goals (mobility impairment and the need to do shopping). In the second model, the appraisal of health may depend on the point of reference (someone with asthma and practicing professional sport, although in other activities the person may be fully capable). In the third model, the scope of achieved goals may be an indicator of health, i.e. the more a person achieves, the healthier they feel. Evaluation in the fourth model is associated with an internal hierarchy of values, which usually leads to reassignment of the importance of goals. In this case, health is perceived as the ability to adapt ambitions to abilities and conditions.

Therefore, health can be evaluated in terms of the assessment of one's own abilities, or the importance of the undertaken and achieved life goals. A person evaluates not only his or her own previous and planned achievements, but also the existential and spiritual dimension of their life. This involves activation of the personal resources that enable assigning greater value to the goals achievable regardless of the limitations. Sometimes an ill person achieves a higher level of satisfaction with life than during the time before the illness [2, 10].

Different authors list different phenomena under the "social support" category. These may include formal structures of the social network, activity expressed in providing or receiving assistance (provided and received support), or a subjective estimation of the possibility of receiving help (perceived social support).

In the psychology of health, the most important aspect of support is perceived social support [16]. However, according to some researchers social support should be considered a personal variable [3, 16]. The perceived support results from the impact of the environment. People with a high level of perceived support are more problem solving oriented, and more competent. Clearly the consistence between expectations and the actually received support may be of great importance, both in the course of the disease and in the recovery period.

Research questions

1. What are the most common mechanisms of coping with difficulties associated with living with a chronic disease?

2. Do these mechanisms change with time and are they associated with the assessment of satisfaction with one's life?

Table 1. Reliability of Proactive Coping Inventory (PCI) scales
Tabela 1. Rzetelność skal Inwentarza Proaktywnego Radzenia Sobie (PCI)

Scales	Cronbach's alpha in studies			N items
	Polish	Canadian	Polish-Canadian	
Active coping	0.87	0.85	0.80	14
Reflecting over the problem	0.86	0.79	0.80	11
Strategic planning	0.74	0.71	0.71	4
Prevention	0.79	0.83	0.79	10
Instrumental support seeking	0.81	0.85	0.84	8
Emotional support seeking	0.72	0.73	0.64	5
Avoidance	0.67	0.61	0.74	3

Material and methods

The study involved two groups: healthy and chronically ill patients. The first group comprised 80 people who felt healthy, did not take any medicines continuously, were not in therapy due to any conditions, were not invalids and did not require rehabilitation or care. The second group comprised 182 chronically ill people diagnosed as: patients with ischaemic disease, following one myocardial infarction (N = 41), patients receiving continuous treatment due to primary arterial hypertension (N = 35), patients receiving treatment due to a malignant neoplasm (N = 36), patients with diabetes (N = 33) and patients with bronchial asthma (N = 37). The duration of the disease varied between one year and several years (M = 10.37; SD = 8.08). 62 patients were ill for 5 years, 52 patients were ill for 6-10 years, and 68 patients were ill for 11 years or more. All the subjects were under constant medical care due to the consequences of their conditions.

The healthy people were slightly younger (M = 48.02, SD = 6.86) than the chronically ill people (M = 53.03, SD = 7.97). The number of men and women in both groups was similar: the group of healthy people comprised 41 women and 39 men, while the group of ill people comprised 95 women and 87 men.

The study was conducted in the years 2011-2015, individually in the patients' homes or in a hospital ward. Many people declared a need for contact outside the study; therefore, meetings were often divided into two or three sessions. The time required to fill in the questionnaires was usually less than an hour.

Proactive Coping Inventory (PCI) was used as the research tool. It is a multidimensional questionnaire comprising 55 items in 7 subscales [6].

The proactive coping scale combines goal setting with individual methods of goal attainment cognitions and behaviour.

The reflective coping scale describes simulation and contemplation about a variety of possible behavioural alternatives by comparing their imagined effectiveness; it comprises an analysis of the problem and its sources, and generating hypothetical plans of action.

Strategic planning focuses on the process of generating a goal-oriented schedule of action in which extensive tasks are broken down into manageable components

Preventive coping deals with the anticipation of potential stressors and the initiation of preparation before these stressors develop fully. Preventive coping is distinct from proactive coping, as it applies to a potential threat in the future by considering previous knowledge and experience.

Seeking instrumental support focuses on obtaining advice, information and feedback from people in one's social network when dealing with stressors.

Seeking emotional support: a person tries to lower (downregulate) temporary anxiety by discovering the emotions of others, evoking empathy and seeking companionship. It is emotional self-regulation with the assistance of significant others.

Avoidance coping: this consists of eluding action in a demanding situation by delaying; this scale is very short (it consists of only three statements), so its reliability

might be limited, but its results, as demonstrated by authors, can be good. The indicators of reliability are presented in Table 1.

The method has been in use for a few years and its results are still under validation; however, it appears to be particularly useful in studies regarding the mechanisms of coping with difficult and stressful situations. Coping with the effects of an illness is especially important in chronically ill patients, where the approach to the disease, appraisal of personal resources and perceived social support significantly contribute to satisfaction with one's life.

Results and discussion

The level of disease acceptance was determined using the Disease Acceptance Scale (Table 2). For obvious reasons, this tool was not used in healthy volunteers.

A relatively high level of disease acceptance is expressed by patients with diabetes and hypertension. The lowest degree of acceptance is observed in oncological patients. Significant statistical differences are found between the group of oncological and hypertensive patients ($t = 2.19$; $p < 0.05$) and diabetics ($t = 2.25$; $p < 0.05$).

Neither the age of the individuals ($F = 0.81$; $p = 0.82$) nor the duration of the disease ($F = 1.11$; $p = 0.33$) affected the level of disease acceptance. A slight increasing trend could be observed in acceptance, or rather a reconciliation with the situation, during the second stage (between 6 and 10 years of illness duration), but as the disease continues then the acceptance of the unsatisfactory health status reduces.

The means of coping with stress and obstacles are very important in a constantly difficult situation of chronically ill people. Which of them are more typical for healthy people, and which for chronically ill people? Does the type of disease affect the preferred strategies? These questions could be important in the analysis of the issue of quality of life.

The methods of coping with difficulties were measured using the Proactive Coping Inventory (PCI). The scores obtained in the study groups are presented in Table 3.

There were slight differences in the methods of coping, both between the healthy and ill people, and between the various groups of chronically ill people. The only aspect in which the ill people differed significantly from the healthy people was in instrumental support ($t = 2.58$; $p < 0.01$). Patients used this mechanism of dealing with stress and difficulties more often, and attempted to gather the largest possible amount of information about the disease, its causes and course, as well as methods of treatment. However, a certain tendency for increased use of strategic planning, and a higher level of activity was

observed in healthy people. The scores obtained by healthy people most closely matched those of people with diabetes. Slightly reduced coping scores, especially regarding reflective and proactive coping, were observed in patients with neoplastic diseases and asthma.

Table 2. Disease acceptance (AIS scale) in the study groups:

Tabela 2. Akceptacja choroby (skala AIS) w badanych grupach chorych: wyniki średnie average results

Disease acceptance	M	SD
Ischaemic disease	24.66	7.33
Arterial hypertension	25.30	6.13
Neoplastic disease	21.55	7.55
Diabetes	25.30	5.73
Asthma	23.50	8.13
F; p	1.62	0.17

Along with the course of the disease, two coping strategies were used increasingly often: reflective processing of difficulties ($t = 2.35$; $p < 0.05$) and prevention ($t = 2.46$; $p < 0.05$). These strategies were most extensively used in the first few years following the onset of the disease, and then their intensity decreased. Among all the seven assessed methods of coping with difficulties, seeking emotional support significantly correlated with general satisfaction with life ($r = 0.26$; $p < 0.05$), whereas avoidance negatively correlated with general satisfaction ($r = -0.24$, $p < 0.05$).

The relationship between general satisfaction and coping strategies was observed in two of them: avoidance ($r = -0.26$; $p < 0.05$) – the negative value indicates that the studied people did not prefer behaviours consisting in eluding difficulties or delaying action – and active coping, orientation on obtaining targets and implementing effective solutions ($r = 0.27$; $p < 0.05$).

Conclusions

- Along with the duration of the disease, two coping strategies were applied increasingly often: reflective processing and prevention. These strategies were most extensively used in the first few years following the onset of disease.
- In chronic diseases, the most important type of support was the emotional support from significant others.
- Eluding real problems by avoiding and postponing important matters indefinitely was a strategy with detrimental effects on satisfaction with life during a chronic disease.

Table 3. Ways of coping with difficulties: summary of results

Tabela 3. Sposoby radzenia sobie z trudnościami: zestawienie wyników

Coping methods	Healthy subjects		Ischaemic disease		Hypertension		Neoplastic disease		Diabetes		Asthma	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Proactive	35.57	3.05	34.44	3.71	34.21	5.18	33.71	4.75	35.79	3.65	34.38	3.96
Reflective	30.33	3.77	29.10	5.47	29.30	5.14	27.68	6.52	31.06	4.21	29.16	3.73
Strategic planning	11.60	3.53	10.37	1.84	9.64	1.80	9.55	2.23	10.91	1.49	10.03	2.31
Prevention	27.05	3.48	26.54	3.92	25.85	3.81	25.26	4.69	27.21	2.79	26.06	4.16
Instrumental support	19.36	2.84	19.56	3.59	21.21	2.94	20.42	3.58	21.09	3.34	20.38	4.40
Emotional support	12.98	2.14	13.05	2.58	14.27	2.17	13.55	2.51	13.79	2.16	13.19	2.76
Avoidance	7.05	1.23	7.58	1.41	7.33	1.65	7.16	1.34	7.15	1.20	7.44	1.54

Table 4. Correlations between satisfaction and life satisfaction, and ways of coping**Tabela 4. Korelacje satysfakcji i zadowolenia z życia ze sposobami radzenia sobie**

Coping methods	Psychological variables			
	Life satisfaction		Satisfaction	
	Healthy subjects	Ill subjects	Healthy subjects	Ill subjects
Proactive	0.17	0.21**	0.27*	0.27***
Reflective	0.07	0.19**	0.05	0.39***
Strategic planning	0.06	0.33***	0.08	0.31***
Prevention	0.18	0.13	0.04	0.26***
Instrumental support	0.19	0.14	0.01	0.21**
Emotional support	0.26*	0.20**	0.10	0.36***
Avoidance	0.24*	0.06	0.26*	0.03

*p < 0.05

**p < 0.01

***p < 0.001

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Efficacy of everolimus and axitinib in the second-line treatment of patients with metastatic renal cell carcinoma

Skuteczność leczenia ewerolimusem i aksyтынibem u chorych na rozlanego raka nerkowokomórkowego w drugiej linii leczenia

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Abstract. Today, everolimus and axitinib remain the only drugs reimbursed by the Polish National Health Fund in patients with metastatic renal cell carcinoma (RCC) after a lack of success on tyrosine kinase inhibitor. The aim of the study was to compare the antitumor efficacy of everolimus and axitinib in terms of overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR). A retrospective analysis was conducted in consecutive patients with metastatic RCC who started second-line therapy with everolimus or axitinib at the Department of Oncology, Military Institute of Medicine between January 2014 and July 2017. A total of 46 patients received everolimus and 32 received axitinib in the study. Median OS, median PFS, ORR and DCR were 12.5 months, 3.1 months, 0% and 46% in the everolimus group, and 13.7 months, 5.6 months, 3% and 59% in the axitinib group. No significant differences were found for OS, PFS, ORR and DCR. Everolimus and axitinib had similar antitumor efficacy in the assessed population.

Key words: axitinib, everolimus, metastatic renal cell carcinoma, overall survival, progression-free survival, objective response rate

Streszczenie. Wstęp. Ewerolimus i aksyтынib są aktualnie jedynymi lekami refundowanymi przez Narodowy Fundusz Zdrowia u chorych na rozlanego raka nerkowokomórkowego (RCC) po uprzednim niepowodzeniu leczenia inhibitorem kinaz tyrozynowych. Cel pracy. Porównanie skuteczności przeciwnowotworowej ewerolimusu względem aksyтынibu mierzonej czasem przeżycia całkowitego (OS), czasem wolnym od progresji choroby (PFS), odsetkiem obiektywnych odpowiedzi (ORR) i współczynnikiem kontroli choroby (DCR). Materiał i metody. Analizę retrospektywną przeprowadzono wśród kolejnych chorych na rozlanego RCC, u których rozpoczęto drugą linię leczenia z użyciem ewerolimusu lub aksyтынibu w Klinice Onkologii WIM w okresie od stycznia 2014 do lipca 2017 roku. Wyniki. W badaniu wzięło udział 46 chorych leczonych ewerolimusem i 32 leczonych aksyтынibem. Mediana OS oraz mediana PFS, ORR i DCR wyniosły odpowiednio 12,5 miesiąca i 3,1 miesiąca, 0% i 46% dla ewerolimusu oraz 13,7 miesiąca i 5,6 miesiąca, 3% i 59% dla aksyтынibu. Nie wykazano istotnych różnic w zakresie OS, PFS, ORR i DCR. Wnioski. W badanej populacji ewerolimus i aksyтынib charakteryzowały się porównywalną skutecznością przeciwnowotworową.

Słowa kluczowe: aksyтынib, ewerolimus, rozlaniany rak nerkowokomórkowy, czas przeżycia całkowitego, czas wolny od progresji choroby, odsetek obiektywnych odpowiedzi

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Background

Renal cancer is the ninth most frequent malignant neoplasm in adults, and the thirteenth most common cause of death globally [1]. Its most frequent histological type is renal cell carcinoma (RCC), accounting for approximately 80-90% of all cases [2]. In non-metastatic RCC, the only therapeutic option that may lead to recovery is surgical removal of the primary lesion. About 30% of patients are diagnosed with a synchronous metastatic disease, and in another 30% a failure of the radical surgical treatment is observed, resulting in dissemination of the neoplastic disease [3].

Presently, in patients with metastatic RCC, the treatment of choice is systemic treatment using molecularly targeted therapies, whose goal is to extend survival and offer the best quality of life. Sunitinib and pazopanib are used in the first-line treatment. They are tyrosine kinase inhibitors (TKI), and their angiogenic effect is associated with blocking of the vascular endothelial growth factor (VEGF) receptors. The first-line therapy also involves non-specific immunotherapy with the use of interferon alpha combined with bevacizumab, an anti-VEGF monoclonal antibody [4-6]. The effectiveness of these therapies, expressed by the median progression-free survival (PFS) and median overall survival (OS), is approximately 10 and 23 months, respectively [7]. If the disease progresses, approximately 50% of patients are qualified for second-line treatment, which may include the following: (1) other TKI: axitinib, cabozantinib or sorafenib; (2) everolimus, which is a mammalian target of rapamycin (m-TOR) inhibitor; (3) immunotherapy with nivolumab, a monoclonal antibody against programmed-death receptor-1 (PD-1) and (4) a combination of everolimus and lenvatinib (TKI) [8].

Everolimus was approved by the American Food and Drug Administration (FDA) in 2009, based on a study by Motzer et al. that demonstrated a significant extension of PFS in a group of patients receiving everolimus (median: 4.9 months) compared to the placebo group (median: 1.9 months). Also, the relative hazard ratio for disease progression was reduced by 67% (hazard ratio [HR] = 0.33; 95% confidence interval [CI]: 0.25–0.43; $p < 0.001$). Everolimus was not associated with a significant OS improvement compared to the placebo (median: 14.8 vs 14.4 months, HR = 0.87; 95% CI: 0.65–1.15; $p = 0.162$). However, it should be noted that 80% of patients from the placebo groups received everolimus after disease progression. The objective response rate (ORR), defined according to Response Evaluation Criteria in Solid Tumors (RECIST), was limited in both groups (2% and 0%, respectively) [9]. Axitinib was approved by the FDA in 2012, based on a study by Rini et al., which revealed

its superiority over sorafenib in terms of PFS (median: 6.7 vs 4.7 months, HR = 0.665; 95% CI: 0.544-0.812;

$p < 0.001$) and ORR (19% vs 9%, $p = 0.001$), without a significant effect on OS (median: 20.1 vs 19.2 months, HR = 0.969; 95% CI: 0.800-1.174; $p = 0.374$) (10).

Recently, FDA approved cabozantinib, nivolumab and a combination of lenvatinib and everolimus for the second-line treatment in patients with metastatic RCC in whom a prior TKI therapy failed. All these options proved more effective than everolimus in terms of OS, ORR and PFS (except for nivolumab) [8]. American and European oncological societies recognised them as reference therapies for this indication [11, 12]. In Poland they are not easily accessible, as they are not financed by the National Health Fund. The reimbursed treatment options include everolimus and axitinib, although the therapies have never been compared in a prospective clinical trial. Therefore, potential differences between everolimus and axitinib in antineoplastic effectiveness should be explored as they are of particular importance to Polish oncologists, who usually have access to limited therapeutic options, compared to global standards.

Aim of the study

The aim of the study was to compare the antineoplastic effectiveness of second-line everolimus and axitinib in patients with metastatic RCC hospitalised in the Department of Oncology, Military Institute of Medicine, between January 2014 and July 2017.

Material and methods

The retrospective analysis involved consecutive patients with metastatic RCC treated in the Department of Oncology, Military Institute of Medicine in Warsaw. The inclusion criteria were as follows: (1) histopathologically confirmed RCC, (2) metastatic stage of the disease confirmed in a CT examination, (3) previous nephrectomy or parenchyma saving procedure, (4) failure of first-line therapy based on TKI, (5) introduction of the second-line treatment with everolimus or axitinib in the period from January 2014 to July 2017, and (6) no previous adjuvant and/or neoadjuvant therapy. The study endpoints included: (1) OS defined as the time from introduction of everolimus or axitinib to death from all causes, (2) PFS defined as the time from introduction of everolimus or axitinib to progressive disease (PD), determined according to RECIST version 1.1 or death from all causes, (3) ORR defined as a rate of patients with partial response (PR) or complete response (CR), and (4) disease control rate (DCR) defined as the rate of patients obtaining PR, CR or stable disease (SD).

The descriptive statistics included median values and range for quantitative variables, and frequency and

percentage values for qualitative variables. The Mann-Whitney U-test was used for quantitative variables and Pearson's chi-square test (or Fisher's exact test, if the expected value was no more than 5 in a given field of the contingency table) were used for qualitative variables to assess the differences between the group of patients receiving everolimus and those treated with axitinib. The Kaplan-Meier estimator was used to determine the survival function and median OS and PFS. The probability of survival was compared between the groups using the log-rank test, and univariate and multivariate Cox proportional hazards regression analysis, considering the age and sex of patients, first-line treatment PFS (< 6 months vs \geq 6 months), and prognostic groups according to International Metastatic Renal Cell Database Consortium (IMDC) [13]. If differences were found in patients' characteristics, an adjusted Kaplan-Meier estimator and log-rank test with inverse probability weighting were used. Pearson's chi-square test (or Fisher's exact test) were used to assess ORR and DCR. Results of analyses (two-tailed) with P values of less than 0.05 were considered statistically significant. The statistical calculations were conducted using Stata (StataCorp, USA) version 14.2 and R (The R Foundation for Statistical Computing, Austria), version 3.2.5.

Information about patients was collected from individual medical histories. The study was approved by the Bioethical Committee of the Military Institute of Medicine. Patient's consent was not required, due to the retrospective character of the study.

Results

78 patients were included in the study. 46 patients (59%) received everolimus, and 32 patients (41%) received axitinib. Detailed patient characteristics are presented in Table 1. At the moment of introduction of the second-line treatment, there were no significant differences between the study groups regarding the assessed variables, with the exception of ECOG performance status, which was higher in the everolimus group. In both groups the percentage of male patients was higher (60%). The patients were most often classified into the "intermediate risk" IMDC prognostic group (49% of all patients). In most

cases, the first-line treatment was sunitinib (68%). There were no differences in the frequency of individual first-line therapies, or in their antineoplastic effectiveness measured by ORR and DCR. However, patients treated with axitinib had a significantly longer first-line PFS than those treated with everolimus (median: 17.8 vs 11.7 months, $p = 0.043$).

Median follow-up time was 22.7 months (95% CI: 17.9–25.5) for the entire cohort, 24.1 months (95% CI: 16.7–35.4) in the group of patients receiving everolimus, and 20.5 months (95% CI: 11.0–25.5) in the group of patients receiving axitinib ($p = 0.094$). Median OS and PFS were 12.5 months (95% CI: 7.8–14.8) and 3.1 months (95% CI: 2.5–6.0), respectively, in the group of patients receiving everolimus, and 13.7 months (95% CI: 7.4–26.7) and 5.6 months (95% CI: 2.7–7.8), respectively, in patients treated with axitinib. The survival curves according to the received second-line treatment are presented in Figure 1. No significant differences were found between the groups in therapeutic efficacy expressed by OS and PFS (unadjusted log-rank test $p = 0.395$ and $p = 0.359$; adjusted log-rank test $p = 0.434$ and $p = 0.208$). In univariate Cox regression, axitinib therapy, compared to everolimus, was associated with statistically insignificant reduction of hazard ratios, both regarding death, and progressive disease, by 22% (HR = 0.78, 95% CI: 0.44–1.39; $p = 0.369$ and HR = 0.78; 95% CI: 0.46–1.33; $p = 0.362$, respectively). Following the adjustment for the sex and age of patients, first-line treatment PFS (\geq 6 months vs < 6 months), and IMDC prognostic groups, the effect of a second-line therapy on OS and PFS was statistically insignificant HR = 0.68; 95% CI: 0.38–1.23; $p = 0.203$ and HR = 0.68; 95% CI: 0.39–1.18; $p = 0.165$, respectively) [Tab. 2].

CR was not identified in either group. PR was observed in one patient (3%) in the axitinib group, and in none of the patients in the everolimus group (0%). SD as the best response to therapy was found in 21 (46%) patients treated with everolimus, and in 18 (56%) patients receiving axitinib. No significant differences were demonstrated in ORR (0% vs 3%, $p = 0.410$) or DCR (46% vs 59%, $p = 0.510$) for patients treated with everolimus or axitinib, respectively.

Table 1. Patient characteristics at second-line treatment initiation**Tabela 1. Charakterystyka pacjentów w chwili rozpoczęcia drugiej linii leczenia**

Variable	Everolimus (N = 46)	Axitinib (N = 32)	p
Age (years): median (range)	62 (36-79)	61 (48-76)	0.528
Male, n (%)	24 (52)	23 (72)	0.080
Time from diagnosis to treatment initiation under 1 year: n (%)	19 (41)	15 (47)	0.626
Sarcomatous component: n (%)	3 (7)	1 (3)	0.640
No. of organs with metastases: median (range)	3 (1-6)	3 (1-7)	0.821
Location of metastases: n (%)			
Lungs	33 (72)	24 (75)	0.525
Lymph nodes	22 (48)	14 (44)	0.915
Bones	12 (26)	10 (31)	0.767
Liver	6 (13)	7 (22)	0.377
Adrenal glands	8 (17)	3 (9)	0.587
Brain	0 (0)	0 (0)	0.300
Local relapse	14 (30)	9 (28)	0.402
Other kidney	6 (13)	3 (9)	0.732
ECOG performance status: n (%)			0.046
0	14 (30)	3 (9)	
1	31 (68)	27 (85)	
2	1 (2)	2 (6)	
Haemoglobin <LLN: n (%)	10 (22)	11 (34)	0.216
Adjusted calcium >ULN: n (%)	1 (2)	2 (6)	0.565
LDH >1.5 × ULN: n (%)	18 (39)	9 (28)	0.315
neutrophils >ULN: n (%)	2 (4)	2 (6)	1.000
Platelets >ULN: n (%)	5 (11)	6 (19)	0.344
MSKCC prognostic group: n (%) favourable			0.311
Intermediate	14 (31)	5 (16)	
Poor	30 (65)	26 (81)	
IMDC prognostic group: n (%)			0.348
favourable	20 (43)	10 (31)	
Intermediate	22 (48)	16 (50)	
Poor	4 (9)	6 (19)	
First-line TKI: n (%)			0.111
sunitinib	30 (65)	23 (72)	
Pazopanib	10 (22)	9 (28)	
Sorafenib	6 (13)	0 (0)	
First-line PFS (months): median (95% CI)	11.7 (6.2-16.5)	17.8 (8.2-24.4)	0.043 ^a
First-line PFS (<6 months): n (%)	14 (30)	8 (25)	0.600
First-line ORR: n (%)	8 (17)	10 (31)	0.153
First-line DCR: n (%)	38 (83)	29 (91)	0.510

a Long-rank test

ECOG – Eastern Cooperative Oncology Group, LLN – lower limit of normal, LDH – lactate dehydrogenase, ULN – upper limit of normal, MSKCC – Memorial Sloan-Kettering Cancer Center, IMDC – International Metastatic Renal Cell Database Consortium, TKI – tyrosine kinase inhibitor, PFS – progression-free survival, CI – confidence interval, ORR – objective response rate, DCR – disease control rate

Discussion

Introduction of molecularly targeted therapies to clinical practice in the last decade significantly improved the prognosis of patients with metastatic RCC. This progress extended median OS to 30 months in patients receiving two lines of treatment, and even to 40 months in those who receive three lines of treatment [14]. On the other hand, a large number of therapeutic options raises questions as to which therapy is the best at a given stage of systemic treatment. For years, based on the results of third phase clinical trials, the recommended second-line therapies were everolimus and axitinib, which demonstrated antineoplastic effectiveness superior to placebo and sorafenib, respectively [9, 10]. However, these medicines were never compared in a prospective head-to-head clinical trial. Moreover, such a comparison is not to be expected, as therapies superior to everolimus have become available, e.g. cabozantinib, nivolumab, and a combination of lenvatinib and everolimus [8]. Nevertheless, the comparison of everolimus and axitinib in terms of effectiveness is still required, especially in Poland and other countries where the newest therapies are not easily available due to a lack of reimbursement.

Table 2. Results of multivariate Cox regression for overall survival and progression-free survival
Tabela 2. Wyniki wieloczynnikowej regresji Coxa dla przeżycia całkowitego i czasu wolnego od progresji choroby

Variable	OS		PFS	
	HR (95% CI)	p	HR (95% CI)	p
Second-line treatment				
Everolimus	1	0.203	1	0.165
Axitinib	0.68 (0.38 - 1.23)		0.68 (0.39 - 1.18)	
Sex				
Male	1	0.459	1	0.327
Female	0.80 (0.44 - 1.44)		1.32 (0.76 - 2.32)	
Age (years)				
	0.99 (0.97 - 1.03)	0.970	0.97 (0.94 - 1.01)	0.090
First-line PFS				
≥ 6 months	1	0.953	1	0.223
< 6 months	0.98 (0.53 - 1.83)		0.69 (0.38 - 1.25)	
IMDC prognostic group				
Favourable	1	0.056	1	
Intermediate	1.87 (0.98 - 3.54)	<	0.89 (0.51 - 1.57)	0.894
Poor	6.47 (2.53 - 16.68)	0.001	3.42 (1.37 - 8.52)	0.008

OS - overall survival, PFS - progression-free survival, HR - hazard ratio, CI - confidence interval, IMDC - International Metastatic Renal Cell Database Consortium

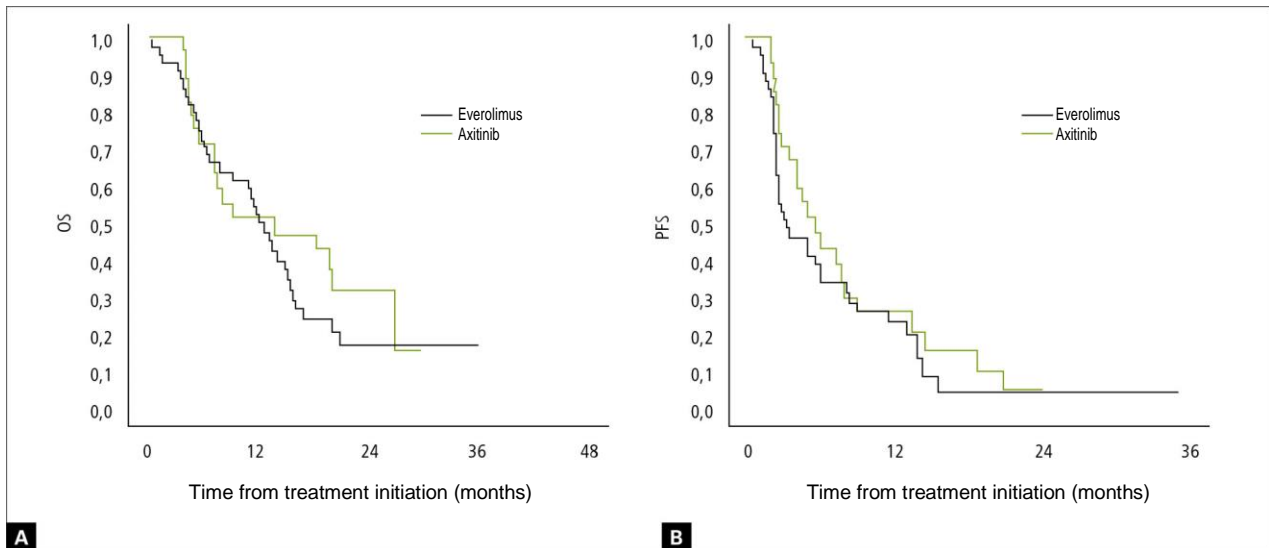


Figure. Kaplan-Meier curves for (A) overall survival (OS) and (B) progression-free survival (PFS) stratified by second-line treatment

Figure. Krzywe Kaplana-Meiera dla (A) przeżycia całkowitego (OS) oraz (B) czasu wolnego od progresji choroby (PFS) względem leku drugiej linii

This comparative analysis of the effectiveness of everolimus and axitinib is based on the authors' experience of the Department of Oncology, Military Institute of Medicine, a leading Polish centre treating patients with metastatic RCC. It demonstrates that the groups of patients treated with everolimus did not differ significantly from those treated with axitinib in terms of most clinical and pathological characteristics, with the exception of a better performance status in patients receiving everolimus, and the first-line PFS, which was longer in patients receiving axitinib. This may be due to a higher propensity to use second-line TKIs if a long-term response was obtained to a first-line TKI [15]. The analysed treatment outcomes appeared to be slightly worse than those presented in the registration studies of both medicines. Median OS and PFS of patients receiving everolimus were 12.5 and 3.1 months, compared to 14.8 and 4.9 reported by Motzer et al. Median OS and PFS of patients treated with axitinib were 13.7 and 5.6 months, compared to 15.2 and 4.8 months in the study by Rinni et al. [10]. In both studies everolimus demonstrated nearly no potential to reduce the size of neoplastic lesions, whereas the potential of axitinib to reduce lesions was a sixth of that in the studied population than in the registration study of this product [9, 10]. However, it should be emphasised that third phase clinical studies usually include selected patients who meet strict inclusion criteria, and their treatment outcomes are generally better than those obtained in the population of patients treated in everyday clinical practice [16].

Basic analyses revealed an absence of significant differences between everolimus and axitinib in terms of effectiveness, measured by PFS, OS, ORR and DCR. These results are in compliance with retrospective reports by other authors. Sherman et al. in their study applied data-weighting analysis of the patients from registration studies on everolimus and axitinib, in whom prior sunitinib therapy failed. The median PFS was 4.7 months (95% CI: 3.5 – 10.6) for everolimus and 4.8 months (95% CI: 4.5 – 6.4) for axitinib [17]. In a single-centre study by Guida et al. no differences were found between everolimus and axitinib in terms of OS (median: 21.5 vs 14.9 months, $p = 0.23$), PFS (median: 5.3 vs 7.7 months, $p = 0.39$) and DCR (69% vs 73%, $p = 0.31$), whereas regarding ORR, a higher activity of axitinib was reported (24.4% vs 3.7%, $p = 0.002$) [18]. Based on multi-centre data, Vogelzang et al. demonstrated that the type of second-line therapy (everolimus or axitinib) was of no consequence for OS (HR = 1.16; 95% CI: 0.74 – 1.82) and PFS (HR = 1.16; 95% CI: 0.85 - 1.59).

Similarly to the presented study, the time of the first-line treatment had no prognostic significance for OS and second-line PFS [19].

Despite the limitations of this study, including its retrospective character and relatively limited number of patients, the obtained results are consistent with previous literature reports, and provide valuable information for Polish oncologists, whose choice of second-line therapies is limited due to the reimbursement policy to two options: everolimus or axitinib. The demonstrated similar level of effectiveness of both medications suggests that the choice should be based on other criteria, such as therapy's toxicity profile or potential comorbidities [20].

Conclusions

In the study involving patients of the Department of Oncology, Military Institute of Medicine, treated due to metastatic RCC following a failure of a prior systemic TKI therapy:

- no significant differences between the antineoplastic effectiveness of everolimus and axitinib were found in terms of OS, PFS, ORR and DCR;
- in patients treated with axitinib the first-line PFS was longer, and ECOG performance status at the initiation of the second-line therapy was worse than in the patients receiving everolimus. Apart from that, no significant differences were observed in patient characteristics between the two groups.

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Uromodulin serum concentration in patients with chronic kidney disease, stages 3 to 5

Correlations between markers of glomerular filtration rate and markers of calcium-phosphate and bone metabolism

Stężenie uromoduliny w surowicy pacjentów z przewlekłą chorobą nerek w stadiach III–V

Korelacje z parametrami przesączania kłębuszkowego i markerami gospodarki wapniowo-fosforanowej oraz kostnej

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Abstract. Uromodulin in physiological conditions is the most abundant urinary protein. This protein is exclusively produced in the kidneys by cells in the thick ascending limb of the loop of Henle and the early distal tubule. This creates the opportunity to study extending uromodulin use in patients with chronic kidney disease (CKD) in various stages of progression as the serum marker associated with renal tubules dysfunction. The aims of the study were to demonstrate the correlations between serum uromodulin and commonly used renal markers and various measures of glomerular filtration rate in patients with CKD. An additional intention was to check whether there were any correlations between serum uromodulin and the markers of calcium-phosphate and bone metabolism in these patients. The study groups consisted of 119 subjects with CKD, stages 3 to 5. The control group consisted of 32 healthy subjects. Kidney function, calcium-phosphate and bone metabolism markers were determined in all subjects. The conducted analyses demonstrated statistically significant differences between the average concentration of serum uromodulin in the study groups and in the control group (control group 188.2 ±72.5 ng/ml, stage 3 70.9 ±40.0 ng/ml, stage 4 37.3 ±15.7 ng/ml, stage 5 18.7 ±14.1 ng/ml [p = 0.000]). The results of the study show clearly statistically significant correlations between serum uromodulin concentration and the measures of glomerular filtration rate expressed as the equations CKD-EPI Cystatin C and CKD-EPI Creatinine-Cystatin C in the analysed groups with CKD stages 3 to 5. The authors demonstrated statistically significant correlations between serum uromodulin concentration and markers of bone metabolism in stage 5 CKD. Serum uromodulin concentration may be an additional marker that enriches the assessment of kidney function in various stages of CKD progression. Low serum uromodulin concentration may suggest disorder of bone metabolism in patients treated with dialysis.

Key words: chronic kidney disease, serum markers of kidney function, uromodulin

Streszczenie. Uromodulina stanowi w warunkach fizjologicznych główne białko moczu. Ulega wyłącznie ekspresji we wstępującym ramieniu grubym pętli Henlego oraz w początkowym odcinku kanalika dystalnego nerki. Stwarza to możliwość przeprowadzania badań, które mogłyby rozszerzyć zastosowanie oznaczania uromoduliny w surowicy pacjentów z przewlekłą chorobą nerek (PChN) w różnym stadium zaawansowania jako markera związanego z upośledzeniem funkcji kanalików nerkowych. Celem podjętych badań było określenie związku stężenia uromoduliny w surowicy z rutynowymi markerami dysfunkcji nerek oraz różnymi miarami przesączania kłębuszkowego u pacjentów z PChN w stadiach III–V. Dodatkowym zamierzeniem było

sprawdzenie, czy istnieje korelacja stężenia uromoduliny z markerami gospodarki wapniowo-fosforanowej oraz kostnej u tych pacjentów. Badaniu poddano 119 pacjentów z PChN w stadiach III–V. Grupę kontrolną stanowiły 32 osoby. Wykonane zostały u nich oznaczenia parametrów nerkowych, markerów z zakresu gospodarki wapniowo-fosforanowej i kostnej. Przeprowadzone analizy wykazały statystycznie istotne różnice średnich stężeń uromoduliny w surowicy pomiędzy grupami pacjentów z PChN i grupą kontrolną (grupa kontrolna $188,2 \pm 72,5$ ng/ml, stadium III $70,9 \pm 40,0$ ng/ml, stadium IV $37,3 \pm 15,7$ ng/ml, stadium V $18,7 \pm 14,1$ ng/ml [$p = 0,000$]). Stężenia uromoduliny w surowicy były wyraźnie statystycznie istotnie skorelowane z miarami przesączania kłębuszkowego wyrażonymi równaniami CKD-EPI Cystatin C i CKD-EPI Creatinine-Cystatin C w badanych grupach w stadiach III–V PChN. Wykazano statystycznie istotne korelacje w stadium V choroby pomiędzy stężeniem uromoduliny i parametrami gospodarki kostnej.

Stężenie uromoduliny w surowicy może być dodatkowym markerem wzbogacającym ocenę funkcjonowania nerek w różnych stadiach zaawansowania PChN. Małe stężenie uromoduliny w surowicy może wskazywać na zaburzenia metabolizmu kostnego u chorych leczonych nerkozastępczo.

Słowa kluczowe: uromodulina, przewlekła choroba nerek, markery nerkowe w surowicy

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Background

Uromodulin, also referred to as the Tamm-Horsfall protein, is a glycoprotein, the most abundant protein in physiological urine [1]. In 1950, Igor Tamm and Frank Horsfall isolated it from urine by precipitation with sodium chloride, and discovered that the protein had the ability to inhibit virus-induced haemagglutination. In 1985, Muchmore and Decker isolated a glycoprotein in the urine of pregnant women, demonstrated its immunosuppressive properties, and named it uromodulin. Only two years later studies by Pennica et al. (sequential analysis), followed by the work of Olczak et al. (analysis of the carbohydrate part of the uromodulin molecule in pregnant and non-pregnant women) revealed that the Tamm-Horsfall protein and uromodulin were the same protein [2]. Uromodulin is expressed only in the thick ascending limb of the loop of Henle and in the early renal distal tubule. It regulates the water and electrolyte metabolism in the thick ascending loop of Henle. Previous studies demonstrated a protective function of uromodulin in urinary tract infections and, its preventive effect on the formation of renal stones, as well as its role in the immunological processes taking place in the kidneys [3]. Uromodulin may be an antioxidant, and protect the kidney against ischaemic damage. The protein's negative effect was observed in progressive renal failure in the course of multiple myeloma in cast nephropathy. A relationship was also demonstrated between uromodulin (its reduced concentration in urine) and other renal diseases, such as reflux nephropathy, lupus nephritis, tubulointerstitial nephritis or polycystic

kidney disease [2]. Many studies analyse mutations in the uromodulin gene. They are classified as autosomal dominant tubulointerstitial kidney diseases: uromodulin-associated kidney disease (UAKD), familial juvenile hyperuricemic nephropathy (FJHN), and medullary cystic kidney disease type 2 (MCKD2) [4-6].

A certain amount of uromodulin passes into the blood circulation. Its function is not yet fully understood. Further studies are required to increase the usefulness of serum uromodulin determination in the diagnosis of impaired renal function and the integrity of renal parenchyma and the associated diseases. For this purpose, new markers are still being researched, as the generally available ones, such as creatinine or cystatin C, have certain limitations, especially in the later stages of chronic kidney disease (CKD).

The aim of the study was to analyse the correlation between uromodulin concentration and common renal parameters, as well as glomerular filtration rates in the serum of patients with stage 3–5 CKD. In addition, the correlation between uromodulin concentrations and the markers of calcium-phosphate and bone metabolism were analysed in these patients, as the associated disorders increase along the disease progression.

Material and methods

119 patients with stage 3 to 5 CKD were examined. This group included 44 patients treated with haemodialysis or peritoneal dialysis (stage 5) at the dialysis unit, 39 stage 4 patients, and 36 stage 3 patients, treated at the nephrology clinic. They were all treated at the Military

Institute of Medicine in Warsaw. The control group consisted of 32 individuals, for whom the renal parameters and markers of calcium-phosphate and bone metabolism were determined. Serum concentrations of creatinine, urea, uromodulin, cystatin C, total calcium, calcium ions, inorganic phosphates, magnesium, albumin, prealbumin, C-reactive protein (CRP), intact PTH (iPTH), 25-hydroxyvitamin D (25(OH)D), alkaline phosphatase (ALP), bone alkaline phosphatase (BAP), osteocalcin, total procollagen type 1 amino-terminal propeptide (total P1NP), isomerised C-terminal telopeptide of type I collagen (β -CrossLaps) were determined. The following indices of glomerular filtration were listed: eGFR (estimated glomerular filtration rate), GFR based on creatinine concentration (CKD-EPI creatinine - chronic kidney disease epidemiology collaboration creatinine), cystatin C concentration (CKD-EPI cystatin C), creatinine and cystatin C concentration (CKD-EPI creatinine-cystatin C). The demographic data and relevant information were obtained from the Department of Nephrology and Dialysis and from the Clininet system of the Military Institute of Medicine in Warsaw. They included patient age, stage of CKD, causes of CKD, duration of dialyses, calcium preparations, vitamin D or calcimimetics used. The study group and the control group were selected without any age or sex restrictions. In the control group, the exclusion criterion was a history of diabetes, untreated or unstable arterial hypertension, renal diseases, hyperparathyroidism or hypoparathyroidism, and use of vitamin D or calcium preparations.

The study was approved by the Bioethical Committee of the Military Institute of Medicine in Warsaw, no. 10/WIM/2016 from 17/02/2016).

The material for tests (venous blood) in most patients was collected in the morning in closed-system vacuum test tubes. In patients undergoing haemodialysis, the blood was drawn before the dialysis. Biochemical and immunochemical tests were usually performed on the same day. The remaining material was frozen at -70°C , and used for further specialist tests within 3 months after collection. In patients undergoing haemodialysis, peritoneal dialysis, or in the patients treated in the nephrology clinic the tests were performed using the remaining (unused) blood that was supplied to the laboratory for standard tests. Subjects from the control group had approximately 10 ml of blood collected, following their written consent, for the necessary tests.

Methods

Uromodulin concentrations were determined using an Uromodulin ELISA kit produced by Euroimmun. In most assays ready reagent kits for automatic analysers by

Beckman and Roche Diagnostics were used to determine concentrations of creatinine, urea, cystatin C, total calcium, inorganic phosphates, magnesium, albumin, ALP, CRP, iPTH, 25(OH)D, osteocalcin, total P1NP and β -CrossLaps. BAP was performed using immunoenzymatic IDS Ostase BAP EIA test, and an ionised calcium concentration was determined with the use of a Siemens series 900 blood gas analyser. The glomerular filtration rates were calculated using the formulas: eGFR – shortened MDRD (modification of diet in renal disease) formula, CKD-EPI Creatinine (2009), CKD-EPI Cystatin C (2012), and CKD-EPI Creatinine-Cystatin C (2012).

Statistical methods

The obtained data were analysed using Statistica software. Descriptive statistics were used to characterise individual study groups. The normality of distribution was examined using the Shapiro-Wilk test. Correlations were found with the use of non-parametric tests (Spearman's correlations). The significance of differences between the groups was determined by Kruskal-Wallis test. The ROC curve illustrated the diagnostic usefulness of uromodulin in the study groups. The relationships between uromodulin concentration and other renal parameters were presented with the use of linear regression.

Results

Table 1 presents the characteristics of all the study groups and the control group. Significant statistical differences were observed between the mean values of most of the determined or calculated parameters in the three study groups and in the control group, with the exception of patient age and magnesium concentration. In addition, significant differences in prealbumin concentrations were observed only between the control group and other patients. The number of male and female subjects was not significantly different between the study groups and the control group, so there were no statistically significant differences regarding sex ($p = 0.1001$). Mean serum uromodulin concentrations differed significantly between the study groups and the control group, and differed clearly between individual study groups. The results were less dispersed the more advanced the CKD stage, (Fig. 1).

The obtained test results demonstrated statistically significant correlations between serum uromodulin concentrations and the glomerular filtration rates, expressed as CKD-EPI Cystatin C and CKD-EPI Creatinine-Cystatin C in the study groups in stages 3 - 5 CKD (Fig. 2).

In addition, our analyses helped to observe statistically significant correlations in individual CKD

stages between uromodulin concentration and cystatin C concentration or bone metabolism markers. All the correlations are presented in Table 2.

Table 1. Characteristics of study groups
Tabela 1. Charakterystyka grup badanych

	CKD stage 3 (n = 36)	CKD stage 4 (n = 39)	CKD stage 5 (n = 44)	Control group (n = 32)	p
Age (years)	65 ± 10	64 ± 11	62 ± 13	59 ± 14	0.0842
Uromodulin ng/ml	70.9 ± 40.0	37.3 ± 15.7	18.7 ± 14.1	188.2 ± 72.5	0.000
Cystatin C mg/l	1.8 ± 0.3	2.8 ± 0.5	5.5 ± 1.1	1.0 ± 0.1	0.000
Creatinine, µmol/l	159.1 ± 17.7	256.4 ± 53.0	592.3 ± 194.5	79.6 ± 17.7	0.000
eGFR ml/min/1.73 m ²	39.6 ± 7.0	21.5 ± 4.1	8.7 ± 3.0	84.8 ± 15.5	0.000
CKD-EPI Creatinine ml/min/1.73 m ²	38.0 ± 7.9	20.5 ± 4.1	7.9 ± 2.7	84.6 ± 15.6	0.000
CKD-EPI Cystatin C ml/min/1.73 m ²	37.5 ± 11.4	20.3 ± 5.2	8.3 ± 2.7	79.0 ± 13.9	0.000
CKD-EPI Creatinine-Cystatin C ml/min/1.73 m ²	37.0 ± 8.9	19.4 ± 4.0	7.5 ± 2.2	82.3 ± 12.9	0.000
Urea mmol/l	11.5 ± 4.4	17.1 ± 4.5	19.6 ± 5.9	5.7 ± 1.6	0.000
Total Ca mmol/l	2.4 ± 0.1	2.3 ± 0.3	2.2 ± 0.2	2.4 ± 0.1	0.0000
Ionised Ca mmol/l	1.18 ± 0.04	1.17 ± 0.05	1.10 ± 0.10	1.16 ± 0.09	0.0002
Phosphorus mg/dl	3.5 ± 0.6	3.8 ± 0.7	4.9 ± 1.3	3.4 ± 0.5	0.0000
Mg mg/dl	2.1 ± 0.2	2.0 ± 0.3	2.0 ± 0.4	2.1 ± 0.1	0.2697
Albumin g/l	44.0 ± 3.0	41.0 ± 4.0	37.0 ± 4.0	43.0 ± 6.0	0.0000
Prealbumin mg/dl	31.1 ± 7.1	30.0 ± 7.0	29.2 ± 6.8	26.6 ± 4.3	0.0372
CRP mg/dl	0.5 ± 0.5	1.3 ± 1.8	0.8 ± 0.7	0.2 ± 0.3	0.0000
iPTH pg/ml	79.2 ± 47.3	189.7 ± 127.2	500.1 ± 441.8	38.8 ± 12.8	0.000
25(OH)D ng/ml	21.1 ± 11.4	16.6 ± 9.7	11.9 ± 9.5	22.9 ± 7.9	0.0000
ALP U/l	82.6 ± 28.5	103.9 ± 47.1	142.3 ± 88.7	73.9 ± 24.9	0.0000
BAP µg/l	15.5 ± 7.3	18.9 ± 9.3	33.6 ± 36.8	13.9 ± 5.7	0.0000
Osteocalcin ng/ml	29.5 ± 17.4	70.7 ± 49.3	287.7 ± 355.6	19.2 ± 7.8	0.000
Total P1NP ng/ml	51.1 ± 17.8	92.0 ± 54.8	600.1 ± 1247.1	47.3 ± 17.3	0.000
β-CrossLaps pg/ml	507.5 ± 299.3	922.3 ± 389.1	2097.8 ± 1213.4	361.9 ± 171.9	0.000

The data are presented as means ± standard deviation.

p – significance level

The tests did not demonstrate any statistically significant correlations between uromodulin concentrations and the parameters of calcium-phosphate metabolism in the study groups. In patients with stage 5 CKD uromodulin concentrations negatively correlated with the duration of dialyses ($r = -0.3705$; $p = 0.0133$) and with the use of calcium preparations ($r = -0.3225$; $p = 0.0328$).

The Receiver Operating Characteristic (ROC) curve method was used to analyse the potential diagnostic usefulness of uromodulin concentrations in stage 3 - 5 CKD patients (Tab. 3). The sensitivity of the test for stage 3 was > 70%, and for stages 4 and 5 it was > 95%. The specificity of the test in all cases was > 95%.

Discussion

Most recent studies on uromodulin focused primarily on its concentration in urine. Numerous relationships were found between uromodulin secretion and other markers of renal diseases, including the genetic character of disorders [7]. Many publications are available about serum uromodulin concentrations and its relationship with various stages of CKD, although previously serum uromodulin concentration was presented as a marker of early renal damage.

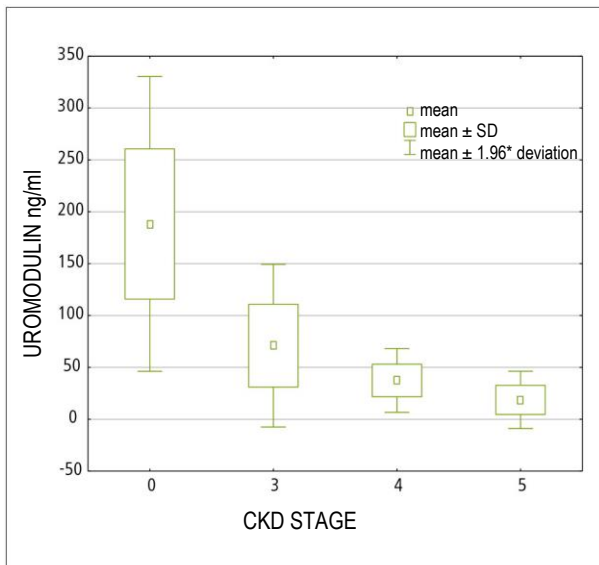


Figure 1. Serum uromodulin concentration in patients with CKD (stages 3 to 5) and in the control group

Rycina 1. Stężenie uromoduliny w surowicy pacjentów z PChN (III,- V, V stadium) oraz w grupie kontrolnej

Our studies indirectly confirm that serum uromodulin concentration may be a marker of the function of renal tubules in patients with different stages of CKD, and may help to distinguish the patients with normal renal function. This is illustrated by the highly statistically significant differences in the concentrations between the control group (188.2 ± 72.5 ng/ml) and the groups with stage 3 (70.9 ± 40.0 ng/ml), stage 4 (37.3 ± 15.7 ng/ml) and stage 5 CKD (18.7 ± 14.1 ng/ml). Reduction of uromodulin concentrations at the higher CKD stages might be used to extend the monitoring of patient status. This test (as are other renal parameters) is limited by patient age, and the associated reduced number of active nephrons. This was demonstrated by a group of researchers who conducted similar studies in a group of patients aged 71 ± 7 years old [1]. A weak, but statistically significant correlation between age and uromodulin was also revealed by Steubl et al. [8]. However, our studies did not demonstrate this relationship, similarly to the analyses by other researchers, e.g. Scherberich et al. [9]. The discrepancy is probably due to the differences in age and the sizes of the study groups. The study by Scherberich et al. also demonstrated that both in children and in adults without any diagnosed renal disorders, serum uromodulin concentration is a fixed parameter [9].

Uromodulin acts contrary to other renal parameters (such as creatinine, cystatin C or urea). Its concentration decreases with deterioration of the kidney function. It is positively correlated with eGFR, CKD-EPI Cystatin C and CKD-EPI Creatinine-Cystatin C. Most studies support these correlations [8, 10-12]; however, Prejczar et al. reported that in one of their study groups serum

uromodulin concentrations correlated positively with serum creatinine concentrations, and negatively with eGFR [10]. In our study we demonstrated statistically significant correlations between uromodulin concentration and CKD-EPI Cystatin C, CKD-EPI Creatinine-Cystatin C in stages 3 to 5 CKD, and between uromodulin and cystatin C in stages 3 and 5. Statistically significant correlations between uromodulin and eGFR measured by CKD-EPI Cystatin C and CKD-EPI Creatinine-Cystatin C may demonstrate the superiority of uromodulin testing in certain cases, in which different diets or extreme differences in muscle mass may affect other test results. Uromodulin can also help to identify patients at a higher risk of the complications associated with chronic comorbidities, such as diabetes or cardiovascular events. Fedak et al. presented a strong positive correlation, following a logarithmic transformation, between serum uromodulin concentration and CKD-EPI Creatinine-Cystatin C in all stages of CKD ($r = 0.82$; $p < 0.001$) [13].

The absence of statistically significant correlations between uromodulin and the retention of nitrogenous waste in the individual stages of CKD in our study may indicate that uromodulin, due to the site of its production, determines primarily the function of the renal tubules, and not glomeruli. This could also be supported by the results indicating a positive correlation between urine uromodulin concentration and eGFR, but only with eGFR < 90 ml/min/1.73 m². Therefore, uromodulin is not likely to become an alternative marker for the assessment of glomerular filtration [14]. Numerous reports indicate that serum uromodulin concentrations may be a potential marker of disturbed kidney function in the early phase of the disease, when other parameters, such as concentrations of creatinine, cystatin C and urea, are not affected. It would suggest that the first stage of renal impairment, regardless of its cause, starts with damage to the renal tubules in the ascending loop, and results in a reduced serum uromodulin concentration. Therefore, the early stages of kidney disease, until the glomerular filtration rate decreases, may remain undetected [8]. Only cystatin C is mentioned as a good marker in early stages of diabetic nephropathy, but it does not apply to all patients with CKD [15].

In stage 5 CKD, uromodulin concentration statistically significantly correlates negatively with the duration of dialysis therapy in this group of patients. The longer a patient is treated with dialysis, the lower the uromodulin concentration that is observed. This may be due to a further reduction in the already impaired renal function. Moreover, the correlation between a reduced uromodulin level and an increased quantity of calcium preparations taken by these patients may confirm the glycoprotein's relationship with disease progression.

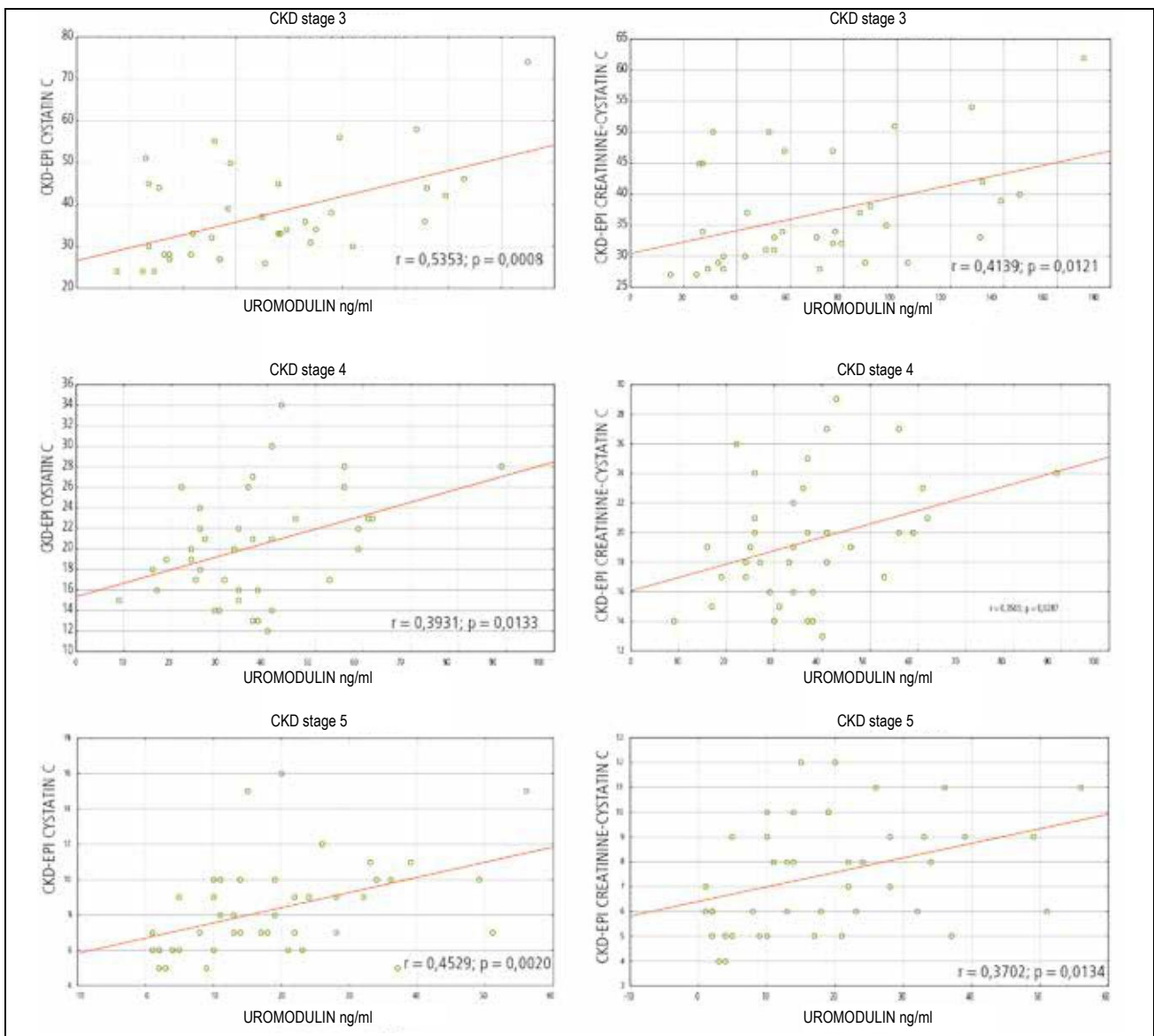


Figure 2. Correlations between uromodulin concentration and CKD-EPI Cystatin C, and uromodulin concentration and CKD-EPI Creatinine-Cystatin C in stages 3 to 5 of CKD

Rycina 2. Korelacje pomiędzy stężeniem uromoduliny a CKD-EPI Cystatin C oraz stężeniem uromoduliny a CKD-EPI Creatinine-Cystatin C w stadiach III–V PCHN

Uromodulin correlated negatively with the markers of bone metabolism in patients with stage 5 CKD. Along with the progression of CKD, calcium-phosphate metabolism is disturbed, and changes in the bone system occur. This is reflected in study results by increased concentrations of ALP, BAP, osteocalcin, total P1NP and β -CrossLaps. Higher correlations between uromodulin and the markers of bone metabolism in the entire study group with CKD (stages 3-5) compared to stage 5 indicate that the changes in bone system take

place already before the renal replacement therapy is introduced. Halankar and Shalia described a negative correlation ($p < 0.01$) between serum uromodulin concentration and serum phosphate concentration, and with the product of $Ca \times P$ (one of the causes of mineral bone disorders in the course of CKD) [12].

Table 2. Correlations of uromodulin concentration and parameters of glomerular filtration and biochemical indicators of bone homeostasis in patients with stages 3 to 5 CKD – Spearman rank correlation (r)

Tabela 2. Korelacje stężeń uromoduliny z parametrami przesączania kłębuszkowego i biochemicznymi wskaźnikami metabolizmu kostnego u pacjentów z PChN w stadiach III–V – korelacje rang Spearmana (r)

	CKD-EPI Cystatin C	CKD-EPI Creatinine Cystatin C	Cystatin C	ALP	BAP	Osteocalcin	Total P1NP	β-CrossLaps	25(OH)D
CKD stage 3	0.4804**	0.3887*	0.5124**	0.0312	0.0295	0.1791	0.0791	0.2112	0.1498
CKD stage 4	0.3454*	0.3435*	0.3118	0.0522	0.0989	0.1441	0.0287	0.0469	0.2595
CKD stage 5	0.5276***	0.4208**	0.5142***	0.3057*	0.4138**	0.3589*	0.4202**	0.3335*	0.0845
CKD stages 3 - 5	0.8630***	0.8552***	0.8642***	0.6258***	0.4145***	0.6888***	0.6440***	0.6882***	0.4203***

*p < 0.05

**p < 0.01

***p < 0.001

Table 3. Analysis of ROC curve for uromodulin – patients with stages 3 to 5 CKD

Tabela 3. Analiza krzywej ROC dla uromoduliny – pacjenci III–V stadium PChN

CKD stage	Cut-off point	AUC	AUC 95% CI	p
3	90.0 ng/ml	0.939	0.899-0.990	0.0000
4	62.0 ng/ml	0.999	0.997-1	0.0000
5	56.0 ng/ml	1	1	0.0000

AUC – area under the curve ROC, CI – confidence interval, p – level of significance

The ROC curve analysis confirms that uromodulin is a test that is potentially useful in the diagnosis of CKD. The proposed cut-off point for healthy individuals is > 100 ng/ml for the Euroimmun kit used in the study. Results below this value should suggest impaired renal function [16]. According to our studies, a concentration < 90 ng/ml may indicate stage 3, < 62 ng/ml may indicate stage 4, and < 56 ng/ml may indicate stage 5 CKD. Staubl et al. tested 335 subjects and determined their urine and serum uromodulin concentrations. The AUC value for serum uromodulin was considerably higher than for uromodulin in urine. This relationship was confirmed for stage 1 CKD compared to the control group, and for stages 3 to 5 [8]. Our study results do not suggest, however, that serum uromodulin concentration enables a precise identification of the stage of the disease. Serum uromodulin concentration assay may be sometimes useful in the assessment of other pathological processes in CKD, e.g. changes in the bone system, as demonstrated by the correlation between uromodulin level and the concentrations of the markers of bone metabolism (stage 5) observed in the study. However, the usefulness of uromodulin for this purpose requires further confirmation.

It has been reported that in patients with early-stage CKD and low serum uromodulin concentrations the risk of disease progression and end-stage renal failure is higher than in patients in stages 3 and 4 CKD and with higher uromodulin concentrations [11]. Low serum uromodulin concentration may be a prognostic factor in indicating a possible future deterioration of the renal function [17]. It is also suggested that high uromodulin concentrations are associated with low risk of eGFR reduction, a reduced risk of death due to a renal disease, a decreased risk of acute renal damage, as well as with a lower risk of urinary tract infections in elderly patients [18].

Despite all this research, the role of uromodulin in the pathogenesis of renal impairment has not been fully understood. However, some studies explore the possibility of using uromodulin in other diseases than CKD. Serum uromodulin concentration was determined in patients with early acute pancreatitis. Acute kidney damage is one of the complications of this disease. It appeared that in this case, the uromodulin concentration statistically significantly correlates with deteriorating kidney function. Unfortunately, its concentration does not predict the severity of pancreatitis, or the occurrence of

acute kidney damage [19]. There are reports of a relationship between uromodulin and impaired glucose metabolism. Low uromodulin concentrations were observed in prediabetic patients, who later developed diabetes [20]. Other studies have extended our understanding of uromodulin, but as a marker of cardiovascular events in patients with coronary disease. There are studies demonstrating a significant relationship between serum uromodulin concentration and overall survival of these patients. In addition, a coefficient combining creatinine and uromodulin was used to predict the risk of cardiovascular events [21-24].

Conclusions

Serum uromodulin concentration may form an additional marker to complete the assessment of renal function at different stages of CKD, possibly offering a simpler interpretation than other common renal parameters. Moreover, uromodulin may be useful in the evaluation of CKD complications, e.g. bone system disorders. Further research in this direction is necessary, as the role of serum uromodulin has not been completely explored.

Limitations

This study is limited by a low number of subjects in study groups. To measure GFR, instead of a "gold standard", eGFR was used, based on the available standard tests. This shortcoming was compensated by the use of additional parameters: cystatin and creatinine.

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Life satisfaction vs physical fitness and health behaviour of Special Forces soldiers

Satysfakcja z życia a sprawność fizyczna i zachowania zdrowotne żołnierzy komandosów

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Abstract. In the context of the effectiveness of professional military service, individual behaviours during leisure time as determining the overall satisfaction with life become increasingly important. The aim of the study was to assess the relationship between the level of overall life satisfaction and physical fitness and the healthy behaviour of soldiers in Special Forces units. The study involved 596 servicemen. Standardized psychological tests were used to assess the level of life satisfaction and health behaviour. Physical fitness was assessed using the test trials annually performed in the Polish Armed Forces. All the analysed categories of health behaviour showed a statistically significant positive relationship ($p < 0.05$) with life satisfaction level. Life satisfaction is to the greatest extent linked to a positive attitude, and in the least to health practices. No significant correlation has been demonstrated between satisfaction with life and physical fitness tests. Health-promoting activities should be promoted in the army because they contribute to the overall increase in satisfaction with life. The mental health of soldiers is a matter requiring more extensive research and in-depth analyses. Apart from annual physical fitness tests, the subjective level of quality of life and health behaviour should be assessed.

Key words: life satisfaction, professional soldiers, health-promoting behaviour, physical fitness

Streszczenie. Wstęp. W kontekście efektywności zawodowej służby wojskowej coraz większego znaczenia nabierają indywidualne zachowania w czasie wolnym, które determinują ogólną satysfakcję z życia. Celem niniejszej pracy było zbadanie związku ogólnej satysfakcji z życia ze sprawnością fizyczną i zachowaniami zdrowotnymi żołnierzy Jednostki Specjalnej Komandosów. Materiał i metoda. Badaniem objęto 596 żołnierzy zawodowych. Użyto standaryzowanych testów psychologicznych oceniających poziom satysfakcji z życia i zachowań zdrowotnych. Do oceny sprawności fizycznej wykorzystano próby testowe stosowane corocznie w polskiej armii. Wyniki. Wszystkie analizowane kategorie zachowań zdrowotnych wykazały dodatni istotny statystycznie związek korelacyjny ($p < 0,05$) z poziomem wskaźnika satysfakcji z życia (SWLS). Satysfakcja w największym stopniu związana jest z pozytywnym nastawieniem psychicznym, a w najmniejszym z praktykami zdrowotnymi. Nie wykazano istotnego związku satysfakcji z życia z testami sprawności fizycznej. Wnioski. Należy popularyzować zachowania prozdrowotne w wojsku, gdyż przyczyniają się one do poprawy ogólnej satysfakcji z życia. Problematyka dobrostanu psychicznego żołnierzy jest kwestią wymagającą szerszych badań i pogłębionych analiz. W wojsku poza corocznym testowaniem sprawności fizycznej powinno się oceniać również subiektywny poziom jakości życia i zachowań zdrowotnych.

Słowa kluczowe: satysfakcja z życia, żołnierze zawodowi, zachowania zdrowotne, sprawność fizyczna

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Background

Soldiers in elite military units are subject to a significant psychophysical burden. Stress, often experienced in the military, contributes to numerous anti-health behaviours and mental health issues. Many active soldiers and veterans suffer from depression and suicidal thoughts [1]. This is partially due to the fact that the environment of supervision and control, typical for the army, is highly stress-inducing. In the United States, over 27% of soldiers suffer from significant levels of stress and from depression, which is reflected in reduced work effectiveness [2]. Hourani et al. [3] report that for soldiers their work is associated with much more stress than their family (out-of-work) life. Military personnel with a high level of stress are exposed to considerably more mental health problems, and demonstrate reduced work effectiveness, compared to the employees with lower stress levels.

Some professions require significant personal engagement and subordination of many aspects of life to achieve effective performance at work. Military service, especially in special forces, requires a high level of physical fitness and resistance to mental stress.

In the context of the professional effectiveness of soldiers, their individual behaviour in their leisure time, which determines general satisfaction with life, becomes increasingly important.

Satisfaction with life is defined as a general evaluation of satisfaction with one's own achievements and living conditions [4]. It is one of the indicators of quality of life. Together with other indicators of mental and physical health, it helps to determine if a person develops normally [5]. Work in elite military units creates numerous opportunities to face challenges, which can naturally be stress-inducing, but also offer satisfaction derived from overcoming difficulties, completing tasks, and reaching goals.

Unfortunately, the problems of lifestyle and quality of life of professional soldiers are rarely explored in scientific studies, and when they are, the research concerns veterans, rather than active service soldiers.

Numerous behavioural patterns contribute to a person's lifestyle. From the point of view of health, they may be classified as pro- and anti-health behaviours [6]. For the purpose of this study, the pro-health behaviours comprise all activities undertaken to prevent or detect a disease, or to improve the health status and sense of well-being [7].

One of the lifestyle elements, especially in people working in the military, is maintaining a high level of physical fitness, understood not only in the context of purely motor skills or the mechanistic biological or

physiologically-medical aspects, but also as a behavioural and cultural phenomenon. Therefore, following Osiński [8], physical fitness may be also defined as a certain level of motor self-sufficiency and independence, demonstrated in various external situations (while solving problems in the physical and social environment).

Physical fitness is particularly important for soldiers, as it determines the effectiveness of their professional work; therefore, unified fitness tests are conducted annually in the Polish Army. Physical fitness is determined by different factors, including the level of physical activity and other health behaviours [9]. It is also considered a measure of professional potential, e.g. of health. It is one of the factors that help to achieve optimal quality of life [10]. In this context, studying the relationship between the level of motor skills and satisfaction with life seems to be justified.

The aim of the study was to assess the general level of life satisfaction and its correlations with physical fitness and the health behaviour of Special Forces soldiers.

Material and methods

This study involved 596 professional soldiers serving in the Special Forces Unit in Lubliniec.

To assess the level of life satisfaction, the Satisfaction With Life Scale (SWLS) by Diener et al. was used [4]. A Polish adaptation of this tool, developed by Juczyński [11], was applied. It is a questionnaire comprising 5 statements. The subjects assessed, on a scale from 1 to 7, the degree to which the statements apply to their life. General indicator of life satisfaction was calculated as the aggregate sum of all the scores. The range of test scores lie between 5 and 35 points. The higher the score, the higher the level of life satisfaction it reflects. According to the test's instructions, the general score was converted to sten scores. A 1-4 sten score was considered low, a 5-6 sten score was considered average, and a 7-10 sten score was considered high. The internal consistency of the SWLS test was based on a Cronbach alpha of 0.85 (the author of the Polish version of this research tool declares a reliability indicator of 0.81).

In the second part of the study, health behaviour was assessed using Health Behaviour Inventory (HBI) by Juczyński [11]. This is a tool based on self-reporting, comprising 24 statements describing various health behaviours, whose frequency is evaluated on a scale of 1 to 5. The general indicator of the intensity of health behaviour is an aggregate sum of all the scores. The range of test scores lie between 24 and 120 points. The higher the score, the more pro-health the behaviour it

reflects. Following the test procedure, scores in four behaviour categories were calculated: "healthy eating habits" (HEH), "preventive behaviours" (PB), "positive mental attitude" (PMA) and "pro-health habits" (PHH). The general indicator of health behaviour was converted to a sten score. A 1-4 sten score was considered low, a 5-6 sten score was considered average, and a 7-10 sten score was considered high. The internal consistency of the HBI test was based on a Cronbach alpha of 0.88 (the author of this research tool declares a reliability indicator of 0.85).

The evaluation of physical fitness was conducted using the results of mandatory annual fitness tests, performed in standardised conditions, described in the Minister of the National Defence resolution on physical fitness testing of professional soldiers [12]. The tests included: (a) 3000 m run (to test circulatory and respiratory capacity) - the time was measured with an accuracy of 1 second, (b) pull-ups on a bar (to test the strength of arm muscles and the shoulder girdle) - the number of properly performed pull-ups was measured, (c) shuttle run 10 x 10 m (to test running speed and agility) - the time was measured with an accuracy of 0.1 second, (d) sit-ups from a supine position for 2 minutes (to test the strength of the body core muscles) - the number of properly performed sit-ups was measured. The individual elements of the test were assessed in the range from 2 to 5 (2 - unsatisfactory, 5 - very good), using different criteria in various age groups (in 5-year ranges).

The anonymous tests were performed, following the principles of fitness testing, by one trained person, who was also a physical education coach. The test was approved by the commander of the Special Force Unit. The collected data were analysed using an MS Office Excel 2010 spreadsheet and Statistica 10 software. T-Student's test was used to analyse the significance of differences between the means, and the relationships between the analysed variables were analysed using Pearson's linear correlation (r). In the analyses, the results for which probability was below the adopted level of significance of 0.05 ($p < 0.05$) were considered significant.

Results

The mean general satisfaction with life score (SWLS) in the studied group of soldiers was 21.57. The maximum value in the population was 33, and the minimal score was 8. After converting the raw results to sten scores, representing the mean satisfaction with life, a mean

value of 5 was obtained for the entire study group. Table 1 presents the structure of the satisfaction with life levels (low, average, high). The most common score was average (38.5%), followed closely by a high score (38.2%), and the least common result was a low score (23.1%). The differences between the presented satisfaction with life level are statistically significant; however, no correlations were found between satisfaction with the life and age of the subjects ($r = -0.0060$; $p = 0.883$).

The general health behaviour indicator (HBI) in the studied soldiers was 81.85. The maximum value in the population was 119, and the minimal score was 36. Converting the results to sten scores resulted in three level of health behaviour: low (23.49%), average (39.43%) and high (37.08%) (Tab. 2). The differences between the individual levels of HBI were statistically significant ($p < 0.05$). Table 3 presents four indicators of individual behaviour categories, i.e. HEH, PB, PMA and PHH.

No statistically significant correlation was observed between the general HBI and the age of subjects ($r = 0.045426$; $p = 0.268$). However, along with age, the "healthy eating habits" and "pro-health habits" scores were raised (the correlations were statistically significant), whereas the "preventive behaviours" and "positive mental attitude" scores were lowered (no statistical significance at $p < 0.05$).

The general fitness assessment obtained by the soldiers on the basis of the four tests was 4.40 (on a scale of 2 to 5). A total of 278 (46.6%) subjects received grade "good", of whom 159 soldiers (26.6%) achieved the maximum score in the general physical fitness assessment. The physical fitness score was unsatisfactory only in 4 soldiers. The results and grades in individual fitness tests are presented in Table 4. The highest grade (4.82) was obtained in the test of the strength of core muscles (sit-ups from a supine position), whereas the lowest grade (3.85) was achieved in the test of endurance (3000 m run). The level of fitness in the studied group decreased with age, with the exception of the shuttle run, where a very weak, but statistically significant negative correlation was observed. In this test soldiers maintained their physical fitness the longest, whereas the greatest reduction in fitness with age was observed in strength-testing exercises (sit-ups and pull-ups).

Table 1. Level of life satisfaction of examined soldiers

Tabela 1. Poziom wskaźnika satysfakcji z życia badanych żołnierzy

	Level of life satisfaction indicator (SWLS)				*difference with $p < 0.05$		
	Low	Moderate	High		Low-average	Low-high	Average-high
N	138	230	228	t	29.140*	47.048*	32.156*
%	23.15%	38.59%	38.26%	df	366	364	456
x	14.45	20.50	26.94	P	0.0000	0.0000	0.0000

Table 2. Level of health behaviours of examined soldiers

Tabela 2. Poziom zachowań zdrowotnych badanych żołnierzy

	Level of health behaviour indicator (HBI)				*difference with $p < 0.05$		
	Low	Moderate	High		Low-average	Low-high	Average-high
N	140	235	221	t	24.998*	40.658*	30.890*
%	23.49%	39.43%	37.08%	df	373	359	454
x	63.57	78.79	96.67	P	0.0000	0.0000	0.0000

Table 3. Level of individual indicators of health behaviour of examined soldiers

Tabela 3. Poziom poszczególnych wskaźników zachowań zdrowotnych badanych żołnierzy

Health behaviour indicator	Studied soldiers (Special Force Unit)			
	x	SD	Max.	Min.
Health behaviour indicator (HBI)	81.85	13.46	119	36
Healthy eating habits (HEH)	3.23	0.67	5	1.17
Preventive behaviours (PB)	3.35	0.85	5	1.33
Positive mental attitude (PMA)	3.7	0.65	5	2
Pro-health habits (PHH)	3.37	0.7	5	1.2

All the analysed categories of health behaviour demonstrated a positive statistically significant correlation ($p < 0.05$) with SWLS levels. The strongest correlation was observed between satisfaction with life and positive mental attitude, and the weakest relationship was found between the satisfaction and pro-health habits. No significant correlation between satisfaction with life and physical fitness tests was found. The tested motor skills do not correlate with the general health behaviour indicator. Only in the strength-testing exercises (sit-ups and pull-ups) was a statistically significant, although not pronounced, negative correlation with "healthy eating habits" and "pro-health habits" observed ($p < 0.05$).

Table 4. Results of physical fitness tests of examined soldiers

Tabela 4. Wyniki testów sprawności fizycznej badanych żołnierzy

Physical fitness tests	Studied soldiers (Special Force Unit)			
	x	SD	assessment	general assessment of physical fitness
3000 m run	13.56	2.58	3.85	4.40
Sit-ups from a supine position (cm)	64.87	6.79	4.82	
Pull-ups on a bar (no.)	13.25	3.06	4.69	
Shuttle run (s)	28.91	1.34	4.50	

Discussion

In the present socio-economic situation, the interest of young people in military service is increasing. This is a result of numerous reforms, including the elimination of mandatory military service in 2009, and complete professionalization of the Polish Armed forces.

Table 5. Correlations between the analysed variables
Tabela 5. Związki korelacyjne pomiędzy analizowanymi zmiennymi

Variables	Age	SWLS	HBI	HEH	PB	PMA	PHH	3000 m run	Sit-ups	Pull-ups on a bar
SWLS	0.00									
HBI	0.04	0.39*								
HEH	0.11*	0.33*	0.81*							
PB	0.07	0.30*	0.85*	0.58*						
PMA	0.00	0.40*	0.83*	0.51*	0.72*					
PHH	0.12*	0.27*	0.76*	0.57*	0.43*	0.50*				
3000 m	0.22*	0.01	0.05	0.05	0.01	0.03	0.07			
Sit-ups	0.69*	0.00	0.03	0.10*	0.05	0.03	0.10	0.21*		
Pull-ups on a bar	0.63*	0.01	0.07	0.13*	0.00	0.02	0.10*	0.27*	0.58*	
Shuttle run	0.09*	0.00	0.01	0.02	0.00	0.00	0.04	0.17*	0.09*	0.09*

* Correlations statistically significant at $p < 0.05$

Polish studies on candidates for military service indicate that the values they cherish the most include "having a preferred job or profession", followed by a "life full of adventures and travel", and a "good financial status" [13]. It seems clear that professional stability and social benefits may encourage young people to join the Armed Forces, especially when the job market is in a state of a constant flux. In addition, service in elite military units is associated with special prestige and recognition in society. Unusual lifestyle and the opportunity to experience extreme situations entices many young people to choose a future in the Special Forces. However, the preliminary conditions for joining this formation include very good health status, high level of physical fitness, and psychological resilience to stress-inducing situations. It appears that not all candidates realise the mental burden associated with the military service or the consequences of long-term work in an environment that requires permanent mental and physical alertness.

The high level of physical fitness reported in this study is largely due to the significant fitness and health potential the young soldiers presented when they joined the Armed Forces. The annual fitness tests conducted for the uniformed services mobilise soldiers to work on their physical capacity and maintain it at the highest possible level, as significant motor skills and agility are among the key competences in the army.

Lenart [14], using tests resembling those for professional soldiers, demonstrates results similar to those reported in this study; however, he emphasises the significant differences in the presented level of fitness between different components of physical capacity,

depending on the military specialisation. Similarly, Bzdawski et al. [15] and Wajer et al. [16] report the high level of motor skills of Polish soldiers. In every army physical fitness is a focus of particular attention and control; therefore, large investments are made in training infrastructure, equipment and training programmes to increase certain motor competences.

The army promotes health through its physical fitness standards and regular controls, e.g. body weight monitoring [17]. It should be noted that the level of physical fitness is determined by a range of health behaviours, which are parts of lifestyle, and an active one in particular.

It appears that the organisational culture of the army helps to popularise many pro-health behaviours. However, the problem of health-promotion in the army has been noticed only recently, and special wellness programmes are being introduced [18]. The military unit where this study was conducted offers a well-developed sports and recreational infrastructure, e.g. a club for amateur runners, known across the country, which organises events promoting an active lifestyle.

Various activities to compensate for the stress-inducing working conditions are very important for the quality of life of soldiers, and for their mental status. Studies demonstrate that positive emotions are of crucial importance in the army, as they help to develop psychological resilience in those adaptive situations associated with high psychophysical requirements, contributing to good health and psychological well-being [19].

Many researchers emphasise that preventive activities and prophylactic programmes for soldiers

returning from military mission are particularly important [20].

The studied soldiers presented a higher level of health behaviour (HBI = 81.85) than the general population of adult men in Poland (HBI = 78.50). The Special Forces soldiers also achieved higher results in all the analysed categories of behaviour. The greatest difference was observed in PMA, and the smallest in PB.

Pro-health behaviour is highly desirable in a military environment. The subject literature most frequently analyses the hazardous, anti-health behaviours that, as it appears, are not rare. They result from stress, and are a form of coping with it. Burnett-Zigler et al. [21] point to a high rate (36%) of soldiers abusing alcohol. A particularly high exposure to cruelty or life-threatening situations in combat operations is associated with alcohol abuse after returning home [22]. The risks related to alcohol abuse and the post-traumatic stress disorder are often found simultaneously in war veterans [23]. In his long-term study [24, 25] involving 150 thousand soldiers, Bray noticed a decreasing trend in the use of tobacco or illegal drugs, but also the increased abuse of prescription medications, habitual drinking, post-traumatic stress disorder and suicidal thoughts.

Pflanz et al. [2] suggest that elimination of the sources of stress should be a priority for the army, in order to ensure the mental health of soldiers. Physical activity plays an important role, as it helps to maintain psychological balance and prevent depression [26].

The people working in the army, particularly in the Special Forces, are not random, but carefully selected for their psychological aptitude. Wilcove [27] reports that as many as 825 of officers in the American Army are satisfied with their military lifestyle. They declare that relationships with their children have the greatest effect on the quality of their lives. The majority of them (73%) understand the importance of general satisfaction with life, and believe that it is reflected in the quality of professional work.

A considerable engagement in professional work, and perceiving it as passion, appears to determine a high level of satisfaction with life. Many researchers emphasize the relationship between general satisfaction with life and professional work [28]. Vittersø [29] demonstrates in his studies, however, that a pleasant atmosphere correlates more closely with satisfaction with life than engagement in performing tasks does. Therefore, pleasure derived from activity can improve life satisfaction.

The level of satisfaction with life in the studied soldiers (SWLS = 21.57) was slightly higher than the mean result for a normalised group reported by the author of the Polish version of the applied research tool (SWLS = 20.11).

Parker et al. [30] demonstrated in their studies that physical aptitude is one of significant predictors of satisfaction with life. However, in our studies the level of physical fitness does not correlate with the SWLS level. Satisfaction with life is associated with activity, taking action (health behaviour), and not with its results (physical fitness). It may be assumed that the soldiers presenting a high level of fitness do not consider physical capacity as a value, since they take it for granted. A similar observation applies to health, conditioning effective daily functioning: the value of health grows when its resources decrease. Numerous studies indicate that with age the meaning of physical fitness as the determinant of life satisfaction increases [31].

Conclusions

- Pro-health behaviour in the Armed Forces should be promoted, as it contributes to general satisfaction with life.
- Although no statistically significant relationship was demonstrated between the results of physical fitness tests and life satisfaction, fitness should be considered as a measure of health and potential necessary to maintain and develop physical capacity, directly associated with professional effectiveness. Creating opportunities to present one's physical fitness, e.g. during sports and recreational events, and to derive satisfaction from achievements in this area is also recommended.
- Apart from annual physical fitness tests, the army should also evaluate soldiers' subjective perception of their quality of life and health behaviour.
- The problem of the mental well-being of soldiers requires extensive studies and deep analysis.

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Insulin resistance and its laboratory correlations in males with metabolic syndrome

Insulinooporność i jej laboratoryjne korelaty u mężczyzn z zespołem metabolicznym

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Abstract. Metabolic syndrome (MS) occurs with high frequency in the general population. Most of the definitions of MS do not include insulin resistance (IR); therefore, IR occurrence in MS is not extensively examined. The aim of this study was to determine the frequency of IR in males with MS, association of IR with adipokines and cardiometabolic risk factors. In 86 males with MS, we determined serum fasting insulin and glucose (FG) and calculated IR using homeostatic model assessment (HOMA-IR). Three adipokines (adiponectin, leptin, adipocyte fatty acid binding protein [A-FABP]) and several cardiometabolic risk factors (total cholesterol TC, LDL-cholesterol [LDL-C], HDL-cholesterol [HDL-C], triglycerides [TG], apolipoprotein B [apoB], apolipoprotein A-I [apoA-I]), glycated haemoglobin (HbA1c) were also determined. IR (HOMA-IR ≥ 3.4) was found in nearly half of the patients. Fasting insulin strongly correlated with HOMA-IR (Spearman $R = 0.973$, $p < 0.001$) and was also the strongest IR predictor: insulin cut-off 13.4 mIU/L predicted HOMA-IR ≥ 3.4 with 96% sensitivity and 94% specificity, AUC 0.993, $p < 0.0001$). Leptin significantly correlated with HOMA-IR ($R = 0.482$, $p < 0.001$) and independently predicted IR at cut-off 9.02 ng/ml with 79% sensitivity and 59% specificity, AUC = 0.728, $p = 0.0001$. Fasting insulin and to some extent leptin are worthwhile additions to MS for predicting IR in males with this syndrome.

Key words: cardiometabolic risk factors, insulin resistance, leptin, metabolic syndrome

Streszczenie. Zespół metaboliczny (ZM) występuje z dużą częstością w populacji ogólnej. Większość definicji ZM

nie uwzględnia oporności na insulinę (IR), dlatego też występowanie IR w ZM nie zostało wyczerpująco zbadane. Celem naszego badania było określenie częstości występowania IR u mężczyzn z ZM oraz związku IR ze stężeniami adipokin i kardiometabolicznych czynników ryzyka. U 86 mężczyzn z MS oznaczono stężenie insuliny oraz glukozy na czczo (FG) i obliczono IR metodą oceny homeostazy HOMA-IR. Oznaczono również stężenia trzech adipokin (adiponektyna, leptyna, adipocytowe białko wiążące kwasy tłuszczowe [A-FABP]) i kilka kardiometabolicznych czynników ryzyka (stężenie cholesterolu całkowitego [TC], cholesterolu frakcji LDL [LDL-C], cholesterolu frakcji HDL [HDL-C], triglicerydów [TG], apolipoproteiny B [apoB], apolipoproteiny A-I [apoA-I]) oraz odsetek hemoglobiny glikowanej (HbA1c). IR (HOMA-IR $\geq 3,4$) stwierdzono u niemal połowy naszych pacjentów. Stężenie insuliny na czczo było silnie skorelowane z HOMA-IR (Spearman $R = 0,973$, $p < 0,001$) i równocześnie było najsilniejszym predyktorem IR: punkt odcięcia 13,4 mIU/l przewidywał HOMA-IR $\geq 3,4$ z 96% czułością i 94% swoistością, AUC 0,993, $p < 0,0001$). Stężenie leptyny było wyraźnie skorelowane z HOMA-IR ($R = 0,482$, $p < 0,001$) i niezależnie przewidywało IR dla punktu odcięcia 9,02 ng/ml z 79% czułością i 59% swoistością, AUC = 0,728, $p = 0,0001$. Stężenia insuliny na czczo i w pewnym stopniu leptyny są cennym uzupełnieniem zespołu metabolicznego do przewidywania IR u mężczyzn z tym zespołem.

Słowa kluczowe: zespół metaboliczny, insulinooporność, leptyna, kardiometaboliczne czynniki ryzyka

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Background

Overweight and obesity are very common not only in developed countries, but also globally, in some cases affecting even 30% of the general population [1, 2]. Metabolic syndrome (MS) refers to obesity associated with the disturbed metabolism of lipids and carbohydrates, and unstable arterial blood pressure [3, 4]. These abnormalities result in cardiovascular disorders, renal impairment, diabetes, neuropathy and other pathologies [5-7]. Metabolic syndrome, as a clinical syndrome, has various definitions. The one offered by the International Federation of Diabetes (IDF) is simple to use, and thus it is the most popular one [8]. It comprises arterial hypertension, central obesity, and disturbed carbohydrate and lipid metabolism. The World Health Organisation (WHO) definition [9] also includes insulin resistance as the most important diagnostic criterion. The European Group for the study of Insulin Resistance (EGIR) confirmed the importance of insulin resistance in MS, defining it as serum insulin concentration > 75 percentile in the non-diabetic population [10]. However, the RISC study questioned identification of increased insulin concentrations with insulin resistance [11].

Insulin resistance is a state of impaired biological response of tissues to insulin with respect to the metabolism of carbohydrates, lipids and proteins, conditioned by the combined effect of numerous genes (polygenicity) and environmental factors (primarily diet and physical activity) [12]. It is difficult to determine the frequency of insulin resistance in MS due to the varied diagnostic criteria and differences (environmental and genetic) between populations.

There are many methods of testing insulin resistance. They usually require a lot of work and are tedious for the patient. The most reliable results can be obtained using a metabolic clamp (the test involves a continuous infusion of insulin and simultaneous administration of glucose, to ensure constant euglycaemia) [13]. Homeostasis Model Assessment - Insulin Resistance (HOMA-IR) is another method of estimating insulin resistance based on the concentration of insulin and fasting glucose. It was developed by Matthews et al. [14], and it uses the following formula: $HOMA-IR = (\text{insulin } [\mu\text{U/ml}] \times \text{glucose } [\text{mg/dl}]) / 405$. In people with normal glucose tolerance the indicator does not exceed 3.2 [15]. In a large-scale epidemiological study on insulin resistance and MS in Poland the determined HOMA-IR value for the upper limit of the third quartile [16] was 3.4.

It appears that insulin resistance is one the principal mechanisms of carbohydrate and lipid metabolism disorders in MS, and it can occur years before their clinical manifestation [17]. Insulin resistance and hyperinsulinemia are considered independent risk factors

for diabetes and cardiovascular diseases due to the associated changes in the fat tissue, liver and striated muscles, expressed by changes in blood concentrations of the adipokins, lipoproteins, liver enzymes, inflammatory markers and components of the haemostatic system [5].

The relationship between insulin resistance and classic cardiometabolic risk factors is not fully understood; therefore, the diagnosis of insulin resistance based on IDF criteria is limited. This may lead to underestimation of the cardiovascular risk in patients with MS.

Aim of the study

The aim of this study was to determine the frequency and severity of insulin resistance in males with metabolic syndrome, and to find correlations between its measures and selected laboratory parameters recognised as cardiometabolic risk factors or risk-modifying factors. The study involved determination of the following analytes: concentrations of adipocyte proteins (adiponectin, leptin and adipocyte fatty-acid binding protein [A-FABP]), glucose, glycated haemoglobin rate (HbA1c), concentrations of total cholesterol, LDL fraction (LDL-C) and HDL fraction (HDL-C), triglycerides (TG), apolipoprotein B (apoB), apolipoprotein A-I (apoA-I), aminotransferases and high-sensitivity C-reactive protein (hs-CRP). Another aim of this study is to establish, indirectly, whether there are pathobiochemical premises to include the determination of insulin concentrations in the differential diagnosis of the risk of diabetes and cardiovascular disease in males with metabolic syndrome, or if the previous standard tests are sufficient. In addition, a secondary purpose of the study was to determine if such assessment should include another biochemical marker that would be highly correlated with the indicators of insulin resistance (a surrogate marker for these measures). The closest relationships may be found with concentrations of certain adipokines, whose relation with insulin resistance in metabolic syndrome is not often described, with the exception of adiponectin, and is unclear.

Material and methods

The analysis included 86 males diagnosed in the Military Institute of Medicine with MS using the IFD criteria [8]. Patient characteristics are presented in Table 1. None of the subjects had a history of diabetes, chronic kidney disease, thyroid disorders or cardiovascular disease. Nearly all the patients (n = 80, 93%) had arterial hypertension, and 55 of them (68.8%) were using hypotensives.

In the physical examination and medical history the following constitutive factors were considered: body mass index (BMI), waist circumference, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DB). Based on the medical history, physical examination and the results of previous or current laboratory tests, cardiovascular risk based on SCORE charts was calculated for each patient (10-year risk of a fatal cardiovascular event).

Laboratory tests were performed using fasting peripheral venous blood, collected in the morning (7:00 – 9:00). Concentrations of the following parameters were determined: urea, creatinine, fasting glucose (FG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoproteins B and A-I, glycated haemoglobin (HbA1c), insulin, adipocyte proteins: adiponectin, leptin and adipocyte fatty acid-binding protein. Prediabetes was diagnosed based on the HbA1c rate, according to the ADA criterion > 5.7% [18].

Routine biochemical assays were performed with standard methods, using a Roche Integra 800 analyser and reagents. LDL-C concentration was calculated according to the Friedewald's formula [19]. HbA1c, apoA-I and apoB concentrations were determined with the immunoturbidimetric method, using Roche Diagnostics reagent kits and Cobas 501 analyser, and insulin concentrations were determined by immunoelectrochemiluminescence (ECLIA), using a Cobas 6000 analyser. C-reactive protein (hs-CRP) concentration was assessed by a highly sensitive immunofluorometric assay using Siemens reagents (CardioPhase® hsCRP) and BN2 analyser produced by the same manufacturer. The upper limit of reference range for insulin concentration is 24.9 mU/l. Insulin resistance was determined according to the formula: $HOMA-IR = (\text{insulin } [\mu\text{U/ml}] \times \text{glucose } [\text{mg/dl}]) / 405$.

Concentrations of adipocyte proteins were determined by the ELISA methods. Serum adiponectin concentration was determined using Human Adiponectin Platinum ELISA ready reagent kits produced by eBioscience. The range of adiponectin in healthy blood donor was 1309-13 928 ng/ml (manufacturer's data). Serum concentrations of adipocyte fatty acid-binding proteins (A-FABP) was determined using Human Adipocyte FABP ELISA kits produced by BioVendor. According to the manufacturer, the normal range for AFABP is 9.58 ± 16.32 ng/ml (mean \pm 2 SD). Serum leptin concentration was determined using Leptin (Sandwich) ELISA reagent kits produced by DRG. The normal value range for men is 3.84 ± 1.79 ng/ml.

Table 1. Clinical characteristics and incidence of MS components according to IDF in the studied group

Tabela 1. Charakterystyka kliniczna i częstość występowania cech ZM według IDF w badanej grupie

Parameter	Mean \pm SD
Age (years)	43.5 \pm 9.6
Waist circumference (cm)	111.7 \pm 8.9
BMI (kg/m ²)	32.4 \pm 3.7
SBP (mm Hg)	142.3 \pm 16.4
DBP (mm Hg)	90.5 \pm 10.1
TG (mg/dl)	240.5 \pm 124.7
HDL-C (mg/dl)	41.2 \pm 8.7
FG (mg/dl)	100.0 \pm 10.0
MS feature	% (n)
Waist circumference	100 (86)
Arterial hypertension	93 (80)
Increased triglyceride concentration	77.9 (67)
Reduced HDL-cholesterol concentration	51 (44)
Abnormal fasting glucose concentration	47.7 (41)
Hypotensive treatment	63.9 (55)
Hypolipidemic treatment	27.9% (24)
3 features of the syndrome present	39.5% (34)
4 features of the syndrome present	34.9% (30)
5 features of the syndrome present	25.6% (22)

BMI - body mass index, DBP - diastolic blood pressure, FG - fasting glucose, HDL-C - HDL-cholesterol, SBP - systolic blood pressure, TG - triglycerides, MS- metabolic syndrome

Statistical analysis

The statistical analysis was performed using and Statistica 12.0 (StatSoft Inc.). Data distribution was assessed visually on histograms, and using the Shapiro-Wilk test. The results for quantitative variables were expressed numerically and as percentages, whereas for continuous variables they were presented as mean \pm SD (standard deviation). The results of lipoprotein determination were neglected in patients receiving hypolipidemic treatment. Due to the asymmetrical distribution of a few analytes (insulin, leptin, adiponectin and aminotransferases), nonparametric Spearman's method was used to assess correlations between concentrations of the studied substances (for all of them), and logarithmic transformation was used for multiple regression. Only the results unaffected by hypolipidemic treatment (n = 62) were used in the assessment of correlations between lipid concentrations and other laboratory parameters.

Table 2. HOMA-IR and laboratory parameters not included in the IDF definition in the studied group**Tabela 2. HOMA-IR i parametry laboratoryjne nie objęte definicją ZM wg IDF w badanej grupie**

	Mean ± SD (median)
HOMA-IR ⁸⁰	4.10 ± 2.49 (3.27)
Fasting glucose ⁸⁰ (mIU/l)	16.31 ± 9.49 (13.60)
Adiponectin ⁸⁴ (ng/ml)	7565 ± 5274 (6041)
Leptin ⁸⁴ (ng/ml)	12.42 ± 8.78 (9.77)
A-FABP ⁸⁵ (ng/ml)	27.46 ± 13.37 (24.9)
HbA1c ⁸⁶ (%)	5.81 ± 0.36 (5.75)
ALT ⁸⁵ (U/l)	44.3 ± 20.0 (39.0)
AST ⁸⁶ (U/l)	29.75 ± 10.72 (28.00)
TC ⁶² (mg/dl)	234.7 ± 44.8 (232.0)
LDL-C ⁶² (mg/dl)	140.2 ± 38.4 (139.5)
apoB ⁶² (g/l)	1.15 ± 0.25 (1.17)
apoA-I ⁶² (g/l)	1.54 ± 0.26 (1.52)
hs-CRP ⁶² (mg/l)	2.29 ± 2.19 (1.25)
SCORE ⁸⁶ (%)	2.77 ± 3.30 (1.00)

A-FABP - adipocyte fatty acid binding protein, ALT - alanine aminotransferase, apoA-I - apolipoprotein A-I, apoB - apolipoprotein B, AST - aspartate aminotransferase, HbA1c - glycated haemoglobin, HOMA-IR - insulin resistance indicator, LDL-C - concentration of low density protein cholesterol, hs-CRP - high-sensitivity C-reactive protein, SCORE - indicator of a 10-year risk of death due to cardiovascular causes, TC - total cholesterol concentration, numbers in the upper index - number of cases

Results

A total of 67 subjects (78%) had elevated TG concentrations, and 44 subjects (51%) had reduced HDL-C levels. Abnormal FG concentration was observed in nearly half of the patients. Table 2 presents the results of laboratory tests that are not included in the definition of MS.

The results presented in Table 2 (medians) indicate that insulin resistance (HOMA-IR ≥ 3.4) was found in almost half of the patients, slightly over half of the subjects had prediabetes (HbA1c ≥ 5.7%), nearly 1 in 2 patients had elevated ALT, and in 2 out of 3 subjects hypercholesterolemia was observed (LDL-C > 100 mg/dl). ApoB concentrations were elevated (≥ 1.33 g/l) in 15 subjects (24.2%). ApoA-I concentrations in patients who were not receiving hypolipidemic treatment were within the reference range for healthy males (> 1.04 g/l). Elevated A-FABP concentrations (> 25.9 ng/ml) were observed in 37 patients (43.5%).

Table 3. Correlations of HOMA-IR and insulin with glycemia, concentrations of adipokins and other laboratory markers of cardiometabolic risk, and SCORE risk assessment**Tabela 3. Korelacje HOMA-IR i insuliny z glikemią, stężeniami adipokin i innymi markerami laboratoryjnymi związanymi z ryzykiem kardiometabolicznym oraz skalą SCORE**

Parameter	HOMA-IR R _s	Insulin R _s	Glucose R _s	HbA1c R _s
Age (years)	0.006	0.095	0.320**	0.215*
Waist circumference (cm)	0.353**	0.358**	0.130	0.192
BMI (kg/m ²)	0.398***	0.404***	0.108	0.141
HOMA-IR	-	0.973***	0.417***	0.222*
FG (mg/dl)	0.417**	0.244*	-	0.339**
Fasting glucose (mIU/l)	0.973***	-	0.244*	0.178
Adiponectin (ng/ml)	0.127	0.139	0.031	0.218*
Leptin (ng/ml)	0.482***	0.501***	0.049	0.246*
A-FABP (ng/ml)	0.209	0.234*	0.012	0.046
HbA1c (%)	0.222*	0.177	0.339**	1.000
ALT (U/l)	0.293**	0.344**	0.039	0.160
AST (U/l)	0.272*	0.279*	0.129	0.173
hs-CRP (mg/l)	0.119	0.050	0.208	0.097
TG (mg/dl)	0.103	0.163	0.156	0.066
HDL-C (mg/dl)	0.142	0.229	0.288*	0.017
TC (mg/dl)	0.178	0.127	0.317*	0.073
LDL-C (mg/dl)	0.139	0.084	0.316*	0.065
apoB (g/l)	0.237	0.204	0.211	0.032
apoA-I (g/l)	0.123	0.192	0.167	0.079
No. of syndrome features	0.307*	0.231*	0.436***	0.216*
SCORE	0.082	0.125	0.164	0.175

A-FABP - adipocyte fatty acid binding protein, ALT - alanine aminotransferase, apoA-I - apolipoprotein A-I, apoB - apolipoprotein B, AST - aspartate aminotransferase, BMI - body mass index, FG - fasting glucose concentration, HbA1c - glycated haemoglobin, HDL-C - HDL cholesterol, HOMA-IR - insulin resistance indicator, hs-CRP - high-sensitivity C-reactive protein, LDL-C - low density lipoprotein cholesterol, TG - triglycerides, R_s - Spearman's correlation coefficient, *p < 0.05, **p < 0.01, ***p < 0.001 (correlation coefficients regarding the parameters included in the HOMA-IR formula are italicised), SCORE - indicator of a 10-year risk of death due to cardiovascular causes, TC - total cholesterol

Table 4. Sensitivity and specificity of insulin resistance diagnosis (HOMA-IR>3.4) using parameters associated with metabolic syndrome Tabela 4. Czulość i swoistość wykrywania oporności na insulinę (HOMA-IR>3.4) z wykorzystaniem parametrów związanych z zespołem metabolicznym

	Cut-off point	Sensitivity (%)	Specificity (%)	AUC	p
Circumference (cm)	113	72	65	0.714	0.0002
BMI (kg/m ²)	32.1	76	71	0.742	0.0000
Leptin (ng/ml)	9.02	79	59	0.728	0.0001
A-FABP (ng/ml)	19.7	84	42	0.644	0.0195
FG (mg/dl)	106	44	90	0.697	0.0009
Insulin (mIU/l)	13.4	96	94	0.993	0.0000
ALT (U/l)	47	58	76	0.712	0.0002
Factors (no.)	4	77	52	0.637	0.0288

A-FABP - adipocyte fatty acid-binding protein, ALT - alanine aminotransferase, AUC - area under the curve, ROC - receiver operating characteristics, BMI - body mass index, FG - fasting glucose concentration

Hyperleptinaemia (leptin concentration > 5.63 ng/ml) was observed in over 75% of patients. Serum hs-CRP concentration associated with increased cardiovascular risk (≥ 3.0 mg/l) was found in 18 (29%) patients who did not receive hypolipidemic treatment. High cardiovascular risk (SCORE $\geq 5\%$) was observed in 18.6% of the entire group.

A very strong correlation was found between HOMA-IR and insulin concentration, and a moderate correlation was reported between HOMA-IR and FG, which was expected, as these parameters are included in the mathematical formula. However, the considerably more pronounced relationship of insulin resistance with insulin concentration than with FG is noteworthy (Tabs. 3-4).

The results showed particularly strong correlations between leptin and HOMA-IR, insulin concentration, BMI and waist circumference (Tab. 3). The measures of obesity correlated more strongly with leptin than with HOMA-IR and insulin concentrations. A slightly weaker, but still significant, correlation was observed between leptin concentration and HbA1c (Tab. 6). The analysis of predictive values of certain parameters confirmed the key importance of insulin concentration for insulin resistance. Glycaemia, although mathematically related to HOMA-IR,

demonstrated high specificity, but relatively low sensitivity (Tab. 4).

Table 5. Parameters affecting HOMA-IR (except insulin concentration) - multiple regression models Tabela 5. Parametry wpływające na HOMA-IR (poza stężeniem insuliny) - modele regresji wielorakiej

Parameter	B	Standard error b	β	p
Model 1.				
Free term			4.0800	0.0008
Circumference	0.0159	0.1059	0.0004	0.8805
Log[Glu]	0.3662	0.1053	2.0776	0.0008
Log[Lept]	0.4763	0.1011	0.3719	0.0000
Log[ALT]	0.2677	0.0940	0.3196	0.0058
Log[HbA1c]	0.8255	0.1001	0.7024	0.4126
No. of factors	0.1003	0.0940	0.0251	0.3367
	R	R²	R² adjusted	
Correlation	0.6879	0.4732	0.4267	0.0000
Model 2.				
Free term			4.919	0.0000
Circumference	0.2402	0.1026	0.0062	0.0220
Log[Glu]	0.3982	0.0975	2.1715	0.0001
Log[ALT]	0.2213	0.1019	0.2656	0.0333
	R	R²	R² adjusted	
Correlation	0.5693	0.3242	0.2960	0.0000

P - standardised regression coefficient, B - regression coefficient, Log[ALT] - logarithm of the activity of alanine aminotransferase, Log[Glu] logarithm of glucose concentration, Log[Lept] - logarithm of leptin concentration, R - correlation coefficient, R² - determination coefficient,

In the multiple regression model, including the parameters correlated with HOMA-IR (except for insulin), leptin concentration correlated most strongly with this measure of insulin resistance, rendering waist circumference insignificant in this model (Tab. 5). Leptin concentration accounted for approximately 40% of the HOMA-IR variability. Waist circumference became a significant predictor of HOMA-IR after elimination of leptin from model 1.

Adiponectin concentration, contrary to expectations, did not correlate significantly with insulin resistance or with insulin concentration. A negative correlation was found between adiponectin concentration and glycated haemoglobin rate ($R_s = -0.218$, $p = 0.024$). A strong correlation was observed between adiponectin concentration and ADL-C and apolipoprotein A-I concentration (Tab. 6).

Table 6. Correlations between concentrations of adipokins, measures of obesity, HDL components, and age (Spearman's method)
Tabela 6. Korelacje między stężeniami adipokin, miarami otyłości, składnikami frakcji HDL oraz wiekiem (metoda wg Spearmana)

	Age	Adiponectin	Leptin	A-FABP	ApoA-I	HDLC
Age (years)		0.151	0.162	0.112	0.213	0.272*
Circumference (cm)	0.098	0.090	0.395***	0.357***	0.027	0.063
BMI (kg/m ²)	0.023	0.031	0.466***	0.326*	0.022	0.057
Adiponectin (ng/ml)	0.151	-	0.208	0.022	0.523***	0.424***
Leptin (ng/ml)	0.162	0.209	-	0.442***	0.181	0.260*
A-FABP (ng/ml)	0.113	0.022	0.442***	-	0.031	0.163
ApoA-I, (ng/ml)	0.213	0.523***	0.181	0.104	-	0.793***

A-FABP - adipocyte fatty acid-binding protein, ApoA-I - apolipoprotein A-I, BMI - body mass index

A-FABP concentration demonstrated a clear relationship with body mass index, but slightly less pronounced than the correlation between leptin and BMI. A visible correlation between the activity of aminotransferases, especially ALT (activity increased to > 41 U/l in 40% of the subjects), and insulin concentration and insulin resistance is noteworthy. Aminotransferase levels positively correlated with waist circumference ($R_s = 0.345$, $p = 0.0014$ for ALT and $R_s = 0.388$, $p = 0.0003$ for AST). A statistically significant relationship between ALT activity and HOMA-IR was confirmed in the multiple regression analysis (Tab. 5). Lipoprotein components did not correlate significantly with insulin concentration or insulin resistance.

Discussion

In the studied group of patients with MS insulin resistance was observed in nearly half of the patients, and hyperinsulinaemia in 13% of the subjects. Despite the fact that MS has been a focus of interest of researchers for over two decades, the data regarding the frequency of insulin resistance and its severity in this syndrome is relatively limited, while the available information is largely ambiguous [5]. According to the WHO definition, insulin resistance is the essential condition for the diagnosis of MS [9]. However, the epidemiological studies using a metabolic clamp method to determine insulin resistance demonstrated that this condition is found only in 33% of patients with MS [20]. Karnchanasorn et al. did not observe insulin resistance in 32% of Caucasian patients with metabolic syndrome, and concluded that it is not a necessary component of the syndrome, although it is a risk factor in MS [21]. In a study conducted in Poland in the general population ($n = 2673$, without excluding diabetics) insulin resistance was observed in 48% of subjects [16]. In our study group insulin resistance was found in approximately half of the patients. The presented results are therefore consistent with the outcomes of a large epidemiological study, and confirm that MS

diagnosis based on the IDF criteria is not always synonymous with insulin resistance [22].

In the studied group insulin concentrations of > 13.4 mU/l predicted HOMA-IR ≥ 3.4 with very high sensitivity and specificity. Similar benefits of assessing fasting insulin to determine various measures of insulin resistance, including HOMA-IR were demonstrated in a group of obese patients by Pang KM et al. [23].

In the class of adipocyte proteins, the strongest predictor of insulin resistance measures was leptin concentration. Hyperleptinaemia was observed in the majority of patients, which is consistent with the reports indicating that it is an independent predictor of MS [24]. The cut-off point for leptin concentration suggestive of insulin resistance in our study was 9.02 ng/ml (79% sensitivity, 59% specificity, AUC - 0.728), and was slightly higher (6.45 ng/ml, 71.4% sensitivity, 60.2% specificity, AUC of 0.716) than the cut-off point for identification of any two cardiometabolic risk factors in a population study by Gijon-Conde et al. [25]. The physiological relationship between leptin and insulin is very complex. Leptin, a protein hormone (16-kDa) secreted by adipocytes (thus the relationship with BMI and waist circumference), affects the hypothalamus, reducing appetite and increasing the energy output of the organism. In physiological conditions, it inhibits the synthesis and secretion of insulin by pancreatic polypeptide cells. Insulin stimulates the secretion of leptin from adipocytes. Leptin also stimulates gluconeogenesis, increases the sensitivity of hepatocytes to insulin, and glucose uptake by the muscles [26]. Very often hyperleptinaemia in obese patients, despite the lack of proportional reduction of appetite, leads to a diagnosis of leptin resistance [27] due to an impaired effect of the hormone on the central nervous system [28]. Some researchers suggest it may be secondary to hyperinsulinaemia and insulin resistance [29, 30]. However, a recent metaanalysis including 13 epidemiological studies [31] did not confirm the hypothesis that increased leptin concentration is a cardiovascular risk factor. Due to its strong correlation

with insulin concentration, insulin resistance and obesity measures, leptin is the best (except for insulin) candidate for extended characteristics of metabolic syndrome, as indicated also by other researchers [24].

Adiponectin was another protein synthesised in adipocytes that we analysed. In physiological conditions, this protein increases tissue sensitivity to insulin and demonstrates anti-atherosclerotic and anti-inflammatory effects [32]. Its negative correlation with insulin and insulin resistance was not statistically significant, as data from previous studies had suggested [33, 34]. Similarly to our study, no statistically significant correlation between adiponectin and insulin or HOMA-IR was found by Yadav A. et al. in a group of healthy individuals [35] or by Nakatani H. et al. [36] in a group of young males. Kaser S. et al. [37] did not find a relationship between concentrations of adiponectin or its isoforms and sensitivity to insulin. Disturbing factors should be considered while interpreting these results, as adiponectin concentration is reduced in obesity, metabolic syndrome and type 2 diabetes [38]. Moreover, some hypotensive medications frequently used in our group of patients, e.g. angiotensin-converting enzyme inhibitors (ACE-I), may increase serum adiponectin concentration [39]. An indirect sign of potential anti-atherosclerotic properties of adiponectin was demonstrated in our study in a clear, positive and significant correlation between adiponectin and HDL-C concentrations, and an even stronger correlation with the fraction's protein component, apolipoprotein A-I. This is consistent with reports of other researchers [40, 41]. Therefore, it appears that HDL fraction components may be good predictors of adiponectin concentration in metabolic syndrome, eliminating the need to determine this hormone.

The third adipokine assessed in our study was adipocyte fatty acid-binding protein (A-FABP), whose blood serum concentration positively correlated with leptin, waist circumference and BMI (the strongest relation), and with insulin (weaker correlation), but not with insulin resistance. A strong correlation between A-FABP and waist circumference, BMI and the amount of visceral fat tissue was demonstrated recently by HUNG et al. [42]. The usefulness of A-FABP in the diagnostics of MS was examined by Stejskal and Karpisek M. [43], who established that at the cut-off point of 16.4 µg/l the sensitivity was 40%, and specificity 99%. These values were similar to those observed in our study. Our results indicate indirectly that A-FABP does not provide any additional information to that obtained through leptin assay, as they are strongly and positively correlated.

The positive correlation between aminotransferases and HOMA-IR and insulin concentration, as well as the relationship between ALT and HOMA-IR in our multiple

regression models confirmed that hepatic dysfunction plays a role in insulin resistance in MS [44-46]. Non-alcoholic fatty liver disease, considered a hepatic manifestation of MS, is the most common civilizational disease of the liver [47].

Standard parameters of lipid metabolism (TC, HDL-C, LDL-C and TG) did not correlate significantly with HOMA-IR and insulin concentrations, and did not distinguish significantly insulin resistant patients from other subjects. Similarly, Kakita et al did not find any correlation between TC and HDL-C concentrations and the indicators of insulin resistance in males with MS [48]. The SCORE scale, associated with lipids and other classic risk factors, did not correlate with insulin resistance.

Conclusions

Insulin resistance measured according to HOMA-IR is observed in almost half of the males with metabolic syndrome, and it is highly correlated with serum fasting glucose concentration. Therefore, determination of fasting insulin suffice to predict insulin resistance in this group of patients.

Leptin is the second most potent predictor of HOMA-IR, considerably more reliable than waist circumference or concentration of adipocyte fatty acid-binding protein.

Adiponectin concentration was not significantly correlated with obesity measures or insulin resistance, but demonstrated a strong positive correlation with HDL cholesterol and apolipoprotein A-I concentrations, as well as a negative correlation with glycated haemoglobin rate, which may indirectly indicate its anti-atherosclerotic properties.

Concentrations of lipoprotein components and SCORE cardiovascular risk assessment did not correlate with the severity of insulin resistance. Therefore, the traditional, classic risk factors do not reflect an increased risk of insulin resistance.

Determination of insulin concentration in MS patients together with assessment of insulin resistance are necessary to fully estimate the risk of diabetes and cardiovascular diseases, and to introduce targeted prophylaxis of these conditions.

Diagnostic and prognostic determination of leptin in MS should still be studied, due to its strong pathophysiological relationship with insulin and adipocyte activity in the organism.

Clinical implications

Metabolic syndrome in males seems to be highly heterogeneous in terms of cardiometabolic risk. In the studied sample over 20% of subjects had abnormal

fasting glucose levels, together with increased HbA1c and insulin resistance. Considering the fact that coexistence of insulin resistance and MS extends the syndrome's predictive value in the assessment of cardiovascular risk (it doubles the risk), the evaluation of disturbed tissue sensitivity to insulin is entirely justified. Our study indicates that, among many parameters associated with cardiometabolic risk, the assessment of insulin concentration may demonstrate the highest added value and, if not available, it is followed by determination of leptin and ALT.

Summary

Insulin resistance measured by HOMA-IR model was found in nearly half of males with metabolic syndrome, and correlated particularly strongly with insulin concentration. Leptin was the second strongest predictor or insulin resistance, far better than other laboratory and clinical indicators, including adiponectin and A-FABP. The predictive value of leptin in insulin resistance increased if alanine aminotransferase was introduced in the multiple regression model. Studies on the significance of insulin resistance in complex pathophysiological disorders associated with MS contribute to an improved estimation of cardiovascular risk in this group of patients.

Limitations

The number of studied patients was not high, but sufficient for a reliable assessment of significant relationships and differences between the examined biochemical parameters. On the one hand, the studied group was homogeneous (i.e. "pure metabolic syndrome", without significant comorbidities and disorders that could affect the results in uncontrolled way). On the other hand, it limited the potential extrapolation of the results on patients other than those with MS. The fact that the analysis included only males, due to the specificity of the research work at the Military Institute of Medicine, may also affect the interpretation of the results.

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Hyperammonaemia as a rare cause of severe consciousness disorders in intensive care units

Hiperamonemia jako rzadka przyczyna ciężkich zaburzeń świadomości na oddziale intensywnej terapii

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Abstract. Consciousness disorders occur in most patients admitted into intensive care units. One of their rare causes may be hyperammonaemia. A 28-year-old male was admitted to the intensive care unit due to a consciousness disorder of unspecified origin. Alcohol, drug or other psychoactive medicament poisoning was excluded. In childhood he was diagnosed with hyperammonaemia type 2 – for many years he has not been following the recommended therapy. On admission he was drowsy, without any logical contact, sometimes excited. Cerebral oedema was excluded after performing a CT scan. In laboratory blood tests it was alleged that only hypoglycaemia (40 mg/dl), high ammonia concentration (140 mcg/dl) and hyperbilirubinemia (3.52 mg/dl) were present. A sedative, continuous infusion of glucose, an appropriate diet and intravenous medicines reducing ammonia serum concentration were applied. Consciousness disorders were still observed, therefore it was decided to start continuous venovenous hemodiafiltration – this caused the general state of the patient to improve, and the patient was discharged home. Hyperammonaemia should be considered to be one of the causes of consciousness disorders. Quick and correct diagnosis and treatment allows doctors to avoid damage to the central nervous system and the patient's death.

Key words: hyperammonaemia, genetics, diet therapy, metabolism

Streszczenie. Zaburzenia świadomości występują u większości pacjentów przyjmowanych na oddziały intensywnej terapii (OIT). Jedną z ich rzadkich przyczyn może być hiperamonemia. Na OIT został przyjęty 28-letni pacjent z zaburzeniami świadomości o niejasnym pochodzeniu. Wykluczono zatrucie alkoholem, lekami oraz środkami psychoaktywnymi. W dzieciństwie rozpoznano u niego hiperamonemię typu 2 – od wielu lat nie stosował zalecanej terapii. W chwili przyjęcia podśpiał, bez kontaktu logicznego, okresowo pobudzony. W tomografii komputerowej głowy wykluczono obrzęk mózgu. W badaniach laboratoryjnych krwi z odchyłen stwierdzono jedynie hipoglikemię (40 mg/dl), duże stężenia amoniaku (140 µg/dl) oraz hiperbilirubinemię (3,52 mg/dl). Włączono sedację, ciągle wlew glukozy, odpowiednią dietę; podano dożylnie leki zmniejszające stężenie amoniaku w surowicy, a wobec utrzymujących się zaburzeń świadomości rozpoczęto ciągłą hemodiafiltrację żylną-żylną, uzyskując w ciągu kilku dni poprawę stanu umożliwiającą wypisanie pacjenta do domu. Hiperamonemia musi być rozpatrywana jako jedna z przyczyn zaburzeń świadomości. Szybkie rozpoznanie i wdrożenie właściwego leczenia pozwala uniknąć uszkodzenia ośrodkowego układu nerwowego i śmierci pacjenta.

Słowa kluczowe: hiperamonemia, genetyka, metabolizm, leczenie dietą

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Background

Ammonia is a toxic product of the decomposition of amino acids, the basic components of proteins. It is

produced in most human tissues. After coupling with glutamate to form non-toxic glutamine, it is transported in the blood to the liver, where it is transformed in the enzymatic urea cycle (Fig. 1) into urea, excreted through

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the kidneys with the urine. Another important source of ammonia involve the intestinal bacteria that use urease to degrade urea to ammonia.

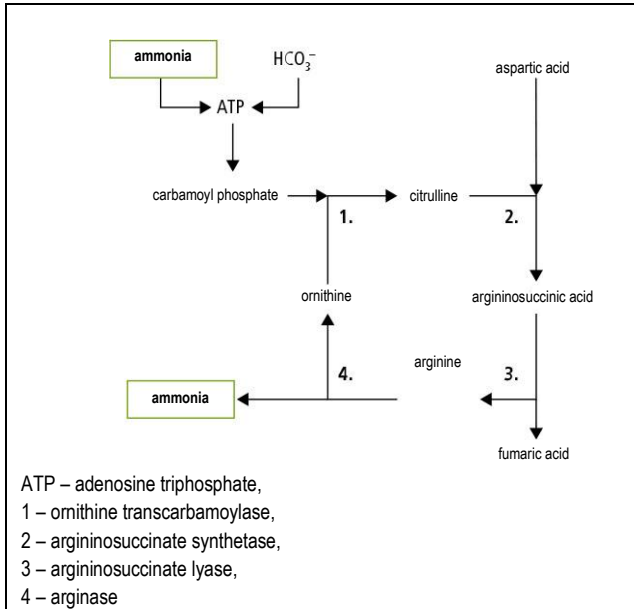


Figure. Reactions of the urea cycle (own work)

Rycina. Reakcje cyklu mocznikowego (opracowanie własne)

Through the portal vein, ammonia passes directly into the liver. The kidneys also can produce ammonia and release it either to the bloodstream, or to the urine, which helps to regulate the acid-base balance in the organism [1]. Ammonia is particularly toxic for the brain. It easily crosses and damages the blood-brain barrier, disturbs neurotransmission processes and the cellular metabolism of the central nervous system (CNS), resulting in cerebral oedema [2].

Hyperammonaemia is a condition characterised by an increased concentration of ammonia in the blood serum, leading to CNS impairment, and often to death. According to the underlying cause, it can be classified as primary and secondary, or congenital and acquired (Tab. 1) [2].

Hyperammonaemia is diagnosed on the basis of increased serum ammonia concentration ($>70 \mu\text{g/d}$), and the occurrence of symptoms such as consciousness disorders, generalised convulsions, vomiting and coma. Diagnosis and treatment of the disease is often delayed, which may result in permanent damage to the CNS and death. Different types of consciousness disorders are observed in ICU patients. They are most frequently caused by a water and electrolyte imbalance or metabolic disorders (e.g. hypoglycaemia, hyponatraemia or hyperammonaemia). In most ICUs ammonia concentrations are not routinely determined. As a result, the diagnosis of this potentially fatal disease may be

considerably delayed or even impossible, and hyperammonaemia should always be considered in differential diagnostics of patients with severe consciousness impairment, especially of unclear aetiology.

A case report

A 28-year-old male was admitted to the ICU at the Central Clinical Hospital of the Ministry of Internal Affairs and Administration due to severe consciousness disorder of unspecified origin, preceded by intensive nausea and vomiting. On admission, the patient was in a generally poor condition, lucid, unresponsive to verbal stimuli, temporally and spatially disoriented, drowsy, temporarily agitated and aggressive. His respiratory and cardiovascular status was stable. Basic laboratory and imaging diagnostics were performed in the Hospital Emergency Department (HED). Blood tests revealed only hypokalaemia (2.8 mmol/l), hypoglycaemia (40 mg/dl) and hyperbilirubinaemia (3.52 mg/dl). The following assays were conducted: concentrations of ethyl alcohol, non-edible alcohols and a full toxicology panel (amphetamine, cannabinoids, mephedrone, tricyclic antidepressants, opioids, benzodiazepines). All the test results were negative. Computed tomography of the brain did not reveal any abnormalities. Despite the normalisation of kalaemia and glycaemia, consciousness impairment continued to increase, and the patient was admitted to the ICU. The medical history collected a few hours after the patient's mother revealed that in the family there were several cases of young men dying from unspecified causes. The patient was diagnosed in childhood with type II hyperammonaemia associated with an enzymatic defect of the urea cycle (ornithine transcarbamoylase deficiency). For many years the patient did not comply with the recommended therapy, including a special diet. He did not receive treatment for any other chronic diseases, and denied using stimulants. The physical examination did not demonstrate any significant abnormalities. On admission to the ICU, the ammonia concentration was $140 \mu\text{g/dl}$ (normal range: $35\text{--}70 \mu\text{g/dl}$). The patient was assessed using the prognostic scales available for intensive therapy (Tab. 2).

At the ICU, due to agitation, analgosedation with intravenous infusion of dexmedetomidine was introduced. The applied management strategies included passive oxygen therapy through a facial mask, balanced fluid therapy, including continuous intravenous infusion of 10% glucose solution, administration of medicines reducing ammonia concentrations (sodium benzoate and sodium phenylacetate), arginine and infusion of 15% mannitol to prevent cerebral oedema. The gastrointestinal tract was decontaminated with rifaximin.

Parenteral nutrition was introduced, as well as enteral nutrition with considerably reduced protein input (< 5

citrate and ultrafiltration of 50-100 ml/h, according to the fluid balance. After 5 days the renal replacement therapy

Table 1. Classification of hyperammonemia [2]

Tabela 1. Klasyfikacja hiperamonemii [2]

Hyperammonaemia			
primary	secondary	congenital	acquired
Deficiency of one enzyme in the urea cycle	Deficiency of enzymes or mediators of metabolic pathways other than the urea cycle, associated with transformation or distribution of ammonia	Genetic defect resulting in enzyme deficiency in metabolic pathways associated with ammonia	Other causes
Type 2 (the most frequent) - ornithine transcarbamoylase deficiency	Organic acidemias - disturbed metabolism of branched-chain amino acids (propionic, methylmalonic and isovaleric acidemia)	Urea cycle enzyme defects (primary hyperammonaemias)	Liver insufficiency (toxic, alcohol-induced, post-inflammatory, ischaemic end other)
	Liver damage	Hyperinsulinism-hyperammonaemia syndrome	Drug-induced (e.g. sodium valproate)
		Organic acidemias (secondary hyperammonaemias)	Growth of gastrointestinal bacterial flora

g/d), and high energy value (2500-3000 kcal). After the introduction of the treatment, the patient's condition briefly improved, and no neurological deficits were observed. The ammonia concentrations oscillated near the upper limit of normal. Between days 3 and 4 of hospitalisation, the patient's condition rapidly deteriorated, including loss of consciousness, weakened tendon reflexes and defence reflexes in the pharynx, and tachypnoea of up to 25 breaths per minute.

Table 2. APACHE II (Acute Physiology and Chronic Health Evaluation II), SOFA (Sequential Organ Failure Assessment)

Tabela 2. Skale APACHE II (Acute Physiology and Chronic Health Evaluation II) i SOFA (Sequential Organ Failure Assessment)

Prognostic scale	No. of points	Estimated mortality (%)
APACHE II	15	22
SOFA	5	<33

A thoracic x-ray image presented the parenchymal densities in the lungs, while a computed tomography of the head excluded cerebral oedema. Laboratory tests showed abnormal ammonia concentrations of 800 µg/dl and CRP concentrations, increased by a factor of 10 compared to the values on admission (88.9 mg/dl; normal range: < 5 mg/dl) with normal procalcitonin concentration (PCT; normal range: < 0.5 ng/l). The patient was diagnosed with nosocomial pneumonia complicating a hyperammonaemic crisis. He underwent orotracheal intubation, received analgesia (propofol, pentanyl) and adaptive support ventilation, with 30% oxygen in the inspired mixture. Broad spectrum antibiotic therapy (ampicillin and sulbactam), and continuous veno-venous haemodiafiltration (CVVHDF) were introduced, together with anticoagulation with

cycle and sedation were discontinued, and the patient was extubated. The neurological examination did not reveal any abnormalities. Ammonia concentration was reduced to the normal range, inflammatory markers were decreased, and inflammatory lesions in the lungs regressed in the imaging tests. An oral diet developed by a dietician was introduced, the patient received instructions regarding lifestyle, and in a generally good condition was discharged home on day 20 of hospitalisation.

Discussion

Consciousness disorders are one of the most frequent symptoms in patients admitted to ICUs. It is estimated that up to 80% of patients in these units demonstrate different types of consciousness disorders [4]. Higher mortality and longer hospitalisation are reported in this group, compared to patients without consciousness impairment [5]. The most frequent causes of consciousness disorders include: CNS impairment (e.g. haematomas, strokes, cerebral oedema, neuroinfections), water-electrolyte imbalance and metabolic imbalance (e.g. dehydration, metabolic acidosis, hypoglycaemia, hyponatraemia, hypernatraemia, uraemia, hyperammonaemia), intoxication (with medications, e.g. hypnotic agents, opioids, antidepressants, carbon dioxide, alcohol, narcotic drugs), sepsis, various types of shock, severe anaemia, alcohol withdrawal syndromes and other. Diagnostics of consciousness impairment includes basic laboratory tests (peripheral blood count, electrolytes, CRP, PCT, arterial blood gasometry, aminotransferases, bilirubin, urea, creatinine, general urinalysis), and basic toxicological tests. The most important imaging studies

include computed tomography of the head, which helps to eliminate most abnormalities in the CNS. In the case of suspected neuroinfection, the cerebrospinal fluid is also assessed [4].

Depending on the results of these tests, accurate diagnosis can be established, and proper management may be introduced. Ammonia concentration is not a routine test, and it is unavailable in most Polish hospitals. In the presented case it was difficult to establish the cause of severe consciousness impairment, as all the principal reasons were excluded in additional studies. Only the family history allowed the selection of the right diagnostic procedures.

Type 2 hyperammonaemia is the most common primary hyperammonaemia in the world. It is inherited recessively. The gene responsible for the disease is located on the X chromosome, so the disorder is usually observed in males. It is estimated to affect 1-9 people per 100,000 [2]. The disease often manifests already in infancy, in the form of lower energy, irritation, reduced reaction to stimuli, reluctance to eat, difficulty with sucking, and vomiting. Sometimes convulsions and ataxia are observed in children. Delayed diagnosis leads to cerebral oedema and death due to herniation of the deep cerebral structures in the natural holes in the skull, resulting in arrested circulation [2]. As expression of the gene coding ornithine transcarbamoylase may vary, in some patients the first symptoms of the disease may occur later in life, but typically before 40 years of age. Their onset is often prompted by fasting, excessive physical effort, severe infection, or following a high-protein diet for a long time (sportsmen).

The treatment of the disease consists in preventing hyperammonaemia and providing alternative ways of excreting ammonia from the organism. A low-protein diet is recommended. Energy value (calories) in the diet is obtained through the supply of sugar and fat; essential amino acids are supplemented (especially arginine, participating in the urea cycle). Apart from dietary restrictions, medications accelerating excretion of ammonia from the organism are used (sodium phenylbutyrate, phenylacetate and benzoate). In the case of the hyperammonaemic crisis observed in the presented patient, probably due to pneumonia, a protein-free diet is used; energy is obtained from continuous administration of glucose and lipids, and gastrointestinal decontamination with rifaximin or neomycin is conducted, to eliminate intestinal bacteria producing large quantities of ammonia. Arginine preparations and medicines accelerating ammonia elimination are also infused intravenously [2]. The fastest and most efficient methods of eliminating ammonia from the blood are renal replacement therapies [7]. Due to the limited number of described cases of

hyperammonaemia, there is no consensus as to when the renal replacement therapy should be introduced. It seems that it should be considered in patients with severe hyperammonaemia (ammonia concentration exceeded by over a factor of three); in patients with the symptoms of encephalopathy resistant to treatment or persisting for many hours, and in patients with cerebral oedema [7]. Intermittent haemodialysis are the treatment of choice, but in patients in very serious condition, with cardiovascular insufficiency or cerebral oedema it appears that continuous veno-venous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF) should be performed, avoiding rapid fluid shifts. The duration of therapy is not established. The key aspect is the resolution of consciousness disorders, not only the reduction of blood ammonia concentration. Together with renal replacement therapy, the conservative treatment described before should always be applied [7].

Prognosis in type 2 hyperammonaemia is serious. It may be improved by prompt diagnosis and following recommendations regarding nutrition and pharmacotherapy. In the case of problems with the management of the disease or its severe recurrences, therapeutic options include orthotopic liver transplantation [2].

Conclusions

Hyperammonaemia is a very rare and difficult to diagnose cause of severe consciousness disorders. Determination of ammonia concentration should be obligatory in all patients with consciousness impaired due to unspecified causes, especially when the results of basic laboratory tests are normal. Patients with suspected hyperammonaemia should be treated in general hospitals with access to a full-profile laboratory. A prompt and proper therapy allows the avoidance of serious neurological complications and the death of patients with this disease.

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Ormond's Disease – a case report

Choroba Ormonda – opis przypadku

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Abstract. Retroperitoneal fibrosis, also called Ormond's Disease, is a chronic inflammatory process, characterized by the development of combined fibroid and inflammatory tissue in the retroperitoneal space. Typically, lesions are located in the retroperitoneal space of the abdominal arteries, iliac arteries, ureters, and sometimes the duodenum or kidneys. In the majority of cases the disease is primary (idiopathic retroperitoneal fibrosis – IRPF), rarely is secondary to drugs, malignancy, radiotherapy or infections. RPF is an uncommon condition, mostly affecting people in their 50s, and prevalent in males. Diagnosis can be made on the basis of clinical manifestation and results of the medical imaging. If the clinical presentation is unusual or the location of fibrosis is untypical, the biopsy of the fibroid should be made to confirm the recognition. Currently, there is no recommendation for the treatment of the RPF, with therapy schemes largely based on the experience of specialized centres and rare publications. The article presents the case of 62-year-old female hospitalized in the Department of Internal Diseases and Rheumatology due to inflammation of the peripheral joints, who was diagnosed as RPF during conventional diagnostics. The patient was successfully treated with an immunosuppressive therapy.

Key words: retroperitoneal fibrosis, Ormond's disease, fibroid, immunosuppression

Streszczenie. Włóknienie zaotrzewnowe (RPF), zwane chorobą Ormonda, jest przewlekłym procesem zapalnym, charakteryzującym się tworzeniem włóknisto-zapalnej masy tkankowej w przestrzeni zaotrzewnowej. Zmiany typowo zajmują okolice przestrzeni zaotrzewnowej aorty brzusznej, tętnic biodrowych oraz moczowodów, niekiedy dwunastnicy czy nerek. W większości przypadków choroba ma charakter pierwotny (idiopatyczne włóknienie zaotrzewnowe [IRPF]), rzadziej wtórny (polekowy, w przebiegu chorób nowotworowych, radioterapii, zakażeń). RPF należy do chorób rzadkich, najczęściej dotyczy osób około 5. dekady życia, częściej chorują mężczyźni. Rozpoznanie ustala się na podstawie obrazu klinicznego oraz wyników badań obrazowych. W przypadkach o nietypowym przebiegu lub umiejscowieniu zmian wykonuje się biopsję masy włóknistej w celu potwierdzenia histopatologicznego. Aktualnie nie istnieją wytyczne leczenia RPF, schemat postępowania terapeutycznego opiera się na własnych doświadczeniach ośrodków specjalistycznych oraz nielicznych publikacjach. W artykule opisano przypadek 62-letniej kobiety hospitalizowanej w Klinice Chorób Wewnętrznych i Reumatologii z powodu zapalenia stawów obwodowych, u której w toku diagnostyki rozpoznano RPF. Zastosowano leczenie immunosupresyjne, z dobrym efektem.

Słowa kluczowe: włóknienie pozaotrzewnowe, choroba Ormonda, masa włóknista, immunosupresja

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Background

Retroperitoneal fibrosis (RPF), also referred to as Ormond's disease is a chronic inflammatory process characterised by deposition of fibrous inflammatory tissue in the retroperitoneal space [1]. The lesions typically form in the retroperitoneal space around the abdominal aorta, iliac arteries and ureters, sometimes

also around the duodenum or kidneys [1, 2]. In most cases the disease is idiopathic (idiopathic retroperitoneal fibrosis - IRPF), and in rare cases it is secondary to drugs, neoplastic diseases, radiotherapy or infections [1, 3]. Retroperitoneal fibrosis is a rare disease, found in 1.38 per 100,000 people; however, due to its often asymptomatic character, this frequency may be underestimated [3]. RPF usually affects patients between

50 and 60 years old, and it is more often diagnosed in males [3]. Presently, no guidelines for the treatment of RPF are available. Therapeutic management is based on the experience of specialist centres, and that of a few publications [4, 5].

A case report

A 62-year-old patient was admitted to the Department of Internal Diseases and Rheumatology of the Military Institute of Medicine in June 2017 (medical history no.: 2017/46637), due to polyarticular pain with a slight oedema of the metacarpophalangeal joints (MCP II, III of the right hand). The patient had a history of arterial hypertension and spinal discopathy of the L5/S1 section. She received the following chronic treatments: pantoprazole (20 mg/d), prednisone (2.5 mg/d), tribemutine (100 mg/d), amlodipine (5 mg/d), ramipril (5 mg/d), indapamide SR (1.5 mg/d), and metoprolol (75 mg/d). In March 2017, the patient was diagnosed with undifferentiated arthritis, and started therapy with prednisone (2.5 mg/d), methotrexate (15 mg/week orally), and folic acid (15 mg/week). After approximately 1.5 months of treatment, the patient developed a rash on her hands, so methotrexate was discontinued, and 2 g/day of sulfasalazine was introduced. Prednisone was continued, resulting in alleviation of the articular pain. The physical examination at the admission revealed an itchy skin rash over the whole body, and a small oedema of the MCP II and III joints of the right hand. The laboratory tests demonstrated: ESR of 34 mm/h, normal CRP, absence of rheumatoid factor and anti-cyclic citrullinated peptide antibodies, elevated creatinine concentration (1.1 mg/dl), elevated uric acid concentration (6.1 mg/dl), and low concentration of vitamin D³ (22 ng/ml). X-ray examinations of the hand and feet joints did not demonstrate destructive lesions in the bones, and ambulatory thoracic x-ray did not demonstrate any abnormalities. An abdominal ultrasound examination revealed a solid, hypoechoic tissue in the retroperitoneal space, surrounding a 60-70 mm long section of the aorta and the inferior vena cava, well-defined, without visible vasculature; the image suggested retroperitoneal fibrosis. Diagnostic tests included computed tomography (CT) of the abdominal cavity, which demonstrated an abnormal soft tissue infiltration in the retroperitoneal space, paraspinally, along the midline, measuring 67 × 40 × 94 mm. The infiltration covered the aorta, renal arteries, and, partially, the inferior vena cava and the left renal vein. The upper pole of the infiltration was visible at the L1/L2 intervertebral space, the lower one reached the body of L4. A few enlarged inguinal lymph nodes of up to 16 × 11 mm were also described (Fig. 1). After the analysis of the



Figure 1. Computed tomography of abdomen before treatment
Rycina 1. Tomografia komputerowa jamy brzusznej przed leczeniem

history and additional test results, the diagnosis of retroperitoneal fibrosis (Ormond's disease) was established. The prednisone dose was increased from 2.5 mg to 60 mg/day, with instructions to reduce the dose gradually. The patient was qualified for treatment with cyclophosphamide infusions; initially 6 infusions of 1 g were planned. Due to the potentially drug-induced character of the skin rash, sulfasalazine was discontinued.

During the treatment a gradual deterioration in renal parameters was observed: creatinine concentration increased (maximum of 1.5 g/dl), and eGFR decreased to 37 ml/min/1.73 m², which prompted discontinuation of angiotensin-converting enzyme inhibitor. A total of 6 infusions of cyclophosphamide with a 600 mg mesna were administered: the first one on 29/06/2017 (1 g *i.v.*), the second one on 01/08/2017 (750 mg), the third one on 07/09/2017 (750 mg), the fourth one on 09/10/2017 (750 mg), the fifth one on 14/11/2017 (750 mg *i.v.*), and the sixth one on 29/01/2018 (750 mg, with administration delayed due to sinusitis). The cyclophosphamide doses were adjusted to the patient's age and degree of renal sufficiency. No adverse effects of the treatment were observed. In January 2017 methotrexate was re-introduced, but since it was followed by a rash outbreak, the medicine was discontinued after a few days. During hospitalisation in March 2018, a control abdominal CT was performed, revealing a persistent soft tissue, ill-defined infiltration area, demonstrating homogeneous contrast enhancement, located



Figure 2. Computed tomography of abdomen after treatment
Rycina 2. Tomografia komputerowa jamy brzusznej po leczeniu

retroperitoneally around the aorta, from the level of the renal arteries to the aortic bifurcation.

A visible reduction in lesions compared to the previous test was observed – the infiltration was 26 × 54 mm, a change from the previous 39 × 68 mm. The infiltration area covered the renal arteries (with preserved lumen), left renal vein (minimally narrowed), and inferior vena cava (suspected narrowing). The infiltration did not cover the common iliac arteries or ureters (Fig. 2). Moreover, quite numerous fibroses were found at the base of the lungs, and an unspecified nodule or post-inflammatory densities of 3 mm were found in segment 8 of the right lung. Due to regression of lesions in the abdominal CT, observed reduction of ESR (23 mm/h), creatinine (1.1 mg/dl) and eGFR (53 ml/min/1.73 m²), maintenance treatment with mycophenolate mofetil was introduced at an initial dose of 1 g/day, with instructions to increase the dose to 2 g/day after two weeks. The patient is under the constant care of the Rheumatology Clinic of the Military Institute of Medicine. Another hospitalisation at the Department of Rheumatology is planned in 6 months, for a follow-up and potential treatment modification.

Discussion

Retroperitoneal fibrosis probably develops in the course of an immunological reaction. This hypothesis is supported by the frequent coexistence of other autoimmune diseases, such as glomerular nephritis,

rheumatoid arthritis, nodular arteritis, autoimmune thyroiditis, and primary biliary cholangitis [1, 6, 7]. In recent publications RPF is often considered one of the manifestations of IgG4-dependent diseases [1, 8]. In most cases RPF initially is asymptomatic, or presents only non-specific symptoms (fever, reduced body weight, and weakness). In more advanced stages, the symptoms include abdominal pain, back pain in the lumbar region, oedema of the lower limbs, oedema of the scrotum, and, less often, temporary claudication, intestinal ischaemia and signs of intestinal obstruction [1, 4]. In laboratory tests the inflammatory parameters are elevated (ESR and CRP), sometimes anaemia and leukocytosis is observed. If ureters are compressed, the parameters of nitrogen retention are elevated, and proteinuria and haematuria may occur. In addition, the following are frequently found: rheumatoid factor (RF), anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-thyroid peroxidase antibodies (anti-TPO) [1, 4], and HLA-DRB1-03 antigen; these factors are often associated with diseases of autoaggression [1, 6, 7]. The diagnosis is based on the results of imaging tests. Usually, the first study is abdominal ultrasound (US), revealing a hypoechogenic or isoechogenic mass involving the organs in the retroperitoneal space, and in the case of compressed ureter, signs of hydronephrosis are observed [2]. However, the key examinations in the diagnostics of retroperitoneal fibrosis are computed tomography (CT) and magnetic resonance imaging (MRI), which allow the periaortic fibrous inflammatory mass to be presented. Fibrosis is typically located in the preaortic area, and laterally from the aorta, without causing its displacement [2]. The fibrous mass frequently involves the ureters and the inferior vena cava, rarely infiltrating other organs in the retroperitoneal space, such as duodenum and kidneys [2]. Other abnormalities that can be visualised in CT and MRI include hydronephrosis, deep vein thrombosis and involvement of the renal vessels [2]. 18F-FDG positron emission tomography (PET) is another useful test that helps to detect the foci of infection or neoplasm, and conduct a metabolic assessment of the fibrous mass, used to determine the disease activity [2]. Usually the diagnosis is based on the clinical presentation and results of imaging tests. If during the course of the disease the location of the lesions is atypical, the fibrous mass is biopsied for histopathological confirmation [9]. Currently, there are no guidelines regarding the treatment of RPF. Therapeutic management is based on the experience of specialist centres, and a few publications [4, 5]. Pharmacological treatment is based on corticosteroids, usually prednisone at an initial dose of 1 mg/kg b.w./day, gradually reduced, in some cases following methylprednisolone infusions. In order to accelerate the dose reduction of prednisone (to

limit the risk of adverse events), tamoxifen is introduced [4, 13], or immunosuppressants, such as azathioprine [4], cyclophosphamide [4, 10], methotrexate [4, 11, 12] and mycophenolate mofetil [4, 14]. In the case of ureter stenosis or hydronephrosis, surgical treatment is recommended (JJ stenting of the ureters or nephrostomy) [15]. A good response to treatment means that abdominal pain subsides, CRP and ESR decrease, eGFR normalises, and a CT/MRI examination reveals regression or arrested growth of the fibrous inflammatory mass. Patients must remain under constant supervision due to the risk of disease recurrence. Periodic assessment of the clinical status and inflammatory parameters, as well as monitoring of the renal function, are recommended. In addition, control imaging tests are performed, primarily CT and MRI, less often PET [4, 16]. In the presented case the patient's age and sex were atypical. Moreover, the first symptoms reported were pain and oedema of the joints (non-specific for RPF), which led to the diagnosis of unclassified arthritis. Only when diagnostic abdominal US and CT were introduced was the diagnosis changed to RPF. The diagnosis was established at an early stage of the disease, and implementation of treatment prevented further progression. Due to the aggressive pharmacological therapy (6 cyclophosphamide infusions) not only was the disease inhibited, and the fibrous mass in the retroperitoneal space reduced, as shown in the follow-up abdominal CT scan (Figs. 1–2), but surgical treatment was not required. Presently, maintenance therapy with mycophenolate mofetil at 2 g/day is administered together with the glucocorticosteroid treatment. It should be emphasised that, despite the effectiveness of the previous therapy, the patient requires further follow-up and the constant care of the Rheumatology Clinic.

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Cardiac tamponade – a rare complication of acupuncture

Tamponada serca – rzadkie powikłanie zabiegu akupunktury

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Abstract. Aesthetic and natural medicine has recently been growing in popularity in Poland. Although severe complications are rare, they can be fatal. We present the case of a 44-year-old female with cardiac tamponade caused by damage to the right ventricle with an acupuncture needle. She underwent acupuncture and mesotherapy with her own plasma a few hours before collapse, which caused admission to the hospital. Due to the rapidly developing shock the patient was admitted to the intensive care unit. A cardiac tamponade was diagnosed and the patient was transferred to the cardiosurgical operation theatre. Sternotomy was performed and the tamponade was drained. The right ventricle perforation was sutured. The patient condition improved and she was discharged home in good condition after a 12-day treatment.

Key words: acupuncture, complication, cardiac tamponade, shock

Streszczenie. Zabiegi medycyny estetycznej i naturalnej cieszą się w Polsce coraz większą popularnością. Poważne powikłania tych zabiegów zdarzają się rzadko, ale mogą zakończyć się zgonem. W artykule opisano przypadek 44-letniej kobiety z tamponadą serca spowodowaną uszkodzeniem prawej komory serca igłą do akupunktury. Pacjentka poddała się zabiegom akupunktury oraz mezoterapii osoczem własnym na kilka godzin przed zaszabnięciem, które było przyczyną przyjęcia do szpitala. Ze względu na objawy rozwijającego się wstrząsu została przyjęta na OIT, gdzie rozpoznano tamponadę serca i przekazano pacjentkę na blok operacyjny kardiologii. Wykonano sternotomię, odbarczono worek osierdziowy, a następnie zszyto perforację prawej komory. Po zabiegu stan pacjentki uległ poprawie. Po 12 dniach leczenia pacjentka została wypisana do domu w stanie dobrym.

Słowa kluczowe: akupunktura, powikłanie, tamponada serca, wstrząs

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Background

Complementary or natural medicine is very popular in Poland. Acupuncture is a therapy originating from traditional Chinese medicine. Despite numerous controversies regarding its effectiveness, the popularity of acupuncture in Europe is increasing. It is estimated that 200 million acupuncture procedures are performed globally every year [1]. However, even apparently safe and harmless procedures are associated with a risk of fatal complications.

Cardiac tamponade, following tension pneumothorax and pulmonary embolism, is the third most common cause of obstructive shock. The pericardial fluid exerts

pressure on the right ventricle and impairs right ventricular filling. It results in reduced end-diastolic volume, decreased cardiac output, and, as a consequence, diminished supply of oxygen to cells, which leads to shock. Untreated cardiac tamponade is often fatal. Its symptoms (hypotension, muffled heart sounds, and excessive filling of the jugular veins) create a classic Beck's triad [2]. They are accompanied by tachycardia and paradoxical pulse, i.e. reduced pulse amplitude during inspiration. These symptoms do not occur in every case, which significantly impairs the diagnosis of cardiac tamponade, especially when no data in the patient's history indicate this particular disease. The most frequent causes of cardiac tamponade include:

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penetrating thoracic injury, dissecting aortic aneurysm, cardiac muscle rupture following myocardial infarction, collection of effusion in inflammatory and neoplastic diseases, and iatrogenic causes (endovascular procedures, central catheterisation, and complications following cardiocirculatory procedures) [2]. Transthoracic ultrasound is the gold standard in the diagnostics of this condition, as it confirms within seconds the presence of pericardial fluid, and allows one to assess the symptoms of pressure on the right cardiac ventricle [3]. If immediate cardiocirculatory intervention is not possible, the treatment of choice involves pericardiocentesis, i.e. puncture of the pericardium, and aspiration of the fluid. It reduces temporarily the pressure in the pericardium, and improves the haemodynamic conditions [2, 3].

Case report

A forty-four year-old female was admitted to the Hospital Emergency Department (HED) after a fainting episode. The patient reported chest pain radiating to both arms. She denied any chronic diseases. On the day of the episode the patient received aesthetic procedures: acupuncture and autologous plasma mesotherapy of the neck and chest. The patient's general condition at admission was severe. She presented with impaired consciousness, dyspnoea, tachycardia of 120/min., and hypotension of 80/50 mm Hg. No other abnormalities were found in the physical examination. The HED physician noticed an acupuncture needle in the thoracic wall in the right parasternal area, and removed it. The laboratory tests performed at the HED revealed: lactic acidosis with pH of 7.2 and base deficit of 10 mmol/l, lactate concentration of 10.9 mmol/l (N 0.9 – 1.7 mmol/l), D-dimer concentration of 1055 µg/l (N <500 µg/l), high-sensitivity troponin concentration of 27.3 µg/ml (N <15.6 µg/ml). A radiological examination of the chest did not demonstrate any pathological signs. The treatment included oxygen supplementation through a face mask, and, due to hypotonia, infusion of adrenalin. As the consciousness impairment, as well as the cardiovascular and respiratory insufficiency were increasing, the patient was admitted to the Intensive care Unit (ICU) with a diagnosis of anaphylactic shock induced by the plasma used during the mesotherapy.

At the admission to the ICU the patient was in a very severe general condition, lucid, agitated, and confused temporally and spatially. The mean arterial pressure was 40/30 mm Hg. The skin was pale, cool and sweaty. The patient underwent orotracheal intubation, and received pressure-controlled synchronised intermittent mandatory ventilation (P-SIMV) with 30% oxygen in the inspired mixture, and continuous positive end-expiratory pressure of 8 cm H₂O. To support the cardiovascular system,

Table. Results of laboratory tests performed on admission to the intensive care unit

Tabela. Wyniki wybranych badań laboratoryjnych wykonanych przy przyjęciu na oddział intensywnej terapii

Test	Normal range	Patient's results
Aspartate aminotransferase (AST)	5-31 U/l	245 U/l
Alanine aminotransferase (ALT)	<32 j/l	281 U/l
Total bilirubin	0.3-1.2 mg/dl	0.55 mg/dl
Activated partial thromboplastin time (APTT)	25.4-36.9 sec.	43.1 sec.
Prothrombin time (PT, INR)	0.9-1.2 sec.	1.65 sec.
D-dimer	<500 µg/l	6834 µg/l
Fibrinogen	200-393 mg/dl	100 mg/dl
Creatinine	0.5-0.9 mg/dl	1.37 mg/dl
Leukocytes	4.5-10 thousand/µl	22.35 thousand/µl
Haemoglobin	12-16 g/dl	10.3 g/dl
Platelets	150-400 thousand/µl	216 thousand/µl
pH	7.35-7.45	7.216
pO ₂	72-107 mm Hg	165 mm Hg
pCO ₂	35-45 mm Hg	32 mm Hg
Base deficit (BE)	+1.5 -- -1.5 mmol/l	11.2 mmol/l
Lactates	0.9-1.7 mmol/l	12.3 mmol/l
Troponin I	<15.6 µg/ml	216.9 µg/ml
Creatine kinase (CK)	<170 j/l	90 U/l
Creatine kinase - weight (CK-MB)	<25 j/l	59 U/l
Myoglobin	19-51 ng/ml	67 ng/ml
C-reactive protein	<5 mg/l	2.5 mg/l
Sodium	135-145 mmol/l	138 mmol/l
Potassium	3.5-5 mmol/l	3.19 mmol/l

increasing doses of noradrenalin (up to 0.38 µg/kg b.w./min) and adrenalin (up to 0.17 µg/kg b.w./min) were administered. The patient also received analgesia with morphine and midazolam infusions, steroids and antihistamines. The laboratory test results at the admission are presented in the table. The thoracic X-ray of the patient, interpreted as normal, is presented in Figure 1.

As the applied treatment did not result in an improvement, extended diagnostics were performed. Thoracic computed tomography examination was performed to exclude pulmonary embolism. The study revealed a large quantity of pericardial fluid (Figure 2). No embolic material was found in the pulmonary arteries, and no other pathological lesions were observed in the chest.

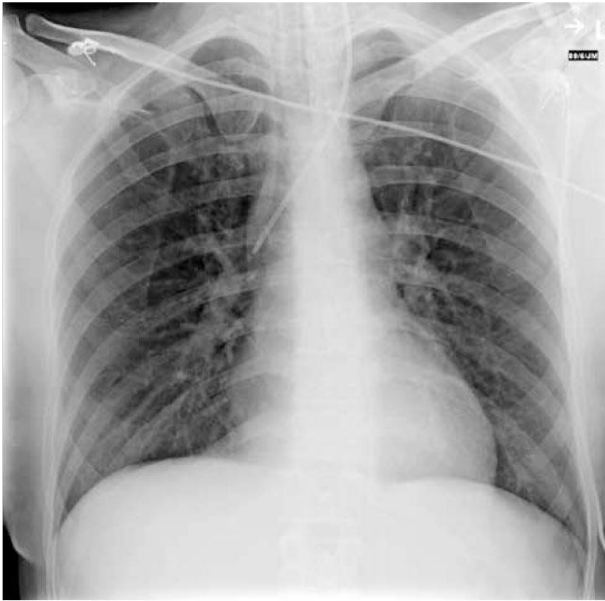


Figure 1. Patient's chest x-ray interpreted as normal
Rycina 1. Wynik RTG klatki piersiowej pacjentki – opisany jako prawidłowy



Figure 2. Chest CT scan showing fluid in pericardium
Rycina 2. Wynik badania tomografii komputerowej klatki piersiowej z widocznym płynem w worku osierdziowym

An urgent ultrasound examination of the heart confirmed tamponade; a large quantity of pericardial fluid and symptoms of pressure to the right ventricle were revealed.

The patient was immediately transferred to the operation theatre of the Department of Cardiosurgery. Subxiphoid pericardiectomy was performed, and a profuse outflow of fresh blood was observed. The decision to perform a sternotomy and mediastinal revision was made. After decompression of the tamponade the cardiovascular system quickly stabilised, allowing the reduction in the doses of catecholamines. Cardiac surgeons located a 1 cm-long hole in the right ventricle of the heart, and sutured it. The total blood loss during the procedure was 2,000 ml. Afterwards, the patient was transferred to the ICU. On the first day after the procedure the patient's condition quickly improved: acidosis disappeared, and lactate concentrations normalised. Laboratory markers of multiorgan failure subsided. Doses of catecholamines were gradually reduced, and eventually discontinued. After sedation ceased, the patient regained consciousness, was disconnected from the ventilator, and extubated. From that moment onwards, she breathed spontaneously. In the operating theatre and within 48 hours following the procedure a total of 5 units of blood cell concentrate and 10 units of fresh frozen plasma were transfused. A follow-up cardiac ECHO conducted on the third day of the treatment did not reveal any abnormalities. Blood, urine and tracheal secretion cultures were sterile. The

patient was transferred from the ICU to the cardiosurgical unit. The postoperative period was uncomplicated. On day 6 the chest drains were removed, and on day 12 the patient was discharged in a good condition.

Discussion

The increasing popularity of natural and aesthetic medicine in Poland results in a growing number of associated complications. The World Health Organisation (WHO) monitors the safety of acupuncture and collects data about adverse events [1]. They are observed rarely, in approximately 6% of patients undergoing this type of procedures, and usually they do not require medical intervention. According to Zhang et al., in 2010 the incidence of serious complications of acupuncture, defined as damage to internal organs or the need for hospitalisation, was 0.024% [4]. Numerous cases of pneumothorax caused by this procedure were reported across the world. In 2011, 26 cases of cardiac tamponade due to acupuncture were reported, of which 14 were fatal [5]. The health and life-threatening complications of acupuncture include: pneumothorax, damage to the right atrium of the heart, inferior vena cava, spinal cord, intestine, liver, gallbladder or eyeball, peritonitis, laryngeal nerve paralysis and subarachnoid or extradural haemorrhage with compression of the spinal cord [4]. Complications of acupuncture are not described in the Polish literature.

In the presented case the initial diagnosis was anaphylactic shock due to the plasma used in

mesotherapy; however, as the patient's own plasma was used during the procedure, this diagnosis was not very convincing. Septic shock was also taken into account, but inflammatory markers, such as leukocyte count and concentrations of C-reactive protein and calcitonin were normal, and the physical examination and additional tests did not reveal any signs of infection. Due to an increased concentration of D-dimers, and lack of response to a standard therapy of anaphylactic shock, pulmonary embolism was excluded, and a diagnostic thoracic CT was performed. Unexpectedly, the study revealed a large quantity of pericardial fluid. This diagnosis was surprising, as the physical examination did not demonstrate any typical symptoms of cardiac tamponade. An ultrasound examination would be helpful in differential diagnosis of a shock, but it was not immediately available [6]. Using high doses of catecholamines elevated the arterial pressure, and provided the time to take the patient to the computed tomography laboratory. Further conversation with the people performing mesotherapy revealed that the plasma was injected only in the neck area, so this procedure could not have been the cause of the heart injury. Acupuncture needles, however, were placed in the skin of the chest on both sides of the sternum. The patient left the aesthetic medicine office with one of them still inserted in the chest skin. The needle moved deeper, punctured the chest wall, and tore the right ventricle. It was removed only in the emergency department.

Conclusions

Pericardial tamponade is a very rare, but life-threatening complication of acupuncture, and it should be taken into consideration in each case of hypotonia in a patient who underwent such procedure. Ultrasound examination is the gold standard in the diagnostics of cardiac tamponade, and it should be available in every emergency department [6]. Its use considerably facilitates differentiation of the causes of the life-threatening shock [7]. A prompt diagnosis of cardiac tamponade allows the prevention of cardiac arrest, and, as a consequence, death.

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Use of TIPSTIM to strengthen brain plasticity processes and improve treatment effectiveness – a case report

Zastosowanie aparatu TIPSTIM w celu wzmocnienia procesów plastyczności mózgu i poprawy efektywności leczenia – opis przypadku

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Abstract. Sensory-motor disorders of the upper limb which accompany hemiparesis lead to difficulties in performing precise operations, and disturb self-maintenance and fine motor or manipulating skills. Such disorders can arise due to damage to the central nervous system caused by subarachnoid haemorrhages and as a result of complications during its treatment. The article presents the case of a 39-year-old female with pyramidal, left-sided hemiparesis resulting from the intracerebral haemorrhage from a rupture of the cerebral aneurysms of the anterior communicating artery. Neurosurgical treatment with embolization resulted in secondary disease – ischemic stroke in the callosal commissure. The article focuses on a comprehensive rehabilitation of the patient which took place in the Rehabilitation Hospital with the Sub-Department of Neurological Rehabilitation of the Military Medical Institute. The rehabilitation process was supported by the use of the percutaneous stimulation of sensory endings (rSS) method, using a TIPSTIM device in order to strengthen the brain plasticity processes and improve treatment effectiveness.

Key words: subarachnoid haemorrhage, secondary ischemic stroke, pyramidal hemiparesis, brain plasticity, comprehensive rehabilitation, rSS, TIPSTIM

Streszczenie. Zaburzenia czuciowo-ruchowe kończyny górnej towarzyszące niedowładom połowicznym powodują utrudnienia w czynnościach precyzyjnych, zaburzają procesy samoobsługi oraz umiejętność manipulacji i motorykę małą. Mogą rozwinąć się wskutek uszkodzeń OUN, m.in. jako następstwa krwotoków śródmózgowych i powikłań ich leczenia. W artykule przedstawiono opis przypadku 39-letniej kobiety z niedowładem piramidowym lewostronnym w następstwie krwotoku śródmózgowego z pękniętego tętniaka tętnicy łączącej przedniej. Leczenie neurochirurgiczne metodą embolizacji było powikłane wtórnym udarem niedokrwiennym spoidła wielkiego. W artykule opisano kompleksowe usprawnianie pacjentki w Klinice Rehabilitacji z Pododdziałem Rehabilitacji Neurologicznej WIM. W procesie rehabilitacji kompleksowej zastosowano dodatkowo metodę przezskórnej stymulacji zakończeń czuciowych (rSS) z wykorzystaniem aparatu TIPSTIM w celu wzmocnienia procesów plastyczności mózgu i poprawy efektywności leczenia.

Słowa kluczowe: krwotok śródmózgowy, wtórny udar niedokrwienny mózgu, niedowład połowiczny piramidowy, rehabilitacja kompleksowa, plastyczność mózgu, rSS, TIPSTIM

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Background

A well-conducted and effective neurorehabilitation is a process that uses the plasticity of the brain, enabling regeneration and reconstruction of the damaged neurons, as well as the learning and memorisation processes. The success of the therapy depends on the intensity and quantity of the stimuli provided. In order to enhance and perpetuate the neuroplasticity processes in comprehensive neurorehabilitation, not only kinesiotherapy but also stimulation by physical therapy is used [1]. Studies involving healthy volunteers demonstrate that a few hours of sensory stimulation changes the cortical maps, and the level of excitability of the cerebral cortex in the sites corresponding to the stimulated areas [2]. In this type of stimulation, the goal is to achieve the parameters and dosing regimens that induce synaptic plasticity using two contrary processes: synaptic long-term potentiation (LTP), and long-term depression (LTD). LTP consists in modification of the synaptic connection, and a long-term potentiation of the signal transmission on the level of the synapses. The effectiveness of signal transmission increases, and the information sent from the presynaptic cell induces a stronger reaction in the postsynaptic cell. This mechanism, discovered initially in the hippocampus, occurs in virtually all areas of the brain, and is responsible for short-term memory. LTD is necessary in order to induce and fix the long-term memory processes. IT consists in habituating and familiarising the synaptic connection with the stimulus, until it is completely blocked. Another strong stimulus that activates the auxiliary and intermediate interneurons breaks the block, or even causes the formation of new synaptic connections and dendritic branches. This phenomenon, which probably governs primarily the processes of learning motor tasks, was first discovered in the cerebellum, and then it was observed in the hippocampus and in the cerebral cortex. Triggering this process requires long-term low-frequency impulses. Only when structural changes occur, involving the formation of new synaptic connections with a higher number of receptors and synaptic vesicles, do we observe the process of learning and long-term memory. This is how neurons near the site of injury can adapt and take over the role of the damaged structures, creating new connections and new neural networks. Both processes, discovered and described in 2000 by Erick Kandel, enable the adaptation and modification of neurons near the site of injury, and their taking over the role of the damaged structures. The rSS method uses the ability to initiate the above neuroplasticity processes, observed in direct transcranial microstimulation involving electric and

magnetic stimulation. The studies by Kandel demonstrate that long-term neural stimulation with high-frequency current generates the processes that stimulate postsynaptic potentials, and modifies their size and character [3].

Case report

A 39-year-old female patient, without any other diseases, previously healthy, was admitted to the Department of Rehabilitation for rehabilitation due to the consequences of subarachnoid haemorrhage with intraventricular rupture. The patient was treated by embolization, complicated by a secondary ischaemic stroke in the callosal commissure. Four weeks before the patient was hospitalised because of this complication at the Department of Neurosurgery, where she was admitted urgently due to loss of consciousness, headache and 4 cm neck stiffness. Imaging tests demonstrated a ruptured aneurysm of the anterior communicating artery, associated with an intracerebral haemorrhage. The exact time of onset was unknown; the patient was last seen approximately 24 hours before the incident. Urgent diagnostics and treatment were applied, including cerebral arteriography and embolization of the aneurysm. In the post-operative period the patient demonstrated memory disorders, psychomotor retardation, and a follow-up CT scan revealed an ischaemic foci in the genu and trunk of the callosal commissure. She was diagnosed with pyramidal left-sided hemiparesis, predominantly affecting the upper limb, including reflex syndrome and ipsilateral facial paresis. Rehabilitation started at the Department of Neurosurgery of the Mazowiecki Brodnowski Hospital. On day 18 of hospitalisation, the patient was discharged in an improved condition.

On day 5 after the hospitalisation, a headache recurred, together with nausea and neck stiffness. The patient was examined at the Hospital Emergency Department, where no consciousness disorders or neurological abnormalities were observed. The head CT revealed status post endovascular embolization of the aneurysm of the anterior communicating artery. Compared to the previous test, the following were observed: a trace of partially haemolysed blood in the fissure near the genu of the callosal commissure, hypodense foci consistent with the previous location of ischaemic lesions, haemolysed haematoma near the frontal horn of the left lateral ventricle, and a slight dilation of the ventricular system in the area of parietal and frontal horns. The middle structures were not displaced, and ventricle III was not dilated. There were no indications for neurosurgical intervention. After

several hours of observation and resolution of symptoms, the patient was discharged with the recommendation of further follow-up and motor rehabilitation, as well as discontinuation of the previous anticoagulation treatment - Clexane 0.4 ml qd. No other anticoagulants were introduced.

The patient was admitted to the Department of Rehabilitation 4 weeks after the onset of symptoms. The physical examination did not demonstrate any abnormalities, the cardiac function was regular, approximately 78-80/min., blood pressure was normal - 110/80 mm Hg. The patient was lucid, auto- and allopsychologically oriented, verbally responsive, with retrograde amnesia regarding the events around the onset of the disease. She did not present signs of aphasia, and was able to form complex sentences, with preserved language function. The neurological examination revealed dysfunction of the upper and lower left limb, in the form of reduced muscle strength and a partial restriction of active movements. The muscle tension was slightly increased. The deep reflexes were brisk, symmetrical, and the Babinsky sign was negative. Impaired superficial sensation and proprioception were observed in the upper left limb - dysmetria of 2 cm in the finger-to-nose test. The psychological assessment did not reveal impaired abstract thinking, deficits in visual gnosis or in the ability to acquire new information and learn. The patient's mood was adequate, her appearance was normal, and she was motivated to continue rehabilitation. Attention fatigue was observed, as well as slight problems with visual field searching, reduced operational memory, and slightly weakened visual and motor coordination. In manipulation the patient revealed deficits in bilateral hand coordination with a preserved grasping function, but without a writing grip, and with a complete inability to write with the left hand. All these functions were preserved in the upper right limb. It was established in the interview that the patient was right-handed. The diagnosis was moderate pyramidal left-sided hemiparesis, without pain syndrome, predominantly affecting the upper limb, and with ipsilateral paresis of the facial muscles.

The rehabilitation included:

- kinesiotherapy – passive exercises, passive-active exercises, active exercises without load, active exercises with support, slow active exercises, balance exercises, learning and re-learning of gait, elements of PNF,
- logopaedic therapy – rehabilitation of active and passive speech,
- occupational therapy – improving manual skills, graphomotorics, eye-movement coordination, visual-motor coordination, bilateral hand coordination,
- psychological therapy,

- massage.

In addition, as one of the elements of comprehensive rehabilitation, repetitive sensory stimulation (rSS) was introduced with the use of TIPSTIM device. rSS uses the brain's neuroplasticity, affecting the processes of learning and rehabilitation, through repeated, adequate doses of sensory stimulation. Properly adjusted parameters of sensory receptor stimulation induce and facilitate the processes of reorganising the neural connections in the sensory cortex on the CNS, and result in improved sensorimotor behaviours [4].

Discussion

In the presented case of pyramidal left-sided syndrome resulting from intracerebral haemorrhage with secondary ischaemic stroke in the callosal commissure the main problem of the patient was impaired hand function, memory and associative disorders, and disturbed visual-motor coordination. The clinical symptoms depending on the site of injury due to the haemorrhage included reduced muscle strength and range of active voluntary movements, increased spasticity, and excessive deep reflexes. As a result of injury to the callosal commissure, the processes of integration of information from both hemispheres were disturbed. The treatment was started four weeks after the cerebral incident. A comprehensive rehabilitation was introduced: kinesiotherapy, massage, occupational therapy, neurologopaedic and neuropsychological treatment. In addition, the rSS method was used. The procedure was performed every day, for 4 weeks, 5 days a week, 45 minutes a day on the hand affected by paresis. During the procedure, the patient could conduct any activity that would not interfere with the device's work, or rest. The following stimulation parameters were applied: discharge of 20 Hz, lasting 1.4 seconds, with 5-second intervals and the time of impulse amplification and decrease of 0.3 second and 0.2 seconds. The intensity of stimulation oscillated between 6.4-14.4 mA for the median nerve, and 3.3–10.4 mA for the ulnar nerve. The impulses were supplied by two channels: for the median nerve (fingers 1-3), and the ulnar nerve (fingers 4 and 5), using 1 × 4 cm electrodes woven into a special glove. The intensity of application was set so that the impulses were painless, and the patient perceived them as neutral or pleasant [5].

In parallel to the conventional therapy, the patient underwent neuroplasticity stimulation. On the day of introducing the therapy, half-way through the treatment, and on the day of its completion, the function of the paretic hand and the healthy hand was examined and tested, superficial and deep sensation were assessed, to evaluate the effects of repeated sensory stimulation, and the muscle strength was measured with a dynamometer.

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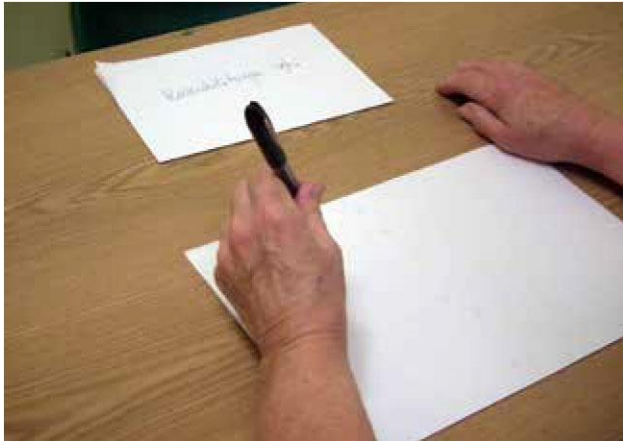


Figure 1. Reproducing of text containing script letters – “hand rehabilitation”

Rycina 1. Odwzorowanie tekstu złożonego z liter pisanych – „rehabilitacja ręki”

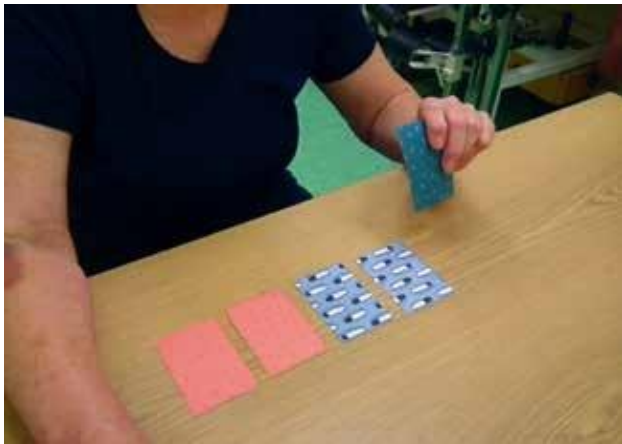


Figure 2. Turning five 6 × 9 cm cards upside down
Rycina 2. Odwrócenie 5 kart o wymiarach 6 × 9 cm



Figure 3. Putting five coins of different dimensions into a container of diameter 5 cm and 4 cm high

Rycina 3. Zebranie pięciu monet różnej wielkości do pojemnika o średnicy 5 cm i wysokości 4 cm



Figure 4. Picking up five beads with table spoon and putting them to a container of diameter 5 cm and 4 cm high

Rycina 4. Zebranie pięciu koralików łyżką stołową do pojemnika o średnicy 5 cm i wysokości 4 cm

The assessment of daily activities and the function of the hand consisted in a 6-point Jebsen-Taylor test, modified according to our design. The study involved measurement of the time of individual tests, assessment of the superficial and deep sensation, and of the muscle strength. Each test was performed by the patient three times, both with the paretic and the healthy hand. The result of each consecutive measurement was recorded and averaged in an Excel spreadsheet, as well as illustrated photographically (Figs. 1-8).

As a result of the therapy, after two weeks of stimulation the patient demonstrated a visible improvement in general physical fitness and in manual

function, especially with regard to grasping function and graphomotor skills. The muscle strength of the paretic limb also increased considerably. Before the therapy, the patient could not hold a writing tool, had significant problems with holding and manipulating a spoon, and with the tweezer grip. The greatest improvement was observed in the gripping and graphomotor function, expressed in a significantly shorter time of performing a task: rewriting a text, collecting beans with a spoon, and moving containers between fields. The precision grip also improved: collecting coins into a container and stacking coins. A slight change was observed in the ability to turn cards.



Figure 5. Stacking five 1 zloty coins
Rycina 5. Ułożenie pięciu monet jednozłotowych w stosik



Figure 7. Examination of deep feeling
Rycina 7. Badanie czucia głębokiego



Figure 6. Moving five containers of the dimensions mentioned above from a work surface to surfaces marked on 1.5 × A4 format sheet of paper
Rycina 6. Przeszawianie pięciu pojemników o wymiarach jak poprzednio z blatu na pola oznaczone na powierzchni 1.5 kartki A4



Figure 8. Examination of surface feeling
Rycina 8. Badanie czucia powierzchniowego

rSS was applied for another two weeks. After that time no significant changes were found in writing grip, precision grip, and in muscle strength. With regard to superficial and deep sensation, a clear improvement was observed after the first two weeks of stimulation. After another two weeks of rSS, the test for sensation did not reveal any difference with relation to the healthy side, or the previous test. It was observed that rSS as an additional method in a complex rehabilitation process results in a visible improvement with regard to motor and sensory functions of the paretic hand after 10 days of application, and may be a valuable addition to the conventional therapy. Extending the period of stimulation by another 10 days did not bring a spectacular further improvement. The functions of the healthy right hand (the dominant one in this case) were moderately improved, and remained within the normal physiological range. The efficiency of

the left upper limb, and time of performing tasks with the paretic hand, approached the parameters obtained by the healthy – dominant – hand.

Conclusions

A comprehensive neurological rehabilitation using the processes of cerebral plasticity enables the recovery of patients with impaired CNS, e.g. due to strokes. The presented case involved an intracerebral haemorrhage from a ruptured aneurysm. After the intracerebral haemorrhage, as a result of a procedure, the patient experienced an ischaemic stroke with subsequent moderate left-sided hemiparesis and dysfunction, primarily of the upper limb, as well as memory and association deficits. The treatment process was focused on the recovery of the manipulative function of the upper

limb, bilateral hand coordination and visual-motor coordination, and improvement of self-sufficiency. Transdermal rSS stimulation with the use of TIPSTIM after the presented cerebral incident may be an additional, complementary element of rehabilitation. It appears that 10 days of such therapy results in a visible improvement in sensation, proprioception, and hand function. Extension of the stimulation by another 10 days did not further improve the paretic limb's function. This method requires further observation and research involving a larger number of patients, preferably in double-blind, placebo-controlled studies.

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Modern dental care for military units in the armies of the world – a literature review

Współczesne zabezpieczenie stomatologiczne jednostek wojskowych w armiach na świecie – przegląd piśmiennictwa

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Abstract. There are differences in medical backup in different armies around the world. This is why it is important to get to know the structure and organization of medical backup in other armies. This knowledge will help improve our own dental treatment among the soldiers of the Polish Army system in the future. Each country has an individual approach implemented for this issue. This is due to the structural differences in the army itself, financial contributions for dental care, cultural differences, and experience in missions. The backup varies between the soldiers' homeland and that on a mission to a foreign country. Frequently the social and living conditions there are drastically different than those of the native country. These are not only the differences noticed by the authors of this article, there also exist nuances in the decision-making process in the area of the ability to serve inside the home country and outside its borders, and the manner in which highly specialized staff can serve in the structures of military dentistry.

Key words: dental backup, field hospital, organizational structure, stabilization missions

Streszczenie. Zabezpieczenie medyczne w armiach świata jest różne, dlatego ważne jest poznanie struktury i organizacji zabezpieczenia medycznego w armiach obcych państw. Pomoże to w przyszłości poprawić system leczenia chorób jamy ustnej u żołnierzy Wojska Polskiego. W każdym kraju podchodzi się do tego zagadnienia w sposób indywidualny, co podyktowane jest różnicami strukturalnymi w samym wojsku, nakładami finansowymi przeznaczonymi na zabezpieczenie stomatologiczne, różnicami kulturowymi czy też doświadczeniem misyjnym. Inaczej bowiem wygląda zabezpieczenie w kraju stacjonowania żołnierzy, a inaczej na misji w obcym państwie. Często okazuje się, że warunki bytowo-socjalne są tam odmienne od tych znanych w rodzimym kraju. Nie są to jedyne różnice zauważone przez autorów powyższego artykułu. Dostrzeżono również niuanse w sposobie orzekania o przydatności do służby zarówno w kraju, jak i poza nim oraz w sposobie pozyskiwania wysokospecjalistycznej kadry, mogącej pełnić służbę w strukturach stomatologii wojskowej.

Słowa kluczowe: zabezpieczenie stomatologiczne, szpital polowy, struktura organizacji, misje stabilizacyjne

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Introduction

Military dentistry is an inextricable element of military medicine, and it is not possible to discuss one without taking the other into account. This is the reason why it is crucial to understand how health care, particularly dental care, functions in other armies of the world. A thorough analysis and comparison of different situations with the situation of the Polish army should allow improvements in the condition of health care in the same.

The level of dental backup varies in different armies of the world. In some armies it is at a high level, with military dental clinics in operation, whereas others lack a sufficient infrastructure or personnel – officer-physicians

who can provide sufficient care in military units. There is also a significant difference between dental care within Poland and that provided on international missions. All these details have a decisive impact on the efficiency of the level of military health care and the care a soldier may receive.

Dental backup in the Polish Army

In 2002, the Military Medical Academy and the Medical Academy in Lodz were merged to form the Medical University of Lodz. Within the structures of this entity, there is a military – medical faculty aimed at the academic formation of the future military medical staff for

the Polish Army, in collaboration with the Military Medical Training Center in Lodz. The intention was to draw military physicians from civilian structures as well, in the form of voluntary transfers to the army. However, this system had little attraction for civilian doctors and, consequently, lacked effectiveness. This situation led to a decrease in the number of physicians in the Polish Army [1]. In 2008, the main reason for doctors to leave the army was retirement. This constituted 77.02% of all cases of leaving the army in the medical corps [1]. Such a condition was caused by the lack of attractiveness of work in the army, heavy workload, problems with concluding specializations in medical fields, and low earnings in comparison to colleagues working in civilian structures of medical care, and the need for extensive availability of army physicians [1]. Changes made at the beginning of the 21st century aimed at improving the operation of military health care by adjusting it to the reality of professionalization of the Polish Army, have, in truth, limited or even impaired it [1]. The current dental care system implemented in the Polish Army does not function properly, and there is a lack of active officer physicians. At present there are 36 military dentists (as of 2016), a number smaller than that of military pharmacists or veterinarians. In many military units the dental offices have been closed, as until recently there were no legal possibilities to open such points in accordance with the Act of 15 April 2011 on Healthcare Institutions [2] or there were a lack of sufficient dental personnel. Often the equipment of dental offices, because it is not being used, is transferred to commercial divisions and subsequently liquidated or sold by the Military Property Agency to the civilian market. Also, the positions of dentists in the Polish Army, which remain unfilled, are routinely liquidated by unit commanders or transformed into other positions [1]. This means that dentists have no clear or precisely defined path of professional development, let alone a military career [1]. These are the primary reasons why doctors and dentists leave the army [1].

According to the latest provisions of law, a dentist can specialize in an area of their choice 15 days a month, while the remainder of the time must be spent at a military unit. The specialization is not required by the unit commander or supervising physician. The specialization is carried out at a hospital or a military clinic which is nearest to the doctor's / officer's residence [1]. However, not every voivodship has such facilities. The author of this article had to carry out his specialization at a military clinic located 120 km away from the home unit. It should be mentioned that such training is non-chargeable on the basis of a volunteering agreement. This means that all the commuting, accommodation and compulsory specialization courses must be covered by the military physician.

Currently doctors may specialize in all areas of dentistry. However, few hospitals have maxillofacial surgery wards or clinics where such specializations in dental surgery or maxillofacial surgery may be carried out. These are the clinical hospitals in Wrocław and Bydgoszcz, and the Military Medical Institute in Warsaw. Additionally, specializations in dental surgery and other areas may be conducted in clinics that operate at military hospitals (in Szczecin, Krakow, Warsaw, Bydgoszcz, and Wrocław), and the Military Institute of Aviation Medicine in Warsaw and the Central Military Health Service Center, "CePeLek", which is also located in Warsaw.

Under the current military decision-making process in the Polish Army, the condition of one's dental hygiene is one of the decisive factors as to whether a person may or may not serve outside the country. A person with tooth decay should not be qualified as fit for an international mission [3]. Even one instance of tooth decay may disqualify a person from being sent on a mission. If such a person is already on a mission, however, they should be evacuated from the battlefield.

The operation of a dental office at home is not the same as on missions. For the latter, the need for dental care is very pressing. For example, the Polish Military Contingent in Afghanistan had an operating dental practice. It formed a part of the Polish Field Hospital stationed in Ghazni. It was a reference level 2+ unit, namely, a field hospital extended to include a pharmacy, dental office, and emergency room. The staff of the dental office included one officer – a dentist and one nurse (a civilian or non-commissioned officer). There was no CT scanner and no prosthetic laboratory in the field hospital [4]. It was possible that a dentist would serve on a mission without any specialization. The principal activities included conservative and root-canal treatment, extraction of uncomplicated teeth, and plaque removal. If there were any complicated dental cases (for example, extractions of impacted teeth), such patients were sent for scheduled treatment to the Dental Clinic in Bagram, where American specialists served [4-5].

In the French army, however, the procedure of treating patients on missions was radically different. If any dental problems emerged among the staff serving on a mission, they were immediately evacuated in the MEDEVAC (Medical Evacuation) medical helicopter to the nearest French base with an operational dental care practice. For example, during the mission in Mali in the period from February 2013 to May 2013, 15.7% of the cases of air evacuation (MEDEVAC) were due to dental reasons [7].

In the Polish Military Contingent the situation was quite different. If a soldier was stationed in a smaller base where there was no Polish Field Hospital, they had to wait for road transport, which, in turn, was organized

after several days of waiting. During this time, the patient remained under the care of a paramedic, who would administer the painkillers available in the paramedic's backpack. To summarize, a dental patient was not an evacuation priority for the Polish Military Contingent. Due to financial reasons, medical helicopters were not called for such cases. Such patients, in spite of the pain, had to wait patiently for the convoy evacuation to the Polish Field Hospital in Ghazni [5, 6].

Dental backup in the United States Army

The method of classification in allied armies is much more restrictive than in Poland. A soldier with untreated teeth has no right to go abroad. Additionally, it should also be stated that soldiers in the home country have guaranteed dental care provided by the state. For example, in the US Army, there are hospitals in military bases with adequately equipped and staffed dental practices [8].

The US Army should be considered a model to follow as dental care there is at a very high level. Cases of dental problems among US soldiers occur very rarely. Having been on a mission twice, the author noticed only a few cases of dental interventions among American personnel in the base of Ghazni. This demonstrates that the verification process in the United States is very efficient and admits no possibilities of cheating, as often happens in military medical boards in Poland. The strength of the system is also backed up by a centralized and fully computerized system for the verification of the soldiers who remain in active service and in the National Guard [8]. Also, the Canadian army has such a computerized system for its patient base [9]. This considerably facilitates the decision-making process regarding the ability to serve outside the country (mission to Iraq) and within its borders [8]. It should be mentioned that in numerous American bases there are hospitals with dental offices [10]. The clinic in Fort Hood in Texas is one such example [11]. Dental problems among American soldiers are thoroughly treated. For candidates who wish to be sent on international missions, the verification process is very restrictive. The command does not want to generate additional costs related to the dental treatment of soldiers stationed in the theater of operations. Such treatment is the source of problems related to medical evacuation or provision of specialized equipment or materials. It is estimated that during the mission to Iraq from June to July 2011, the United States Army spent as much as 21.9 million dollars on the treatment of dental cases and other non-battle injuries. It should be stated that the process of treatment for many of those issues has not yet been completed which shall certainly generate still higher costs [12].

The entity responsible for health care in the US army is the Army Medical Department Center and School

(AMEDDC&S). This is the center that coordinates the training and further work of all the military physicians, including dentists, inside the country and outside its borders. On the other hand, the U.S. Army Dental Command (DENCOM) is the entity responsible for dental care itself. It is subordinate to the command of the military health care, U.S. Army Medical Command (MED-COM). DENCOM is divided into areas of responsibility where dental centers and prosthetic laboratories operate. They are to provide care for all the American soldiers stationed in bases in the USA and outside it (Germany, Italy). The United States Army has six areas of responsibility. DENCOM's principal tasks include the treatment of decayed teeth, preventive dental care, scientific research, training of subordinate employees, and sending specialized dental staff on international missions [13].

Currently, in the United States there are 29 dental clinics. They are to provide assistance for the soldiers stationed in the garrisons inside the country. Their principal activities include conservative dental care (principally amalgam fillings), dental surgery (without implants), dental prophylaxis with the instructions of hygiene, and basic periodontal treatment (descaling). Dental practices of this kind can also perform imaging diagnostics, bite-wing and panoramic dental x rays [14].

For the expeditionary forces, on the other hand, is the Expeditionary Medical Support System (EMEDS). It is a highly specialized unit that consists of physicians and mid-level personnel intended to operate outside the country. It was first used during the flood in Houston in 2001. This aim of this unit is to secure the medical and sanitary needs of soldiers both inside the country and on missions, and to provide care to the victims of natural disasters. Apart from the personnel, this medical group includes all the hospital infrastructure. EMEDS Basic is sent abroad when the contingent number exceeds 2,000 people. This team also includes a dentist. It is a lower level of reference of medical teams sent outside the United States. The following one is called EMEDS + 25, and provides health care for groups of 5,000 people [11, 15]. In this unit, within the structures of the dental clinic, dentists perform complex surgical procedures, including extractions of impacted third molar teeth. It is generally permitted for a dentist who has determined professional experience and has undergone adequate training to perform complex tooth extractions [10].

Dental backup in the Canadian Army

The Canadian Army has a special division whose purpose is to manage matters related to the training and activity of military dentistry, called Canada for Dental Service (CFDS). It forms a part of the Canadian Military Forces. The structure of this unit includes 119 officers, some of whom are dentists, and the rest perform administrative tasks. Non-commissioned officers also

take part in the provision of dental care. There are 201 of them, including dental technicians and hygienists. The dental service also employs 110 civilians: dentists, hygienists, assistants, nurses, and receptionists. Officers of the dental care use uniforms of the Land Forces, despite the type of force in which they serve. Since 1995, the dental service has been commanded by an officer of the rank of Brigadier General. This year also marked the decrease in the military ranks in the medical command due to financial reasons [9, 16]. Currently, Canadian dentists are subordinate to a colonel, and not, as it had been before, to the Brigadier General. The commanding unit managing dental care is commanded by a colonel from the main headquarters in Ottawa. There are 26 dental divisions under his command, including two in Europe. Three major centers are qualified as dental clinics and are commanded by officers with the rank of lieutenant colonel. Apart from general dentists, there are prosthetists, periodontists, and maxillofacial surgeons in service in those clinics. The smallest clinics located in military units are commanded by captains or majors. There are few specialists in these small facilities. This is why when a more difficult case emerges, such a patient is sent to a facility with a higher reference level. The patient may be directed to a larger military clinic, a civilian clinic, or a private practice [9, 16]. In general, the tendency is to achieve full dental health in soldiers who serve in line units. The dental condition is assessed with the use of NATO STANAG 2466 standards [6, 9, 10, 16]. CFDS subdivisions must be able to help any soldier anywhere in the world, particularly those on international missions [9, 16].

This is the reason why the division of assistance for the soldiers in need outside the borders of Canada is rather specific. There are three reference levels for dental clinics on missions. The first one provides emergency aid to patients with pain related to stomatognathic system. The second level, called the sustaining level, is intended for urgent cases. The third level, on the other hand, is a specialized level where patients with complicated problems of the stomatognathic system are directed. Specialists, such as maxillofacial surgeons, treat patients on this highest reference level. Up until recently, dentists also could use clinics located on two floating hospitals, namely HMCS (Her/His Majesty's Canadian Ship) "Protecteur" and HMCS "Preserve". It is thanks to them that the entire spectrum of tests, including x-rays (without panoramic images) could be performed. However, at present both ships have been withdrawn from service. Activities aimed at obtaining new ships with technical backup are currently under way [9, 16].

Expeditionary forces have two systems of dental clinics at their disposal [9, 16]. Those are: a road-based

transport clinic, Dental Special Equipment Vehicle (SEV) and an air transport clinic, Air Transportable Dental System (ATDS). The latter is also used by air forces. The road transport clinic (SEV), also known as the Mobile Dental Clinic (MDC), is a self-sufficient unit that can operate together with mission forces. It consists of non-armored 2.5 ton trucks equipped with an air-conditioned clinic section. The module is furnished with full dental equipment, tools, materials and personnel which operates this mobile clinic. The staff consists of a two-person dental team: the doctor and a dental assistant. A tent with reception and waiting room can be optionally installed nearby. In order to secure power needs, a 10 kW power generator is used. Unfortunately, the whole set is quite heavy and slow, which is why there are certain limitations to its mobility in mountainous areas. Setting up all the materials takes approximately 60 minutes after which the staff is ready to work. The other type of providing dental care on mission is the system based on air transport (ATDS). It may be used during short-term operations as all the equipment fits into a 400-pound box. It is intended for emergency treatment, which is why a great advantage of this type of clinic is its compact size and speed of transport. The set may be laid out in a tent or an abandoned building. Its principal parts are: a dental chair, an air compressor generating high pressure connected to it, and dental tools. The entire set is powered by a 5 kW power-generating device. Additionally, the entire module can be equipped with a portable x-ray set [9, 16].

Dental backup in the Army of Great Britain

The British Army has a system called Defense Medical Services (DMS). Its jurisdiction covers all the military health service in different types of forces (Navy, Land Forces, Aviation, and Special Forces). A part of the DMS is the Defense Dental Services (DDS). A total of 1,085 people serve in this unit, namely, dentists-officers, dental hygienists, dental assistants, technicians, and nurses. The majority of procedures are carried out in the dental centers inside and outside the country, especially created for that purpose. The main headquarters of the DDS and the entire DMS are in Staffordshire and they cover 12 smaller medical districts located in Great Britain, and also Germany and Cyprus. Defense Dental Services also conduct activities on military missions outside home units. The purpose of the activities of those dental offices on missions is to ensure an operational stomatognathic system for the soldiers who serve in the theater of war operations [17]. The forces stationed outside the national borders also have at their disposal outpatient services and hospitals located on warships, where dental offices also operate. Up until recently, the

British Army had three floating hospitals of this kind. They were located on HMS (Her Majesty's Ship) Ark Royal (currently withdrawn from service), RFA (Royal Fleet Auxiliary) Argus, and HMS Ocean. Thanks to them, the British Army is able to guarantee dental care for soldiers while the forces are moving in the area of war operations [18].

To become an officer-dentist in the British Army, one must graduate from a civilian dental higher education institution or be a dentistry student on a military scholarship (the army covers the costs of the entire process of education). Then, after completing the third year of studies, the candidates go through a verification process before the committee from the Royal Army Dental Corps. This classification process allows one to participate in an 11-week basic training program, Professionally Qualified Officers' Commissioning Course in the Royal Military Academy, in the town of Sandhurst. This course familiarizes the cadets with basic expressions and commands used in the army and military drill and rules to follow while handling weapons. The training is very difficult and exhausting for the cadets. Once having successfully completed the training and obtaining promotion to the rank of lieutenant, the students are qualified to participate in the Army Medical Services Entry Officers Course (EOC), where they study the specifics of working as a military dentist. After having completed this part of the training, the officers receive a promotion to the rank of captain and begin their service in a dental office in a military unit. It is then that the military part of the training process is over. The officer's salary in the rank of captain is £ 67,000 a year. It depends, however, on the function performed in the military structures and it can be much higher than that [19].

Dental backup in the Army of the Czech Republic

Armed forces of Czech Republic have a very extensive system of health care in place. Both soldiers and recruits are treated in military hospitals located all over the country. Principal military hospitals include those located in Bechyne, Hradec Kralove, Prague, Prostějov, Práslavica, Vyskov, Zatec, Brno and Olomouc. Their activity is financed from the resources provided by the Ministry of Defense and the general health insurance fund. Nevertheless, these hospitals also provide assistance to civilians, which constitutes almost 90% of all the services. Dental clinics operate at those hospitals. The main clinical hospital is the one located in Prague. Its task is to train future professionals of military medicine [20]. Currently, 17 dentists, including 9 officers, are employed for the needs of the army. The professional training of a dentist lasts 5 years.

Expeditionary forces, on the other hand, have two field hospitals at their disposal. Those medical units are equipped with tents and containers that can be transported to any region of the world. Their structure also includes a mobile dental practice. For evacuation processes, road armored transporters and aircraft (Casa C-295 and Airbus A-319 CJ) are used. It is very helpful given the involvement of the Czech Army in the military conflicts in the world within the NATO and UN peace missions [20].

Conclusions

The above-described examples demonstrate differences in the armed forces of different countries. However, every army that wants to be a force to be reckoned with in the international arena must have medical units in its structure. A characteristic that medical services in different countries share is its universality. Apart from medical activity, they also have scientific and educational structures. Some countries involved in operations outside their borders have subdivisions adapted in such a way that they can provide assistance on international missions. Another difference is the manner in which medical care staff is obtained for the army. Some countries do this on the basis of civilian physicians who sign contracts with the army after completing their medical training. Others, on the other hand, train their own physicians in military higher education institutions. Despite numerous shortcomings and deficiencies, the Polish Army does not lag behind other countries' military forces. However, besides having adequate structures and subdivisions, it lacks personnel to man the structures. An additional problem for every soldier serving in a line unit is a lack of operational outpatient services or a dental clinic at the site where they are stationed. For example, in the Lodz voivodship, there is no military hospital or clinic that can provide services for the army. This is why soldiers must seek assistance in private dental practices at their own expense or use the public healthcare system outside the walls of their military unit. In the 21st century, a sad reflection comes to mind – medicine goes further and further away from the soldier serving on the first line.

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Oral health with regard to malocclusion in young males – a review

Stan zdrowia jamy ustnej z uwzględnieniem wad zgryzu u młodych mężczyzn – przegląd

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Abstract. Examination of masticatory organ condition is often carried out in different age groups, by gender. A characteristic group for research is young males, and in this paper particular attention was paid to the condition of the masticatory system of males applying for admission to the army. The article is based on the analysis of papers describing the condition of the masticatory system in young males, carried out in various voivodeships and by different authors over a 15 year period. The aim of the work is to present oral health, taking into account malocclusion in young males, based on modern literature.

Key words: malocclusion, soldier, young male

Streszczenie. Badania stanu narządu żucia przeprowadza się często w różnych grupach wiekowych z podziałem na płeć. Charakterystyczną grupę do badań stanowią młodzi mężczyźni, a w przedstawianej pracy szczególną uwagę zwrócono na stan narządu żucia mężczyzn starających się o przyjęcie do wojska. Artykuł opiera się na analizie prac dotyczących stanu narządu żucia u młodych mężczyzn, przeprowadzanych w różnych województwach i przez różnych autorów na przestrzeni 15 lat. Celem pracy jest przedstawienie stanu zdrowia jamy ustnej z uwzględnieniem wad zgryzu u młodych mężczyzn na podstawie współczesnego piśmiennictwa.

Słowa kluczowe: wada zgryzu, żołnierz, młody mężczyzna

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Background

For many years epidemiological studies have been conducted in Poland to assess masticatory organ defects in young men, and their effect on dental aesthetics, as well as broadly defined stomatognathic system disorders, especially in the temporomandibular joints. The studies have been performed in different regions and professional environments, e.g. in military recruits or students of various higher education facilities. In studies conducted over 25 years ago by Malajewska et al. [1] in a group of 227 male students of the Maritime School, aged 20–24 years old, the malocclusion rate was 25.1%. In 1995, Malepszy et al. [2] studied 240 subjects aged 18

years old from three environments: a large city, a small town, and an urban area. They assessed the masticatory organ parameters of 30 males in each group. In most of the subjects (70.8%) malocclusion was observed, with the majority of defects assessed as severe (57.7%). Only 12.9% of the subjects with defects received orthodontic treatment. A similar rate of malocclusion was observed in the Lubelskie voivodeship at 81%, and in the Gdańsk area at 71.2%, whereas lower rates were reported for the students of Pomeranian Medical University, at 39.42%.

Aim of the study

The aim of the study is to summarise the current literature data regarding this issue.

Material and method

Publications from the last 15 years were analysed regarding a homogeneous group of young men. The key words included: "soldier", "young male", "malocclusion" and "temporomandibular dysfunction". The PubMed and Google Scholar Internet browsers were used. Several reports were obtained, from which 18 publications were selected.

Results

Relatively few reports regarding the frequency of malocclusion in young men applying for professional military service are available in the Polish literature. In 2006, a study involving 100 recruits aged 18–23 years old was conducted to assess the presence of malocclusion in this group of subjects, who were from southern and western Poland. 50 subjects had normal occlusion, 41 had distal occlusion, and 8 had mesial occlusion. Only in 1 case was the occlusion perfect, which suggests a significant neglect in the area of orthodontic prophylaxis and treatment [3]. A study involving 300 recruits aged 19–26 years old assessed malocclusion and speech defects. In 174 subjects malocclusion was found, and in 163 subjects malocclusion and dental defects were observed. Moreover, a significant relationship was established between open occlusion and speech defect, which is important from the perspective of military service [4]. The incidence of malocclusion in the group of 300 young adult males from the Lower Silesia region was 91%. The most frequently observed defect was rotation [5]. In 2008, the occlusion of 720 military recruits from the West Pomeranian voivodeship was analysed. In approximately 70% of them malocclusion was observed, predominantly due to dental defects - crowding due to insufficient space in the dental arches. Frączak et al. [6] reported that, similarly to previous years, the dental and periodontal condition required decisive therapeutic intervention, and expansion of the educational programme, to comply with the WHO recommendation for the year 2000. According to these authors, there was a legitimate concern that the goals would not be achieved in this age group. A study of 25 soldiers, conducted to determine the requirements in terms of orthodontics, demonstrated that 20 of them needed orthodontic treatment due to pronounced disto-occlusion [7].

Repeated analysis of temporomandibular joint disorders (the first in 104 newly recruited soldiers and the

second at the end of their military service) demonstrated that initial isolated symptoms of dysfunction in a relatively short period (8.5 months) developed into several simultaneous articular symptoms. Kamiński et al. [8] confirmed the effect of military service on the prevalence of masticatory organ dysfunction. They observed an increase by 8.7% in the frequency of pain associated with mandibular movements, a reduction of mandibular mobility by 3.8%, and an increase of bruxism by 0.8%. The prevalence of masticatory organ dysfunction in soldiers increased from 23.1% in recruits to 34.6% in soldiers completing their service.

Studies regarding oral health and the condition of mandibular joints in students were conducted for many years. At one university in Warsaw, the dysfunctions and parafunctions associated with malocclusion and occlusion disorders were analysed. The study involved 79 male students with full dentition or individual deficits, in whom a relationship was found between articular dysfunctions and malocclusion. Masticatory organ dysfunctions were observed in 57% of the students, while in 43% no symptoms of dysfunction were found. The symptoms of masticatory organ dysfunction were more frequent in students with malocclusion and disturbed occlusion, especially in subjects with complex or transverse defects. The assessment included occlusal parafunctions (clenching, grinding, and teeth tapping) and non-occlusal parafunctions (lip and cheek chewing, fingernail biting, and chewing gum). Occlusal parafunctions occurred in 33 students, and non-occlusal ones in 51 students, most often in the case of malocclusion relative to the frontal plane [9, 10]. An analysis conducted in soldiers in Wrocław demonstrated a greater severity of temporomandibular joint dysfunctions in young soldiers [11]. In subsequent years, studies regarding temporomandibular joint dysfunction in young adult males (recruits from the Lower Silesia region) demonstrated that 239 out of the 300 subjects had no serious dysfunctions [12]. In 2013, in Łódź, 95 patients were examined (25 males and 70 females, aged 15–68 years old) using different diagnostic criteria to assess dysfunction of the masticatory organ. In the International Headache Society test, temporomandibular joint noise occurred in 33 subjects, reduced range of jaw movement in 31 subjects, pain during jaw movements in 62 subjects, difficulty opening the mouth in 62 subjects, occlusal parafunctions in 60 subjects, and non-occlusal parafunctions in 27 subjects. In the Dvorkin and LeResche test, noise was observed in 33 subjects, difficulty opening the mouth in 25 subjects, trismus in 6 subjects, and temporomandibular joint pain in 41 subjects. Occlusal parafunctions were found in 60 individuals, and non-occlusal parafunctions in 27 subjects. The International Headache Society test is

useful in screening and epidemiological studies, whereas the Dvorkin and LeResche test finds better application in clinical diagnostics for the type of masticatory organ dysfunction [13].

In 2011, the centre in Wrocław assessed the therapeutic needs regarding the aesthetic component of the index of orthodontic treatment need (IOTN). The research project included 55 higher education students. In an intraoral examination the maxillary profile, facial profile and Korkhaus lip step were assessed, and the depth of the mentolabial sulcus was evaluated. Students assessed subjectively a fitting photograph representing the aesthetic component (AC) of the IOTN. The study revealed a correlation between the accuracy of the selected aesthetic component and awareness of the defect. The treatment need consistent with the IOTN aesthetic component was confirmed [12]. In another study, conducted by Minch et al. in a group of 25 students of the Medical University in Wrocław and 25 soldiers, the collected data demonstrated more cases of malocclusion in the soldiers, a higher subjective need to treat malocclusion in students, and differences between the groups regarding the subjective and objective orthodontic treatment needs [14].

In the orthodontic assessment control of the development of different elements of the face and implementing relevant corrections is important. Physical appearance greatly affects proper functioning in social, private and professional life. Strzałkowska and Lekan emphasise this aspect [15]. The appraisal of one's own appearance is important for adequate functioning in professional life, so functionally and aesthetically successful orthodontic treatment is of high importance. Small defects, as many authors report, do not result in a negative aesthetic perception. A similar opinion is expressed by patients following orthodontic treatment in whom subtle disorders remained, or recur with time. Exacerbation or intensification of the defect, according to numerous authors, significantly lowers the aesthetic appreciation, and has a negative effect on the person's attractiveness [16-18]. Individuals who find themselves in a high need of orthodontic treatment demonstrate low levels of macro-, mini- and micro-aesthetics, i.e. of oral aesthetics, and have low self-esteem. Aesthetic changes in the face area may affect the quality of life. For young people, physical attractiveness is an important factor contributing to social relations [19, 20].

Summary

The analysis of the literature data revealed that the level of malocclusion, occlusal and non-occlusal parafunctions, and dysfunctions of temporomandibular joints in young males is relatively high. However, the

degree of malocclusion does not reflect the actual situation in males applying for military service, as the requirements regarding health status are defined in the Regulation of the Minister of Health [21] of 08/01/2010 regarding the pronunciation of fitness to perform military service. In chapter 6, with regards to the oral cavity, paragraph 25 mentions congenital or acquired maxillary or mandibular deformity that impairs mastication, and chronic diseases of the temporomandibular joint that significantly impair mastication. "Maxillary and mandibular deformities" include such defects as real mandibular prognathism, maxillary or mandibular protrusion, laterogeny, prognathism, micrognathism, open occlusion or combined maxillary and mandibular defects, comprising real mandibular prognathism with micrognathism, and other defects resulting in lack of interaction between opposing chewing surfaces of the antagonistic teeth. While pronouncing fitness for professional military service, the following aspects should be considered: the degree of damage to the dentofacial system, e.g. maxillary or mandibular deficits, incorrect fusion of a fracture, lack of fusion, deficits of the chin, lips or cheeks, mandibular contraction, deficits or scarring of the tongue, glossopharyngeal nerve paralysis, and associated complications, such as facial deformation that affects interactions with other people, or drooling due to inability to close the mouth completely. In these conditions of the masticatory organ, speech and mastication disorders are also evaluated. Candidates for professional military service are referred to dental examination including an assessment of malocclusion and oral health in order to pronounce the candidate as "fit" or "unfit for military service" in various military formations. No studies regarding orthodontic aspects of oral health have been conducted in the Greater Poland region in males applying for professional military service

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Diagnostics of pituitary adenomas using ^{11}C -methionine PET

Diagnostyka gruczolaków przysadki techniką PET z ^{11}C -metioniną

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Abstract. The gold standard for pituitary adenoma diagnostics is magnetic resonance imaging. In special cases, such as postoperative changes, multiple adenomas or ectopic hormonal activity, this method may be insufficient. Positron emission tomography with ^{11}C -methionine is a non-invasive imaging scan that allows us to visualize lesion metabolism.

The results of recent studies indicate the high sensitivity and specificity of this method, and its usefulness in identifying the active lesion or differentiating recurrence from iatrogenic changes.

Key words: pituitary gland, pituitary adenoma, PET, positron emission tomography, methionine, Cushing's disease, acromegaly

Streszczenie. Złotym standardem w diagnostyce gruczolaków przysadki jest badanie rezonansu magnetycznego.

W szczególnych przypadkach, takich jak zmiany pooperacyjne, mnogie gruczolaki lub ektopowe wydzielanie hormonów przysadki, badanie to może jednak nie być wystarczające. Badanie pozytonowej tomografii emisyjnej z użyciem ^{11}C -metioniny jest nieinwazyjną metodą obrazowania, która pozwala zobrazować metabolizm zmiany. Wyniki badań z ostatnich lat wskazują na dużą czułość i swoistość metody oraz jej przydatność we wskazywaniu zmiany aktywnej lub zróżnicowaniu wznowy i zmian jatrogennych.

Słowa kluczowe: przysadka, gruczolak przysadki, PET, pozytonowa tomografia emisyjna, metionina, choroba Cushinga, akromegalia

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Background

Pituitary adenomas are among the most common tumours of the CNS, accounting for approximately 10-15% of all intracranial tumours [1, 2]. The traditional classification distinguishes adenomas of ≤ 10 mm and those of > 10 mm. The data regarding their occurrence in the general population are often incongruous. Metaanalysis by Ezzat et al. indicates that the prevalence of adenomas is 16.7%, most of which are microadenomas; the prevalence of macroadenomas in the general population is estimated at 0.16–1.2% [3].

They are usually benign. Hormonally active adenomas typically secrete prolactin, less often ACTH, growth hormone or gonadotrophic hormones, while only occasionally producing TSH. Approximately 16% of them demonstrate a mixed activity. A large number of adenomas do not secrete hormones, and apart from the mass effect they have no clinical importance [2].

The gold standard in the treatment of pituitary adenomas is magnetic resonance, which allows us to assess precisely the tumour location and size. However, there are also cases of multiple adenomas, or ectopic secretion of pituitary hormones, where disorders are not caused by a single pituitary adenoma, or one of multiple tumours. In addition, due to constant improvement in the quality of imaging, magnetic resonance imaging (MRI) lesions with no clinical significance are visible, so-called "incidentalomas", which complicates the diagnostic process (especially in patients with ambiguous results from hormone tests), and may result in a misguided decision to apply surgical treatment of a pituitary adenoma. In such case, catheterisation of the petrosal sinuses may be helpful, but this test has certain restrictions, such as its invasive character and limited availability. Recent reports indicate that ^{11}C -methionine PET (MET-PET) could be an alternative test.

Description of the method

Positron emission tomography (PET) with methionine labelled with radioactive carbon is a non-invasive method of visualising CNS tumours, including pituitary lesions. ^{11}C -methionine is a pharmaceutical agent with a high uptake by most types of pituitary adenoma, and relatively low uptake by the surrounding CNS tissue. Its uptake indicates an increased metabolism of amino acids. The tracer is administered intravenously, and then recorded by the PET scanner. The image created through computer processing indicates the sites of increased tracer uptake, in this case corresponding to the increased metabolism of amino acids. The procedure is associated with a limited exposure to radiation. The estimated effective dose is approximately $5.2 \mu\text{Sv}/\text{MBq}$ of administered radiotracer (usually 200–555 MBq, 4 MBq/kg b.w. is administered), which means approximately 1.5 mSv for a patient weighing 70 kg, with the acceptable annual exposure being 50 mSv.

PET presents the organ's function, so in the case of multiple adenomas it helps to identify the hormonally active lesion. If the lesion demonstrated in MR is clinically insignificant, using a functional PET test and the exclusion of hormonal activity of the tumour may prevent an unnecessary operation. Moreover, a whole-body scan can localise the source of ectopic hormone secretion.

It should be noted that a healthy pituitary gland also demonstrates methionine collection in the PET test, but to a lower degree than adenomas.

Clinical application

Cushing's disease

Cushing's disease is caused by elevated cortisol concentration in the blood serum due to oversecretion of corticotropin (ACTH) by the pituitary adenoma. Over 80% of all ACTH-secreting pituitary tumours are microadenomas. Cushing's disease is diagnosed based on the presence of characteristic symptoms and laboratory markers of ACTH-dependent Cushing's syndrome of pituitary origin. In each case an MRI examination of the pituitary gland is necessary [4, 5].

In primary diagnostics of corticotropic adenomas, MET-PET and MR results are highly consistent. Zize Feng et al. [6] compared in his study the results of MRI and PET examinations with histopathological tests results in 45 patients, of whom 15 had ACTH-secreting adenomas. In the group of 15 subjects all showed an increased methionine uptake in the pituitary gland, in most cases consistent with the adenomas presented in the MRI. In two subjects in this group the MRI results were ambiguous; in both cases the PET scan was consistent with the histopathological test results. The

study was limited by its retrospective character, and the solely qualitative assessment of the PET results.

Using MET-PET both in *de novo* diagnosed adenomas, and in recurring tumours was assessed by Kolouri et al. [7]. The study involved 20 patients: 10 during primary diagnostics, and 8 with a recurring adenoma. In two patients ectopic ACTH secretion was observed. In the group of newly diagnosed adenomas, increased methionine uptake was demonstrated in 7 out of 10 subjects, which was consistent with the results of rapid acquisition MR imaging and histopathological tests, whereas in classic MR reconstruction only four lesions were presented. In all ten patients a transsphenoidal surgery was performed. Interestingly, out of three patients with a negative PET result, only one benefited from the procedure.

Patients with suspected recurrence are difficult to assess using magnetic resonance imaging, as the image following radiotherapy or post-operative lesions often resembles a recurrence. In a study by Kolouri et al., in the group of patients with recurrence, the PET results were positive in 5 out of 8 subjects, similarly to the MRI results.

The use of methionine PET in the diagnostics of recurring pituitary adenomas was analysed by Tang et al. [8]. Their study involved 33 patients following pituitary gland surgery with suspected recurrence based on laboratory test results or the presence of lesions in the MRI scans. This group included 8 patients operated on due to an ACTH-secreting adenoma. Only in 1 of the 8 cases was adenoma distinguished from post-operative lesions in an MRI, whereas the PET result was positive in all of them. Based on these results, a gamma-knife procedure was performed in 6 patients, resulting in improved laboratory test results in 4 subjects. It should be noted that this is the oldest of the presented studies (from 2005), and since then the quality of imaging has improved considerably.

Apart from a qualitative assessment, PET enables a quantitative evaluation of the tracer uptake in the lesion through the analysis of SUV indicators. In a study by Ikeda et al. [9], out of 39 patients who had been operated on due to Cushing's disease, the presence of ACTH-secreting adenoma was confirmed histologically in 35 subjects, and this group was further analysed. The preoperative 1.5T and 3.0T MRI tests, and in 11 patients MET-PET tests, were compared. In all cases an increased methionine uptake in the pituitary tumours was demonstrated, with SUV_{max} of 1.8 - 6.9 for adenomas, which was above the background level. The mean SUV_{max} value for the pituitary gland itself was 1.3 ± 0.23 , slightly higher than in healthy individuals (0.74 ± 0.18), probably due to the increased uptake in the tumour.

As previously mentioned, the Cushing's syndrome symptoms may be triggered by ectopic ACTH secretion. PET is a whole-body test, which enables the tracing of abnormalities outside the CNS. In a study by Kolouri et al. [7] two such cases were described. Both patients demonstrated a limited uptake in the pituitary gland; in one of them PET demonstrated a foci in the intestine, confirmed as a neuroendocrine tumour, and in the other subject a primary breast cancer was detected.

Acromegaly

Acromegaly is a disease caused by oversecretion of the growth hormone. The treatment consists of the surgical removal of the adenoma and/or administration of somatostatin analogues. Complete removal of the lesion is not always possible, especially in the case of microadenomas [10]. In their study Rodriguez-Barcelo et al. [11] assessed the usefulness of MET-PET in the diagnostics of growth hormone-secreting adenomas in two groups: 6 patients with a primary diagnosis of acromegaly (3 of them were later transferred to the other group), and 11 patients following surgical treatment. Apart from visual analysis, a semi-quantitative method was applied, evaluating the ratio of SUV_{max} of the adenoma to SUV_{max} of the grey matter in the opposite hemisphere (SUV_{max}/SUV_{cglm}). The limit value was set at 1.5. In the group of non-operated patients, the proposed index was positive in subjects with macroadenomas, but negative in those with microadenomas, although the focus of increased uptake, correlating with the lesions presented in MRI, was visible in all 3 cases. It indicates that uptake depends on the size of the lesion. Most patients received somatostatin analogues during the study. In the study group, after the procedure half of the patients did not demonstrate the symptoms of active acromegaly. In 1 of them the SUV_{max}/SUV_{cglm} index was positive, and in others it was negative. In this subgroup the MRI test did not reveal recurrences in any of the 7 cases. In the subgroup of patients with active acromegaly, the SUV_{max}/SUV_{cglm} index was positive in 6 out of the 7 patients. In 3 cases the MRI results did not offer an unambiguous differentiation between recurrences and post-operative lesions. Both the sensitivity and specificity of ^{11}C -methionine PET for a recurrence of GH-secreting pituitary adenoma was 86%. In other studies Feng et al. [6] report a consistency of 86% between MET-PET results and the histopathological material.

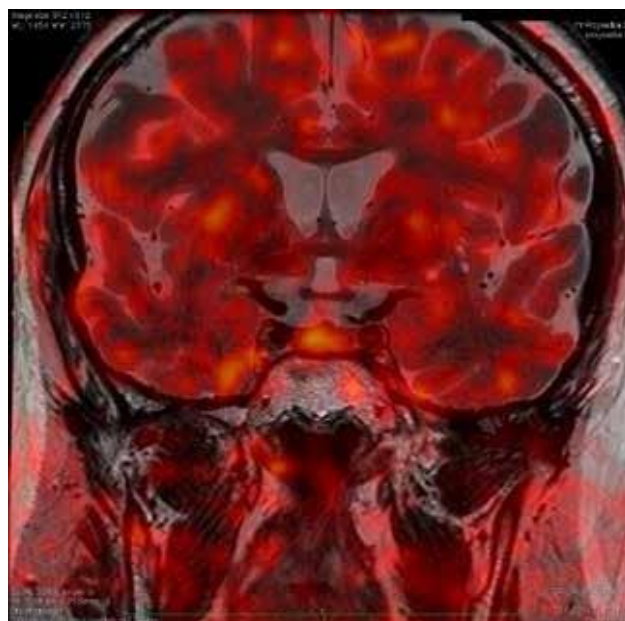


Figure 1. Patient with Cushing's disease. Fusion of MRI and PET images. Focal uptake of ^{11}C -methionine in the right part of pituitary gland concordant with adenoma location is visible. Own data.

Rycina 1. Pacjentka z chorobą Cushinga. Fuzja obrazów MRI i PET. Widoczny obszar wzmożonego wychwytu ^{11}C -metioniny po w prawej stronie przysadki odpowiadający gruczolakowi. Materiał własny.

Tang et al. [8] in their study had only 4 patients with recurrence following the treatment of GH-secreting adenoma. Half of the results were consistent with the MRI results; in other cases the result of magnetic resonance was negative, and therapeutic decisions were based on the PET results.

Other indications

Prolactinoma is the most common pituitary adenoma. However, it is not often mentioned in the context of MET-PET tests. Feng et al. [6] report a high consistency of 100% between MET-PET results and the histopathological material.

Tang et al. [8] demonstrated the method's usefulness in the diagnostics of *prolactinoma* recurrence, obtaining positive results in 8 out of 10 studied patients.

The same study included also the only report regarding MET-PET in TSH-secreting adenomas - the rarest type. In the studied group was 1 patient with a recurrence of secondary hyperthyroidism. In this case the PET test was positive, and the MRI was negative.

Conclusions

The gold standard in imaging diagnostics of pituitary adenomas is the magnetic resonance test. In individual cases the diagnostics may be extended to include

Usefulness of laboratory tests in the diagnostics of cerebrospinal rhinorrhea

Przydatność badań laboratoryjnych w diagnostyce płynotoku nosowego

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Abstract. Cerebrospinal rhinorrhea occurs when there is a fistula between the anterior skull base and the nasal cavity, tympanic cavity and sinuses. It commonly occurs following head trauma or as a result of intracranial surgery. Cerebrospinal fluid leakage is a rare condition that can lead to the development of serious consequences, such as meningitis. This article reviews the laboratory diagnostic of cerebrospinal rhinorrhea, including the detection of glucose and chloride in nasal discharge. This was the traditional method used to diagnose CSF leak, but has a poor positive predictive value. The article also describes the use of prostaglandin D synthase, commonly known as beta trace protein and beta 2 transferrin to detect CSF leak.

Key words: beta trace protein, beta 2 transferrin, cerebrospinal fluid, cerebrospinal rhinorrhea

Streszczenie. Płynotok nosowy powstaje na skutek wytworzenia przetoki pomiędzy przednią częścią podstawy czaszki a jamą nosową, bębenkową oraz zatokami. Dzieje się to najczęściej w następstwie urazów głowy, a także zabiegów chirurgicznych. Wypływ płynu mózgowo-rdzeniowego jest rzadkim stanem, który może prowadzić do poważnych konsekwencji, m.in. w postaci zakażenia opon mózgowo-rdzeniowych. W niniejszej pracy przedstawiono diagnostykę laboratoryjną płynotoku nosowego, która obejmuje wykrywanie glukozy i chlorków w wydzielinie. Testy te są tradycyjnymi metodami pozwalającymi zdiagnozować płynotok, ale mają małą dodatnią wartość predykcyjną. Opisano również wykorzystanie syntazy prostaglandyny D2, powszechnie znanej jako białko beta trace oraz beta 2 transferyny w detekcji obecności płynotoku.

Słowa kluczowe: płynotok nosowy, płyn mózgowo-rdzeniowy, beta 2 transferyna, białko beta trace

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Background

Rhinorrhoea is a pathological condition manifested by a leak of the cerebrospinal fluid (CSF) through the nasal cavity due to a fistula in the areas where the bones of the cranial base are the thinnest. The damage usually occurs between the inside of the skull, and the vault of the nasal cavity and ethmoid, frontal sinus, sphenoid sinus, or tympanic cavity. In the latter case, the fistula forms as a consequence of an interrupted tympanic roof, which results in discharge flow to the throat [1, 2].

A CSF leak is usually a result of mechanical injury caused by traffic accident, or a surgical procedure in the area of the nasal cavity and sinuses. The fistula may also be caused by a neoplastic process that leads to damage of the cranial bones, and interruption of the dura, which protects the brain [2]. Cerebrospinal leak usually presents as a watery, colourless discharge, flowing with varying intensity from the nose, ear, conjunctival sac, or down the posterior pharyngeal wall [3]. Figure 1 presents classification of rhinorrhoea according to aetiology [1, 2].

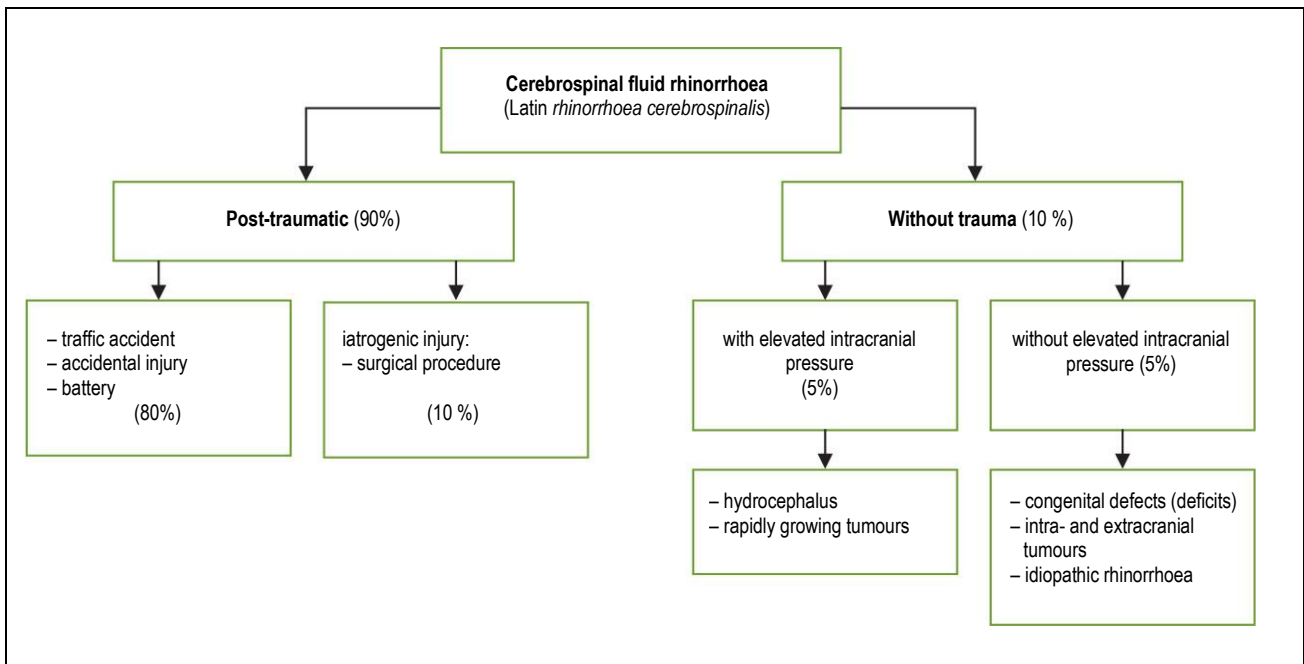


Fig. 1. Classification of cerebrospinal rhinorrhoea [1,2]

Ryc. 1. Klasyfikacja płynotoków nosowych [1,2]

Cerebrospinal fluid rhinorrhoea does not always occur directly after a trauma. Late demonstration of the symptoms of injury may be due to a haematoma, oedema or tissue inflammation that may block the outflow of CSF through the fistula [2]. The diagnosis may also be delayed when the leak is insignificant over a long period or hardly noticeable, and the only symptoms are associated with recurrent meningeal infections. It poses many diagnostic problems, and prevents an accurate diagnosis. According to the time from the injury to the onset of symptoms, cerebrospinal leaks are classified as:

- direct (immediate) - manifesting within 48 hours,
- early - occurring within a month,
- late - occurring up to 3 months following the trauma,
- delayed - manifesting after several months, or even years [1, 2].

As a result of damage to the meninges and bones protecting the brain, the likelihood of complications increases with the duration of the CSF leak [2]. The deficit enables the infection from the nasal cavity and sinuses to pass to the cranial cavity [4]. It may lead to meningitis, encephalitis or brain abscess [2]. It is estimated that approximately 10% of CNS infections are associated with existing fistulas [5]. Most frequently identified pathogens causing this type of infections are

Haemophilus influenzae and *Streptococcus pneumoniae* [1].

Cerebrospinal fluid rhinorrhoea presents as an uncontrollable, usually unilateral, discharge of watery, transparent discharge from the nasal cavity, that intensifies while leaning the head forward, and when the head is moved back, or the body is in a supine position, the need to swallow frequently occurs. The discharge is commonly mistaken for rhinitis and allergic catarrh, which is the main diagnostic problem [1, 2], due to the fact that cerebrospinal fluid leak is a very rare condition.

Diagnosis of cerebrospinal fluid rhinorrhoea – diagnostic strategy

The diagnostics of a CSF leak is based on two basic stages, in which the presence of cerebrospinal fluid in the discharge is confirmed, and the deficit is located.

Diagnosis

- Medical history – collecting detailed medical history
- Physical examination – laryngological consultation, endoscopic examination, Queckenstedt's test, Valsalva's test, halo sign – double ring
- Laboratory tests

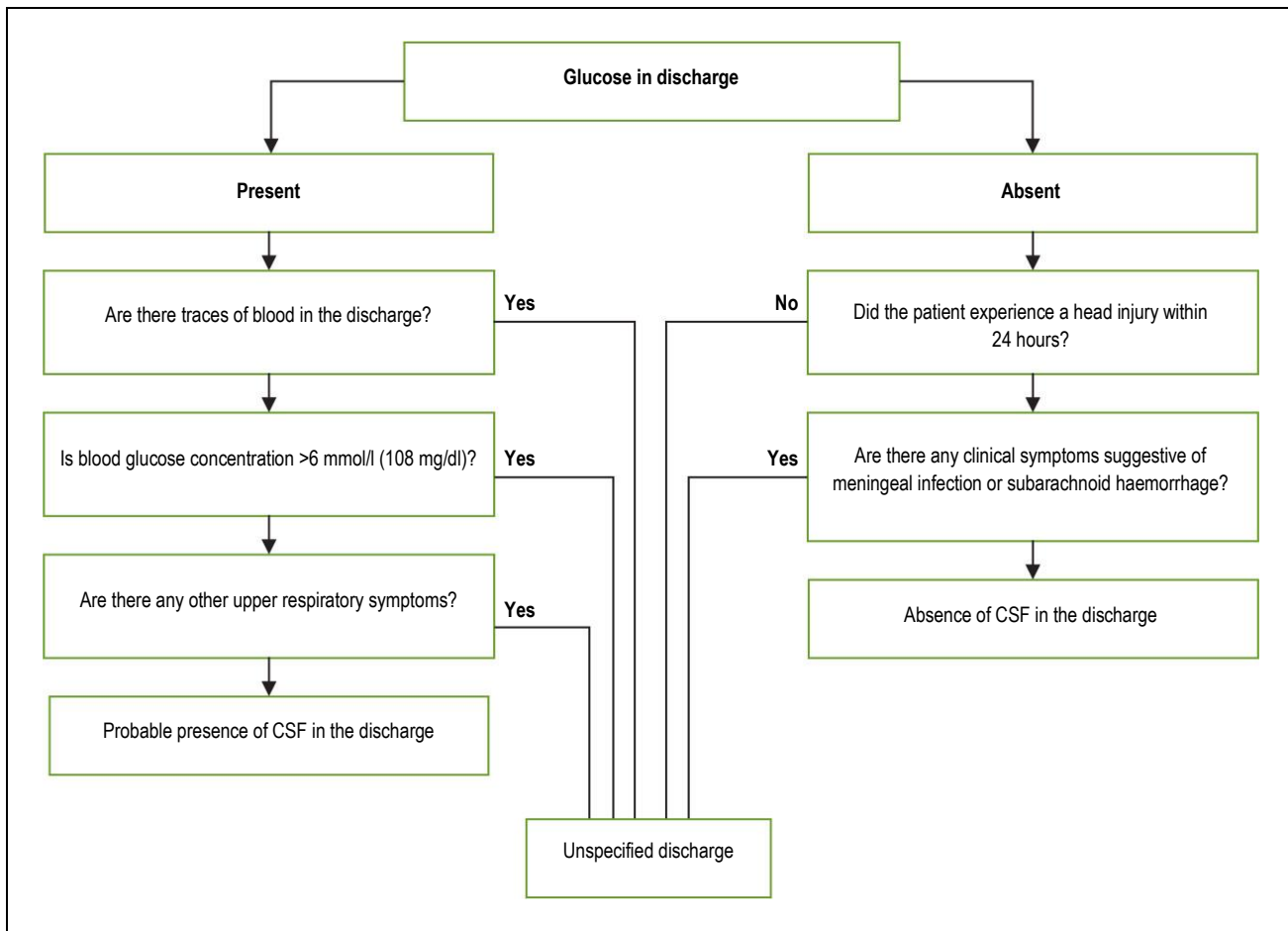


Fig. 2. Scheme for diagnostic algorithm in the evaluation of rhinorrhea after a head injury [6]

Ryc. 2. Algorytm diagnostyczny wspomagający ocenę wydzieliny z nosa po przebytych urazie głowy [6]

Location of cerebrospinal leak

- Imaging diagnostics: computed tomography (CT), magnetic resonance (MR)
- Isotope diagnostics – scintigraphic examinations
- Tests using tracers (fluorescein) [2]

Laboratory diagnostics

The traditional method of detecting CSF in the rhinorrhoea involves determination of glucose concentration with the use of easily available and inexpensive peroxide glucose test strips [1]. They are used for the semi-quantitative measurement of glucose in the discharge, based on the intensity of colour of the test strip. The normal glucose content in the cerebrospinal fluid is approximately 40 mg/dl, i.e. around 60% of its blood concentration, whereas the glucose level in the rhinorrhoea is much lower (within 10 mg/dl). However, using a dry strip test in the diagnostics of rhinorrhoea is associated with a significant error margin, so this technique may be considered only as an

"orientational" screening test. The presence of reductive substances in the tears and in the nasal discharge can lead to false-positive results, as in the case of contamination of the leak with blood. Meningitis or subarachnoid haemorrhage, on the other hand, is associated with a risk of false-negative results, due to the use of glucose by bacteria and the cells present in the CSF [6].

In order to minimise the interfering factors, a diagnostic algorithm was developed to optimise the interpretation of glucose measurement in the discharge (Fig. 2). It was intended primarily for the personnel of emergency departments in those centres where laboratories do not have tests for specific identification of CSF leak [6].

Another "orientational" test involves the determination of chloride concentrations in the discharge. High levels of this analyte indicate the presence of cerebrospinal fluid, whereas low levels exclude it. As a reminder: normal chloride concentration in the CSF is 120 -130 mmol/l.

Both this test and glucose determination must be confirmed in CFS-specific analyses [2].

Beta-2 transferrin

Determination of beta-2 transferrin (B2Trf) remains the most sensitive and specific marker of fistula formation in the diagnostics of cerebral rhinorrhoea [1]. Transferrin (Trf) is a glycoprotein of low molecular weight (~78 kDa), binding and transporting iron in the blood. It consists of a single polypeptide chain, and two branched oligosaccharide chains [7]. This protein is not a homogeneous molecule, and can be found in several polymorphic forms in the serum and other body fluids [8]. The oligosaccharide chain includes: sialic acid residues, galactose, N-acetylglucosamine and mannose. Depending on the presence of individual components, the protein has 9 isoforms: from asialotransferrin to octasialotransferrin [7, 9]. The isoform that reaches the highest serum blood concentration is tetrasialotransferrin, which accounts for 64–80% of the circulating transferrin, whereas desialotransferrins, including asialo- (< 0.5%), monosialo- (< 0.9%) and disialotransferrin (< 2.5%), are found in minimal quantities [7]. The sialylated forms of the protein that are present in the serum in the highest concentrations form beta-1 transferrin (B1Trf). In the cerebrospinal fluid, the dominant form is asialotransferrin, referred to as beta-2 transferrin (accounting for ~25% of the total Trf pool). Other isoforms found in the CSF originate in the serum, from which they diffuse, in a limited concentration, through the blood-brain barrier [9, 10].

B2Trf is CSF-specific, but it is also found in the vitreous body of the eye and in perilymph, although in much lower quantities. The protein is not present in the catarrhal discharge, saliva or tears, which can be used in the diagnostics of cerebrospinal fluid rhinorrhoea [1]. Contrary to other markers of fistula, B2Trf reaches such low blood concentrations that it is not detected by the available tests [11], with the exception of certain physiological or pathological conditions, such as rare disorders of the glycoprotein metabolism, or alcoholic liver disease, in which concentrations of desialylated forms of transferrin increase. This process is associated with the reduced activity of liver glucosyltransferase [8, 11, 12].

The method most frequently used to detect B2Trf is separation by polyacrylamide gel electrophoresis or agarose gel electrophoresis, combined with protein immunofixation, conducted in an alkaline environment [8, 11, 13]. This method uses the fact that a higher amount of sialic acid in the Trf molecule increases the total negative charge of this protein, which, during electrophoretic separation, migrates faster towards the

positive electrode (anode), until the molecule obtains an isoelectric point, i.e. a neutral electric charge [8]. Forms present in the cerebrospinal fluid, devoid of sialic acid, obtain a more "positive" total charge. Therefore, they are immobilised in the gel closer to the negative electrode (cathode) [8, 14]. In addition, using specific anti-Trf antibodies makes the method more sensitive (sensitivity of approximately 93%), and more specific (specificity of ~97%) than most tests previously used in the diagnostics of cerebrospinal fluid rhinorrhoea [11].

However, immunoelectrophoresis is very expensive, due to a limited availability of the specialist equipment and a low number of determinations. Moreover, the test is time-consuming; the procedure lasts approximately 2-4 hours, depending on the test kit used, and requires a lot of work, as the samples need to be processed manually, especially in the initial and final phases of the test [13]. The search for new techniques in the diagnostics of CSF rhinorrhoea was also motivated by problems with the interpretation of the results obtained from samples contaminated with blood. Due to considerably higher concentrations of beta-1 transferrin in the blood serum, when the nasal discharge containing CSF was contaminated with blood, the bands of individual Trf isoforms "blended" on the gel. It is estimated that 2% of blood in the sample results in the b1Trf concentration is so high that electrophoretic separation is unreadable [11].

Beta trace protein

Beta trace protein (BTP) was first described by J. Clausen in 1961 [15]. He presented a monomeric glycoprotein from the lipocalin family, consisting of 168 amino acids. They create a protein of low molecular weight, depending on the degree of its glycosylation (23–29 kDa). Determination of the amino acid sequence of BTP helped to demonstrate its activity as prostaglandin D2 synthase, which catalyses the conversion of prostaglandin H2 to D2 [15].

BTP is synthesised primarily in the epithelial cells of the choroid plexus, and is one of the main proteins found in the cerebrospinal fluid, next to albumin [1]. Therefore, it is a CSF-specific polypeptide, despite the fact that it is also found (in lower concentrations) in other body fluids, e.g. in the serum [16]. The reference ranges for this protein in the cerebrospinal fluid and in the serum are 4.5 - 22.5 mg/l (2.5 - 97.5 percentile) and < 0.7 mg/l (95. percentile), respectively [13, 17].

Due to the high BTP concentration in the CSF, this parameter can be used as a marker of cerebrospinal fluid rhinorrhoea. Its advantage consists in the fact that, similarly to b2Trf, BTP is not present in the catarrhal discharge or in the tears [12, 13].

Initially, BTP was determined using rocket immunoelectrophoresis with the sensitivity of ~91%, and nearly 100% specificity [12, 13]. However, this technique, as in the case of b2Trf, required a lot of work and was time-consuming. As a consequence, the waiting time for the results was long, and was associated with potential complications related to the fistula. Therefore, alternative methods were sought.

With time, immunonephelometry was introduced for BTP determination. It used latex molecules coated with polyclonal, usually rabbit, and antibodies against human beta trace protein [18]. The method was not only much faster than electrophoresis (determination took 12–15 minutes, compared to 2–4 hours of electrophoretic separation), but also less labour-consuming, due to complete automation of the process [13]. Moreover, the measuring range was increased (0.25–15.8 mg/l), which enabled the detection of even small quantities of CSF in the discharge [13].

Despite numerous literature reports and guidelines, the diagnostic values for this test are still controversial. In recent years, many cut-off points were proposed for a definite determination of CSF presence in the discharge. Currently, researchers favour the BTP content of 1.30 mg/l [17]. A diagnostic algorithm was also presented to increase the method's sensitivity to 98.3%, with a specificity of approximately 98%, and to minimise the risk of the false-negative results which occurred with the earlier suggested cut-off values of 2.0–3.0 mg/l (Figure 3) [19]. It involves an analysis of the blood serum and discharge collected at the same time.

However, the nephelometric method has certain limitations. BTP undergoes glomerular filtration, and is considered a marker of residual kidney function, so in patients with renal dysfunctions increased serum BTP concentrations may be expected, approximately 1.2–6.6 mg/l [17]. Therefore, while interpreting the algorithm presented above, the patient's renal status should be taken into account, and the test results in which BTP concentration is ≥ 1.30 mg/l, and the discharge BTP concentration to serum BTP concentration ratio is < 2.0 , should be properly described [13, 17]. In addition, in the case of fresh trauma, when the discharge is contaminated with blood, interference may occur, resulting in false high results [19].

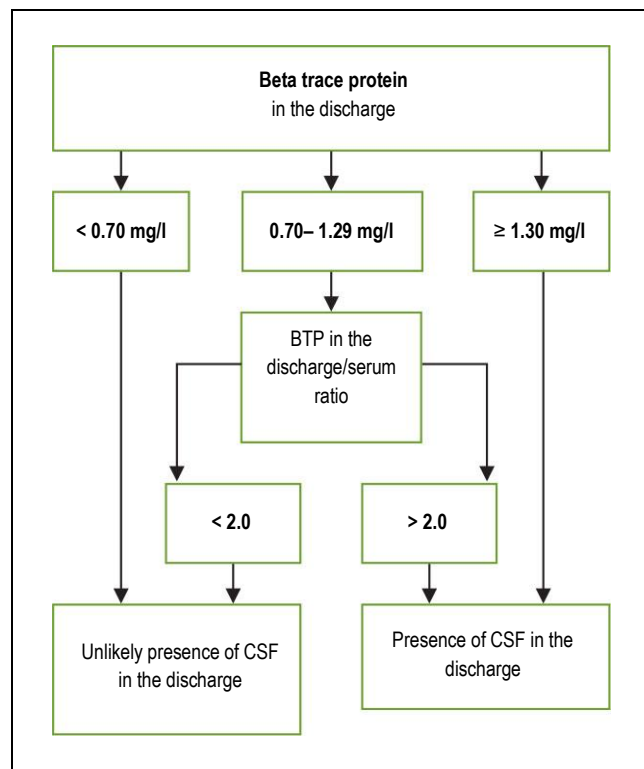


Figure 3. Algorithm to assist interpretation of the results of beta trace protein measurement [17]

Rycina 3. Algorytm pozwalający zinterpretować wynik pomiaru białka beta trace [17]

Conclusions

Due to potential complications in the form of meningitis, intracranial oedema, brain abscess or other neurological complications [4], cerebrospinal fluid rhinorrhoea should be considered an immediate life-threatening condition. Unfortunately, despite numerous publications discussing this problem, a fast and accurate diagnosis is still difficult. Laboratory tests play an important role in the diagnostics of cerebrospinal fluid rhinorrhoea, as they constitute, together with physical examination and medical history, the first step in the diagnostic process. The initial laboratory analyses, with the use of fast and inexpensive tests, include determination of glucose and chloride concentrations. They are not the decisive parameters, but may put the diagnostic process on the right track. The obtained results should be confirmed using CSF-specific biomarkers: beta-2 transferrin and beta trace protein. Due to the long waiting time for the results of the first test, it is usually disregarded in the diagnostic process and imaging tests are used instead. However, advances in the methods of BTP determination may significantly accelerate the diagnostic process.

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Hyperbaric oxygen therapy – a new therapeutic option in central retinal artery occlusion

Terapia hiperbaryczna – nowa opcja leczenia zamknięcia tętnicy środkowej siatkówki

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Abstract. Central retinal artery occlusion is an ophthalmological emergency with a poor prognosis. It is characterized by painless, monocular loss of vision, progressing even within minutes. The most common cause of a central retinal artery occlusion is an embolus originating in the carotid arteries or cardiac chambers. Other causes may include a thrombosis *in situ* in the central retinal artery. The natural history of visual outcomes in central retinal artery occlusion is poor. Thus, correct diagnosis and immediate treatment is crucial. Unfortunately, conventional methods of treatment bring no satisfying effects. New therapies are under investigation, one of them being hyperbaric oxygen therapy. This involves inhaling 100% oxygen under increased and fixed pressure. This article discusses the principles of hyperbaric oxygen therapy in central retinal artery occlusion, indications for use and factors limiting its effectiveness.

Key words: central retinal artery occlusion, hyperbaric oxygen therapy, “cherry-red spot” sign

Streszczenie. Zamknięcie tętnicy środkowej siatkówki jest nagłym stanem okulistycznym o złym rokowaniu. Typowym objawem jest bezbolesna jednooczna utrata widzenia, postępująca nawet w ciągu kilku minut. Najczęstszą przyczyną zamknięcia tętnicy środkowej siatkówki jest zator pochodzący z tętnic szyjnych lub zastawek serca. Przyczyną może być również zakrzep tworzący się *in situ* w tętnicy środkowej siatkówki. Naturalny przebieg zamknięcia tętnicy środkowej siatkówki jest niekorzystny, dlatego kluczowe jest szybkie ustalenie właściwego rozpoznania i włączenie leczenia. Niestety konwencjonalne metody postępowania w zamknięciu tętnicy środkowej siatkówki nie dają satysfakcjonujących wyników, poszukuje się więc nowych sposobów leczenia. Jednym z nich jest terapia hiperbaryczna, polegająca na oddychaniu 100% tlenem podawanym w warunkach stałego zwiększonego ciśnienia. W artykule omówiono założenia terapii hiperbarycznej w zamknięciu tętnicy środkowej siatkówki, wskazania do jej zastosowania i czynniki ograniczające jej efektywność.

Słowa kluczowe: zamknięcie tętnicy środkowej siatkówki, tlenoterapia hiperbaryczna, objaw „wiśniowej plamki”

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Central retinal artery occlusion (CRAO) is an ophthalmological emergency with poor prognosis. It was first described by Graefe in 1859 [1]. The typical symptom of CRAO is painless, monocular loss of vision, progressing even within minutes. The prevalence of CRAO is estimated at 1 to 8-9 episodes per 100,000 people [2, 3]. It is most frequently caused by an embolus originating in the carotid arteries or cardiac chambers. It may also be a consequence of a thrombus forming *in situ* in the central retinal artery [4]. Due to the differences in

therapeutic management, rapid differentiation between thromboembolic origin of CRAO and vasculitis is required [2-4]. The retina is a photosensitive membrane with the greatest oxygen use per weight unit in the organism. As a result, it is very sensitive to hypoxia. Sudden CRAO leads to retinal hypoperfusion and progressive damage to the membrane cells [5]. The scope of retinal injury depends on the degree of collateral circulation and the duration of the ischaemia. Experimental studies on animals demonstrated that retinal damage due to

hypoxia is fully reversible only within approximately 100 minutes of its onset [5].

The diagnostic procedures in CRAO include: blood tests (complete blood count, biochemistry, coagulation parameters) and determination of inflammatory parameters (erythrocyte sedimentation rate, acute phase proteins). In sudden loss of vision, usually a head computed tomography is performed to exclude intracranial haemorrhage. Ophthalmological diagnostic tests in suspected CRAO include fluorescein angiography (FA) to assess the blood flow in the retinal vessels. Electroretinography allows us to evaluate the degree of bioelectric function impairment in the retina due to CRAO [2-5]. The natural course of CRAO is unfavourable. In over 90% of patients visual acuity (VA) is reduced to finger counting or worse. Only in approximately 10% of cases does vision improve [6]. Patients often report a history of transient, short episodes of vision loss, and atherosclerosis before CRAO. In the test of retinal function, vision usually oscillates between light perception and finger counting. In addition, the direct pupillary reflex is disturbed [7]. Ophthalmoscopic examination of the eye fundus reveals retinal pallor, and a cherry red-spot sign is observed in the macula, i.e. the foveola is darker than the surrounding tissue. The retina has a dual blood supply. Photoreceptors and pigment epithelium receive blood through the choroid, and the remaining layers are supplied by the central retinal artery. The red-cherry spot sign is due to the fact that the foveola contains only photoreceptors, nourished by the choroidal vasculature. The rest of the retina is pale due to ischaemia caused by occlusion of the central artery. One can also observe in the eye fundus the fragmentary blood flow in the retinal arterioles, but the embolic material is rarely visible [8].

Management of CRAO is complex [9-11]. Improvement in both the retinal blood supply and retinal function was observed after immediate eye massage (to induce changes in the intraocular pressure, and move the embolic material), reduction of the intraocular pressure (using medications: acetazolamide, hyperosmotic agents: mannitol, anterior chamber paracentesis), and hyperventilation [9-13]. Intra-arterial fibrinolytic agents were also administered [14-16]. The effectiveness of local intra-arterial fibrinolytic therapy was assessed in a multi-centre, randomised, prospective study (the European Assessment Group for Lysis in the Eye – EAGLE study), involving 82 patients with CRAO within 20 hours from symptom onset. Unfortunately, the effectiveness of this treatment was similar to standard management, but the risk of complications was considerably higher (37% of cases) [2].

Another interesting therapeutic option is hyperbaric oxygen therapy (HBOT) [17]. The first reports regarding

the use of a hyperbaric chamber in ophthalmology date back to 1965 [18, 19]. In CRAO, the internal layers of the retina supplied by the central retinal artery die, which results in the loss of vision. However, these layers may receive sufficient amount of oxygen through diffusion from the choroidal circulation if the partial pressure of oxygen is increased. For recanalisation to occur, proper partial pressure of oxygen must be maintained for at least 72 hours. Due to oxygen supplementation, the choroidal vessels may provide a sufficient supply for the internal layers of the retina through diffusion. This allows us to preserve the viability of the retinal ganglion cells, even when the retinal vessels have been completely occluded. During the hyperbaric therapy the serum oxygen content increases by a factor of 20-30. In natural conditions, 60% of the retinal oxygen requirement is covered by the choroid. With increased oxygen partial pressure, the choroid can cover 100% of retinal oxygen requirement.

Hyperbaric therapy is a non-invasive treatment method. It consists in breathing 100% oxygen administered at a constant ambient pressure, increased to over 1 atmosphere [20-23]. The therapy takes place in a special hyperbaric chamber, which enables an efficient saturation of the tissues with oxygen. During HBOT, the arterial oxygen pressure is approximately 2000 mm Hg. The oxygen passes to the erythrocytes, and its concentration rises in the serum, lymphatic system and cerebrospinal fluid. The hyperbaric chamber is used in the following indications: decompression disease, gas emboli, carbon monoxide intoxication, gas gangrene, necrotising soft tissue infection, musculoskeletal injury, multiorgan injury, thermal burn, post-radiation soft tissue injury, post-radiation bladder damage, sudden deafness, chronic bone inflammation, and diabetic foot syndrome. Absolute contraindications include untreated pneumothorax and use of certain medications (adriamycin, disulfiram, cisplatin, sulfamylon). Relative contraindications for HBOT include upper respiratory infection, fever, pregnancy, epilepsy, bronchial asthma, emphysema, chronic obstructive pulmonary disease, heart failure, previous operations to the sinuses, ear and chest, diffuse neoplastic disease and claustrophobia [20-26].

The hyperbaric therapy is approved by FDA in the treatment of CRAO [20-26]. Its highest efficiency occurs when applied 8 - 12 hours after the onset of CRAO symptoms.

Hadanny et al. assessed the effectiveness of HBOT, and determined the parameters of irreparable retinal damage in CRAO [23]. The observation involved 232 patients with CRAO treated in the years 1999-2015 in the Centre for Hyperbaric Medicine in Tel Aviv. The data was collected retrospectively, and included age, sex, chronic

diseases, medications used, ophthalmological diseases, time from symptom onset to the initiation of treatment, visual acuity, eye fundus examination, intraocular pressure, protocol of the hyperbaric therapy, and adverse events. CRAO was diagnosed based on the symptoms and the results of eye fundus examination. The following inclusion criteria were applied: age over 18 years old, occlusion of the central retinal artery unrelated to vasculitis, symptoms persisting for less than 20 hours, baseline best corrected visual acuity (BCVA) > 0.5 logMAR, i.e. Snellen < 0.32. The exclusion criteria included: presence of cilioretinal artery, lack of data regarding BCVA, BCVA < 0.5 logMAR (Snellen > 0.32), occlusion of the central retinal artery due to vasculitis, iatrogenic occlusion of the central retinal artery, occlusion of a branch of the central retinal artery, and other final diagnosis [23]. The hyperbaric treatment protocol was based on inhalation of 100% oxygen at 2-2.4 atm. Three 90-minute therapeutic sessions were applied within the first 24 hours, followed by one session daily. The treatment was discontinued when VA did not improve after two consecutive sessions. Patients from the control group received classic therapy of CRAO: eye massage, anterior chamber paracentesis, and pharmacological treatment: oral acetylsalicylic acid, acetazolamid and β -blocker drops locally. The patients were carefully diagnosed from a neurological and cardiac perspective, to determine the cause of central retinal artery occlusion. They received cardiac echocardiography and Doppler ultrasound of carotid arteries. Changes in BCVA in the course of HBOT were assessed. VA was evaluated using the logMAR score and Early Treatment of Diabetes Retinopathy Study (ETDRS) charts. A significant clinical improvement was defined as VA improvement by 0.3 logMAR.

Out of 232 patients treated in the hyperbaric medicine centre, a group of 128 subjects met the inclusion criteria, and were included in the final analysis. The mean age of patients was 66.5 years, 69% of them were males. The most common chronic diseases included hypertension and hypercholesterolaemia. Approximately half of the patients received anticoagulants before the episode of central retinal artery occlusion. In 2 out of every 3 patients the origin of the material occluding the artery was not determined. In 11% of cases the source of the embolus was material from the heart. 18% of subjects were diagnosed with atherosclerosis of the carotid arteries. The mean time from the onset of CRAO symptoms to initiation of treatment was 7.8 ± 3.8 hours. The mean number of session in the hyperbaric chamber was 4. In 2 out of 3 subjects the examination of the eye fundus revealed a cherry-red spot. The mean BCVA according to logMAR at the admission was 2.14 ± 0.50 (i.e. finger counting), and as a result of HBOT it improved

significantly to 1.61 ± 0.78 ($p < 0.0001$). 67% of patients in the studied group obtained a clinically significant improvement of vision, i.e. VA improvement by at least 0.3 logMAR. 25% of patients achieved BCVA > 1.0 logMAR (Snellen > 0.1). The percentage of eyes with a significant VA improvement was significantly higher in patients without the red-cherry spot (86% vs 57.6%, $p < 0.0001$). Also the percentage of eyes with BCVA > 1.0 logMAR was significantly higher in the cases without the red-cherry spot (61.0% vs 7.1%, $p < 0.0001$). No correlation was demonstrated between the red-cherry spot sign and the onset of CRAO. HBOT appeared to be safe: only 5.5% of patients experienced minor, reversible adverse events. They included transient problems of minimal intensity, fully subsiding within 2-3 days, such as ear pain, dyspnoea, or nose bleed [23].

Hadanny et al. demonstrated that patients who did not present with the red-cherry spot in the eye fundus at the moment of initiation of treatment obtained a significantly higher improvement of vision compared to subjects who presented with this sign. The presence of embolic material or an interrupted blood column in the arteries at the moment of the patient's arrival did not affect the final visual acuity. The factors that had a statistically significant effect on the final VA included: time between the symptom onset and initiation of treatment, red-cherry spot sign in the eye fundus, and visual acuity at the moment of the patient's arrival. Factors such as age, sex, previous anticoagulation treatment, chronic diseases, intraocular pressure, application of paracentesis, eye massage or the number of sessions in the hyperbaric chamber did not affect the improvement of visual acuity [23].

Periods of tolerance to ischaemia vary considerably between people. For instance, patients with atherosclerosis develop tolerance to longer periods of tissue ischaemia. This resistance depends on the type of vascular occlusion, and on the presence of residual flow, so time cannot be the only parameter indicating an irreversible character of tissue damage. It may be assumed that until the red-cherry spot sign develops, regardless of the time from the symptom onset, the damage can be reversed with hyperbaric therapy [20-23]. Hadanny et al. suggest that when HBOT is easily available, one therapeutic session is justified in patients presenting with the red-cherry spot sign. Treatment in the hyperbaric chamber should be continued only after a significant improvement of vision following the first HBOT session [23].

In the past several years there have been reports of the effectiveness of hyperbaric therapy in the treatment of central retinal artery occlusion. Soares et al. in 2017 described two cases where HBOT was applied [24]. The first patient was a 61-year-old female who received 8

HBOT sessions at 2.4 atm. BCVA improved from finger counting to Snellen 1.0. FA demonstrated normalisation of the blood flow in the eye fundus arteries. As for the systemic comorbidities, increased HbA1c and supraventricular extrasystoles were observed. The second patient, a 69-year-old male, received 9 HBOT sessions at 2.4 atm. BCVA improved from finger counting to Snellen 0.8, and FA revealed a normal flow in the retinal arteries. Atherosclerotic plaques were found in the patient's internal carotid artery.

Menzel-Severing et al. in 2012 published the effects of HBOT in patients with CRAO [25]. It was a retrospective, non-randomised case series. The analysis included all CRAO cases in the period from 1997 to 2010. Two groups were distinguished: 51 patients treated with HBOT and haemodilution, and a control group of 29 patients treated only with haemodilution. Included in the study were patients with VA up to 20/200 within 12 hours from the onset of CRAO symptoms. The mean baseline VA in the combined therapy group was finger counting, and in the control group it was 20/1000. There were no significant differences between the groups with regard to the duration of CRAO symptoms before the initiation of treatment. In the group receiving the combined therapy with HBOT the mean VA improvement was 3 lines on the Snellen chart ($p < 0.0001$). The improvement persisted for over three months of follow-up treatment ($p = 0.01$). In the control group, receiving only haemodilution, the mean VA improvement was 1 line ($p = 0.23$, after three months of follow-up $p = 0.17$). The percentage of eyes that improved by 3 or more lines on the Snellen chart was 38% in the combined therapy group, and 17.9% in the haemodilution group ($p = 0.06$). However, after three months of follow-up no significant differences were found in that respect between the groups (35.7% vs 30.8%; $p = 0.76$). The authors of the study pointed to the need for an extended prospective study with randomisation.

Cope et al. described a series of 11 cases of CRAO in which HBOT was applied in the period between 2005 and 2009 [26]. In 8 cases vision improved, in 53% of patients by 2 or more lines on the Snellen chart.

Summing up, hyperbaric therapy is effective, safe and non-invasive methods of treatment of central retinal artery occlusion. Clearly, the efficiency of HBOT is largely determined by the time from the onset of CRAO symptoms and initiation of treatment. The highest effectiveness of HBOT is obtained before the cherry-red spot sign develops in the eye fundus. However, due to a high inter-individual dispersion of periods of tolerance to ischaemia, even in the presence of the red-cherry spot HBOT may be used, especially in those centres where hyperbaric therapy is available. HBOT may also be a part

of combined therapy with the use of conventional methods of treatment of CRAO.

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Polish Army Honour Book and medical professions

Księga Honorowa Wojska Polskiego a zawody medyczne

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Abstract. The Polish Army Honour Book (previously: Honorary Book of the Minister of National Defence) honours Polish Army soldiers and military institutions and units in terms of special achievements. The authors browsed through both documents in search for soldiers and military institutions honoured with an entry in both of the books for particular achievements related to the field of medicine.

Key words: Polish Army Honour Book, medical professions

Streszczenie. Księga Honorowa Wojska Polskiego (wcześniej Księga Honorowa Ministra Obrony Narodowej) honoruje żołnierzy Wojska Polskiego oraz instytucje i jednostki wojskowe za szczególne osiągnięcia. Autorzy dokonali przeglądu obu dokumentów w celu wyszukania żołnierzy i instytucji wojskowych uhonorowanych wpisem za szczególne osiągnięcia związane z aktywnością medyczną.

Słowa kluczowe: Księga Honorowa Wojska Polskiego, zawody medyczne

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Introduction

The Polish Army Honour Book ("Book") has existed since 2010. The rules for making entries in the Book are specified in the Regulation of the Minister of National Defence of 23 June 2010 on the distinction of soldiers, former soldiers and sub-units, military units and institutions (Dz. U. [Journal of Laws] 2010 no. 124 pos. 841, chapter 8 §32 point 4, chapter 10 §44 and §45), and in the Act of 9 October 2009 on military discipline (Dz. U. [Journal of Laws] 2009 no. 190 pos. 1474, art. 11.1 and 13). Originally, special achievements of the Polish Army soldiers were honoured in the Honorary Book of Military Acts, which was renamed the Honorary Book of the Minister of National Defence in 1989.

The Book commemorates special achievements in the performance of duties, including training in peacetime, as well as acts of sacrifice and courage in active military service after the announcement of conscription, during a

state of emergency, in wartime, and during the performance of duties in a war zone. In the event of the use of the Armed Forces of the Republic of Poland outside the state borders, the entries in the Book refer to the achievements of humanitarian, search and rescue missions [1]. The entries include the achievements and acts of soldiers of various corps and types of service. It illustrates the complexity of the duties of a modern army, as it contains mentions of achievements in combat, as well as those in the field of commanding and training, staff work, organization and scientific research. Dramatic are the entries concerning soldiers who sacrificed their lives in service to the homeland. Both books are kept at the Museum of the Polish Army in Warsaw.

Health care in honorary books

The Book contains 170 entries, and the Honorary Book of the Minister of National Defence has 182 entries. Among the entries referring to soldiers and military institutions of all types of services only a few concern aspects related to medicine: five soldiers and one institution, which makes them even more worth mentioning and appreciating.

Military medical institutions

The medical institution honoured with an entry in the Polish Army Honour Book in 2011 is the 2nd Military Field Hospital in Wrocław, which received a special mention of the Minister of National Defence for achievements in saving the lives and health of soldiers of the Polish Military Contingents. The hospital was established by the decision of the Minister of National Defence of 10 July 2008. It was opened on 1 September 2009. It continues the tradition and achievements of the 2nd hospital of Peacekeeping Operations. The soldiers - employees of that hospital – participated in numerous foreign missions, including medical support for the Polish Military Contingent in Iraq, Afghanistan, Lebanon, Chad and Syria (within the United Nations Disengagement Observer Force on the Golan Heights), international *peace*-support operations of the North Atlantic Treaty Organization and the Polish Military Contingent during the European missions of the European Union Force in Bosnia and Herzegovina, in Cambodia (United Nations Transitional Authority in Cambodia) and in the United Nations Transition Assistance Group in Namibia. The commitment and dedication of the soldiers and other hospital staff in the medical support for the Polish Military Contingents was repeatedly appreciated by the NATO and the US Department of the Army. During the 3rd rotation of the Polish Military Contingent in Iraq, Major Jacek Kostecki MD lost his life and three other members of the medical staff were injured. The 2nd Military Field Hospital is stationed in Wrocław, and additionally it coordinates the activities of three Medical Support Groups: 6 (stationed in Krakow), 10 (stationed in Świętoszów) and 25 (stationed in Tomaszów Mazowiecki) [2].

White staff – soldiers

A nurse, junior Second Lieutenant, Ewa Porząyńska from the 10th Military Clinical Hospital in Bydgoszcz, was honoured with an entry in the Honorary Book of the Minister of National Defence by his decision of 23 July 2003. She was distinguished for exceptional courage, dedication, activity and professionalism during the rescue operation after a Mi-24 helicopter accident on 4 April 2003 in the training area in Drawsko Pomorskie. Three soldiers were killed and six were seriously injured in the

accident. Regardless of the danger, she proceeded to perform a rescue operation, bringing help to the wounded. It was recognized that thanks to her innovative ideas and the use of unconventional methods, the medical support met the requirements of the NATO medical services.

Captain Zbigniew Plak, M.D., assistant physician at the 108th Military Hospital with Outpatient Clinic SP ZOZ in Elk, was distinguished for bravery, sacrifice and dedication in saving human health and life during the stabilization mission of the Polish Military Contingent in Iraq. The decision on the entry into the Honorary Book of the Minister of National Defence was issued on 18 April 2005. Captain Plak participated as a physician in the peacekeeping mission of the Medical Support Group in Karbala. While he was providing medical assistance to Iraqi citizens injured in a car accident, he suffered a serious spinal injury, yet in the following days he continued to perform his professional duties diligently and performed surgeries on Polish soldiers injured in a terrorist attack. A few hours after the end of the surgery, due to the spinal injury he had suffered, he lost feeling in his legs.

By decision of 13 July 2012, Lieutenant Colonel Marzanna Rosińska, M.D., head of the Education Department at the Military Medical Education Center in Łódź was honoured in the Polish Army Honour Book for outstanding achievements in popularizing knowledge of military emergency medicine. Since 1992 she has served in research and education in military healthcare institutions, initially at the Military Medical Academy in Łódź, and since 2002 in subsequent positions at the Military Medical Service Training Center. Among others, Lieutenant Colonel Rosińska worked on the development of training concepts and programs primarily in the field of emergency medicine. Her competences and specialist knowledge ensured the high level of content and form for numerous specialist military publications, including the instructor's handbook "Assisting the wounded on the battlefield - procedures for soldiers". Selected evacuation procedures developed by her team from the Medical Training Center and included in the manual "Medical evacuation of the Rosomak transporter crew" were implemented by the Polish Armed Forces.

Senior Corporal Przemysław Małolepszy, group commander and senior paramedic of the 1st Engineering Battalion of the 5th Engineering Regiment in Szczecin, was honoured with an entry in the Polish Army Honour Book for exceptional bravery and courage while serving in the 5th rotation of the Polish Military Contingent in Afghanistan (decision of 4 August 2010). He served multiple times outside Poland. In 2009, as a paramedic in the 5th rotation of the Polish Military Contingent in Afghanistan, while performing his duties within a

Polish-Afghan patrol he attempted to rescue Captain Daniel Ambrozinski under fire, risking his own life. Despite being injured himself, he continued helping other soldiers from the patrol. Thanks to his courage and sacrifice, the size of the tragedy could be reduced.

The last entry in the Polish Army Honour Book regarding medical staff is the decision of 4 August 2017 on the distinction of Division General Prof. Dr. hab. MD Grzegorz Gierelak, director of the Military Institute of Medicine in Warsaw, for his outstanding medical, educational and managerial achievements. Professor Gierelak developed his medical knowledge in the course of work in successive educational, scientific and managerial positions at the Central Clinical Hospital of the Ministry of National Defence (CSK MON) in Warsaw. Since 2007 he has been the director of the Military Institute of Medicine. During his term of office a number of wards were created and modernized. Also, a unique, specialist unit was created: Clinic of Psychiatry and Combat Stress, which assists veterans of foreign missions in their long and difficult recovery. The long-term dedication of Professor Gierelak his to service and medical, managerial and educational activity has contributed to broadening of the scope and improvement of the quality of medical assistance provided to soldiers and their families, which means a measurable strengthening of the combat capabilities of the Polish Armed Forces.

Summary

Commitment, determination and dedication are the features which are common for the "white staff" of soldiers honoured in the honorary books of the Polish Army. Their work has contributed to saving human life, both by improving the functioning of medical facilities and health care organizations, as well as through direct participation in rescue operations and military missions of international organizations, including NATO.

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Professors on both sides of the Iron Curtain – the *genius loci* of the Jan Sobieski 6th Regional Hospital in Lviv

Profesorowie po obu stronach „żelaznej kurtyny” – *genius loci* 6. Szpitala Okręgowego im. Króla Jana III Sobieskiego we Lwowie

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Abstract. The Jan Sobieski 6th Regional Hospital was one of the ten most important military health care facilities in the interwar period. The unusual atmosphere prevailing in Lviv, where the cultures of various nations merged (Poles, Jews, Germans, Armenians, Russians, Ruthenians and others), inspiring and enriching each other, was also felt in the 6th Regional Hospital. This is how the specific *genius loci* of the 6th Regional Hospital was created. An excellent illustration of this phenomenon is the interesting history of two physicians from the Lviv military clinic, the head of the X-ray Laboratory Alfred Bong (1899–1982) and the senior head of the Ophthalmology Department Witold Starkiewicz (1906–1978), who after the end of World War II, operating in completely different socio-political conditions (US and PL), achieved high professional positions, becoming models and patrons for medical specialists in their field. Today, the legendary King Jan Sobieski 6th Regional Hospital no longer exists, but despite all that its eastern gate, decorated with the “Janina” coat of arms of the Sobieski family, survives and still inspires everyone visiting 26 Łyczakowska Street, further proof of the *genius loci* of this institution.

Key words: 6th Regional Hospital, Alfred Bong (Bonk), Lviv, Witold Starkiewicz, ophthalmology, radiology

Streszczenie. 6. Szpital Okręgowy im. Króla Jana III Sobieskiego we Lwowie to jedna z dziesięciu najważniejszych placówek wojskowej służby zdrowia w okresie dwudziestolecia międzywojennego. Niezwykłą atmosferą panującą we Lwowie, w którym przenikały się kultury różnych nacji (Polacy, Żydzi, Niemcy, Ormianie, Rosjanie, Rusini i inni), wzajemnie się wzbogacając i inspirując, prześlągnięty był także 6. Szpital Okręgowy. W taki właśnie sposób tworzony był swoisty *genius loci* 6. Szpitala Okręgowego. Doskonałą ilustracją tego zjawiska są ciekawe dzieje dwóch medyków lwowskiej lecznicy wojskowej: kierownika Pracowni Rentgenologicznej Alfreda Bonga (1899–1982) i starszego ordynatora Oddziału Ocznego Witolda Starkiewicza (1906–1978), którzy po zakończeniu II wojny światowej, funkcjonując w zupełnie różnych warunkach społeczno-politycznych (USA i PRL), osiągnęli wysoką pozycję zawodową, stając się wzorem i patronem dla medyków swojej dziedziny. Dziś już nie istnieje legendarny 6. Szpital Okręgowy im. Króla Jana III Sobieskiego, lecz wbrew wszystkiemu przetrwała jego wschodnia brama z zachowanym herbem „Janina” rodu Sobieskich, która wciąż inspiruje wszystkich odwiedzających Łyczakowską 26, co jest kolejnym dowodem istnienia *genius loci* tej placówki.

Słowa kluczowe: 6. Szpital Okręgowy, Lwów, Alfred Bong (Bonk), Witold Starkiewicz, okulistyka, radiologia

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Introduction

For over 600 years Lviv was an important centre of Polish science, culture and art. In the interwar period the city was home to the Jan Sobieski 6th Regional Hospital, one of the ten most important military health care facilities. The building was a former monastery of the Order of the Brothers of Saint John of God. There, in 1659, the future king of Poland, then Ensign Jan Sobieski, founded a hospital for soldiers. It is worth emphasising that the founder stipulated that the financial means should be used by the friars to provide care for the poor, in particular "soldiers who fell ill while going to or returning from the army camp". An expression of the great care of Sobieski for the health care of his soldiers was the confirmation of the hospital's foundation and the increase in its financing in the Warsaw constitution of 1685, after he ascended to the throne of the Polish-Lithuanian Commonwealth. The hospital functioned in that form until after the first partition of Poland. It was closed in 1786 by virtue of the decree of the Austrian Emperor Joseph II, as a result of the liquidation of the Order of the Brothers of Saint John of God. The area and buildings were taken over by the Austrian army, which opened its own military hospital there. In 1918, thanks to the determination of the inhabitants of Lviv and their heroic defence of the city against the Ukrainians, the city of Lviv, called *Semper Fidelis*, was returned to Poland. The former military hospital founded by Sobieski was taken over by the Polish military health service, which organised there the 6th Regional Hospital, the main medical centre of the region, and in 1933 named after King Jan III Sobieski. In the years 1921-1939 the facility had 500-1000 beds. There were surgical, internal medicine, infectious disease, gynaecological and obstetric, neurological, laryngological, ophthalmological and dermatological-venereal wards, as well as X-ray and bacteriological laboratories, a pharmacy and a dental clinic. Most of the medical staff were military doctors, although civilian physicians were also employed to fill vacancies. The possibility to cooperate with the clinics of the Jan Kazimierz University (UJK) created favourable conditions for professional development, and was beneficial for both the military health service and the Faculty of Medicine. The unusual atmosphere prevailing in Lviv, where the cultures of various nations (Jews, Germans, Armenians, Russians, Ruthenians and others) merged, enriched and inspired each other, was also noticeable in the 6th Regional Hospital. It was conducive to the proper organisation of work and obtaining good treatment results, which attracted both the patients and the young medical students who wanted to gain experience working with renowned specialists. Relations

built in this way resulted in numerous scientific publications and inventions. They were also an example for the youngest physicians, how to approach daily challenges of a physicians' work in a creative and open-minded way. All this contributed to the *genius loci* of the Jan Sobieski 6th Regional Hospital.

Strong evidence of its existence is the fate of many physicians working in that institution, who absorbed the rules of the Lviv military clinic and were able to cope even under the most difficult circumstances, becoming local leaders and contributing to society. An excellent illustration of this phenomenon are the lives of two physicians of the Lviv military clinic: the head of the X-ray Laboratory, Alfred Bong, and the senior head of the Ophthalmological Ward, Witold Starkiewicz, who after the Second World War functioned in completely different socio-political conditions (USA and Polish People's Republic), and yet achieved high professional positions and became models and patrons for other physicians in their fields [1].

Lviv military physician as a patron of Radiology Centre w Chicago

The first of them, Alfred Kazimierz Bong, was born on 9 September 1899 in Chernivtsi, Bukovina, to the family of Władysław Bong and Zofia nee Dziłich. His father became the station master of the railway station in Borszczów, so his son was educated at the renowned C.K. Middle School No. V in Lviv. It was a school which provided excellent education, as well as patriotic values. Its students included the youngest recipient of the War Order of *Virtuti Militari*, Defender of Lviv, Antoś Petrykiewicz. Alfred Bong graduated in 1917, during the First World War.

After his final exams he was drafted into the Austrian army on 15 September 1917. He served as a recruit in the 24th Field Artillery Regiment. From 2 November to 27 December 1917 he participated in a course for gunners at the School of Artillery Officers in Preszburg (now Bratislava), after which he was promoted to the rank of a bombardier. On 10 May 1918 he was sent to the Italian front, to the 2nd Artillery Battalion of the School Regiment, where he was promoted to the rank of gunnery sergeant (15 August 1918) and became a platoon commander. The culmination of his service in the Austrian army was the promotion to the rank of ensign on 15 October 1918 [2-4].

At the time of the Ukrainian invasion of Lviv in November 1918, he was on vacation in his native Borszczów. His father, the head of the town railway station, refused to carry out the orders of the Ukrainians. Throughout the entire period of the siege of Lviv, Alfred attempted but failed to join the emerging Polish Armed Forces.



Figure 1. Alfred Kazimierz Bong (1899–1982), 1920s (Central Medical Library: KOL L.598)

Rycina 1. Alfred Kazimierz Bong (1899–1982), lata 20. XX wieku (Główna Biblioteka Lekarska: KOL L.598)



Figure 2. Witold Szymon Starkiewicz (1906–1978), as a cadet of the Medical Officer Cadet School in Warsaw, 1930s (courtesy of Professor Joanna Kośmider)

Rycina 2. Witold Szymon Starkiewicz (1906–1978) jako podchorąży Szkoły Podchorążych Sanitarnych w Warszawie, lata 30. XX wieku (udostępnione dzięki uprzejmości Profesor Joanny Kośmider)

The effective relief of Lviv enabled him to join the ranks of the Polish Army as an ensign on 10 June 1919. In the period from 16 July to 10 August 1919 he attended training at the School of Artillery Officers in Rembertów. Then he was appointed the commander of a platoon in the 1st battery of the 8th Heavy Artillery Regiment, where he was promoted to the rank of second lieutenant. He was slightly wounded on 22 October 1919 and treated in an outpatient clinic. At that time he was directed to the course for physicians in Lviv, which he attended until 5 June 1920. At the time of the greatest intensity of Polish-Bolshevik fighting, from 6 June to 30 September 1920, he served on the front as an officer of the camps and administration of Field Hospital 904/305 in the 2nd Lithuanian and Belarusian Division. At the beginning of 1921, he was appointed to a similar position in Auxiliary Medical Company No. 3, from where he was delegated to the Faculty of Medicine of the UJK on 1 October in order to continue his education as a doctor. During the summer break in 1922 he was a deputy doctor at the District Hospital in Lida (1 July - 18 August), 9th Heavy Artillery Regiment (19 August-2 September) and the District Hospital in Siedlce (3-30 September). In October 1922 he was assigned full time to the 6th Medical Battalion with simultaneous continuation of medical studies at the UJK. He was promoted to the rank of second lieutenant as an assistant to a physician on 17 November 1923. He received the diploma of doctor of general medicine at the Jan Kazimierz University in Lviv on 7 November 1925. After a month he was promoted to the rank of lieutenant and appointed to the position of junior doctor in the 54th Infantry Regiment in Tarnopol. His two-year stay in this unit is best summarised by an opinion formulated in 1927 by the deputy commander of the regiment, Lt. Col. Waclaw Piekarski: "He has a very well developed sense of honour and personal dignity. He is energetic and tactful towards his subordinates (...). His

intelligence is vivid and brilliant (...). He is well suited to be the head physician of the regiment. A high level of commitment to values". On 11 December 1927 Bong became a full-time doctor of the 40th Infantry Regiment in Lviv, which enabled him to return to his beloved city and make contact with the physicians of the 6th Regional Hospital at 26 Łyczakowska Street. This resulted in his referral to a specialization course in radiology in this facility, which he attended from 2 October 1928 to 13 January 1929. Later he became the head doctor of the 14th Regiment of Jazłowiecki Ułans, probably the most popular military unit in Lviv, where in January 1930 he was promoted to the rank of captain. His supervisors valued his knowledge, so they did not create any obstacles for him to attend specialisation training in radiology. From 24 February to 31 December 1930 he developed his competences during a specialisation course in the hospital of the Medical Training Centre (CWSan) in Warsaw. There is an official opinion on him from that period, formulated by the commander of the CWSan, General Jan Kollątaj Srzednicki (1883-1944), in which we read: "extremely intelligent and talented, energetic and independent, will make a good, independent supervisor." On 1 January 1931, by the order of the head of medical region VI no. 4122/30, he was appointed head of the 6th Regional Hospital in Lviv. Due to his thirst for knowledge, the new chief physician did not want to stop with the specialisation training available in Poland, but travelled to Vienna, where from 1 January to 28 February 1931 he studied in the clinics under the supervision of the outstanding Austrian radiologist, Professor Guido Holzkecht (1872-1931). In this way he obtained excellent professional training and became one of the best radiologists in Lviv at that time.



Figure 3. Eastern gate of the former 6th Regional Hospital, the portal still features the "Janina" coat of arms of the Sobieski family, 19 October 2017 (by Z. Kopociński)

Rycina 3. Brama wschodnia dawnego 6. Szpitala Okręgowego we Lwowie, na portalu zachowany do dzisiaj herb rodziny Sobieskich „Janina”, 19 października 2017 roku (autor Z. Kopociński)

The crowning achievement of his military and medical career was his appointment as head of the X-ray Laboratory at the 6th Regional Hospital in Lviv on 5 September 1931, which in a short time became one of the best known and most respected X-ray laboratories in the city. The significant role of Captain Bong in the development of military radiology in Lviv is reflected in the opinion on him formulated on 5 September 1934 by the commander of the 6th District Hospital, Colonel Bronisław Stroński, containing the following words: "He is an officer of high individuality and energy, showing outstanding initiative (...) An excellent organiser of the X-ray laboratory with excellent planning ability and purposefulness of actions. He constantly works to

improve and simplify the course of work (...) Thanks to his broad professional knowledge and excellent results he has turned the X-ray laboratory of the local hospital into a first-rate facility. Overall assessment: outstanding". These were not just courteous compliments, but a realistic and accurate assessment of the work of a military radiologist. In the university city with the Faculty of Medicine of the UJK there were many distinguished doctors and it was not easy to gain a high status among them. It makes the level and importance obtained by the X-ray Laboratory of the 6th Regional Hospital and its chief physician even more worth appreciating. One sign of appreciation from his military superiors was his promotion to major on 19 March 1938.

At that time Lviv was an important centre of science, where world-famous scientists from the Lviv school of mathematics: Stefan Banach (1892-1945), Stanisław Ulam (1909-1984) and Hugo Steinhaus (1887-1972) conducted their brilliant projects. The latter was renowned also in medical circles, due to his work on an "intramer" - a device for locating foreign objects inside a human body. Major Bong, who was the head of the Lviv Circle of the Polish Medical Radiological and Physiotherapeutic Society (PLTRiF) and who actively participated in the scientific activities (he was the author of several very interesting publications), together with associate Professor Witold Grabowski from the Internal Medicine Clinic at the UJK invited Professor Hugo Steinhaus to the meeting of the society on 8 May 1938 to deliver a lecture entitled "On the location of objects using X-rays". The idea of this Lviv mathematician impressed the military radiologist so much that he decided to construct a prototype of the "introwizor" and apply it in practice in the X-ray Laboratory of the Jan Sobieski 6th Regional Hospital. In a short time the device was ready and it was used in four procedures to remove foreign objects from the patients' bodies under local anaesthesia. The success was noticed by the Head of the Department of Health in the Ministry of Military Affairs, General Stanisław Rouppert (1887-1945), who invited Major Bong to present the device to an appropriate committee of military specialists. Unfortunately, further work on the implementation of the "introwizor" was interrupted by the outbreak of the Second World War [5-11].

During the defensive war of 1939 Major Bong was assigned to the 5th Infantry Division in the "Pomorze" Army. He fought in all its battles, including those for Warsaw. For his courage and dedication he was awarded the Cross of Valour. After the capitulation of the capital he worked at Ujazdowski Hospital, and at the turn of 1939 he left for health reasons to Krynica, where he stayed in the Main Spa House on Kościuszki Street. In April 1942 he returned to Warsaw and became involved

in resistance activities under the pseudonym "Boniecki". He became the medical director of Independent Poland, a conspiracy organization established by the Warsaw division of the Silesian Insurgents' Union, from June 1943 subordinated to the Home Army. He took part in the Warsaw Uprising, during which he was the commander of the wound dressing point on Emilii Plater and Poznańska Streets. After the fall of the uprising he was taken prisoner, he was sent to the Polish Military Hospital at Stalag IVB Zeithain in Saxony (formerly the Hospital of the Home Army POWs), where together with Doctor Marian Mroczkowski and Doctor Waclaw Sitkowski he led the X-ray Laboratory for the POWs. In the camp he stayed with his wife and nine-year-old son, Jerzy [12-14].

As a result of the shameful treaties of Yalta and Potsdam, Poland lost its sovereignty and a significant part of its territory, including the city of Lviv. Alfred Bong, unable to return to his homeland and refusing to accept the authorities imposed by the Soviets, decided to remain in exile. He changed the spelling of his surname to Bonk. In the years 1947-1949 he developed his professional qualifications at the University Clinic in Göttingen. In 1950 he emigrated to the United States, where he initially worked in Poteau in Oklahoma, and after two years moved to Chicago, where he became the head of the Department of Radiology at Edgewater Hospital. Simultaneously, from 1976, he worked as a Professor of Radiology at the University of Health Sciences in Chicago, where he shared his experience and skills with medical students. He was an active member of many scientific societies, including the American Medical Association, Chicago Radiological Society, Radiological Society of North America, American College of Radiology and British Institute of Radiology. In 1982, to honour his enormous contribution to the development of radiology in Chicago and as an expression of acknowledgement for 30 years of dedication to his work, the Department of Radiology of the Edgewater Hospital received the name of Doctor Alfred Kazimierz Bonk.

In his private life he was happily married to Eugenia, née Frisch (a Lviv dentist), had a son, Jerzy (born in 1935), who continued his father's work as a radiologist. He was honoured for many years of work in the military health service with the Cross of Valour, Silver Cross of Merit, Medal of the 10th Anniversary of Regaining Independence and Medal of Remembrance for the War of 1918-1921. Major Alfred Kazimierz Bonk (Bong) died on 10 May 1982 in Chicago (Illinois) [15].

A Lviv military ophthalmologist as a father of Szczecin ophthalmology

The life of the senior chief physician of the ophthalmology ward of the 6th Regional Hospital in Lviv had a different course.

Witold Szymon Starkiewicz was born on 3 September 1906 in Gołonóg (Dąbrowa Górnicza), to the medical family of Szymon and Kazimiera Starkiewicz. His father was a well-known and respected medical practitioner, the founder of the "Górka" Children's Sanatorium in Busko Zdrój, and became a role model for young Witold. In 1926 Witold Starkiewicz began studies at the University of Warsaw. Initially he studied mathematics, but soon he changed to the Faculty of Medicine [16]. He met medical students from the Cadet School (until 1928 called the Officers Medical School), which probably inspired Starkiewicz to start military service. He obtained a doctor's diploma on 11 June 1932 and a promotion to the rank of second lieutenant with seniority on 1 November 1933, under the 6th SPSan Promotion [17, 18]. In the years 1933-1934 he was a doctor with SPSan, then he became a full-time physician of the 1st Air Regiment in Warsaw, where he was promoted to the rank of lieutenant with seniority on 1 January 1935. In 1936 he attended a specialist training in his favourite field of medicine - ophthalmology at Ujazdowski Hospital, which allowed him to become an assistant in the ophthalmological department at the Institute of Aeronautical Research in Warsaw a year later. In 1937 he received the award of the Retired Officer-Physician Foundation for his scientific paper "On the influence of low altitude aerobatic flights on the functional state of the eye" [14, 17, 18]. He was promoted to the rank of captain with seniority on 19 March 1938, and several months later he was appointed the senior chief physician of the Ophthalmology Ward of the Jan Sobieski 6th Regional Hospital in Lviv.

The position of the head of the ophthalmology ward in one of the ten most important military hospitals at that time was undoubtedly a distinction and an expression of appreciation for the knowledge and professional skills of Captain Starkiewicz. Lviv belonged to a small group of five Polish university cities. At the Medical Faculty of the UJK there was an excellent Ophthalmology Clinic created by Professor Emanuel Machek (1852-1930), and developed by Professor Adam Bednarski (1869-1941). This meant great opportunities for professional and scientific development for a young medical officer. Also the way in which the work was organised in the Lviv military hospital enabled contacts with the civilian health service.

Unfortunately, this promising stage of Starkiewicz's life was brutally interrupted by the outbreak of the

Second World War, following the attack by the Third Reich and the USSR on Poland [11, 20, 21]. Like most professional staff of the 6th Regional Hospital, he received an assignment to a frontline unit, he took command of the 86th mounted platoon of the Podolska Cavalry Brigade, with which he fought, among others, at the Battle of Bzura. After the end of the defensive war of 1939, he was taken prisoner, and until liberation he remained at Oflag IIC Woldenberg. In 1945, again in the Polish Army, he became the head of the ophthalmology ward of the Military Hospital in Warsaw. He was promoted to the rank of major, and a year later he became a lieutenant colonel. At the same time, he was working as an assistant in the Warsaw Ophthalmology Clinic. In 1946 he defended his doctoral dissertation, entitled "On afterimages, particularly in the peripheral field of view. Electrical theory of the phase character of afterimages" and in 1949 his habilitation dissertation entitled "Causes, symptoms and treatment of strabismus" [16, 22]. A year before that he retired from military service and as an associate professor became the head of the Ophthalmology Clinic at the Medical University of Szczecin. He held that position until 1972. Under his management the clinic soon became one of the most important centres of ophthalmology, especially strabology, in Poland.

Starkiewicz developed a "kinesthetic theory of vision", which he used practically as a localisation method in the treatment of strabismus. He worked on the construction of a device replacing eyesight in blind patients under the name "elektrooftalm". It is worth emphasising that these were original experiments, and not just repetitions of research undertaken elsewhere, which is now a common problem of Polish science. In 1957 Witold Starkiewicz obtained the title of professor. In the years 1959-1962 he was the dean of the Medical Academy in Szczecin. He published 111 scientific articles, was the author of 4 monographs and 2 manuals, and 11 inventive projects in the field of physiology of vision and strabology. He was a member of Polish and foreign institutions and scientific societies, including Polish Ophthalmological Society, Société Française d'Ophtalmologie, European Commission for the Study of Strabismus (vice-president in the years 1970-1972) and the Polish Academy of Sciences.

For his outstanding scientific activity he was honoured, among others, with the Officer and Knight's Cross of the Order of Polonia Restituta and the 1st Class Order of the Banner of Work. One of the streets in Szczecin is named after him. In 1985 a hospital in Gryfice was named after Julia and Witold Starkiewicz.

In his private life he was happily married to Professor Julia Helena Starkiewicz née Latkowska (1908-1978), who was a paediatrician. They had two daughters: Ewa

(1936) and Joanna (1938). It is worth noting that both of them obtained a professor title. Lt. Col. Prof. dr. hab. Witold Szymon Starkiewicz died on 14 September 1978. He is buried in the Powązki Cemetery in Warsaw [16, 20, 23, 24].

Conclusions

As a result of the treaties of Yalta and Potsdam, physicians from the Jan Sobieski 6th Regional Hospital, Major Alfred Kazimierz Bong and Captain Witold Szymon Starkiewicz, could not return to Lviv after the Second World War. Their complicated fortunes brought them to two different continents, on either side of the Atlantic, separated by the "Iron Curtain" of hostile political camps. Acting in very different socio-economic situations, yet despite numerous difficulties and obstacles, they managed to achieve great professional success. Alfred Bong (Bonk) was a professor of radiology at the University of Medical Sciences in Chicago, and the Department of Radiology received his name (very few Poles have been honoured in this way in the USA). Professor Starkiewicz created in Szczecin one of the best ophthalmology centres in Poland, and after his death one of the streets in Szczecin as well as a hospital in Gryfice were named after him. Undoubtedly, both of them carried a part of the magical *genius loci* of the Lviv military hospital, thanks to which they were able to realise their ambitions, winning recognition and respect, regardless of the country in which they lived and its social and political systems.

Unfortunately, the legendary Jan Sobieski 6th Regional Hospital no longer exists. What remains is its eastern gate with the "Janina" coat of arms of the Sobieski family, which still inspires visitors to 26 Łyczakowska Street, which is another proof of the existence of the *genius loci* of this institution. When in Lviv, it is definitely worth visiting the street to feel the magic of this amazing place.

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90th Birthday of Professor Telesfor Piecuch

Jubileusz prof. dr. hab. n. med. Telesfora Piecucha

Michał Tyszkowski

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A nestor of Polish surgery, a retired colonel, a professor doctor of medical science, Telesfor Piecuch turned 90 on 27 February 2018

I got to know Professor Telesfor Piecuch as a doctor 26 years ago, when for a short time I was living with him under one roof. At that time he was already a renowned professor, head of the Surgical Clinic of the 4th Military Clinical Hospital in Wrocław. It was around 2.00 a.m. The telephone rang. I heard the professor pick up the phone. I did not hear the conversation clearly, but I understood that there was some problem during a surgical procedure, but the doctor on duty should deal with it easily. After a while I heard him get dressed and leave. That is the kind of leader he was: firm but extremely committed to his work.

I got to know him as a scientist much later, when on the occasion of his 90th birthday, together with his daughter, who is also my wife, we summarised his scientific achievements.

He obtained his doctor's diploma on 3 September 1953 at the Medical Academy in Poznań. As a distinguished student, he received a very interesting job offer from Poznań; however, the authorities decided that he was needed more in Gorzów Wielkopolski, where he worked as an assistant at the Surgical Ward of the Municipal Hospital from 1953 to 1956, and as the head of the emergency ward from 1955 to 1956.





Although he was assigned to these jobs against his will, he did not treat them as a banishment. On the contrary: he used this period to develop professionally, at the same time contributing to the development of the hospital in Gorzów. He was the first to perform endotracheal intubation during anaesthesia before surgery. This procedure has been the norm for many years, but at that time, when patients were anaesthetised with a cloth soaked in ether, it was a real revolution.

Among the many surgeries which he performed at that time during his 24-hour duties, he remembers especially one extremely complicated, a large skull trepanation on a patient who had been kicked by a horse. Although the injuries were very serious, the operation was carried out so well that the patient not only survived, but also regained almost complete physical and mental fitness.

The period of work in Gorzów Wielkopolski, where he also met his future wife, Hanna, ended on 1 October 1956, when after winning the competition for the post of an assistant he was employed at the 3rd Surgical Clinic of the Medical Academy in Wrocław.

For the second time, the authorities had a different opinion on his professional career, and after six months he was conscripted into the army. Fortunately, he did not end up on the training area, but in the Surgical Ward at the Military Regional Hospital in Wrocław. There he met Tadeusz Orłowski, who later was to become a professor, and who persuaded him to continue his career in the army and the Military Hospital in Wrocław. In 1978 he was promoted to the rank of colonel and head of the Surgical Clinic, which he organised at the time when the Military Regional Hospital obtained the status of clinical



hospital. He was in charge of the Surgical Clinic until 1994.

In parallel with the development of his professional career, he developed scientifically. He obtained the first degree of specialisation in general surgery in 1957, and the second in 1960. Before those exams he had attended clinical training at the clinics of Prof. Wiktor Bross, Prof. Jan Nielubowicz, Prof. Adam Piskorz, Prof. Klemens Skóra and Prof. Zygmunt Szydłowski, Prof. Henryk Kuś, Prof. Michał Krauss and Dr. Marian Wruk. He defended his doctoral dissertation in 1967 (supervisor: Prof. Wiktor Bross), and received habilitation in 1976. In 1986 he was appointed a docent and in 1989 an associate professor.

The scientific work of Professor Telesfor Piecuch includes 145 publications (over 40 in *Military Physician*) and 215 speeches at conferences and congresses. He supervised six doctoral theses and one habilitation thesis in medical science. He reviewed 26 doctoral, habilitation and professor theses.

In 1979 he became a member of the Medical Faculty Council of the Military Medical Academy in Łódź. In 1957, he became a member of the Association of Polish Surgeons, including two terms of office as a member of the Board of the Lower Silesian Branch and one term of



office as a member of the Board of the Military Surgeons Section of the Association of Polish Surgeons. In 1968 he became a member of the Thoracic Surgery Section of the Association of Polish Surgeons and in 1983 he became a member of the Oncological Surgery Section of the Association of Polish Surgeons. He organised many scientific meetings of the Lower Silesian Branch of the Association of Polish Surgeons and conferences of military surgeons.

He also was the Chief Surgeon of the Silesian Military District. For half a year in 1976 he served in the UN armed forces as the head of the surgical ward of the field hospital in Ismailia, Egypt, and as the deputy commander of that hospital.

He has fond memories of working in Egypt. The purpose of the mission was to organise a field hospital to save the lives and health of soldiers injured in combat. During his six-month stay, he did not have to perform any such surgery. The most frequently conducted surgeries were the consequences of car accidents involving UN soldiers, which took place on the road leading through the Sinai Peninsula. Upon his return he became a member of the Association of Veterans of UN Peacekeeping Missions.

Professor Telesfor Piecuch is a general surgeon in the best sense of the term. His interests include gunshot wounds, multi-organ injuries, surgical treatment of thyroid

diseases, adrenal glands, breast cancer, biliary tract diseases, oesophagus, stomach, large intestine, abdominal hernia, lower limb varicose veins, peripheral artery surgery, lumbar and thoracic sympathectomy, pulmonary tissue resection and surgical treatment of mediastinal tumours.

He performed a huge number of surgeries during his career, but a few of them deserve a special mention, since they were either particularly difficult or rarely performed in Polish hospitals:

- surgery of a large cavernous haemangioma in the rectum of a boy using the colo-anal pull-through procedure,
- sewing a heart wound in a patient stabbed with a knife – the surgery was successful and the patient recovered,
- surgeries in aortic arch syndrome,
- surgeries in patent ductus arteriosus,
- surgeries in coarctation of the aorta,
- resection of mediastinal seminoma.

Professor Telesfor Piecuch also contributed to the development of the computerisation of medicine. At a time when computers were starting to gain popularity and no one even thought about hospital IT systems, he developed and implemented - with the help of IT specialists - a system of registration and documentation of surgical procedures, which enabled recording and statistical analysis of surgeries at a higher level than current HIS systems.

Professor Telesfor Piecuch was awarded, among others, the Knight's Cross of the Order of Polonia Restituta, the Golden Cross of Merit, the United Nations Medal, the Gold Medal "For merits for the defence of the country" and the Honorary Badge "For exemplary work in the health service".

Medicine was not his childhood dream. He wanted to become a pilot, he even took a gliding course, but a sight defect thwarted those plans. Both in his youth and later he was a very active man. He practiced rowing, basketball, tennis, mountain tourism, and swimming, he learned to play the violin, and he belonged to the scouts. To this day, he is passionate about photography and gardening. He has a wife, Hanna, a son and daughter, and two adult granddaughters.