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Effect of immunomodulatory therapy using INF-β, GA and DMF on inhibition of relapsing-remitting multiple sclerosis

Wpływ terapii immunomodulującej z zastosowaniem INF-β, GA i DMF na zahamowanie aktywności rzutowo-remisyjnej postaci stwardnienia rozsianego

Katarzyna Gocyła-Dudar, Adam Stępień

Department of Neurology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; head: Prof. Adam Stępień MD, PhD

Abstract. The disease-free status defined in terms of the NEDA-3 parameter is increasingly used in clinical practice as a treatment goal in the therapy of multiple sclerosis (MS). The aim of the study was to evaluate the effect of the first line drugs on the persistence of NEDA-3 status in patients with relapsing-remitting MS. The retrospective study involved a group of 222 patients with relapsing-remitting multiple sclerosis treated with first line drugs in the Multiple Sclerosis Center at the Neurological Department of the Military Medical Institute in 2010–2017. In more than half of the patients, no clinical or radiological signs of disease activity were observed in the annual treatment cycles. NEDA-3 status was maintained in 37.26% of patients after two years and in 14.94% of patients after five years of treatment. The lack of oligoclonal bands in the cerebrospinal fluid proved to be a favourable prognostic factor affecting the prolongation of the duration of NEDA-3 status in the treated patients. The maintenance of NEDA-3 status in patients treated with first line drugs for over 3 years of therapy is rare.
Keywords: first line drugs, multiple sclerosis, NEDA-3

Streszczenie. Wstęp. Brak klinicznych i radiologicznych oznak aktywności choroby, jakimi jest wskaźnik NEDA-3, jest coraz częściej stosowany w praktyce klinicznej jako cel leczenia stwardnienia rozsianego (SM). Celem badania była ocena wpływu leków pierwszej linii na utrzymywanie się statusu NEDA-3 u chorych z rzutowo-remisyjną postacią SM. Methods. Badaniem retrospektywnym objęto grupę 222 chorych z rzutowo-remisyjną postacią SM leczonych lekami pierwszej linii w Poradni Stwardnienia Rozsianego przy Klinice Neurologicznej WIM w latach 2010–2017. Wyniki. U ponad połowy chorych nie odnotowano klinicznych ani radiologicznych oznak aktywności choroby w poszczególnych rocznych cyklach leczenia. Status NEDA-3 utrzymywał się u 37,26% pacjentów po 2 latach i 14,94% chorych po 5 latach leczenia. Brak prążków oligoklonalnych w płynie mózgowo-rdzeniowym okazał się korzystnym czynnikiem prognostycznym, mającym wpływ na wydłużenie czasu utrzymywania się statusu NEDA-3 u leczonych chorych. Wnioski. Utrzymywanie się statusu NEDA-3 u chorych leczonych lekami pierwszej linii przez ponad 3 lata terapii jest rzadkie.
Słowa kluczowe: NEDA-3, stwardnienie rozsiane, leki pierwszej linii

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Introduction

Multiple sclerosis (MS) *(sclerosis multiplex*) is a chronic, autoimmune demyelinating disease of the central nervous system. It typically follows a pattern of relapses and remissions. The treatment goals in relapsing-remitting multiple sclerosis (RRMS) include reduction of relapses, inhibition of the progress of disability, and improvement of the patient's quality of life. First-line medications in RRMS patients include: interferon-β 1a/1b (INF-β), glatiramere acetate (GA), dimethyl fumarate (DMF) and teriflunomide. The NEDA (no evidence of disease activity) measure is used in clinical practice to help assess the effectiveness of therapy in RRMS patients [1].

NEDA is composed of several parameters. The most common one is NEDA-3, which comprises: freedom from relapses over a year period, no clinical progression according to the Expanded Disability Status Scale, and no progression of lesions in MRI tests. Other definitions of NEDA are also in use, e.g. NEDA-2, which comprises only the clinical aspect - relapses and progression of disability, NEDA-4, which includes the above parameters and change in brain volume over time, assessed in MRI test, and NEDA-5, which evaluates concentration of neurofilament in cerebrospinal fluid (CSF). Complete inhibition of MS activity is a very attractive goal, and may provide a useful primary endpoint in clinical trials evaluating the effectiveness of disease modifying therapies (DMT) [2]. Previous cohort studies demonstrated that NEDA status cannot be maintained over time, despite the use of various therapies. This study assessed the persistence of NEDA-3 in patients with relapsing-remitting MS, treated with first-line medications.

Aim of the study

The aim of the study was to assess the effect of first-line immunomodulatory therapies on the persistence of NEDA status in Polish patients with RRMS.

Material and methods

The retrospective study involved 222 adult patients (female and male) diagnosed with relapsing-remitting MS, treated at the Outpatient Multiple Sclerosis Clinic at the Department of Neurology, Military Institute of Medicine in the years 2010-2017 with first-line immunomodulatory medications, according to the current MS treatment programme approved by the Ministry of Health. Relapsing-remitting multiple sclerosis was diagnosed following the McDonald 2010 criteria. The inclusion criteria in the study included: availability of complete clinical data prior to the treatment, including analysis of type-2 oligoclonal bands in CSF at the diagnosis of RRMS, contrast-enhanced head MRI before the treatment (the result of contrast-enhanced head MRI performed within 60 days prior to the treatment), EDSS of <5 at the beginning of treatment, a minimum of one full year of treatment with first-line therapies, availability of contrast-enhanced head MRI test result after each full year cycle of treatment. The exclusion criteria prior to or during the study included other than relapsing-remitting forms of MS, current or planned pregnancy, immunosuppressive therapy used at any time, treatment with a highly active medication, i.e. second-line therapy, patient's clinical status of EDSS >5.0 in a follow-up examination, pending remission, decompensated hepatic failure and other contraindications for treatment continuation listed in the Summary of Product Characteristics of a given medication. Clinical status and the course of MS were assessed during the first visit before the immunomodulatory treatment, and then at control visits during the treatment, every 3 months. Each visit involved a detailed neurological evaluation, assessment of disability level on the EDSS scale, and peripheral blood draw for biochemical tests and complete blood count. After each year of therapy, clinical assessment and laboratory tests were conducted. Control contrast-enhanced head MRI tests and evaluation of the effectiveness of the treatment were also conducted. The attending neurologist then decided whether the treatment was to be continued, or switched to another first-line therapy (INF-β, GA, DMF), following the detailed criteria specified in the drug programme of the Ministry of Health.

Measure definition

The course of the disease was classified following Lublin and Reingold criteria from 1996. The presence of oligoclonal bands in the cerebrospinal fluid was confirmed when at least two oligoclonal bands were found in the CSF, with none in the blood plasma.

Disease relapse was defined as occurrence of new neurological symptoms or exacerbation of the existing ones, reported by the patient or objectively observed at a visit, typical for an acute demyelination episode, persisting for at least 24 hours, after elevated body temperature or infection have been excluded. At least 30 days passed since the last relapse of the disease. Secondary progressive MS was defined as a long-term progression of neurological disability, with an increase of at least 1 point at the EDSS scale, and duration of at least 12 months, unrelated to the disease relapse.

The result of the annual head magnetic resonance test was classified as "no progression" (MRI-NEDA) if the contrast-enhanced head MRI did not reveal the occurrence of new plaques, growth of old plaques, or presence of contrast-enhanced plaques. No evidence of

disease activity was defined according to the NEDA-2 definition, and comprised the following parameters: absence of prolapse and absence of disability progression assessed using EDSS. NEDA-3 also included absence of progression of the lesions in head MRI tests (absence of new/growing lesions in T_2-weighted sequences, and absence of gadolinium-enhanced lesions). NEDA-2, NEDA-3 and MRI-NEDA were assessed after each year of treatment in the five years of follow-up. Persistence of the NEDA-2, NEDA-3 and MRI-NEDA status in the consecutive years of treatment was also analysed.

Following the drug programme, a therapy was considered ineffective, resulting in a switch to a second-line medications, when at least 2 moderate relapses were observed (increase by 1-2 points on the EDSS scale in one or two functional systems, or by 1 point in at least four systems), or 1 severe relapse was observed after the first 6 months of therapy (increase on the EDSS scale higher than in the definition of a moderate relapse, i.e. >2 points), and more than one new contrast-enhanced lesions occurred in the head MRI, or at least 3 new lesions were found in T_2 sequence of the head MRI. The therapy was considered partially ineffective if one of the above criteria was observed. In such cases, a change of therapy to another first-line therapy was acceptable.

Statistical analysis

The studied group was characterised using descriptive statistics. The time to the end of NEDA status was analysed using Kaplan-Meier method, and to compare the NEDA-2 and NEDA-3 results, LongRank test was applied. The prognostic factors for the time to absence of NEDA-2 and NEDA-3 were analysed with the use of Cox proportional hazard regression (multifactorial). The results of the analyses are presented in the tables demonstrating descriptive statistics and number of patients, and the diagrams. A p value of <0.05 was considered statistically significant. The statistical analyses were performed using PQStat version 1.6.6.202.

Results

The study involved 222 patients with RRMS, treated with first-line immunomodulatory therapies. A total of 72.23% of the subjects were female (159/22). The female to male ratio in the studied group was 2.5:1. The median age at the beginning of treatment was 34 years (range of 18 – 58). Mean follow-up period was 48.4 ±15.7 months. Table 1 presents detailed characteristics of the study group before the immunomodulatory treatment.

The percentage of patients with no evidence of disease activity (NEDA-2 status) after each year of therapy remained similar in individual years: 69.82% of patients in the first year of immunomodulatory treatment, 69.81% patients in the second year, and 69.23% of patients in the fifth year of therapy. The lowest value was observed in the fourth year of treatment, at 58.44%. The rate of patients with no clinical and radiological signs of disease activity (NEDA-3) was 56.31% in the first year of treatment, 58.96% in the second year, and 65.89% in the fifth year of therapy. The percentage of patients without radiological signs of disease activity increased from 71.15% in the first year of treatment to 79.58% in the fifth year. Table 2 presents the rate of patients with no evidence of disease activity in individual years of treatment, according to their NEDA-2, NEDA-3 and MRI-NEDA status.

Table 1. Baseline characteristics of study group before immunomodulatory treatment
Tabela 1. Charakterystyka badanej grupy przed rozpoczęciem leczenia immunomodulującego

	Median	Range
Age at diagnosis	31.5	16-57
Age at the beginning of treatment	34	18-58
Relapses in the 2 years before treatment initiation	2	0-5
Degree of disability according to EDSS scale	1.5	0-5
Presence of active lesions in head MRI prior to treatment (N,%)	147/222	66.2%

Table 2. Percentage of patients with no signs of disease activity in each year of immunomodulatory treatment
Tabela 2. Odsetek chorych z brakiem oznak aktywności choroby w poszczególnych latach leczenia immunomodulującego

Years	NEDA-2	NEDA-3	MRI-NEDA
1	69.82%	56.31%	71.15%
2	69.81%	58.96%	75.44%
3	69.89%	64.77%	76.84%
4	58.44%	55.22%	74.58%
5	69.23%	65.89%	79.58%

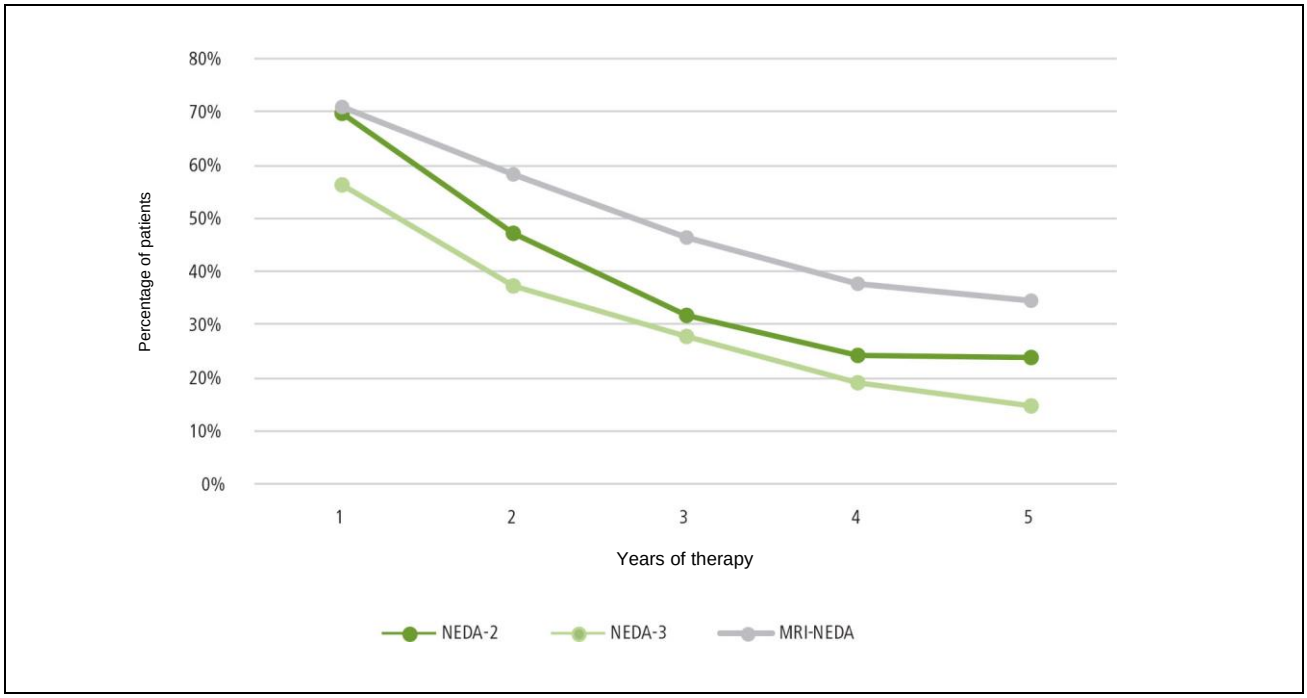

Figure 1. Persistence of NEDA-2, NEDA-3 and MRI-NEDA status over time
Rycina 1. Utrzymywanie się statusu NEDA-2, NEDA-3 oraz MRI-NEDA w czasie

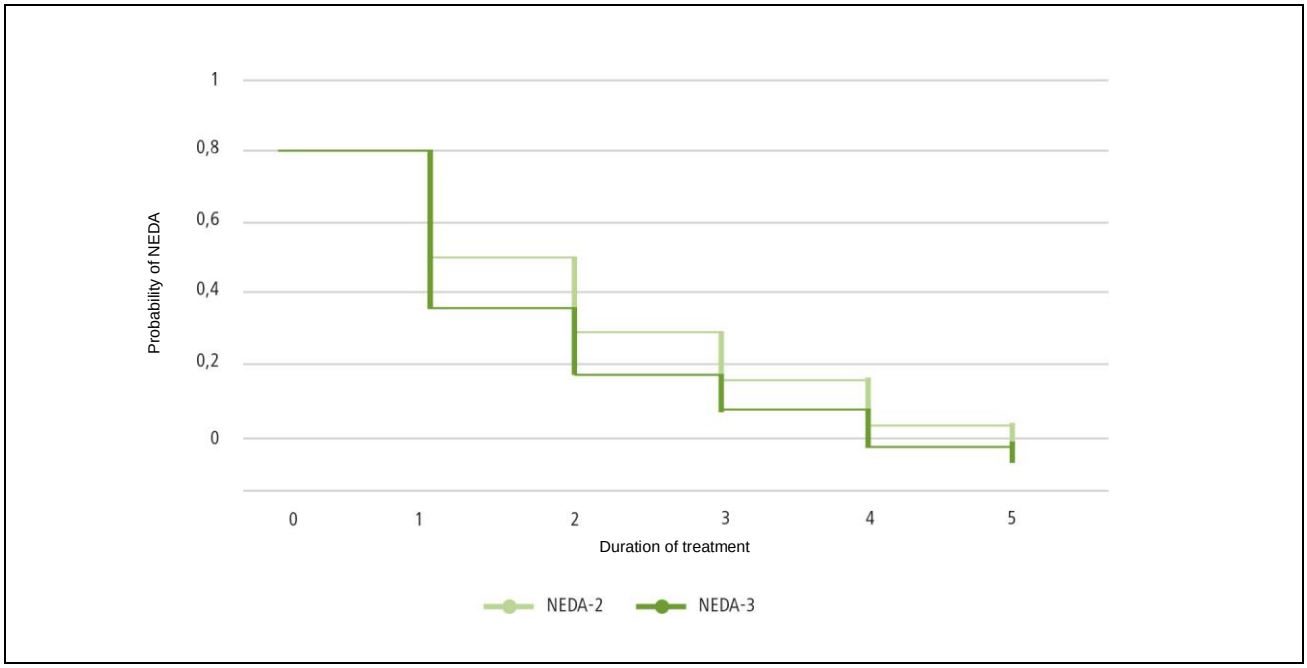

Figure 2. Probability of NEDA-2 and NEDA-3 over time
Rycina 2. Prawdopodobieństwo NEDA-2 oraz NEDA-3 w czasie

Figure 1 presents persistence of the NEDA-2, NEDA-3 and MRI-NEDA status in the consecutive years of treatment. After two years of treatment, the NEDA-2 status was maintained in nearly half of the subjects (47.3%). No evidence of MS activity was observed in 23.85% of patients in the full 5 years of treatment. No evidence of clinical and radiological signs of disease activity (NEDA-3 status) persisted in 37.26% of patients after the first two years of treatment, and in only 14.94% of patients after five years of immunomodulatory therapy. The absence of radiological signs of disease (MRI-NEDA status) was maintained in 58.33% of patients after two years of treatment, and in 23.94% of patients after 5 years.

Based on the Kaplan-Meier analysis of survival, a very significant ($p<0.01$) difference in time to NEDA-3 and NEDA-2 was found (Fig. 2). For NEDA-3, the likelihood of absence of clinical and radiological disease activity decreased with time faster than for NEDA-2. In consecutive years of immunomodulatory therapy, the difference between the likelihood of NEDA-2 and NEDA-3 status disappeared, and after 5 years of treatment the levels of both NEDA measures were similar.

Table 3 presents the effects of the analysed parameters on the time to the end of NEDA-3 status, using the Cox proportional hazard regression. In the model including all the analysed predictors, only the presence of oligoclonal bands significantly reduced the time to the occurrence of disease activity. Demographic or clinical factors, i.e. degree of disability and relapses before the immunomodulatory treatment, did not affect the NEDA-3 status over time.

Table 3. Prognostic factors of time until NEDA-3 failure. Cox proportional hazard regression.
Tabela 3. Czynniki prognostyczne czasu do wystąpienia braku NEDA-3. Regresja proporcjonalnego hazardu Coxa.

	P-value	Hazard ratio	95% CI	+ 95% CI
Sex	0.7994	0.9583	0.6898	1.3313
Age at diagnosis of MS	0.9906	1.0003	0.9582	1.0442
Age at the beginning of treatment	0.9334	0.9981	0.9547	1.0435
Oligoclonal bands	0.0198	1.5265	1.0696	2.1786
EDSS prior to the treatment	0.5163	1.0519	0.9028	1.2257
Relapses in the 2 last year before treatment	0.8850	1.0177	0.8026	1.2905
Relapses in the 2 years before treatment	0.9623	1.0054	0.8032	1.2585

Discussion

It seems that with an increasing number of therapeutic options in prolapsing-remitting MS, the absence of clinical and radiological signs of disease activity, NEDA-3, should be a therapeutic goal in the daily practice of neurologists treating patients with multiple sclerosis. The majority of data regarding long-term absence of clinical and radiological signs of disease activity come from *post hoc* analysis of randomised clinical trials using the available DMT. Few studies demonstrate real-life data from the population of all patients treated in the centres offering therapy for this disease.

In this analysis of RRMS patients receiving first-line medications within the Polish healthcare system the rate of patients with NEDA-2 was approximately 70% after each year of therapy, except for the effects of treatment after the fourth year, when the NEDA-2 measure was lower (58.44%). In over 70% of patients no progression was observed in annual contrast-enhanced head MRI tests, and the highest rate of MRI-NEDA was found after the fifth year of therapy (79.58%). No evidence of clinical and radiological disease activity (NEDA-3 status) remained at the level of 55.22 - 65.89% for each year of the therapy. The highest value was observed after the fifth year of disease-modifying therapy.

The presented percentage of NEDA obtained in consecutive years confirms the proven effectiveness of first-line therapies in reducing the annual rate of prolapses and disability progression, as well as in improving the MRI results [3]. The obtained results demonstrate that, regarding the radiological signs of disease activity, the benefits of using first-line therapies in RRMS patients increase with time. This is partially explained by the fact that the therapeutic effects of immunomodulatory therapy can only be observed after some delay. Some patients who did not demonstrate a response to therapy after a year of treatment, were switched to another first-line medication. Despite treatment modification, we did not observe any increase in the percentage of patients with NEDA-2 after the fifth year of therapy, compared to the results after the first year of treatment.

Analysing the long-term absence of disease activity in time we found that the ratio of patients with NEDA-3 was 56.31% after the first year of treatment, 37.26% after two

years, and only 14.94% after five years of therapy. In an American study involving 93 patients with RRMS, the percentage of patients with NEDA-3 was 63% in the first year, 38% in the second, 19% in the fifth year, and 12% after 10 years of treatment [4]. Another cohort study reported 46% of patients with NEDA-3 in the first year of therapy, and only 7.9% after 7 years of treatment [5]. In an Italian cohort study, only 9% of patients maintained the NEDA-3 status after 10 years of therapy [6]. In a recently published study involving German patients with RRSM, in a 3-year follow-up the percentage of patients with NEDA-3 was 45% after the first year of treatment, 29% after the second year, and 21% after the third year of therapy [7]. The data demonstrate that the percentage of patients with no evidence of clinical and radiological disease activity in MS patients decreases in consecutive years of treatment. The results of these studies cannot be compared directly, due to differences in the frequency of dosing of various DMTs, use of highly active second-line medications, and inclusion of patients with clinically isolated syndrome (CIS) in some of the studies. Approximately half of the treated population will maintain the NEDA-3 status after the first year of immunomodulatory therapy, over one third of patients will not present any clinical or radiological signs of MS activity after two years of using DMT, and slightly less than 1/6 of all the patients will maintain the NEDA-3 status for another 5 years of immunomodulatory treatment. Similarly to other studies, the long-term persistence of the NEDA status appears to be difficult to assess, due to the floor effect. Most patients cannot maintain the NEDA-3 status in the first two years of therapy [4]. Moreover, it has been demonstrated that persistence of the NEDA-3 status is strongly correlated with the frequency of head MRI tests. The probability of maintaining NEDA-3 in time decreases with increased control of disease activity by head MRI testing [8].

In the presented study we found that the probability of no evidence of clinical and radiological disease activity (NEDA-3) in the first year of treatment decreased significantly faster than in the case of NEDA-2. In further years of immunomodulatory therapy, the difference between the likelihood of obtaining NEDA-2 and NEDA-3 status decreases, and after 5 years of treatment the chances of experiencing no signs of disease activity are comparable. This result may reflect the early effectiveness of first-line therapies with regard to no evidence of disease activity, and the failure of this treatment in the long-term perspective. It has been demonstrated that the absence of signs of MS activity persists longer if highly effective therapies are used [9-11].

The NEDA-3 status in time in patients receiving first-line immunomodulatory therapies was found to be independent of age or disability level assessed by EDSS scale before the treatment, or of the number of prolapses in the previous year or two years prior to DMT. In our analysis the only factor extending the time without clinical and radiological evidence of disease activity was the absence of oligoclonal bands in the cerebrospinal fluid. Similar results were presented by German researchers. They found that neither age, nor the degree of disability before treatment affected the NEDA-3 status after two years of therapy. Huhn et al. demonstrated that the absence of clinical or radiological evidence of disease activity was conditional upon the course of the disease (clinically isolated syndrome vs. relapsing-remitting disease) [7]. The effect of the presence of oligoclonal bands on the NEDA measure in this study seems to confirm the results of previous analyses, demonstrating that the presence of oligoclonal bands has an adverse effect on the course of the disease [12].

In this study majority of subjects received injection therapy. We could not assess separately the effect of oral first-line therapy (teriflunomide, dimethyl fumarate) on the persistence of NEDA, as few patients were prescribed these medications in the study period.

The strength of this study is the fact that is based on a real-life population of patients treated with first-line immunomodulatory therapies within the Polish healthcare system, whereas the retrospective nature is its limitation.

Conclusions

Most patients with RRMS receiving first-line immunomodulatory therapy with first-line therapies do not maintain the NEDA-3 status within the first two years of treatment. Persistence of NEDA-3 for over 3 years of therapy with this type of medications is rarely observed.

Literature

1. Bevan CJ, Cree BAC. Disease activity free status: a new endpoint for a new era in multiple sclerosis clinical research? JAMA Neurol, 2014; 71: 269-270;
2. Traboulsee A, Li DKB, Cascione M, et al. Effect of interferon beta-1a subcutaneously three times weekly on clinical and radiological measures and no evidence of disease activity status in patients with relapsing-remitting multiple sclerosis at year 1. BMC Neurol, 2018; 18 (1): 143
3. O'Connor P, Filippi M., Arnason B., et al. for the BEYOND study group: 250μg or 500 μg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomized, multicenter study. Lancet Neurol, 2009; 8 (10): 889-897;
4. Parks NE, Pittock SJ, Mandrekar J, et al. Population-based study of "no evident disease activity" in MS. Neurol Neuroimmunol Neuroinflamm, 2018; 5: 8495
5. Rotstein DL, Healy BC, Malik MT, et al. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA Neurol, 2014;71:269-270
6. De Stefano N, Stromillo ML, Giorgio A, et al. Long term assessment of no evidence of disease activity in relapsing-remitting MS. Neurology, 2015; 85: 1722-1723

7. Huhn K, Senger D, Ulz KS, et al. No evidence of disease activity status over 3 years in a real-world cohort of relapsing remitting MS patients in Germany. Mult Scler Relat Disord, 2019; 27: 133-138
8. Coyle PK, Reder AT, Freedman MS, et al. Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon β-la in the EVIDENCE study. J Neurol Sci, 2017; 379: 151-156
9. Puthenparampil M, Cazzola C, Zywicki S, et al. NEDA-3 status including cortical lesions in the comparative evaluation of natalizumab versus fingolimod efficacy in multiple sclerosis. Ther Adv Neurol Disord, 2018; 11: 1-9
10. Sormani MP, Muraro PA, Saccardi R, et al. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Mult Scler, 2017; 23: 201-204
11. Prosperini L, Annovazzi P, Boffa L, et al. No evidence of disease activity (NEDA-3) and disability improvement after alemtuzumab treatment for multiple sclerosis: a 36-month real-world study. J Neurol, 2018; 265 (12): 2851-2860
12. Zeman AZ, Kidd D, McLean BN, et al. A study of oligoclonal band negative multiple sclerosis. J Neurol Neurosurg Psych, 1996; 60: 27-30

Totally thoracoscopic ablation with autonomic ganglia ablation and left atrial appendage exclusion for persistent atrial fibrillation

Całkowicie torakoskopowa ablacja przetrwałego migotania przedsionków z ablacją zwojów autonomicznych i usunięciem uszka lewego przedsionka

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Abstract. Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia of high morbidity. Antiarrhythmic drugs and percutaneous catheter ablation procedures have moderate efficacy. The aim of the study was to evaluate midterm results of totally thoracoscopic ablation for persistent and long-standing persistent AF. A total of 34 patients with a mean age of 60 (±9.5) years underwent totally thoracoscopic ablation with left atrial appendage (LAA) occlusion. Mean duration of AF was 87 (±76) months, left atrial dimension was 45 (±9.4) mm and LVEF was 59 (±8)%. In all patients bidirectional block across ablation lines around pulmonary veins was achieved. After 3, 6, 12 and 24 months, 48-hour ECG-Holter recordings and echocardiography were performed. No mortality, stroke or TIA were observed, with 97% of patients in sinus rhythm on discharge from hospital. One patient required sternotomy for effectively managed bleeding from left atrium. At the 6, 12 and 24 month follow-up, 86%, 84% and 100% of the patients, respectively, remained in stable sinus rhythm. Totally thoracoscopic AF ablation with autonomic ganglia ablation with left atrial appendage (LAA) occlusion show high efficacy and low risk of complications at the midterm follow-up.
Key words: ablation, atrial fibrillation, left atrial appendage occlusion, totally thoracoscopic, left atrial appendage exclusion

Streszczenie. Wstęp. Migotanie przedsionków (AF) jest najczęstszą arytmią nadkomorową, związaną z dużą chorobowością. Leki przeciwarytmiczne oraz ablacje przezcewnikowe wykazują ograniczoną skuteczność. Cel. Celem badania była ocena średnio odległych wyników całkowicie torakoskopowej ablacji przetrwałego i przetrwałego długo trwającego AF. Metody. 34 pacjentom w średnim wieku 60 (±9,5) lat wykonano całkowicie torakoskopową ablację AF z usunięciem uszka lewego przedsionka. Średni czas trwania arytmii wyniósł 87 (±76) miesięcy, średni wymiar lewego przedsionka wyniósł 45 (±9,4) mm, a frakcji wyrzucana i lewej komory 59 (±8)%. U wszystkich pacjentów uzyskano dwukierunkowy blok przewodzenia przez linię izolacji żył płucnych. Po 3, 6,12 i 24 miesiącach wykonywano badanie 48-godzinne holterowskie i echokardiograficzne. Wyniki. W trakcie obserwacji nie stwierdzono śmiertelności, udaru ani TIA. 97% pacjentów przy wypisie ze szpitala miało rytm zatokowy. Jeden pacjent wymagał sternotomii z powodu krwawienia z lewego przedsionka, skutecznie zaopatrzonego. Po 6,12 i 24 miesiącach obserwacji u odpowiednio 86%, 84% i 100% pacjentów stwierdzano stabilny rytm zatokowy. Wnioski. Całkowicie torakoskopową ablacja migotania przedsionków z ablacją zwojów autonomicznych i usunięciem uszka lewego przedsionka wykazuje dużą skuteczność i małe ryzyko powikłań w obserwacji średnio odległej.
Słowa kluczowe: migotanie przedsionków, ablacja, całkowicie torakoskopowo, zamknięcie uszka lewego przedsionka

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Objective

The significant development in medical care and improved living conditions are favourable for increased life expectancy in developed and developing countries. However, longer lifespan is connected with greater morbidity. Atrial fibrillation (AF) is recently the most prevalent arrhythmia in the senescent population and has become a growing problem because of its complications and high economic costs [1-3]. Many clinical trials and metaanalyses show that pharmacological treatment has poor long-term results and catheter ablation is moderately effective only in a selected group of patients with paroxysmal AF [4-6]. Surgical ablation shows superior results and the Cox-Maze III procedure is considered a gold standard for treatment of drug-refractory symptomatic AF with a success rate exceeding 90% [5, 7]. However, because of its complexity and requirement for a full sternotomy, it is not widely used, especially for lone AF. Technological progress and the continuous increase in knowledge of pathophysiology of AF allowed the creation of systems for minimally invasive ablation without need for cardiopulmonary bypass and even sternotomy [7-9]. The aim of the study was to evaluate the midterm results of totally thoracoscopic and autonomic ganglia ablation for persistent and long-standing persistent AF.

Methods

Patient recruitment

Between November 2011 and December 2013, 34 consecutive patients of mean age 60 (±9.5) years with persistent and long-standing persistent AF underwent totally thoracoscopic ablation of AF with left atrial appendage (LAA) stapling. Eleven patients (32%) had previously at least one failed percutaneous catheter ablation for atrial fibrillation. The study was approved by the Institutional Review Board.

Operative technique

Ablation was performed using Isolator Synergy Ablation System (AtriCure, Inc., West Chester, Ohio, USA). The patient under general anaesthesia was intubated with a double lumen intratracheal tube and placed in supine position. Firstly, three thoracoscopic ports were placed through the 4th (for camera) and the 6th (working ports) intercostal spaces in the midaxillary line into the right pleura. At this stage the right lung was deflated. The pericardium was opened above the phrenic nerve giving good exposure of the right pulmonary veins together with Waterstone's groove. The oblique and transverse sinuses were bluntly opened to enable placing of the AtriCure Lumitip Dissector (AtriCure, Inc., West Chester, Ohio, USA) with rubber-leader around both upper and lower pulmonary veins (PV). Using rubber-leader bipolar radiofrequency AtriCure Isolator Synergy Clamp (AtriCure, Inc., West Chester, Ohio, USA) was placed around the PV. At least three overlapping ablation lesions are performed at the antrum of the veins. Bidirectional acute conduction block was confirmed by both absence of sensed atrial potentials in the PV and pacing conduction from PV to left atrium. In case of any doubt, an extra ablation lesion around the pulmonary veins was made. Next additional box-like lesions on the posterior wall of left atrium and trigonal line between the roof of the LA and the non-coronary sinus were made with a bipolar linear device (Fig. 1). Subsequently, along Waterston's groove identification of the autonomic ganglia was performed using a high-frequency (1000 Hz, 18V) pacing induced vagal response (transient asystole by A-V block >3 seconds). The stimulation was performed with the Isolator Multifunctional Pen (AtriCure, Inc., West Chester, Ohio, USA). Active GP were mainly found anteriorly near superior vena cava.

In the second step, three thoracoscopic ports were placed in a similar way as on the right side in to the left pleural cavity (Fig. 2). The pericardium was opened above the phrenic nerve to visualize the left pulmonary veins, left atrium and the ligament of Marshall. The ligament of Marshall was carefully dissected with electrocautery. Left PVs were encircled and isolated like on the right side with at least 3 overlapping applications of energy (Fig. 3). After confirmation of the bidirectional block, connecting lines on the posterior wall of left atrium were performed and connected with lines made on the right side to create a box-like lesion pattern.

Left atrium appendage stapling

On the left side, left atrial appendage amputation was performed. Before the procedure and also

intraoperatively a transesphageal echocardiography (TEE) was performed to rule out thrombus in the left atrial appendage. LAA was excised with endoscopic Endo-GIA stapler with the novel Tri-Staple (Covidien, Mansfield, USA) reloads (Fig. 4). The stapler was introduced through the 6th intercostal space above the diaphragm. While clamping the appendage the stapler must be placed very cautiously and precisely, preferably under TEE control, in order not to leave any stump. In case of a stump exceeding 1 cm, an additional "green" reload or big endo-clip can be placed to exclude it.

Follow-up

Baseline characteristics, in-hospital and follow-up data were collected prospectively. In perioperative period patients were under continuous heart rhythm monitoring.

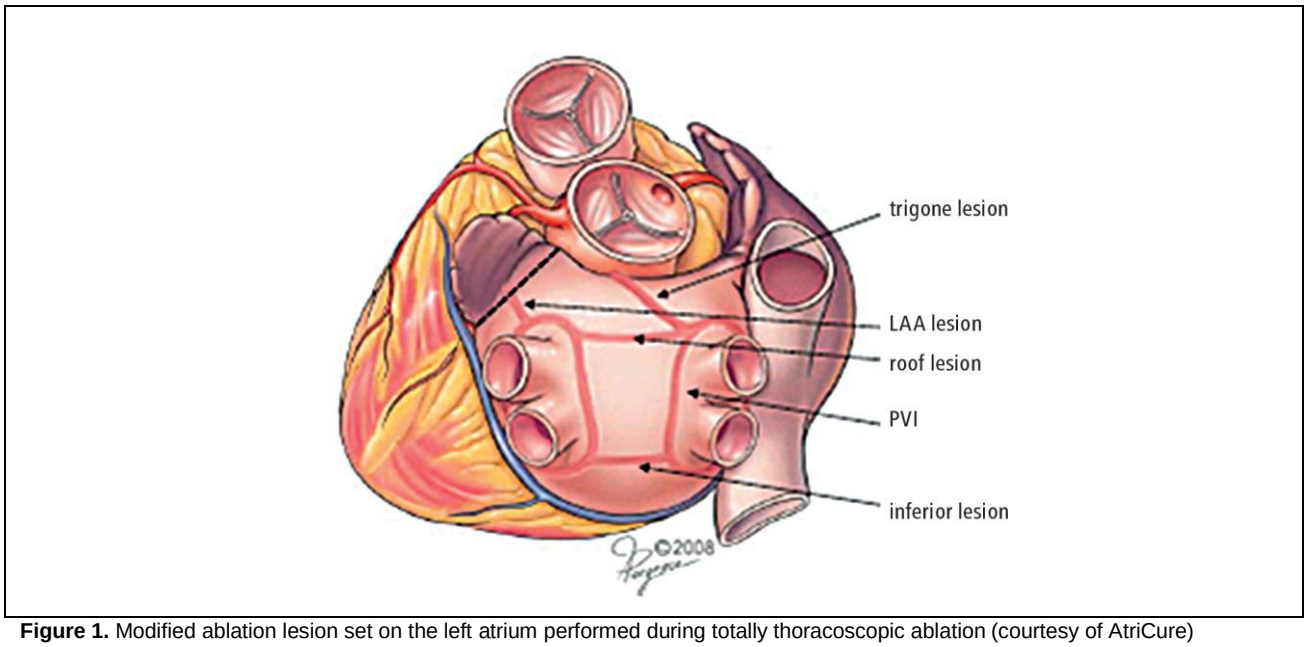

Figure 1. Modified ablation lesion set on the left atrium performed during totally thoracoscopic ablation (courtesy of AtriCure)
Rycina 1. Zmodyfikowany układ linii ablacyjnych w obrębie lewego przedsionka wykonywany podczas całkowicie torakoskopowej ablacji (za zgodą AtriCure)

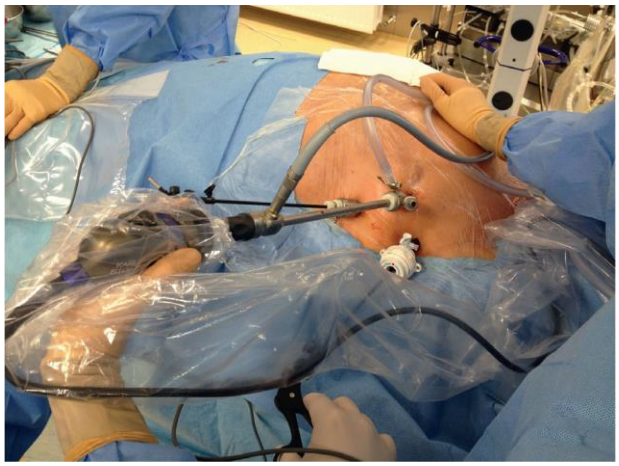

Figure 2. Thoracoscopic set-up on the left side
Rycina 2. Układ torakoskopów po stronie lewej

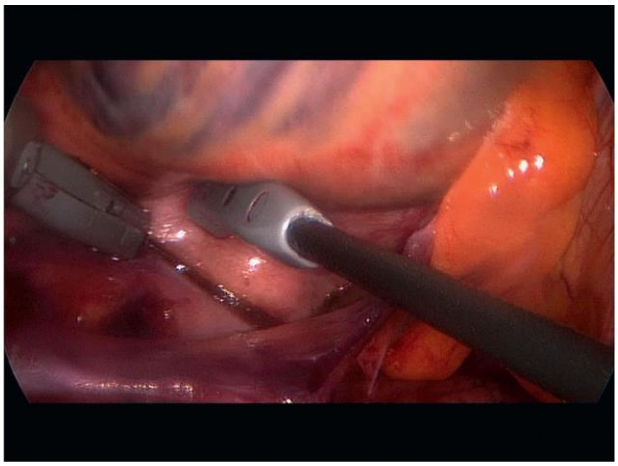

Figure 3. Ablation line around right pulmonary veins
Rycina 3. Linia ablacyjna wokół prawych żył płucnych

At 3, 6, 12 and 24 months, 48-hour Holter-monitoring and echocardiography (TTE) were performed. After ablation, patients were usually discharged on amiodarone or sotalol for 3-6 months. Anticoagulation was administered for at least six months. The decision to discontinue anticoagulation was based on history, confirmation of stable sinus rhythm in two consecutive Holter examinations, CHA2DS2-VASc score below 2 and positive assessment of the atrial transport function. AF episodes after a 3-month follow-up, lasting longer than 30 seconds irrespectively of symptoms and amount, were considered a failure of ablation.

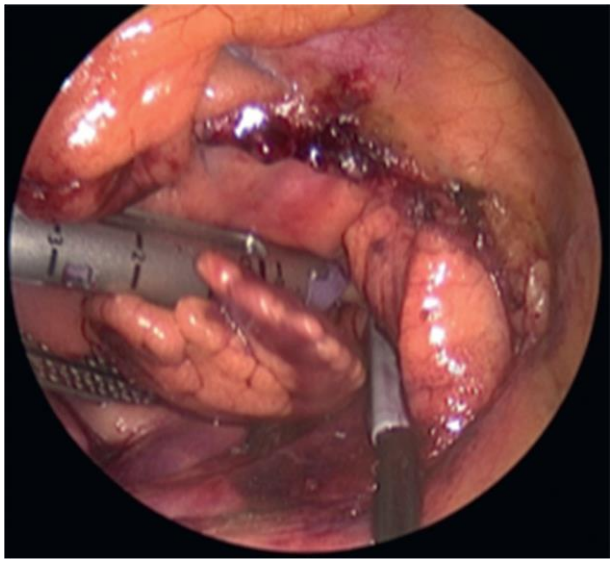

Figure 4. Left atrial appendage stapling
Rycina 4. Wykluczenie uszka lewego przedsionka z użyciem staplera

Results

Patients' characteristics

Detailed clinical characteristics are shown in Table 1. The patients had a mean age of 60 (±9.5) years, with 13 being female (38%). Twenty-five patients (85%) had persistent and 5 patients (15%) had long-standing (>12 months) persistent atrial fibrillation. Six patients (18%) were in arrhythmia on admission to the hospital. All patients had no significant structural heart diseases. Mean time of duration of arrhythmia was 87 (±76) months. Mean EUROScore II and CHA2DS2-VASc score were 0.96 (±0.59)% and 1.9 (±1.3), respectively. Mean serum level of NT-proBNP, troponin I (TnI) and high sensitive troponin I (hsTnI) were 375.7 (±477) pg/ml, 0.014 (±0.029) ng/ml and 0.009 (±0.009) ng/ml, respectively. Mean left atrial dimension and LVEF were 45 (±9.4) mm and 59 (±8)%, respectively. Two patients (6%) reported stroke prior the procedure. Three patients (9%) had an implanted pacemaker or implantable cardioverter-defibrillator. Eleven patients (32%) had at least one previous failed percutaneous catheter ablation. Thirteen patients (45%) were EHRA class 3, and eleven (38%) EHRA class 2b.

Procedural performance and outcome

The protocol was performed in 34 cases and completely achieved in 33 cases. In one female, left-sided ablation and LAA stapling was not feasible due to morbid obesity. In one patient (3%), we did not excise the LAA because of its small size with a very wide base. Mean number of identified GP in a patient was 4 (range 3-6). There was no operative mortality, no stroke or transient ischemic attack, no early or late bleeding requiring revision. One early patient required sternotomy for bleeding from left atrium without further morbidity. After ablation, 31 patients (91%) were in sinus rhythm on admission to the Intensive Care Unit and 33 (97%) on discharge from hospital. Thirteen patients (38%) required electrical cardioversion due to AF. In one case (3%), atrial flutter was observed, also successfully cardioverted to SR.

Table 1. Demographic data
Tabela 1. Dane demograficzne

variable	N	±SD or (%)
age (years)	60	±9.5
sex (male)	21	61
persistent afib (%)	25	73
long-standing persistent (%)	5	15
time of duration (months)	87	±76
arterial hypertension (%)	26	76
diabetes mellitus (%)	7	20
stable coronary artery disease (%)	11	32
chronic obstructive pulmonary disease (%)	1	3
chronic renal disease (%)	2	6
prior hypothyroidism (%)	6	18
prior hyperthyroidism (%)	3	9
cardiomyopathy (%)	1	3
prior stroke/TIA (%)	2	6
pacemaker/ICD (%)	3	9
	mean	**±SD**
NT-proBNP (pg/ml)	375.7	±477
TnI (ng/ml)	0.013	±0.02
hsTnI (ng/ml)	0.0098	±0.0099
EUROScore II	0.96	±0.60
CHADS2	0.82	±0.98
CHA2DS2-VASc	1.97	±1.31
LVEF (%)	58	±9
left atrial dimension (cm)	45	±9.6

Follow up

At the 6, 12 and 24 month follow-ups, 19/22 (86%), 11/13 (84%) and 6/6 of patients remained in stable sinus rhythm, respectively 3/22 (13%), 5/13 (38%) and 2/6 (33%) were off antiarrhythmic drugs (Table 2; Fig. 5). One patient (3%) had an episode of atrial flutter after 6 months, treated with electrical cardioversion. Three patients had episodes of atrial fibrillation in 48-hour ECG-Holter. They were referred to the electrophysiological examination. During the entire follow-up, no incidence of stroke or TIA was noticed. After index procedure in different time points, two patients (6%) required implantation of a pacemaker. One patient with sick sinus syndrome (tachycardia-bradycardia) was electively qualified to a staged procedure with ablation as the first step and pacemaker implantation as a continuation of the treatment. Another patient required early pacemaker implantation because of prolonged episodes of bradycardia postoperatively. However, sinus rhythm returned before discharge. In echocardiography, increase in the left ventricle ejection fraction during follow up (59 ±7%, 64 ±1%, 62 ±5% and 63 ±1.5% in 3, 6, 12 and 24 months, respectively) was observed. Also good left atrial transport function and its restoration in cases with continuous AF before ablation were observed (median E/A = 1.68 ±0.5 cm/s and DT = 207 ±61 ms). Left atrial dimension was 46 (±0.5) mm, 44 (±04) mm, 43 (±0.5) mm and 46 (±0.2) mm,

Table 2. Sinus rhythm (NSR) maintenance, incl. patients off-antiarrhythmic drugs (AAD) at follow-up
Tabela 2. Utrzymanie rytmu zatokowego (NSR) w obserwacji, w tym u pacjentów bez leków przeciwarytmicznych (AAD)

6 months		12 months		24 months	
NSR	NSR off-AAD	NSR	NSR off-AAD	NSR	NSR off-AAD
19/22(86%)	3/22(13%)	11/13(84%)	5/13(38%)	6/6(100%)	2/6 (33%)

respectively. Mean levels of NT-proBNP in FU were 564 (±935) pg/ml, 258 (±237) pg/ml, 255 (±225) pg/ml and 81 (±20) pg/ml, respectively for the time points. No mortality, no stroke or TIA were observed during follow-up.

Discussion

AF is one of the most problematic diseases in developed countries, affecting almost 2% of the population [1, 2]. It causes a high rate of absence at work, economic costs and decreased quality of life. In the longer perspective, the patients have higher risk of cerebrovascular complications, higher rate of heart failure and mortality [3]. Many clinical trials and meta-analysis have proved that pharmacological treatment has poor long-term results and the catheter ablation is moderately effective in patients with persistent forms of arrhythmia [4-6].

The MAZE procedure, proposed by James Cox in 1995, is considered a gold standard for the treatment of drug-refractory symptomatic AF due to its excellent success rate exceeding 90% [5]. However, because of its complexity and requirement for a full sternotomy, it is not widely used, especially for lone AF [7]. To make the procedure easier and feasible for a larger cohort of patients, a number of minimally invasive techniques from bilateral or unilateral minithoracotomy or totally thoracoscopic access have been recently introduced [7-10]. However, in order to obtain similar results these new technologies must fulfil several crucial conditions, mainly regarding ablation pattern protocol and transmurality, especially in an epicardial beating heart setup. Gillinov et al. showed that a sole bilateral pulmonary vein isolation is inferior to both left-sided and complete MAZE operation in persistent AF [14]. The technique described above allows to perform extended left-atrial ablation pattern including not only pulmonary vein isolation but also additional lines on the posterior wall of the left atrium and the trigonal line relevant to the left isthmus line [15, 16]. Employment of bipolar radiofrequency energy assures the transmurality of the ablation lines.

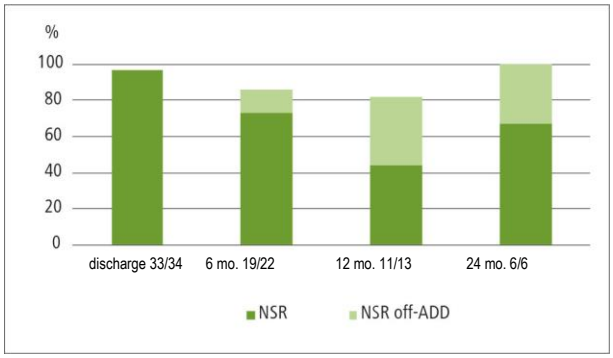

Figure 5. Sinus rhythm (NSR) maintenance, incl. patients off-antiarrhythmic drugs (AAD) at follow-up
Rycina 5. Utrzymanie rytmu zatokowego (NSR) w obserwacji, w tym u pacjentów bez leków antyarytmicznych (AAD)

The autonomic ganglia are located epicardially on the left atrium. It is well known that they can act like a trigger for atrial fibrillation onset [17, 18]. As GP ablation cannot be solely sufficient for restoration of stable SR, however its destruction along with ablation on the left atrium can significantly increase the success rate [18]. In patients with multiple GP, with significant response (transient A-V block) after surgical ablation, stable SR was observed, often with sinus tachycardia lasting for the next few weeks. In some cases we actually saw a return of sinus rhythm during the GP ablation.

Exclusion of the left atrial appendage (LAAE) is gaining additional importance as a prevention of trombo-embolic events and improving the result of ablation in patients with AF. Recent studies indicate that it is not inferior to oral anticoaguation [20]. Thoracoscopic stapling is a safe and reproducible method, however, it is very important to precisely excise the LAA at its base in order not to leave any stump over 1cm. The routine LAAE might contribute to no cerebrovascular incidences in our cohort. Also, the emerged role of LAA in arrhythmia induction and its electrical isolation as a treatment option may explain the very high effectiveness of our ablation protocol with routine LAAE [21].

Moreover, current guidelines require a HEART-TEAM management strategy in patients with persistent AF or patients after failed percutaneous catheter ablation. Therefore, the role of surgical ablation or hybrid procedures is becoming the modern standard for management of AF patients.

Limitations

The main limitation of this study is a small number of patients and a non-randomized trial. The decision regarding further antiarrhythmic and anticoagulation therapy was often managed

by a referring physician. Although we obtained multiple 48-hour ECG-Holter recordings, universal continuous monitoring would be optimal. Moreover, the effects of GP ablation was not investigated.

Conclusion

In our experience, totally thoracoscopic ablation with autonomic ganglia ablation and LAAE for persistent and long-standing persistent AF is safe, feasible and gives good midterm results for the maintenance of the sinus rhythm. It allows the restoration of atrial transport function after the operation, which can improve heart function. Longer follow-up and further studies in this group of patients are necessary.

Literature

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J, 2016;37:2893-2962
2. Calkins H, Brugada J, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. HeartRhythm, 2012
3. Romero JR, Wolf PA. Epidemiology of stroke: Legacy of the Framingham heart study. Global Heart, 2013; 8: 67-75
4. Boersma LVA, Castella M,van Boven W, et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (fast): A 2-center randomized clinical trial. Circulation, 2012; 125: 23-30
5. Cox JL, Boineau JP, Schuessler RB, et al. Modification of the Maze procedure for atrial flutter and fibrillation: rational and surgical results. J Thorac Cardiovasc Surg, 1995; 110: 473-484
6. Weerasooriya R, Khairy P, Litalien J, el al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol, 2011; 57(2): 160-166
7. Yilmaz A, Geuzebroek GSC, Van Putte BP, et al. Completely thoracoscopic pulmonary vein isolation with ganglionic plexus ablation and left atrial appendage amputation for treatment of atrial fibrillation. Eur J Cardiothorac Surg, 2010; 38 (3): 356-360
8. Weimar T, Vosseler M, Czesia M, et al. Approaching a paradigm shift: endoscopic ablation of lone atrial fibrillation on the beating heart. Ann Thorac Surg, 2012; 94 (6): 1886-1892
9. Doty JR, Clayson SE. Surgical Treatment of Isolated (Lone) Atrial Fibrillation With Gemini-S Ablation and Left Atrial Appendage Excision (GALAXY Procedure). Innovations, 2012; 7: 33-38
10. Zembala M, Suwalski P. Minimally invasive surgery for atrial fibrillation. J Thorac Dis, 2013; 5 (Suppl. 6): S704-712
11. Ad N, Holmes SD, Massimiano PS, et al. The effect of the Cox-maze procedure for atrial fibrillation concomitant to mitral and tricuspid valve surgery. J Thorac Cardiovasc Surg, 2013; 146 (6): 1426-1434
12. Schuessler RB, Lee AM, Melby S J, et al. Animal studies of epicardial atrial ablation. Heart Rhythm, 2009; 6 (12, S1): S41-S45
13. Damiano RJ Jr, BadhwarV, Acker MA, etal. The CURE-AF trial: a prospective, multicenter trial of irrigated radiofrequency ablation for the treatment of persistent atrial fibrillation during concomitant cardiac surgery. Heart Rhythm, 2014; 11 (1): 39-45
14. Gillinov AM, Bhavani S, Blackstone EH, et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. Ann Thorac Surg, 2006; 82:502-514
15. Pison L, La Meir M, van Opstal J, et al. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol, 2012; 60: 54-61
16. Muneretto C, Bisleri G, Bontempi L, et al. Successful treatment of lone persistent atrial fibrillation by means of a hybrid thoracoscopic - transcatheter approach. Innovations, 2012; 7: 254-258
17. Doll N, Pritzwald-Stegmann P, Czesia M, et al. Ablation of ganglionic plexi during combined surgery for atrial fibrillation. Ann Thorac Surg, 2008; 86: 1659-1663
18. Mehall JR, Kohut RM, Schneeberger EW, et al. Intraoperative epicardial electrophysiologic mapping and isolation of autonomic ganglionic plexi. Ann Thorac Surg, 2007; 83: 538-541
19. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol, 2011; 57(2): 160-166
20. Holmes DR, Reddy VY, Turi ZG, et al; PROTECT AF Investigators: Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet, 2009; 374: 534-542
21. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an under-recognized trigger site of atrial fibrillation. Circulation, 2010; 122 (2): 109-118

Intravitreal injection of ranibizumab in patients with chronic central serous chorioretinopathy - preliminary reports

Iniekcje doszklistkowe ranibizumabu u pacjentów z przewlekłą centralną surowiczą chorioretinopatią - doniesienia wstępne

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Abstract. Central serous chorioretinopathy (CSC) is an idiopathic disorder which affects young and middle-aged adults, more often males. Usually it is self-limited but sometimes it becomes chronic. Research is still being carried out to find the most effective form of treatment with the fewest complications. The aim was to evaluate the efficacy of intravitreal injections of ranibizumab in patients with chronic CSC. A total of 17 eyes from a group of 17 patients qualified for ranibizumab application were treated. Best-corrected visual acuity, direct ophthalmoscopy, optical coherent tomography (OCT) and fluorescein angiography were performed both during the eligibility visit and during the control visit 1 month after the injection. BCVA improved and central retinal thickness decreased in all patients. Intravitreal injections of ranibizumab can be effective in chronic CSC treatment.
Keywords: central serous chorioretinopathy, ranibizumab

Streszczenie. Wstęp. Centralna surowicza chorioretinopatią (CSC) jest chorobą idiopatyczną dotykającą najczęściej młodych dorosłych lub osób w średnim wieku, częściej mężczyzn. W wielu przypadkach ustępuje samoistnie, jednak czasem przyjmuje formę przewlekłą. Wciąż trwają badania nad opracowaniem najefektywniejszej metody leczenia, obarczonej jak najmniejszymi powikłaniami. Cel. Ocena skuteczności leczenia doszklistkowymi iniekcjami ranibizumabu u pacjentów z przewlekłym CSC. Metody. Badanie przeprowadzono na 17 oczach 17 pacjentów zakwalifikowanych do leczenia ranibizumabem. Pacjentom badano ostrość wzroku (BCVA), przeprowadzano oftalmoskopię pośrednią, wykonywano optyczną koherentną tomografię (OCT) oraz angiografię fluoresceinową (AF) zarówno podczas wizyty kwalifikującej, jak i kontrolnej, po 1 miesiącu od iniekcji. Wyniki. U wszystkich pacjentów doszło do poprawy ostrości wzroku oraz do zmniejszenia centralnej grubości siatkówki. Wnioski. Doszklistkowe iniekcje ranibizumabu mogą być skuteczną metodą leczenia przewlekłego CSC.
Słowa kluczowe: centralna surowicza chorioretinopatią, ranibizumab

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Introduction

Central serous chorioretinopathy (CSC) is an idiopathic disease characterised by serous detachment of the neurosensory retina in the posterior segment. It usually affects young or middle-aged patients, more frequently male than female. Patients with CSC report impaired visual acuity, metamorphopsia, altered perception of colours, micropsia and central scotoma. In most cases the disease is self-contained, and visual acuity is restored after the subretinal fluid is absorbed, typically within 3 to 6 months [1]. Unfortunately, in some patients the process takes many more months. Despite a frequently maintained good visual acuity, they complain about impaired contrast sensitivity and disturbed perception of colours. In a few percent of patients with a long recovery period, visual acuity is irreversibly impaired [2, 3].

CSC is probably caused by increased permeability of retinal vessels, which can be visualised in fluorescein

angiography (FA) as a leak in the pigment epithelial cell layer [4]. In some patients FA reveals multiple focal leaks, or a pathognomonic smokestack image. Sometimes also extrafoveal leaks and retention of subretinal fluid are observed, although they frequently remain unnoticed by patients. In patients with subretinal fluid accumulation persisting for longer periods, restricted or diffused deficits of pigment epithelium are found.

Optical coherence tomography (OCT) offers another method of diagnosing and monitoring CSC. It is valued due to its non-invasive character and repeatable results [5]. In acute CSC, the disease self-limits by reducing the amount of subretinal fluid. Chronic CSC is characterised by prolonged retinal detachment in the posterior segment. It may cause permanent visual impairment. The period of subretinal fluid accumulation resulting in permanent visual damage has not been established.

Ranibizumab is a fragment of recombined humanised monoclonal antibody selective against human vascular endothelial growth factor A (VEGF-A). Intravitreal injection of this medication are used in the treatment of exudative age-related macular degeneration [6], macular oedema following central retinal vein occlusion [7] and diabetic macular oedema [8].

Aim of the study

The aim of the study was to evaluate the effectiveness of ranibizumab in patients with chronic idiopathic CSC.

Material and methods

The study comprised 17 eyes of 17 patients treated with intravitreal injections of ranibizumab at the Department of Ophthalmology, Regional Specialist Hospital in Zgierz from April 2018 to March 2019. The patients were qualified for treatment due to chronic idiopathic CSC. Inclusion criteria comprised a documented persistence of subretinal fluid for over 6 months. Patients with neovascularisation, after retinal photocoagulation, after photodynamic therapy (PDT), after intravitreal injections of triamcinolone or other anti-VEGF preparations, patients with glaucoma or other conditions affecting best-corrected visual acuity (BCVA), e.g. cataract, were excluded from the study. During the visit qualifying for intravitreal injection of ranibizumab, the following tests were performed in all patients: visual acuity test, slit lamp exam, indirect ophthalmoscopy, SOCT (spectral optical coherence tomography), and fluorescein angiography. The qualified patients received a single intravitreal injection of 0.5 ml / 0.05 ml of ranibizumab. The follow-up visit took place a month after the injection. It involved the same tests as the qualification visit.

The results were analysed statistically. For the tests with distribution close to normal values are presented as mean and standard deviation (±SD), and the means were compared using Student's t-test. Statistical significance was set at $p < 0.05$.

The study included 17 eyes in 17 patients, 3 females and 14 males. They all received intravitreal injections of ranibizumab due to chronic idiopathic CSC. Mean age of the patients was 46.7 ± 13.3 years.

Results

Mean visual acuity at the qualification visit was 0.5 ±0.3, and at the follow-up visit – 0.75 ±0.25. The change was considered statistically significant ($p < 0.05$). Visual acuity improved in all the patients. In 88.24% of subjects improvement of at least two lines was observed. The visual acuity did not deteriorate compared to the qualification test in any of the patients (Fig. 1).

A significant reduction of the central retinal thickness in the foveolar was also observed. In the qualification examination the mean retinal thickness in the foveolar was 421.5 µm ±80.5 µm, whereas after treatment it decreased to 239 µm ±36 µm on average, which is statistically significant ($p < 0.05$) (Fig. 2).

In two patients, despite the reduced thickness of central retina, the subretinal fluid was not completely absorbed. They were qualified for another injection.

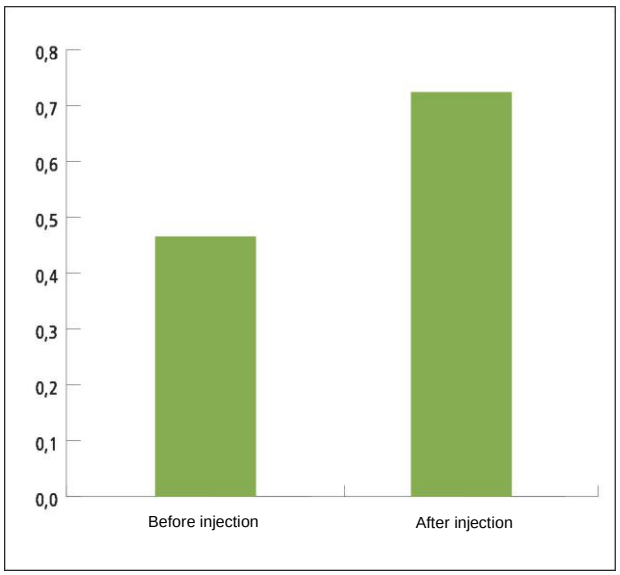

Figure 1. Change in the mean best-corrected visual acuity before and after injection
Rycina 1. Zmiana średniej najlepiej skorygowanej ostrości wzroku przed iniekcją i po iniekcji

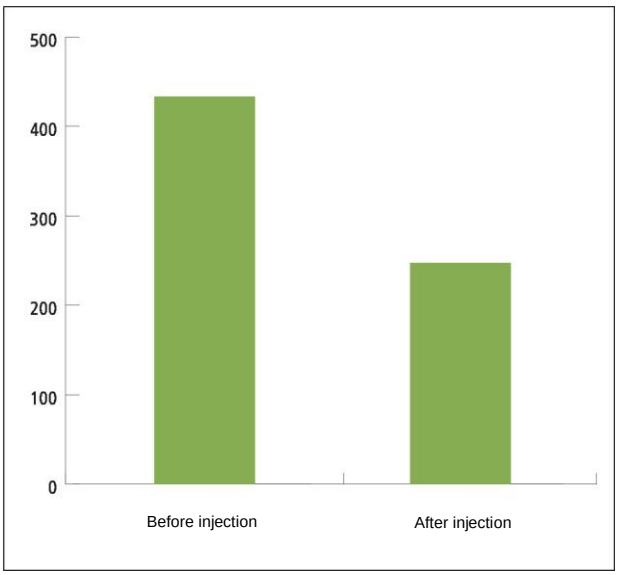

Figure 2. Change in the mean central retinal thickness before and after injection
Rycina 2. Zmiana średniej centralnej grubości siatkówki przed iniekcją i po iniekcji

Discussion

CSC is described as detachment of neurosensory retina with atrophy of retinal pigment epithelium and rearrangement of pigmentation [9]. For a long time it was considered to be a self-limiting disease that does not require treatment, but merely observation [10].

However, recently studies have been conducted to assess the effectiveness of various therapies for CSC.

Cardillo Piccolino et al. [11] established that photodynamic therapy (PDT) can be effective in the treatment of serous macular detachment and improves visual acuity in CSC patients. PDT probably reduces blood flow in choriocapillaries and their permeability. However, the therapy is associated with adverse effects, such as pigment lesions at the application site, and irreversible reduction of blood flow through choriocapillaries. Chan et al. [12] observed development of choroidal neovascularisation at the sites of application of photodynamic therapy, secondary to ischaemia in the choriocapillaries due to PDT in patients with CSC.

Stewart described the risk of choroidal neovascularisation due to argon laser therapy [13]. Researches also used laser beam of 810 nm for transpupillary thermal therapy of CSC. However, Penha et al. [14] reported a case of a 31-year-old male who suffered thermal retinal injury as a result of this treatment. Kim et al. [15] assessed the effectiveness of intravitreal injections of ranibizumab in patients with acute idiopathic CSC (symptoms persisting for less than 3 months). The follow-up examination performed after 6 months demonstrated improvement of visual acuity, reduction of the central retinal thickness, and absence of subretinal fluid.

Shams and Lanchulev [16] established that VEGF regulates angiogenesis and permeability of vessels in the eye. Increased permeability of the choroidal vessels is considered to be the cause of this pathology, so using growth factor inhibitors, such as ranibizumab, to reduce the permeability is justified. It is a common belief that long duration of symptoms adversely affects the prognosis in CSC patients. However, in nearly 90% of the study subjects visual acuity improved by at least 2 lines.

Conclusions

Improvement of visual acuity and of anatomical structure of the retina following intravitreal injection of ranibizumab provide evidence of the effectiveness of this therapy. However, further studies are required to confirm this effectiveness and to develop the perfect dosing regimen for patients with chronic idiopathic CSC.

Literature

1. Wang M, Munch IC, Hasler PW, et al. Larsen. Central serous chorioretinopathy. Acta Ophtalmol, 2008; 86 (2): 126-145
2. Folk JC, Thompson HS, Han DP, et al. Visual function abnormalities in central serous retinopathy. Arch Ophthalmol, 1984; 102 (9): 1299-1302
3. Chuang EL, Sharp DM, Fitzke FW, et al. Retinal dysfunction in central serous retinopathy. Eye, 1987; 1 (1): 120-125
4. Gackle HC, Lang GE, Freissler KA, et al. Clinical, fluorescein angiographic and demographic aspects in central serous chorioretinopathy. Der Ophtalmologe, 1998; 95 (8): 529-533
5. Iida T, Hagimura N, Sato T, et al. Evaluation of central serous chorioretinopathy with optical coherence tomography. Am J Ophtalmol, 2000; 129 (1): 16-20
6. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med, 2006; 355 (14): 1419-1431
7. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Optalmology, 2010; 117 (6): 1124-1133
8. Mitchell P, Bandello F, Schmidt- Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema, Ophtalmology, 2011; 118 (4): 615-625
9. Schaal KB, Hoeh AE, Scheuerle A, et al. Intravitreal bevacizumab for treatment of chronic central serous chorioretinopathy. Eur J Ophtalmol, 2009; 19 (4): 613-617
10. Yannuzzi LA. Type-A behavior and central serous retinopathy. Retina, 1987; 7 (2): 111-131
11. Cardillo Piccolino F, Eandi CM, Ventre L. Photodynamic therapy for chronic central serous chorioretinopathy. Retina, 2003; 23: 752-763
12. Chan WM, Lam DS, Lai TY. Choroidal vascular remodeling in central serous chorio-retinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at primary disease level. Br J Ophthalmol, 2003; 87: 1453-1458
13. Stewart JM. Central serous chorio-retinopathy half dose verteporfin PDT for central serous chorio-retinopathy. Br J Ophthalmol, 2006; 90: 805-806
14. Penha FM, Aggio FB, Bonomo PP. Severe retinal thermal injury after indocyanine green-mediated photothrombosis for central serous chorioretinopathy. Am J Ophthalmol, 2007; 143: 887-889
15. Kim M, Lee S, Lee S. Intravitreal ranibizumab for acute central serous chorio-retinopathy. Ophthalmologica, 2013; 229: 152-157
16. Shams N, Ianchulev T. Role of vascular endothelial growth factor in ocular angiogenesis. Ophthalmol Clin North Am, 2006; 19: 335-344

Association of baroreflex sensitivity and physical fitness based on the assessment of soldiers with different levels of physical fitness

Powiązanie wrażliwości baroreceptorów z wydolnością fizyczną na podstawie oceny żołnierzy o różnym poziomie wytrenowania

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Abstract. Regular physical activity increases the activity of the parasympathetic nervous system, changing the sympathetic-parasympathetic balance towards the latter. An assessment was made of baroreflex sensitivity (BRS) at baseline and during provocative tests in groups of soldiers with average (PW) and above average (PPW) physical fitness in order to identify the BRS parameters that differentiate the two groups. A total of 70 soldiers with PW and 124 healthy soldiers with PPW aged 18-45 years underwent the test. An assessment of BRS at baseline and during provocative tests: controlled breathing test (CBT), handgrip test (CBT) and tilt test (TT) were performed. The most distinguished inter-group differences concerned baseline BRS assessment. Alpha LF and Alpha HF values were higher in the PPW group. During CBT and HGT, no statistically significant differences were noted between the groups. During TT, the differences in PPW group were subtle. The assessment of AUN with BRS enables differentiation of individuals with different levels of physical fitness. The most distinguished differences in BRS parameters were registered at baseline. The assessment of BRS during provocative tests did not show inter-group differences significant enough to consider its performance justified.
Keywords: autonomic nervous system, baroreflex sensitivity, BRS, controlled breathing test, handgrip test, physical fitness, tilt test

Streszczenie. Wstęp. Regularny wysiłek fizyczny zwiększa aktywność części przywspółczulnej autonomicznego układu nerwowego (AUN), przez co zmienia równowagę współczulno-przywspółczulną na korzyść tej drugiej. Cel. Ocena wrażliwości baroreceptorów (BRS) w spoczynku oraz w trakcie testów prowokacyjnych w grupach żołnierzy o przeciętnej (PW) i ponadprzeciętnej wydolności fizycznej (PPW) w celu identyfikacji parametrów BRS różnicujących te grupy. Metody. Przebadano 70 żołnierzy z PW oraz 124 zdrowych żołnierzy z PPW w wieku 18-45 lat. Oceniono BRS w spoczynku i w trakcie testów prowokacyjnych: kontrolowanego oddechu (CBT), zacisku dłoni (HGT) oraz testu pochyleniowego (TT). Wyniki. Najwyraźniejsze różnice międzygrupowe dotyczyły oceny spoczynkowej BRS: w grupie PPW zarejestrowano większą wartość alfa LF oraz alfa HF. W wyniku CBT oraz HGT nie zarejestrowano istotnych statystycznie różnic międzygrupowych. W wyniku TT w porównaniu międzygrupowym w PPW stwierdzone różnice były subtelne. Wnioski. Ocena AUN metodą BRS pozwala różnicować osoby o różnym poziomie wytrenowania. Najwyraźniejsze różnice zaobserwowano w zakresie parametrów BRS rejestrowanych w spoczynku. Ocena BRS w trakcie testów prowokacyjnych nie wykazuje na tyle istotnych różnic międzygrupowych, aby można było uznać ich wykonywanie za uzasadnione.
Słowa kluczowe: BRS, wrażliwość baroreceptorów, wydolność fizyczna, autonomiczny układ nerwowy, test kontrolowanego oddechu, test zacisku dłoni, test pochyleniowy

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Introduction

One of the key tasks of the autonomic nervous system (ANS) is to maintain homeostasis in the organism by regulating interactions between the respiratory system and the cardiovascular system. This is achieved with the use of reflex arcs which start at the anterior area of the ventrolateral medulla oblongata for the sympathetic part and in the posterior area of the ventrolateral medulla oblongata for the parasympathetic part. Regular physical effort increases the activity of parasympathetic ANS, which shifts the sympathetic-parasympathetic balance to the latter at rest and during effort [1-2]. The carotid sinuses and the aortic arch contain baroreceptors, responsible for adjustment of the cardiovascular function to the changing external and internal conditions. The assessment of baroreflex sensitivity (BRS) at rest and during provocative tests is an established method for indirect evaluation of ANS function. Improved BRS is associated with good prognosis in patients with cardiovascular diseases [3-4], and physical activity is one of the methods to enhance BRS [5-6]. However, as no clearly defined conditions for BRS assessment with proven diagnostic value are available, the method is used to a limit extent in daily practice.

Aim of the study

The aim of the study was to assess BRS at rest and during autonomic provocative tests in healthy volunteers (soldiers) with above average and average physical fitness, and to determine which BRS parameters differentiate the two groups. According to the hypothesis, subjects with above average physical fitness should have higher BRS than those with lower fitness, and identification of the parameters and conditions for BRS assessment could be useful in daily practice.

Material and methods

The study group comprised 124 soldiers with above average physical fitness (AAF), serving in special units, and exposed to high psychophysical stress during foreign deployment. The group of soldiers with average physical fitness (AF) included 70 soldiers from regular units. All subjects were 25-45 year old males, and declared to be healthy. The exclusion criteria were: existing cardiovascular, respiratory and neurological conditions, and disorders of the musculoskeletal system that could prevent performing the tests according to the protocol. All subjects were informed about the aim of the study and the methods used to conduct it, and they signed an informed consent to participate in the study. The study was approved by the Bioethical Committee of the Military Institute of Medicine.

Detailed characteristics of the study group are presented in the doctoral thesis of the first author of this article [7]. The study protocol included physical examinations and medical history to identify cardiovascular risk factors (questions about history of early cardiovascular diseases in the family, obesity, abdominal obesity, nicotinism, body mass index based on the body weight and height). Systolic and diastolic blood pressure was measured following the European Cardiac Society guidelines [8], in a quiet room, in a sitting position, after 5 minutes of rest. Each subject underwent an ergospirometric test (ZAN 680 Messgerate GmbH; Germany), after assessment of respiratory exchange to exclude obstruction of the respiratory tract. Next, each subject had an exercise test using a cycle ergometer ramp protocol, combined with simultaneous evaluation of respiratory gases, electrocardiographic changes, and blood pressure measurements. Following the analysis of multiple parameters and diagrams, the physical fitness of subjects was evaluated, using reference values. This study assessed the following parameters: maximal oxygen uptake compared to the predicted values (% pred VO_2 peak), and the actual work load compared to the predicted values (% pred LOAD).

Subsequently, BRS was assessed over time and with regard to frequency, both at rest and during provocative tests: controlled breathing test (CBT) at 15 breaths/minute, showing the effect of forced breathing rate on oscillation of R-R intervals and arterial blood pressure; handgrip test (HGT) to assess the effect of continuous squeezing of a hand dynamometer for 5 minutes on the oscillation of R-R intervals and arterial blood pressure; and the first (5-minute) phase of the tilt test (TT). Following the ESC guidelines, the tilt test was conducted in the morning, to avoid the effect of daily alterations in the sympathetic ANS tension, in a quiet room, with neutral light and ambient temperature. Sequential BRS (seq_BRS), its highest value (Up_BRS) and lowest value (Down_BRS) were determined by analysis of 3 or more consecutive heart beats during which the systolic pressure increased or decreased by 1 mm Hg, and the R-R interval was extended or shortened by 40 ms, as well as Alpha_HF and Alpha_LF BRS were derived as a square root of the ratio of R-R intervals and changes in the systolic blood pressure within the low and high waves. The provocative test pattern is presented in Figure 1. Changes in BRS parameters were also determined as absolute differences (ad_variable) and relative differences (rd_variable), subtracting the resting values before the test from the values obtained during the test.

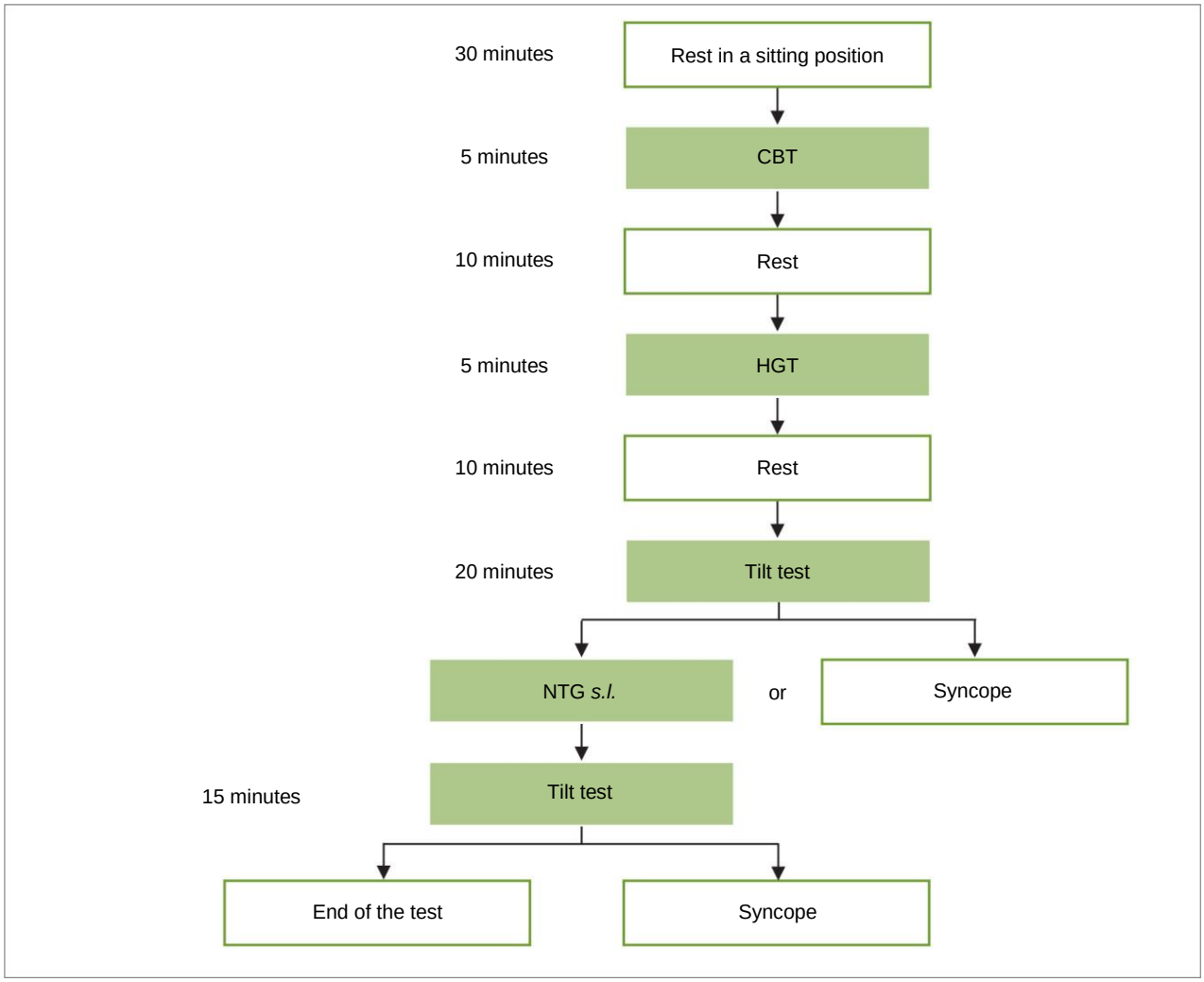

Figure. Provocative test scheme, CBT - controlled breathing test, HGT - handgrip test, NTG *s.l.* - nitroglycerin sublingual
Rycina Schemat wykonania testów prowokacyjnych. CBT - test kontrolowanego oddechu, HGT - test izometrycznego zacisku dłoni, NTG *s.l.* - nitrogliceryna podawana podjęzykowo

Statistical analysis

Statistical analysis was performed using Microsoft Office Excel 2010 and Statistica 12.0 (StatSoft Inc.). The distribution and normality of data were assessed visually, and with the use of Kolmogorov-Smirnov test. Continuous variables were presented as means ± standard deviation, and categorical variables were presented as absolute and relative values (per cent). To analyse the differences between the absolute values t-test was used for variables with normal distribution, and Mann-Whitney U-test for the data that did not follow normal distribution. Statistical significance was set at $p < 0.05$.

Results

Study group characteristics

The baseline characteristics of the groups with above average and average physical fitness is presented in Table 1. Patients in the AAF group were significantly older and had higher body weight and BMI index. They demonstrated lower heart rate at rest, and lower systolic blood pressure. No differences in diastolic pressure were observed.

Table 1. Characteristics and comparison of groups with above average and average physical fitness
Tabela 1. Charakterystyka i porównanie grupy o ponadprzeciętnej i przeciętnej wydolności fizycznej

Parameter	Whole group (n = 194)	AAF (n = 124)	AF (n = 70)	p
Age (years)	33.42 (±6.54)	37 (±4)	26 (±4)	<0.0005
Height (m)	1.79 (±0.06)	1.79 (±0.06)	1.78 (±0.06)	0.422
Body weight (kg)	81.46 (±8.87)	83 (±8kg)	78 (±10)	<0.0005
BMI (kg/m^2)	25.54 (±2.22)	26.07 (±1.87)	24.60 (±2.45)	<0.0005
HR (beats/minute)	64 (±13)	60 (±9)	72 (±15)	<0.0005
SBP (mm Hg)	124 (±12)	120 (±10)	131 (±12)	<0.0005
DBP (mm Hg)	76 (±7)	75 (±7)	77 (±8)	0.057
SBP >140 mm Hg	22 (11.5%)	6 (5%)	16 (23%)	<0.0005
DBP >80 mm Hg	9 (4.7%)	4 (3%)	5 (7%)	0.213

The data are presented as means (± standard deviation) and number of subjects (percentage).

BMI - body mass index, DBP - diastolic blood pressure, HR - heart rate, AAF - above average physical fitness group, AF- average physical fitness group, SBP - systolic blood pressure

Table 2. Baseline BRS parameters in groups of above average and average physical fitness
Tabela 2. Parametry BRS w spoczynku w grupie o ponadprzeciętnej i przeciętnej wydolności fizycznej

Parameter	AAF	AF	p
Alpha_LF	38.55 (±61.67)	28.47 (±18.50)	0.035
Alpha_HF	42.88 (±26.74)	35.19 (±25.98)	0.009
Up_BRS (ms/mm Hg)	34.34 (±20.30)	30.60 (±15.47)	0.383
Down_BRS (ms/mm Hg)	32.95 (±16.10)	32.70 (±22.53)	0.210
Sequence_BRS (ms/mm Hg)	33.82 (±16.05)	32.44 (±19.00)	0.224

Data are expressed as means (± standard deviation).

Alpha_LF - alpha for low frequencies, Alpha_HF - alpha for high frequencies, Up_BRS - the highest value of baroreflex sensitivity, Down_BRS - the lowest value of baroreflex sensitivity, Sequence_BRS - mean value of baroreflex sensitivity

Ergospirometry results

Following the adopted hypothesis, the AAF group achieved higher values in the ergospirometry tests: %pred LOAD *(vs* AF: 115% *vs* 89%, ρ <0.0005), % pred VO_2 peak (116% *vs* 106%, ρ = 0.019), and RER (1.18 vs 1.12, ρ <0.0005).

BRS assessment results

In the assessment of BRS at rest, alpha-LF values were higher in the AAF group, compared to AF: 38.55 *vs* 28.47, ρ = 0035). Also alpha-HF values were higher in the AAF group (42.88 *vs* 35.19, ρ = 0.009). Detailed results are presented in Table 2.

In the CBT results, the following parameters were reduced in the AAF group (before the test vs after the test): 42.88 *vs* 35.52, ρ = 0.009), Down_BRS (32.95 ms/mm Hg *vs* 29.85 ms/mm Hg, ρ = 0.049) and Sequence_BRS (33.82 ms/mm Hg *vs* 30.19 ms/mm Hg, ρ = 0.001). In the AF group the following parameters were reduced: Down_BRS (before the test *vs* after the test): 32.70 ms/mm Hg *vs* 27.37 ms/mm Hg, ρ = 0.006) and Sequence_BRS (32.44 ms/mm Hg *vs* 29.24 ms/mm Hg, ρ = 0.036). Considering the relative and absolute changes in the above parameters, no statistically significant differences between the AAF and AF groups were found during CBT (Table 3).

As for the HGT results, in the AAF group all BRS parameters were significantly reduced, and in the AF group reduction was observed with regard to the following ones (before the test vs after the test): 37.17 *vs* 26.77, ρ = 0.006), Up_BRS (35.88 ms/mm Hg *vs* 26.84 ms/mm Hg, ρ = 0.0006), Down_BRS (31.71 ms/mm Hg *vs* 23.75 ms/mm Hg, ρ = 0.008) and Sequence_BRS (33.27 ms/mm Hg *vs* 24.86 ms/mm Hg, ρ <0.0005). However, considering the relative and absolute changes in the above parameters, no statistically significant differences in BRS were found between AAF and AF groups during HGT (Table 4).

Following tilt test, both groups demonstrated reduction of all the BRS parameters. Intergroup comparison revealed lower absolute reduction of ad_alpha-HF in the AAF group (-28.72 *vs* -22.77, ρ = 0.036), and a lower relative reduction of rd_Down_BRS (-43.94% *vs* 49.73%, ρ = 0.045) (Tab. 5).

Table 3. Comparison of relative and absolute changes in BRS parameters following CBT in groups of above average and average physical fitness
Tabela 3. Porównanie zmian względnych i bezwzględnych parametrów BRS w wyniku CBT w grupie o przeciętnej i ponadprzeciętnej wydolności fizycznej

Parameter	Absolute delta AAF	Absolute delta AF	p	Relative delta AAF (%)	Relative delta AF (%)	p
Alpha_LF	8.61 (±63.62)	1.94 (±15.36)	0.807	1.15 (±47.93)	19.50 (±129.1)	0.797
Alpha_HF	7.36 (±22.43)	2.30 (±17.06)	0.124	6.59 (±57.26)	28.15 (±132.3)	0.065
Up_BRS (ms/mm Hg)	2.69 (±17.48)	1.34 (±12.91)	0.113	0.96 (±44.05)	13.30 (±55.73)	0.117
Down_BRS (ms/mm Hg)	3.10 (±11.83)	5.33 (±17.10)	0.343	5.26 (±39.96)	5.27 (±58.28)	0.332
Sequence_BRS (ms/mm Hg)	3.64 (±10.63)	3.19 (±13.25)	0.677	7.79 (±28.60)	5.18 (±31.92)	0.855

Data are expressed as means (± standard deviation).

Alpha_LF - alpha for low frequencies, Alpha_HF - alpha for high frequencies, Up_BRS - the highest value of baroreflex sensitivity, Down_BRS - the lowest value of baroreflex sensitivity, Sequence_BRS - mean value of baroreflex sensitivity

Table 4. Comparison of relative and absolute changes in BRS parameters following HGT in groups of above average and average physical fitness
Tabela 4. Porównanie zmian względnych i bezwzględnych parametrów BRS w wyniku HGT w grupie o przeciętnej i ponadprzeciętnej wydolności fizycznej

Parameter	Absolute delta AAF	Absolute delta AF	p	Relative delta AAF	Relative delta AF	p
Alpha_LF	6.64 (±18.03)	5.75 (±19.97)	0.901	4.24 (±71.16)	2.34 (±95.82)	0.369
Alpha_HF	8.41 (±28.43)	10.41 (±27.81)	0.498	2.65 (±61.04)	18.15 (±167.5)	0.142
Up_BRS (ms/mm Hg)	4.77 (±34.89)	9.04 (±23.26)	0.266	7.99 (±47.12)	12.04 (±63.50)	0.123
Down_BRS (ms/mm Hg)	5.95 (±15.10)	7.96 (±16.48)	0.800	7.82 (±50.45)	17.34 (±37.76)	0.255
Sequence_BRS (ms/mm Hg)	6.71 (±13.76)	8.41 (±16.96)	0.256	10.87 (±37.65)	17.70 (±42.05)	0.101

Data are expressed as means (± standard deviation).

Alpha_LF - alpha for low frequencies, Alpha_HF - alpha for high frequencies, Up_BRS - the highest value of baroreflex sensitivity, Down_BRS - the lowest value of baroreflex sensitivity, Sequence_BRS - mean value of baroreflex sensitivity

Discussion

The observed higher BRS values at rest in the AAF group indicate a relationship between the above average physical fitness with the ANS function assessed in this study. These findings are consistent with previous reports. Bowman et al. [9] demonstrated that physical effort is associated with higher BRS in elderly subjects. The beneficial effects of physical effort on BRS are confirmed both in interventional studies on humans, and in animal models [10]. Fredericks et al. [11] observed that discontinuation of regular exercise was associated with a reduction in BRS, and decreased physical fitness (based on VO_2 peak). However, some studies find no differences in BRS between subjects demonstrating above average fitness and those exercising recreationally [12, 13].

These discrepancies emphasize the scientific value of studies conducted in homogeneous groups, with the use of advanced diagnostic methods, as in the case of the study conducted in our centre. We decided to verify the usefulness of provocative tests, widely used in the evaluation of ANS function, for the assessment of BRS. It was reported that during the controlled breathing test, at the rate of 6 breaths/minute BRS increased [14-18]. In our study, during CBT with a different breathing rate, contrary to the presented studies, in both groups the Down_BRS and seq_BRS values decreased, but no statistically significant differences in relative changes were found between the groups. However, interpretation of BRS in response to CBT raises doubts, as some authors demonstrate that increased BRS does not indicate modulation of the BRS function due to the change in the breathing rate, but rather represents the relationship between BRS and alterations in arterial pressure oscillation in response to the changed breathing pace [19]. Most available studies [20-24] revealed that during the handgrip test BRS decreased, but its baseline values were restored in the resting phase. In the presented study, consistently with the findings of other authors, HGT resulted in BRS reduction in both groups, and no statistically significant intergroup changes were observed. However, it is noteworthy that the BRS values in the AAF group were higher than in the AF group both before and after HGT. The present study, as well as in

Table 5. Comparison of relative and absolute changes in BRS parameters following TT in groups of above average and average physical fitness

Tabela 5. Porównanie zmian względnych i bezwzględnych parametrów BRS w wyniku TT w grupie o przeciętnej i ponadprzeciętnej wydolności fizycznej

Parameter	Absolute delta AAF	Absolute delta AF	p	Relative delta AAF (%)	Relative delta PW (%)	p
Alpha_LF	15.62 (±16.47)	11.24 (±13.68)	0.075	39.74 (±31.54)	49.60 (±695.3)	0.537
Alpha_HF	28.72 (±24.28)	22.77 (±26.43)	0.036	58.15 (±32.15)	55.22 (±891.8)	0.907
Up BRS (ms/mm Hg)	18.36 (±19.98)	17.57 (±15.09)	0.692	45.81 (±24.97)	47.18 (±31.91)	0.135
Down_BRS (ms/mm Hg)	16.46 (±15.19)	15.93 (±15.46)	0.972	43.94 (±33.23)	49.73 (±35.05)	0.045
Sequence_BRS (ms/mm Hg)	16.77 (±13.45)	16.65 (±15.20)	0.941	46.56 (±21.48)	49.22 (±30.81)	0.106

Data are expressed as means (± standard deviation).

Alpha_LF - alpha for low frequencies, Alpha_HF - alpha for high frequencies, Up_BRS - the highest value of baroreflex sensitivity, Down_BRS - the lowest value of baroreflex sensitivity, Sequence_BRS - mean value of baroreflex sensitivity

other studies available in the literature, demonstrated BRS reduction after verticalisation [25-28]. Similarly to the status before CBT and HGT, the AAF group demonstrated higher BRS at the baseline (higher Alpha_HF and Alpha_LF) compared to the AF group. Although no statistically significant relative and absolute changes were found for most BRS parameters, it should be emphasised that also after verticalisation the BRS in the AAF group was higher. The strengths of this study include the fact that BRS was assessed both with a spectral and a sequential method. The results of both analyses were consistent. The usefulness of provocative tests in the assessment of BRS could be verified. The observed changes are of significant scientific value, but regarding the aim of this study, they do not present any added value in differentiation of subjects with different levels of fitness. Tests at rest, the easiest ones to perform, proved to be sufficient in the detection of significant differences between the study groups.

Limitations

Considering the significant intersubject variability of BRS parameters, the methodological limitations of this study included group size, which could affect the statistical significance of the results. Simultaneously, the groups were considerably more numerous than in other studies available in the literature, involving sportsmen. The only participants in the study were young and middle-aged males, so the results should be carefully applied to other populations. Another limitation is absence of a standardised exercise regimen in the AAF group prior to inclusion to the study. Therefore, the level of physical fitness was verified by ergospirometry, which confirmed a high degree of fitness in special unit soldiers. Moreover, the assessment of ANS function in the study was indirect, and involved using non-invasive tests whose results should be carefully interpreted, and analysed in a broader clinical context.

Conclusions

The assessment of ANS using BRS enables to differentiate between individuals with different levels of physical fitness. The most pronounced differences in BRS parameters were registered at rest. The intergroup differences demonstrated in the assessment of BRS during provocative tests are not significant enough to justify using them to differentiate between individuals with an average and above average physical fitness.

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Literature

1. Konturek SJ. Fizjologia człowieka [Human physiology]. Elsevier Urban&Partner, Wrocław 2007: 1022-1039
2. Lamberts RP, Swart J, Noakes TD, et al. Changes in heart rate recovery after high-intensity training in well-trained cyclists. Eur J Appl Physiol, 2009; 105: 705-713
3. Singh J, Kandala J, Camm A. Non pharmacological modulation of the autonomic tone to treat heart failure. Eur Heart J, 2014; 35: 77-85
4. Modesti P, Ferrari A, Bazzini C, et al. Time sequence of autonomic changes induced by daily slow-breathing sessions. Clin Auton Res, 2015; 25: 95-104

5. Neto OB, de Sordi CC, da Mota GR, et al. Exercise training improves hypertension-induced autonomic dysfunction without influencing properties of peripheral cardiac vagus nerve. Auton Neurosci, 2017; 208: 66-72
6. Costes F, Roche F, Pichot V, et al. Influence of exercise training on cardiac baroreflex sensitivity in patients with COPD. Eur Respir J, 2004; 23 (3): 396-401
7. Wójcik A. Zastosowanie metod oceny neurokardiologicznej w identyfikacji żołnierzy o ponadprzeciętnej wydolności fizycznej. Rozprawa doktorska [Neurocardiological assessment methods in identification of soldiers with outstanding physical fitness. Doctoral thesis]. Military Institute of Medicine, 2019
8. Zasady postępowania w nadciśnieniu tętniczym. Wytyczne PTNT 2015 [Management of arterial hypertension - 2015 PTNT guidelines]
9. Bowman AJ, Clayton RH, Murray A, et al. Baroreflex function in sedentary and endurance-trained elderly people. Age Ageing, 1997; 26 (4): 289-294
10. Machi JF, Bernardes N, Mostarda C, et al. Walking promotes metabolic and baroreflex sensitivity improvement in fructose-fed male rats. Eur J Appl Physiol, 2013; 113 (1): 41-49
11. Frederiks J, Swenne CA, Bruschke AV, et al. Correlated neurocardiologic and fitness changes in athletes interrupting training. Med Sci Sports Exerc, 2000; 32 (3): 571-575
12. Shin K, Minamitani H, Onishi S, et al. Autonomic differences between athletes and non-athletes: spectral analysis approach. Med Sci Sports Exerc, 1997; 29 (11): 1482-1490
13. Foulds HJ, Cote AT, Phillips AA, et al. Characterisation of baroreflex sensitivity of recreational ultra-endurance athletes. Eur J Sport Sci, 2014; 14 (7): 686-694
14. Taggart P, Critchley H, Lambiase PD. Heart-brain interactions in cardiac arrhythmia. Heart, 2011; 97 (9): 698-708
15. Tzeng YC, Sin PY, Lucas SJ, et al. Respiratory modulation of cardiovagal baroreflex sensitivity. J Appl Physiol, 2009; 107 (3): 718-724
16. Modesti PA, Ferrari A, Bazzini C, et al. Time sequence of autonomic changes induced by daily slow-breathing sessions. Clin Auton Res, 2015; 25 (2): 95-104
17. Bothová P, Honzíková N, Fiser B, et al. Comparison of baroreflex sensitivity determined by cross-spectral analysis at respiratory and 0.1 Hz frequencies in man. Physiol Res, 2010; 59 (Suppl 1): S103–111
18. Shin K, Minamitani H, Onishi S, et al. Assessment of training-induced autonomic adaptations in athletes with spectral analysis of cardiovascular variability signals. Jpn J Physiol, 1995; 45 (6): 1053-1069
19. Horsman HM, Peebles KC, Tzeng YC. Interactions between breathing rate and low-frequency fluctuations in blood pressure and cardiac intervals. J Appl Physiol, 2015; 119 (7): 793-798
20. Iellamo F, Pizzinelli P, Massaro M, et al. Muscle metaboreflex contribution to sinus node regulation during static exercise: insights from spectral analysis of heart rate variability. Circulation, 1999; 100 (1): 27–32
21. Florian JP, Simmons EE, Chon KH, et al. Cardiovascular and autonomic responses to physiological stressors before and after six hours of water immersion. J Appl Physiol, 2013; 115 (9): 1275-1289
22. Stewart JM, Montgomery LD, Glover JL, et al. Changes in regional blood volume and blood flow during static handgrip. Am J Physiol Heart Circ Physiol, 2007; 292 (1): H215–223
23. Cunningham DJ, Petersen ES, Peto R, et al. Comparison of the effect of different types of exercise on the baroreflex regulation of heart rate. Acta Physiol Scand, 1972; 86: 444-455
24. Mancia G, Iannos J, Jamieson GG, et al. Effect of isometric hand-grip exercise on the carotid sinus baroreceptor reflex in man. Clin Sci Mol Med, 1978; 54: 33-37
25. Sugawara J, Komine H, Miyazawa T, et al. Influence of regular exercise training on post-exercise hemodynamic regulation to orthostatic challenge. Front Physiol, 2014; 5: 229
26. Laitinen T, Niskanen L, Geelen G, et al. Age dependency of cardiovascular autonomic responses to head-up tilt in healthy subjects. J Appl Physiol, 2004; 96 (6): 2333-1340
27. Chun KJ, Yim HR, Park J, et al. Role of baroreflex sensitivity in predicting tilt training response in patients with neurally mediated syncope. Yonsei Med J, 2016; 57 (2): 313-320
28. Ramírez-Marrero FA, Charkoudian N, Zhong L, et al. Balance between sympathetic response to head-up tilt and cardiac vagal factors in healthy humans. Clin Auton Res, 2007; 17 (4): 227-230

Post-traumatic hernia - a case report

Pourazowa przepuklina płuca - opis przypadku

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Abstract. Lung hernias are rare and late complications of rib fracture. There is a wide range of treatment methods available, from minimally invasive surgery to surgical methods using various synthetic materials or the patient's own muscular flaps. The aim of the study is to present a case of a patient with post-traumatic lung hernia. A hernioplasty with 5 single stitches was performed, bringing together the displaced fragments of the 8th and 9th rib, typical of sternal closure. Three months after the plasty, the results were estimated as good by the surgical team and the patient.
Keywords: lung hernia, post-traumatic complications, Sibson hernia

Streszczenie. Przepukliny płucne są rzadko występującym późnym powikłaniem złamania żeber. Sposób zaopatrzenia jest szeroki: od techniki mało inwazyjnej po techniki z użyciem różnych syntetycznych materiałów albo płatów mięśniowych. Celem pracy jest przedstawienie przypadku chorego z pourazową przepukliną płucną. Methods. Wykonano plastykę przepukliny pięcioma szwami pojedynczymi, zbliżając do siebie rozstąpione fragmenty żeber 8 i 9, typowo jak przy zamykaniu płatki piersiowej. Wyniki. W ocenie zarówno zespołu operacyjnego, jak i chorego efekty plastyki po 3 miesiącach były dobre.
Słowa kluczowe: przepuklina płucna, przepuklina Sibsona, powikłanie pourazowe

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Introduction

Rib fractures are observed in approximately 10% of trauma patients [1], and are among the most common thoracic injuries. They are seen in 40% of patients following thoracic trauma. The consequences of fractures, as well as their treatment methods, are determined by their number, location, and resulting secondary injuries. Early complications of rib fractures include oedema, haematoma and pulmonary contusion. Most rib fractures heal easily and do not leave any sequelae [2]. Late complications include chronic thoracic pain. This study presents a rare case of a late complication of a rib fracture in the form of lung hernia.

Lung hernia is defined as a protrusion of a part of the pulmonary parenchyma and the pleura outside the pleural cavity. The first classification of this condition was introduced by Marel-Lavelle in 1847, and only a few hundred cases have been reported in the literature so far. There is a wide range of treatment methods, from minimally invasive surgery to open surgical methods using various synthetic materials or muscular flaps [3-5]. The patient presented in this study received thoracic surgery due to post-traumatic lung hernia.

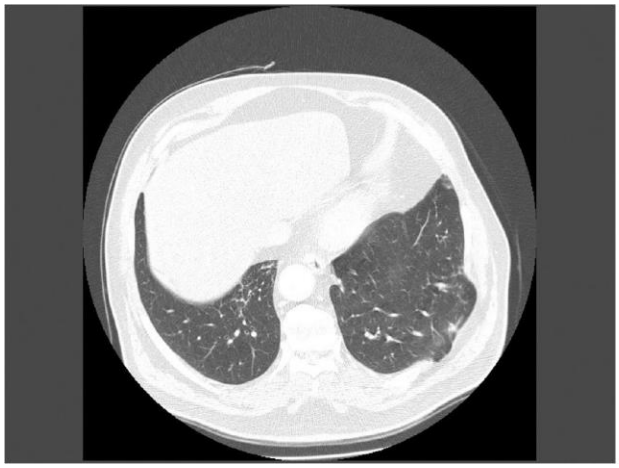

Figure 1. CT scan - cross section of lung hernia
Rycina 1. Przepuklina płucna w obrazie TK w płaszczyźnie poprzecznej

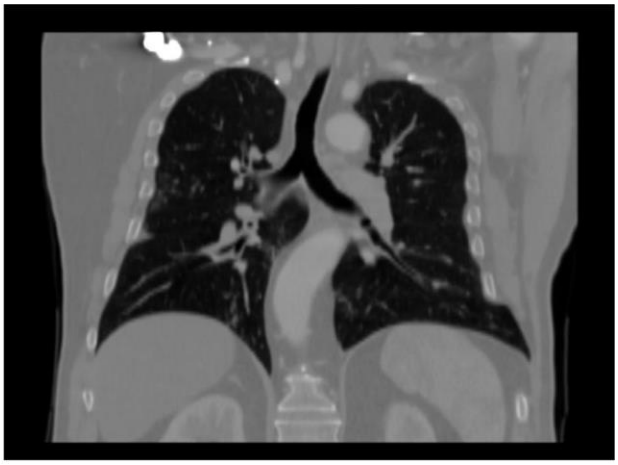

Figure 3. CT scan - coronal plane of lung hernia
Rycina 3. Przepuklina płucna w obrazie TK w płaszczyźnie czołowej

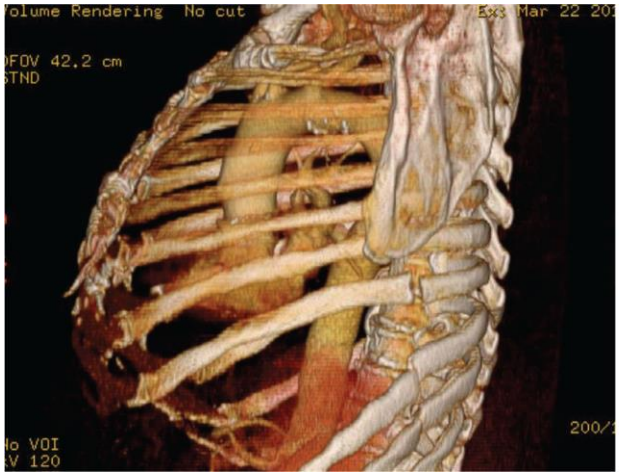

Figure 2. Chest bone reconstruction VRT. Rib defect can be seen
Rycina 2. Rekonstrukcja kośćca klatki piersiowej w 3D z widocznym ubytkiem międzyżebrowym

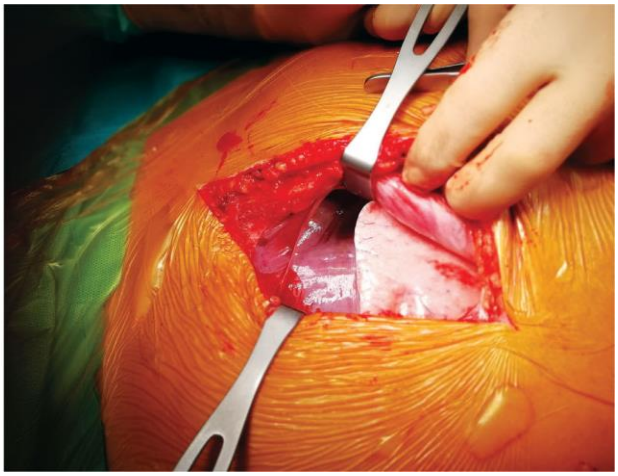

Figure 4. Intraoperative view of lung hernia
Rycina 4. Obraz śródoperacyjny przepukliny płucnej

Case report

A 58-year-old male was referred from the Pain Management Clinic, where he was treated due to post-traumatic thoracic pain, at the Thoracosurgical Clinic. The year before he suffered multiple rib fractures (IV-X) on the left, when a branch fell on him during clear-cutting of cherry trees. A few months after the trauma, a fit of severe coughing resulted in a sudden rib displacement, followed by lung hernia. The 8th rib, fractured in the posterior segment, detached from the costal arch, and moved downwards, creating a large deficit of 5 x 30 cm in the intercostal space. Upon breathing, the lung protruded outside the pleural cavity. This resulted in a significant destabilisation of the thorax, and moving the ribs caused severe pain. The diagnostics included thoracic CT with 3D reconstruction (Fig. 1-3), to improve preparation for the surgery. The symptoms were further increased by patient's obesity (BMI 38), which also affected his general fitness.

The patient was qualified for surgical treatment. Reduction of body weight before the procedure was recommended. Within two months the patient lost 18 kg. The BMI decreased to 32. The patient's fitness increased, his respiratory efficiency increased, and thoracic pain was reduced. The radiological image was confirmed intraoperatively. The 8th and 9th ribs were moved apart, which resulted in the lung slipping outside the pleural cavity during deep inhalation (Fig. 4). After clearing the ribs and preparation of proper muscle layers, fragments

of ribs 8 and 9 were pulled closer together, typically for the closure of thorax with five single sutures. A drain was placed in the pleural cavity through a separate incision. Next, the muscles and skin were sutured in layers. The results of the surgery were good. The procedure was uncomplicated. On the second day after the surgery the drain was removed, and on the third day the patient was discharged.

Discussion and conclusions

Rib fractures rarely result in late complications. This study presents one of them: a lung hernia. The patient was qualified for surgical treatment due to chronic thoracic pain and problems with normal breathing. Lung hernias develop not only as a result of injury, but also following thoracotomy or minimally invasive procedures. According to the literature data, these conditions can be managed with a number of methods [3-5], including video techniques, open surgeries with the use of synthetic materials (e.g. Codubix mesh, Gore-tex, polytetrafluoroethylene or titanium rods), or patient's own muscle flaps. In the presented case a simpler technique was used, typical for classic closure of the thorax during thoracotomy. The results of the procedure after 3 months were considered good both by the surgical team, and the patient. The patient is under the supervision of a Thoracosurgical Clinic.

Literature

1. Wijffels M, Prins J, Polinder S, et al. Early fixation versus conservative therapy of multiple, simple rib fractures (FixCon): protocol for a multicenter randomized controlled trial. World J Emergency Surg 2019; 14: 38
2. Brongel L, Lasek J, Słowiński K. Podstawy współczesnej chirurgii urazowej [Fundamentals of modern trauma surgery]. Wydawnictwo Medyczne Publishing House, Krakow 2008
3. Wiens S, Hunt I, Mahood J, et al. Novel fixation technique for the surgical repair of lung hernias. Ann Thorac Surg, 2009; 88: 1034–1035
4. Forty J, Wells F. Traumatic intercostal pulmonary hernia. Engl Ann Thorac Surg, 1990; 49: 670-601
5. Khalil M, Masala N, Waller DD, et al. Surgical repair of post-traumatic lung hernia using video-assisted open technique. Interact Cardiovasc Thorac Surg, 2008; 7: 506-507

Medical aspects of the threat of radiation sickness in Poland

Medyczne aspekty zagrożenia wystąpieniem choroby popromiennej w Polsce

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Abstract. The probability of radiation sickness occurring in Poland is very small as Poland has a limited number of ionizing radiation sources, while the threats of a terrorist attack with radioactive material or a nuclear war is very low. We cannot, however, exclude its possibility. With over 20 bone marrow transplant centres, Poland could manage even a relatively large-scale radiation accident. Total body irradiation is routinely used in preparation for bone marrow transplantation, and therefore the personnel of such centres have the ability to process irradiated persons. However, in the case of a nuclear bomb attack, when the number of victims could amount to thousands, the available possibilities would be quite limited. It should be stressed, however, that in such a case the problem would also include society, organization and psychology as a whole rather than be limited to the medical aspects. From the medical point of view, it would involve the mass scale introduction of basic principles of care for people with hematopoietic system injuries and provision of end of life care for people with other syndromes of radiation poisoning, whose lives could not be saved.
Key words: nuclear bomb, radioactive contamination, terrorism

Streszczenie. Prawdopodobieństwo wystąpienia choroby popromiennej w Polsce jest bardzo mate ze względu na to, że Polska ma niewielką liczbę własnych źródeł promieniowania jonizującego, a także dlatego, że zagrożenie zarówno radiacyjnym atakiem terrorystycznym, jak i wojną jądrową jest bardzo małe, co jednak nie oznacza, że nie istnieje. Polska, posiadając ponad 20 ośrodków przeszczepiania komórek krwiotwórczych, może zabezpieczyć we własnym zakresie nawet dość duży wypadek radiacyjny. Ponieważ w przygotowaniu do przeszczepienia szpiku wykorzystuje się napromienienie na całe ciało, personel tych ośrodków jest przygotowany do obsługi takich chorych. Natomiast przygotowanie na wypadek wykorzystania bomby jądrowej, w którym porażonych będą tysiące ludzi, jest ograniczone. Trzeba jednak podkreślić, że będzie to w znacznie większym stopniu problemem ogólnospołecznym, organizacyjnym i psychologicznym, niż *stricte* medycznym. Pod względem medycznym będzie to głównie problem wykorzystania na masową skalę podstawowych sposobów opieki nad osobami z uszkodzonym układem krwiotwórczym i zapewnienia godnego umierania osobom z innymi zespołami choroby popromiennej, których nie będzie można uratować.
Słowa kluczowe: bomba jądrowa, skażenie promieniotwórcze, terroryzm

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Introduction

At present, the risk of radiation sickness in Poland (apart from iatrogenic consequences of oncological radiotherapy) appears to be very low, yet it is still present. We have one active reactor, the neighbouring countries have nuclear power stations, we are planning on building our own power stations, and our increasing role in international politics may make Poland a target of terrorist attack; finally, the development of foreign affairs is unpredictable, and we in the zone of potential armed conflict. We also know that our allies, the USA and Germany, are developing plans for protecting people in case of the threat of radiation sickness. This study is based on these documents [1-4].

At least five sources of risk are known:

- terrorist attack or accident involving a nuclear reactor,

- a criminal act involving a powerful source of radiation,
- a terrorist attack using a radiological dispersal device, e.g. dirty bomb,
- explosion of an amateur nuclear bomb,
- explosion (explosions) of nuclear bombs used as a weapon of mass destruction [1].

Moreover, radiation can also be used to eliminate an individual, e.g. as in the case of Litvinenko [5]. Our medical knowledge regarding of the course of post-radiation disorders comes mostly from the analysis of the effects of nuclear explosions in Hiroshima and Nagasaki, and accidents in Chernobyl [6] and Fukushima, while current management procedures that can potentially be used to treat radiation sickness have been developed primarily in haematological centres, especially those offering bone marrow transplantation, where patients receive whole body radiation at doses of up to 12 Gy (grays) for therapeutic purposes [7]. It should also be mentioned that, depending on the type of incident, the consequences of radiation will be accompanied by (frequently dominant) results of mechanical and thermal injuries, external and internal contamination, as well as psychological consequences.

Categories of problems according to type of radiation incident

In the case of accidental or deliberate damage to a nuclear reactor, the consequences are likely to be similar to those in Chernobyl [6] and Fukushima. Serious health problems will be observed in a relatively small number of people (in Chernobyl it was 237 people) in close proximity to the reactor (which practically excludes Poland), whereas the general population may be affected by the fall of radioactive dust (mainly radioactive iodine) from the reactor's cooling system. In such situations, the population at risk should receive iodine preparations, e.g. Lugol's solution, as soon as possible, to block the thyroid gland from absorbing radioactive iodine [8].

In case of a criminal act involving a source of strong radiation, e.g. theft of such a source, victims will be few, and the consequences will depend on the type of source and its contact with the body (bodies) of individuals involved in the incident.

The effects of a terrorist attack with the use of a dirty bomb [4], i.e. a device in which a conventional explosive is to ensure a maximum dispersal of the radioactive isotope from the bomb, are mainly economic (temporary elimination of an economically important place, e.g. a port), due to contamination, and psychological, due to mass panic (if the device is detonated at a site where a large number of people is present at the same time). The area affected by the direct consequences of the incident will be relatively small – a circle of 1 km in diameter [9]. The health effects will mostly include injuries due to the conventional explosive, the absorbed radiation dose will be quite small, and the external contamination will be the main problem. However, depending on the isotope used, radiation sickness may also occur.

The effects of nuclear bomb explosion will depend on its type, power, and the site of detonation, and they will include a full range of health consequences associated with radiation sickness, mechanical and thermal injuries, as well as epidemiological, economic, political, psychological and social consequences. It is believed that various terrorists may construct and detonate a bomb of up to 0.01 kiloton (compared to the 13 kiloton bomb detonated in Hiroshima), whereas larger bombs can be detonated in conflicts involving countries with nuclear weapons. In this case, the three major types of bombs are a neutron bomb, an atomic bomb and a hydrogen bomb.

The most classic ones are atomic bombs, using the effect of uranium or plutonium fission, like the bombs dropped on Hiroshima and Nagasaki. A hydrogen bomb uses fusion of light atom nuclei (e.g. of hydrogen) into heavier ones. It may be much more powerful (with the yield of several megatons), and potentially destroy even large cities; however, it has never been used in armed conflicts before, similarly to a neutron bomb, in which energy is produced as a result of fusion reaction between deuterium and tritium. It is less powerful than the "regular" atomic bomb, and the primary destructive effect is radiation, thus the name "clean bomb". Its force usually does not exceed 1 kiloton [1]. Another problem is the use of munitions containing depleted uranium in armed operations. Depleted uranium has more 235 uranium than natural uranium. Such missiles can better penetrate through armour, but the health consequences will be secondary to wound poisoning with uranium as an element, rather than to radiation (the material is less radioactive than natural uranium). It has been hypothesised that increased morbidity in Iraq was partially due to the use of such munitions by Americans [9]. Depleted uranium is used also in the shields of radiotherapy devices, and in containers for transporting radioactive materials. The effects of documented use of radiation (polonium 210) for the elimination of a former Russian agent, Alexander Litvinenko, were limited to one person, and no environmental threat occurred. However, the victim could not be saved, as polonium, characterised by a long half-life, is incorporated irreversibly into bones, resulting in destruction of bone marrow, including the potentially transplanted material, by alpha radiation It also damages many other organs. Such incidents are usually arranged by national special services, as only they have access to reactors that could provide the isotope [5]. However, theft and use of such material by an employee

of the centre operating the reactor, or by the personnel involved in its transportation, cannot be excluded. For instance, the United States import approximately 8 g of polonium 210 a month from Russia, whereas the lethal dose is a fraction of a milligram [5]. The patient dies after a few dozen to a few hundred days after poisoning with polonium 210 (via the gastrointestinal or respiratory route), depending on the dose.

Radioactive contamination

As mentioned before, this problem will mainly occur in the case of a terrorist attack with the use of a dirty bomb. Any radioactive isotope available for medical or technical purposes can be used to construct one (apart from the conventional explosive). The list of such isotopes is quite long; the most important ones are: americium 241, cobalt 60, caesium 137, iodine 131, iridium 192, radium 226, strontium 90, californium 252, plutonium 238 and plutonium 239, uranium 235 [4] and polonium 210 [5]. Another problem is the fact that radiation is invisible, and if the services addressing the effects of conventional explosion do not have radiation meters, its presence may remain undetected for a long time, resulting in further dispersal of the isotope as a consequence of the natural evacuation of people and objects, such as cars, from the affected area, before radioactive contamination is suspected. Moreover, typical Geiger counters may not detect alpha radiation, due to its limited range. Detectors using zinc sulphide should be used, as close as possible to the suspected surface [9]. In addition, as the discussed situation is still (fortunately) hypothetical, the services, even having obtained a positive reading on the meter, may dismiss it and view it as a result of malfunction of a device that never presented a positive reading before (apparently this was the case with the first signals of the emerging situation in Chernobyl). The consequences of environmental contamination in this situation may be long-lasting, but the medical effects will be quite limited. The decontamination procedure will include mainly washing and a change of clothing [9]. However, this does not apply to polonium 210, which can be lethal at the dose of one microgram [5]. The name “dirty bomb” is also used to refer to a special type of atomic bomb, the cobalt bomb (not to be mistaken with a medical device using the same isotope, cobalt 60). Its explosion may cause a significant contamination of the affected area.

Psychological consequences

All radiation incidents are associated with serious social and psychological consequences, including panic. Firstly, modern society is not accustomed to such events. It would be a completely new and unknown threat; moreover, an invisible one, detectable only by devices that are not easily accessible. A positive example is the reaction of the Polish government after the accident in Chernobyl, when iodine preparations were quickly distributed on a mass scale to convince society that the situation was under control, the services are at work, the preventive measures had been applied, and all people were safe. However, such actions have a positive psychological effects only if morbidity and mortality due to unknown causes are very limited. Similarly, one could imagine using radioprotective agents [10], provided that proper services would have sufficient store of these pharmaceuticals. The medical effectiveness of the mass-scale use of such agents may be questionable, but the psychological effects could be beneficial.

Radiation sickness

The biological effects of explosion of a small bomb, whether one produced by amateur bomb-makers or one used by the military, will be similar, but the medical management will vary, primarily due to the difference in the scale of the problem. The effects of a potential terrorist attack will be smaller in terms of the number of injured, engagement of services eliminating the outcomes, and disorganisation of all other aspects of social life. In other words, the scope of assistance would differ depending whether there were 100 or 100,000 victims.

Typical classification includes three acute radiation sickness syndromes: haematological, gastroenterological and neurological, based on the names of the medical specialisations appropriate to manage them [11-13]. The symptoms of these syndromes partially overlap. Smaller doses of radiation cause haematological syndrome (damage or destruction of bone marrow), moderate doses induce gastroenterological syndrome (damage or destruction of intestinal epithelium), and higher doses result in neurological syndrome (damage to the CNS). As the absorbed dose increases, and the severity of the haematological syndrome intensifies, gastrointestinal symptoms develop: first nausea and vomiting, then diarrhoea and abdominal pain that start to dominate. Next, consciousness disorders develop, followed by loss of consciousness, cardiovascular insufficiency and death. The general symptoms and prognosis are presented in Table 1. The haematological syndrome (doses 2 –10 Gy) develops fully in 10 to 30 days, the gastrointestinal syndrome (doses of 6 — 15 Gy) in 3 to 10 days, and the neurological syndrome (doses >15 Gy) may develop even in a few hours. In addition, cutaneous syndrome is observed in the form of erythematous rash that occurs a few hours after irradiation, and subsides spontaneously. Importantly, in those patients that can be saved with proper medical management the symptoms of radiation

Table 1. Clinical symptoms and prognosis in postirradiation injury [12]
Tabela 1. Objawy chorobowe i rokowanie w uszkodzeniu popromiennym [12]

Doses (Gy)	Prodromal symptoms	Disease symptoms	Prognosis without treatment
0.5 – 1.0	Discreet	Slight reduction in blood cell count	Almost certain survival
1.0 – 2.0	Mild	Early symptoms of bone marrow damage	Survival >90%
2.0 – 3.5	Moderate	Pancytopaenia	Possible survival
3.5 – 5.5	Severe	Pancytopaenia + gastrointestinal injury	Death of approx. 50% of victims in 3.5 – 6 weeks
5.5 – 7.5	Severe	Pancytopaenia + significant gastrointestinal injury	Expected death within 2 – 3 weeks
7.5 – 10.0	Severe	Severe gastrointestinal injury + irreversible pancytopaenia	Expected death within 1 – 2.5 weeks
10.0 – 20.0	Very severe	Severe gastrointestinal injury and irreversible bone marrow damage, consciousness disorders	Certain death within 5 – 12 days
>20.0	Very severe	Cerebrovascular collapse, fever, shock	Certain death within 2 –5 days

sickness are delayed by up to several days, which gives the services time for evacuation and organising assistance. Management of the haematological syndrome in acute radiation sickness will be discussed in a separate study.

Mixed injuries

It is assumed that following explosion of a nuclear bomb, most injuries will belong to one of three categories: burns, mechanical injuries and radiation sickness. Thermal energy accounts for approximately 35% of the total energy released by the bomb, mechanical energy accounts for 50%, and radiation - for 15% [3]. However, it is believed that thermal and mechanical injuries will dominate in the epicentre of the explosion, where also the absorbed radiation dose will be very high, which means that majority of these victims will not be saved, and all the services can do for them is ensuring dignity in death. Further away from the epicentre, the dominant effects will be due to radiation. Table 2 presents the estimated number of casualties and the requirements associated with their management [3]; the data apply to detonation of explosives of 1 and 10 kilotons in a city with the population of approximately 2 million (the size of Warsaw). First of all, the enormous sanitary problem should be emphasised: a possibly prompt burial of a few to several thousands of bodies (both humans and animals). Intensive haematological care requires treatment in conditions similar to those in bone marrow transplantation centres. At the moment in Poland we have a few hundred hospital beds fulfilling such requirements, which covers 1/100 of the expected needs. A similar problem applies to haematologists, as we have 1 specialist per approximately 1,000 victims. In this context, bone marrow transplantations are out of question. The management must be based on possibly prompt evacuation, and ensuring good hygienic conditions. The only factor “facilitating” containment of the problem will be the fact that, as previously mentioned, symptoms will develop only after a few to several days, which will provide the time to undertake the necessary organisational operations. We need to realise that explosion of a 1 kiloton bomb in Warsaw would completely disorganise life in the country, disrupt the functioning of all central authorities, and of the healthcare system, whose key institutions are located in this city, and would be destroyed, at least partially.

Containment of the effect of radiation incident

The tasks associated with containment of the effects of such incident will include those directly related with the site of event, and those regarding the victims, both people and animals. Only the second category will involve the medical services, although close co-operation with other services will be necessary. It should be emphasised that typically the number of least affected individuals is the highest, and the most affected victims are the least group, not the other way round. In the case of less affected patients, the health-related consequences of escaping in panic and of other chaotic actions can significantly exceed the direct effects of a radiation incident; therefore, proper management at the site of the event is of utmost importance, also with regard to reducing the medical consequences.

Table 2. Expected numbers of victims requiring particular level of help after explosion of 1 and 10 KT nuclear bombs in a city with approx. 2 million population [3]*
Tabela 2. Szacowane liczby porażonych wymagających określonego poziomu pomocy w razie wybuchu bomb jądrowych o sile 1 i 10 kiloton w mieście o populacji około 2 milionów [3]*

Category of victims	Radiation dose (Gy)	No. of victims – explosion of 1 kiloton	No. of victims – explosion of 10 kilotons
Mixed injuries	All doses	1000 – 3000	15,000 – 24,000
Immediate deaths	All doses	>7000	>13,000
Palliative care	>10	18,000	45,000
Intensive haematological care	5 – 10	19,500	79,400
Haematological care	3 – 5	33,000	108,900
Internist care	1 – 3	66,000	70,000
Outpatient monitoring	0.5 – 1	82,500	139,000
Epidemiological monitoring	0.25 – 0.5	106,000	147,000
Psychological monitoring for individuals without other injuries	<0.25	>150,000	>270,000

*Based on the Hazard Prediction Assessment Capability Program (HPAC) version 3.21 by Defense Threat Reduction Agency, Fort Belvoir, Virginia, USA

Conclusions

As previously mentioned, the risk of a radiation incident in Poland is very limited, but it exists. The remote likelihood of its occurrence significantly reduces the preparations, thus considerably increasing the potential effects of such an incident, should it occur. If a few, several or a few dozen people were involved in it, the Polish healthcare system, even by introducing improvised measures, should be able to cope with the situation at the highest level, especially given that we could count on prompt assistance from abroad. However, the explosion of a bomb of even 1 kiloton in Warsaw would pose a different challenge, considerably affecting the local ability to manage the process of dealing with the consequences of such an incident. Considering the potential targets for attack, Warsaw appears to be at highest risk, as the attacker will probably attempt to maximise the effects at minimum cost. However, another big city could also be the target if the potential aggressor decides that the defence of Warsaw is organised too well. At least two other management centres should be designated outside of Warsaw, and they should prepare at least outlines for management plans for the site of an incident, as well as management plans for different groups of victims, i.e. direct death casualties, dying individuals, people requiring prompt or delayed evacuation, and the plans for containing mass escape from the area, which could potentially block the evacuation routes. Finally, medical teams must be multi-disciplinary, i.e. haematologists, surgeons and internists, supported by extensive diagnostic facilities, including laboratories.

Literature

1. Mickelson AB, ed. Medical consequences of radiological and nuclear weapons. Office of the Surgeon General, Borden Institute, Fort Detrick, 2013: 1–279
2. Pellmar TC, Rockwell S. Radiological/Nuclear Threat Countermeasures Working Group. Priority list of research areas for radiological nuclear threat countermeasures. Radiat Res, 2005; 163: 115-123
3. Waselenko JK, MacVittie TJ, Blakely WF, et al. Strategic National Stockpile Radiation Working Group. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med, 2004; 140: 1037-1051
4. Rump A, Becker B, Eder S, et al. Medical management of victims contaminated with radionuclides after a "dirty bomb" attack. Mil Med Res, 2018; 5: 27
5. Scott BR. Health risk evaluations for ingestion exposure of humans to polonium-210. Dose Response, 2007; 5: 94-122
6. WHO: Health Effects of the Chernobyl Accident and Special Health Care Programmes. WHO 2006
7. Jędrzejczak WW. Hemograft. Kompendium transplantologii komórek krwiotwórczych [Haemograft. Compendium of haematopoietic cell transplantology] Termedia, 2017: 82-95
8. WHO. Iodine thyroid blocking. Guidelines for use in planning and responding to radiological and nuclear emergencies. WHO 2017
9. Bomanji JB, Novruzov F, Vinjamuri S. Radiation accidents and their management: emphasis on the role of nuclear medicine professionals. Nucl Med Commun, 2014; 35: 995-1002

10. Hofer M, Hoferová Z, Depeš D, Falk M. Combining pharmacological countermeasures to attenuate the acute radiation syndrome – a concise review. Molecules, 2017; 22: E834
11. Dainiak N, Waselenko JK, Armitage JO, et al. The hematologist and radiation casualties. Hematology Am Soc Hematol Educ Program, 2003: 473-496
12. Macià I, Garau M, Lucas Calduch A, López EC. Radiobiology of the acute radiation syndrome. Rep Pract Oncol Radiother, 2011; 16: 123-130
13. Weisdorf D, Chao N, Waselenko JK, et al. Acute radiation injury: contingency planning for triage, supportive care, and transplantation. Biol Blood Marrow Transplant, 2006; 12: 672-682

Is myocardial ischemia a prognostic factor of ventricular arrhythmia occurrence among patients with chronic heart failure?

Czy niedokrwienie jest czynnikiem predykcyjnym arytmii komorowych u chorych ze skurczową niewydolnością serca?

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Abstract. Chronic heart failure (HF) remains a condition with a very poor life prognosis. Implantable cardioverter defibrillators (ICD) are effective in sudden cardiac death (SCD) prevention in patients with reduced left ventricle ejection fraction (LVEF) <35%. Despite of over 30 years of clinical experience, more precise prognostic factors of malignant ventricular arrhythmias are still being sought. Only 30-40% of patients with ICD experience appropriate interventions; others do not benefit from the therapy but are prone to complications. Previous research examining possible ventricular tachycardia and ventricular fibrillation prediction factors has not proven effective. Coronary artery disease is the most frequent cause of CHF, but still the relation of myocardial ischemia, coronary arteries angiographic morphology and the impact of chronic occlusion revascularization on ventricular arrhythmias is uncertain. Coronary artery total occlusion (CTO) seems to be a promising predictor of VT/VF, although further research is necessary to prove this thesis.

Keywords: Chronic heart failure (CHF), chronic total occlusion (CTO), implantable cardioverter defibrillator (ICD), ischemic cardiomyopathy, ventricular fibrillation (VF), ventricular tachycardia (VT)

Streszczenie. Rokowanie w przewlekłej niewydolności serca (HF) jest niepomyślne. Wszczepialne kardiowertery-defibrylatory (ICD) mają udowodnioną skuteczność w zapobieganiu nagłym zgonom sercowym (SCD) u chorych z ciężką skurczową HF ze zmniejszoną frakcją wyrzutową lewej komory (LVEF) <35%. Pomimo ponad 30-letnich doświadczeń wciąż poszukiwane są bardziej precyzyjne czynniki predysponujące do występowania złośliwych arytmii komorowych. Adekwatnych interwencji urządzeń doświadcza zaledwie 30—40% pacjentów zakwalifikowanych do terapii zgodnie z obowiązującymi kryteriami; pozostali nie odnoszą korzyści, są natomiast narażeni na powikłania. Dotychczasowe badania mające na celu identyfikację predyktorów wystąpienia częstoskurczów i migotania komór (VT, VF) nie przyniosły oczekiwanych rezultatów. Najczęstszą przyczyną CHF jest kardiomiopatia niedokrwienna, ale związek niedokrwienia, morfologii zmian w tętnicach wieńcowych i wpływu rewaskularyzacji naczyń przewlekle zamkniętych na potencjał arytmiczny pozostaje nieznany. Wydaje się, że obiecującym czynnikiem prognostycznym wystąpienia VT/VF jest obecność przewlekłej niedrożności tętnicy wieńcowej (CTO), ale konieczne jest potwierdzenie tego w dalszych badaniach.

Słowa kluczowe: przewlekła niewydolność serca (CHF), wszczepialne kardiowertery-defibrylatory (ICD), migotanie komór (VF), częstoskurcz komorowy (VT), kardiomiopatia niedokrwienna, przewlekła całkowita niedrożność (CTO) tętnicy wieńcowej

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Heart failure – definition, epidemiology and prognosis

Heart failure (HF) is a set of symptoms caused by various pathological conditions, and they result in insufficient metabolic supply to tissues, or metabolic supply with increased left ventricular filling pressure. The estimated prevalence of HF is 1-2% of the adult population, but incidence and morbidity increase with age, and affect approximately 10% of people over 70 years of age. Prognosis in HF is unfavourable. Overall one-year mortality in is 7-17% (stable patients and those hospitalised due to exacerbation of the disease, respectively). Causes of death are varied. Some patients die suddenly, whereas in other cases death is a result of the natural course and decompensation of HF. Sudden and unexpected deaths are due to vascular or electric disorders (ventricular arrhythmias, bradycardia, asystole), and often are observed in patients without a significant increase in symptoms. Natural progression of the disease is the principal cause of death in patients at the highest stage (NYHA class IV) [1].

Cardioverter-defibrillators in patients with heart failure: indications and limitations

In at least half of the patients with chronic heart failure the left ventricle ejection fraction (LVEF) is reduced. They are at a particularly high risk of heart rhythm disorders. As they interrupt complex ventricular arrhythmias, implantable cardioverter-defibrillators (ICDs) demonstrate proven effectiveness in preventing sudden cardiac death (SCD). Qualification for this therapy is based on LVEF <35%, although this is not the most precise or repeatable parameter. Despite approximately 30 years of experience in ICD therapy, no better indicators have been identified, and LVEF is the only one correlated with increased risk of SCD [2]. Approximately 30-40% of patients with ICD experience appropriate interventions of the device (i.e. cardioversion, defibrillation or antitachycardia pacing [ATP]) [3]. These are not observed in 2/3 of patients. They do not benefit from ICD, and are exposed to the risk of implantation complications, such as infections, inappropriate interventions, device malfunctions, local complications etc. In a 12-year perspective, the adverse effects in the form of unwanted discharge occur in 20% of patients with the device, lead dysfunction occurs in 17%, and 6% are at risk of ICD-related infection [2]. Psychosocial consequences of ICD treatment, frequently undiagnosed and untreated, also a factor to consider. A total of 8-63% of patients experience anxiety associated with the therapy, and 5-41% suffer from depression. These are typically related to ICD interventions, including unnecessary ones. In extreme cases, post-traumatic stress disorder (PTSD) due to discharges may develop. The effect the awareness of using ICD has on the psyche should be taken into account in all patients. This includes anxiety related with daily activities, in interpersonal interactions, especially intimate ones, limitations in professional work, driving vehicles or practising sports (Fig. 1) [2].

Prognostic factors of ICD intervention

The effectiveness of ICD implantation for prevention of primary SCD in patients with ischaemic cardiomyopathy and severe left ventricular impairment has been confirmed in large randomised trials; implantation of ICD significantly reduces the risk of death [3]. Nevertheless, there is an increasing body of evidence that although LVEF is a marker of HF advancement, its sensitivity and specificity in predicting arrhythmic events is limited. Researchers are looking for more precise predictors and risk factors for ventricular arrhythmias in the form of ventricular fibrillation (VT) / ventricular tachycardia (VT) and appropriate ICD interventions, but previous attempts to identify them have not achieved satisfactory or unambiguous results. Studies examined, for instance, the effect of demographic characteristics (sex, age), comorbidities (arterial hypertension, diabetes, chronic kidney disease, atrial fibrillation), advancement of heart failure (NYHA class), selected laboratory parameters (e.g. inflammatory markers, such as C-reactive protein), and the medications used (mostly beta-blockers). Correlation with tobacco smoking was also analysed. These are only some of the factors that could affect the arrhythmogenic potential, but study results are inconsistent, and require confirmation in further research, due to numerous limitations (Fig. 2) [4-7].

Ischaemic cardiomyopathy and possible revascularisation

The principal cause of left ventricular dysfunction and complex ventricular arrhythmias is coronary disease. The relationship between ischaemia and ICD therapy or deaths due to arrhythmia (apart from recent ischaemia, qualifying for revascularisation) is unknown [8]. No correlation between the stage of coronary disease and the risk of life-threatening heart rhythm disorders have been identified [4]. Many patients with HF had myocardial infarction, or receive revascularisation; however, the normal image of coronary vessels does not exclude the presence of scars, or disturbed coronary microcirculation; therefore, it does not reduce the risk of arrhythmic episodes [1]. Full coronary revascularisation prior to ICD implantation does not eliminate the risk of later incidents due to disease progression, restenosis in the stent after

angioplasty, or occlusion of the coronary artery bypass [8].

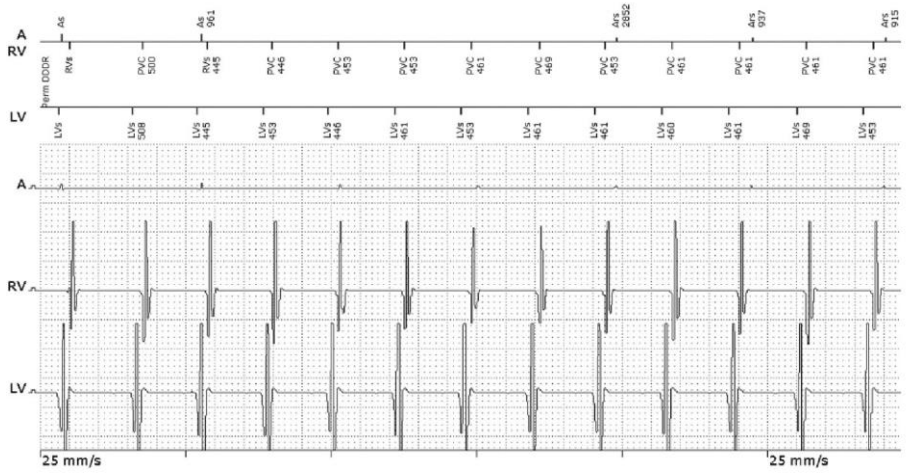

Figure 1. IEGM -ventricular tachycardia in cardiac resynchronization therapy defibrillator (CRT-D) memory
Rycina 1. Zapis wewnątrzsercowy (IEGM) w pamięci kardiowertera defibrylatora z funkcją resynchronizacji (CRT-D) - częstoskurcz komorowy (ventricular tachycardia in CRT-D memory)

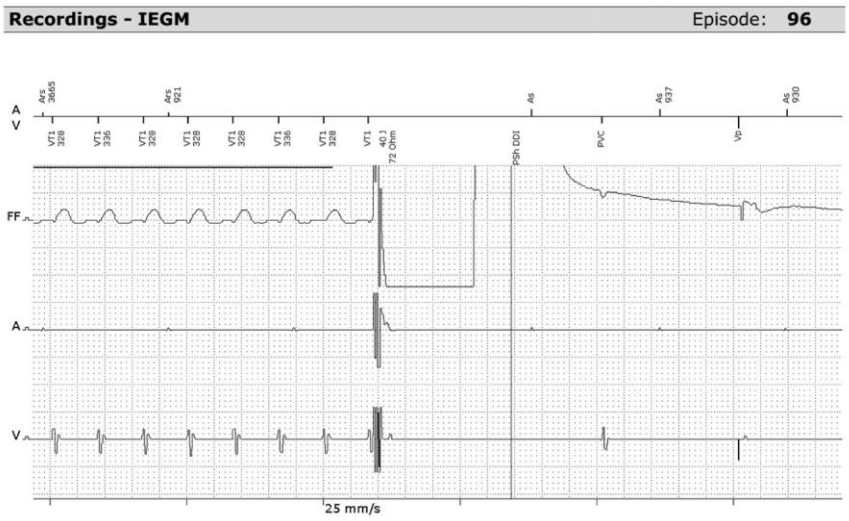

Figure 2. Ventricular tachycardia IEGM; appropriate intervention 40 J
Rycina 2. Zapis IEGM - częstokurcz komorowy; interwencja adekwatna 40 J

In the case of documented ischaemia, revascularisation is clearly the desired method of treatment. In primary prevention, implantation of ICD is delayed for at least 6 weeks after the myocardial infarction, as restored coronary flow may increase LVEF by over 5-6% on average [2]. In secondary prevention, i.e. in patients who experienced sudden cardiac arrest, effective revascularisation reduces the occurrence of life-threatening arrhythmias and SCD, provided the ischaemia is potentially reversible. In patients with extensive scarring in the cardiac muscle and low LVEF, the antiarrhythmic effect is unlikely [2]. Therefore, before ICD is used for primary prevention of SCCD, assessment of the ischaemia and surgical treatment options is necessary [9]. There are no recommendations regarding verification of the ischaemic background after appropriate therapies. Apart from electrical storm, i.e. recurring tachycardia and ventricular fibrillation, when urgent coronarography and interventional therapy are included in relevant guidelines [9], management is based on the practice and experiences of a given centre.

Chronic total occlusion of a coronary artery

It appears that chronic total occlusion (CTO) may be a promising predictor of ventricular arrhythmias. It is defined as the complete obstruction of a main epicardial artery by atherosclerotic plaque. In coronarography there may be a complete absence of flow in the artery, i.e. TIMI 0 *(thrombolysis in myocardial infarction),* persisting for at least 3 months, or functional absence of flow (TIMI 1), demonstrated by a minimal contrast penetration during the test, without filling of the distal segment [10]. Among patients with ischaemic cardiomyopathy, in approximately 30% at least one main coronary artery is permanently occluded [6]. CTO adversely affects the course of the disease, is associated with long-term mortality in patients after myocardial infarction, with more advanced and frequently polyvascular coronary disease, and with worse prognosis, especially in acute coronary syndrome [6, 11].

Large areas of ischaemia (including residual or mute ischaemia) due to chronic occlusion of a main epicardial artery may case tachycardia and ventricular fibrillation even in patients with well-developed collateral circulation. Chronically occluded coronary artery does not have to be associated with myocardial infarction, and thus with the presence of necrosis. VT/VF occurs as a result of two potential mechanisms: presence of scarring in the bed of occluded infarct-related artery (IRA) as a substrate of arrhythmia, and induced myocardial ischaemia resulting in electrical instability triggering arrhythmia [12].

Importance of CTO in predicting ICD interventions

The attempts to determine the effect of CTO on frequency of complex ventricular arrhythmias did not produce consistent results. In 2018, the first metaanalysis examining the risk in patients with coronary CTO and implanted ICD was published. It included six studies and 1423 patients. In conclusion, CTO was considered to be an independent predictor of VT/VF, but only in the group receiving ICD as secondary SCD prevention; no effect of CTO on all-cause mortality was demonstrated in any of the groups. The study did not distinguish between IRA-CTO and CTO in other arteries [13].

The analysis comparing the effect of CTO on mortality and frequency of VT/VF in patients with implanted ICD for primary prevention also did not demonstrate any differences in all-cause mortality, or in occurrence of VT/VF. The comparison involved patients without CTO with patients with CTO who received revascularisation (transcutaneous or cardiosurgical), and with patients with CTO who did not undergo revascularisation. Angiographic assessment was performed only before implantation of ICD; no results of coronarography after appropriate interventions are available [11].

In 2018, the largest metaanalysis so far, including 17 studies (over 55 thousand patients) was published. It confirmed the relationship between CTO and increased risk of VT/VF and appropriated ICD interventions; however, similarly to the studies mentioned above, no relation was found between CTO and increased mortality (due to cardiac causes or all causes) [10].

It is possible that only IRA CTO (i.e. chronically occluded infarct-related artery), as opposed to non-IRA CTO, is associated with arrhythmogenic effect [14]. IRA CTO may be caused by the absence of quick reperfusion in myocardial infarction (primary angioplasty or fibrinolytic treatment), or by generally rare revascularisation. IRA CTO is probably associated with more frequent polyvascular disease and increased risk of heart arrhythmias, especially rapid VT and VF, or appropriate ICD interventions. It also significantly increases the risk of all-cause mortality [10, 14].

Chronic occlusion of different epicardial arteries may have different outcomes. The highest risk has been demonstrated for chronic occlusion of the left anterior descending artery (LAD), followed by right coronary artery (RCA), probably due to the area covered by the vessels [14]. The anatomy of lesions in coronary circulation is very complex, and the course of coronary disease is dynamic.

Moreover, well-developed collateral circulation affects myocardial electrical stability. Non-IRA CTO, even without a direct impact on VT/VF, increases mortality during the next acute coronary syndrome, and is associated with lower LVERF and its further reduction in time, which is a proarrhythmic factor [14, 15].

Prolonged ischaemia in the area supplied by the occluded artery results in myocardial hibernation, i.e. persistent, but potentially reversible function impairment. It also applies to electrical function, and may lead to adverse remodelling. In the bed of IRA CTO the cardiac muscle is replaced by a fibrotic scar with areas of reduced conduction velocity (of key importance for the occurrence of re-entry, the most common mechanism of ventricular arrhythmias in patients with heart failure). The border between the normal and necrotic myocardium is a particularly sensitive area. Revascularisation can improve electrical stability, but due to complex pathophysiology, arrhythmogenic foci may be activated as a result. It is unclear whether the optimal therapy restoring coronary flow may reduce mortality due to arrhythmic episodes, as the effect of successful revascularisation of CTO on the risk of VT/VF has not been confirmed [10].

Moreover, the available literature does not offer data on the impact of the type of acute coronary syndrome (STEMI - ST-elevation myocardial infarction compared to NSTEMI – non-ST-elevation myocardial infarction), the number of experienced episodes, or the type of treatment applied (vascular interventions, cardiosurgical procedures or conservative treatment) on the further occurrence of appropriate ICD interventions.

Conclusions

Chronic HF is an epidemic of our times. Patient care should be optimal, and address the clinical presentation. Medical interventions, from prevention of coronary disease to optimal management of its complications (i.e. advanced ischaemic HF and associated arrhythmias) must be not only effective, but also safe and fully justified.

The effectiveness of ICD in the reduction of SCD risk and improvement of survival in patients with post-infarction HF has been demonstrated in large studies, but they were conducted several years ago [3, 16]. Treatment in the SCD-HeFT study (2005) differed significantly from current HF therapy: only 69% of patients received beta-blockers, and only 20% received an aldosterone antagonist [16]. Optimal pharmacotherapy, i.e. using appropriate doses of disease-modifying drugs, gradually reduces cardiovascular mortality in patients with HF with reduced EF [17]. The most effective combination of medications (i.e. angiotensin receptor-nephrilysin inhibitor [ARNI], sacubitril with valsartan, beta-blocker and aldosterone antagonist, and angiotensin-converting enzyme inhibitor with beta-blocker, aldosterone antagonist and ivabradine) results in the reduction of all-cause mortality (compared to the placebo) by 62% and 59%, respectively [17].

Proper qualification for ICD is a challenge in the therapy of heart failure. In low-risk patients the complications associated with the implanted device may outweigh its benefits. Further studies involving large, representative groups of patients are required to increase treatment effectiveness, individualise therapy, reduce the number of complications, and improve patients' quality of life.

Literature

1. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Eur Heart J, 2016; 37 (27): 14 12
2. Priori S, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J, 2015; 36 (41): 2793-2867
3. Moss AJ, Zareba W, Hall WJ, et al. for the Multicenter Automatic Defibrillator Implantation Trial II Investigators: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med, 2002; 346: 877-883
4. Blumer J, Wolber T., Hellermann J, et al. Predictors of appropriate implantable cardioverter-defibrillator therapy during long-term follow-up of patients with coronary artery disease. Int Heart J, 2009; 50 (3): 313-321
5. Gracieux J, Sanders GD, Pokorney SD, et al. Incidence and predictors of appropriate therapies delivered by the implantable cardioverter defibrillator in patients with ischemic cardiomyopathy: A systematic review. Int J Cardiol, 2014; 177 (3): 990-994
6. Nombela-Franco L, Mitroi C, Fernández-Lozano I, et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). Circ Arrhythm Electrophysiol, 2012; 5 (1): 147-154
7. Feng T, Zhang S, Chen K, et al. Prediction of ventricular arrhythmia events in ischemic heart disease patients with implantable cardioverter-defibrillators. J Mater Sci Mater Med, 2015; 26 (10): 240
8. Elhendy A, Chapman S, Porter T. Association of myocardial ischemia with mortality and implantable cardioverter-defibrillator therapy in patients with coronary artery disease at risk of arrhythmic death. J Am Coll Cardiol, 2005; 46 (9): 1721-1726
9. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J, 2019; 40 (2): 87-165
10. Chi WK, Gong M, Bazoukis G, et al. Impact of Coronary Artery Chronic Total Occlusion on Arrhythmic and Mortality Outcomes: A systematic review and meta-analysis. JACC Clin Electrophysiol, 2018; 4 (9): 1214-1223
11. Raja V, Wiegn P, Obel O, et al. Impact of chronic total occlusions and coronary revascularization on all-cause mortality and the incidence of ventricular arrhythmias in patients with ischemic cardiomyopathy. J Cardiol, 2015; 116 (9): 1358-1362
12. Werner G, Fritzenwanger M, Prochnau D, et al. Determinants of coronary steal in chronic total coronary occlusions donor artery, collateral, and microvascular resistance. J Am Coll Cardiol, 2006; 48 (1): 51-58
13. Wang Z -Q, Qiang H , Luo X , et al. Meta-analysis of risk of ventricular arrhythmias and all-cause mortality in patients with chronic total occlusion of a coronary artery and/or implantable cardioverter-defibrillator. 2018; 121 (10): 1149-1154
14. Di Marco A, Anguera I, Teruel L, et al. Chronic total occlusion in an infarct-related coronary artery and the risk of appropriate ICD therapies. J Cardiovasc Electrophysiol, 2017; 28 (10): 1169-1178
15. Claessen B, van der Schaaf R, Verouden N, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC Cardiovasc Interv, 2009; 2 (11): 1128-1134
16. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med, 2005; 352: 225-237
17. Komajda M, Böhm M, Borer J, et al. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. Eur J Heart Fail, 2018; 20 (9): 1315-1322

Role of preoperative psychological assessment of patients with morbid obesity treated surgically

Znaczenie przedoperacyjnej oceny psychologicznej chorych na otyłość olbrzymią leczonych chirurgicznie

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Abstract. Due to its high effectiveness in treating obesity, and because of the growing number of overweight patients, bariatric surgery has become increasingly popular recently. The World Health Organization warns that obesity is the most dangerous form of chronic disease, one which does not tend to recede spontaneously and has alarming consequences not only in terms of physical health but also for psychological and social functioning. Therefore, obesity needs to be treated as a serious threat. Nowadays, bariatric surgery is considered to be the most effective method of treating morbid obesity. A meticulous diagnosis and assessment of the psychological condition of morbid obesity patients is essential for effective treatment. It allows better understanding of the mechanisms contributing to obesity in patients, and selection of appropriate interventions aimed at increasing the effectiveness of bariatric surgery.
Keywords: morbid obesity, psychological qualification, psychopathology

Streszczenie. W ostatnich latach zauważa się ogromne zainteresowanie chirurgią bariatryczną. Sytuacja ta związana jest ze zwiększeniem częstości występowania problemów z nadmierną masą ciała oraz z dużą skutecznością chirurgicznego leczenia otyłości. Światowa Organizacja Zdrowia alarmuje, że otyłość jest obecnie najgroźniejszą chorobą przewlekłą, która nie ma tendencji do samoistnego ustępowania, a jej konsekwencje są groźne nie tylko dla zdrowia somatycznego, ale również dla funkcjonowania chorego w sferze psychicznej i społecznej. Otyłość powinna być bezwzględnie leczona. Obecnie najskuteczniejszą metodą leczenia otyłości olbrzymiej jest chirurgia bariatryczną. Do uzyskania efektów leczenia chirurgicznego niezbędna jest skrupulatna diagnoza i ocena stanu psychicznego pacjentów cierpiących z powodu otyłości olbrzymiej. Pozwala to na lepsze zrozumienie mechanizmów przyczyniających się do rozwoju nadmiernej masy ciała operowanych pacjentów oraz na dobór odpowiednich interwencji mających na celu zwiększenie skuteczności chirurgii bariatrycznej.
Słowa kluczowe: otyłość olbrzymia, kwalifikacja psychologiczna, psychopatologia

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Introduction

Excessive body weight is becoming global epidemic. Obesity is a problem for a great number of people in all age groups, both in developing and highly-developed countries [1]. Obesity is not considered to be a mental disorder, as opposed to other eating disorders. It is classified as an endocrine, nutritional and metabolic disease (E66.0 – E66.9) [2]. The condition is characterised by body weight increased by fat tissue [3]. According to World Health Organisation, obesity is the most dangerous chronic disease, one that can cause many complications [4-8]. Obesity is typically treated conservatively by introducing dietary restrictions and

physical activity [9]. However, according to scientific research, conservative treatment does not ensure permanent body weight loss. Bariatric surgery offers a chance for successful therapy in morbid obesity and its complications [10-13]. Post-operative body weight loss is associated with improved health parameters in patients, in the somatic and the psychological sphere [10, 11]. Unfortunately, in approximately 20% of patients the body weight reduction is not permanent, which is largely attributed to psychological factors [14-16].

European and Polish guidelines regarding indications and contraindications for bariatric surgeries

The European guidelines regarding qualification of patients for the surgical treatment of obesity have been developed by a multispecialty team of experts. Based on these recommendations, the Bariatric and Metabolic Surgery Section developed the Polish guidelines for qualification of patients for bariatric surgeries. The procedures established by the interdisciplinary team cover indications and potential contraindications for bariatric procedures, as well as post-surgical management [17, 18].

Based on the above guidelines, indications for surgical treatment of obesity include the body weight criterion: BMI >40 kg/m^2 or BMI >35 kg/m^2 with concurrent complications of obesity, such as diabetes, arterial hypertension, lipid disorders, cardiac diseases, sleep apnoea, osteoarticular disorders and others. Bariatric surgery is indicated in patients who did not achieve long-term body weight reduction with conservative treatment. The above recommendations apply to adult patients under 65 years old; patients in other age groups are considered on an individual basis by the qualifying physician taking account of potential benefits and risks of the surgery [18, 19].

The main contraindications for the procedure include lack of cooperation between the patient and the therapeutic team during and after the bariatric treatment. Cognitive disorders and addiction to psychoactive substances and alcohol (due to absence of internal mechanisms of impulse control) also disqualify patients. At least a year of abstinence is required prior to the surgery. Operation is also contraindicated in pregnant women, patients with unstable mental disorders, and those suffering from concurrent conditions that are directly life-threatening [18, 19].

Psychological qualification

Bariatric surgery is a method supporting treatment of morbid obesity. Bariatric treatment has no effect on nutritional habits and behaviours of obese patients which significantly affect disease development. According to study reports, in approximately 60-70% of cases excessive body weight is a result of abnormal nutritional behaviours and limited physical activity [20]. The role of a psychologist in treatment of obesity varies, depending on the phase of therapy. Three phases of treatment are distinguished:

- qualification,
- preparation,
- post-operative phase [21].

Complex correlations are at play between the patient's mind and the disease, resulting in the progression of obesity. The aim of psychological assessment of patients who suffer from morbid obesity is to establish when and how the disease started, determine the dominant nutritional behaviours, the course of previous treatment, and if any attempts to reduce body weight were made. Also important is the social functioning of the obese patient, and potential support they could receive to change the health-related behaviours. In addition, the psychologist assesses the cognitive strategies regarding the patient's attitude to eating, cognitive distortions, expectations associated with eating, and the patient's belief in their ability to cope with difficult situations. The goal of the therapeutic process is not to disqualify a patient from the procedure, but to stop the vicious circle of excessive eating. Identifying the source of disorder helps to optimise the safety of patients undergoing surgery, and effectiveness of surgical treatment of obesity. "The road to change" involves modification of abnormal nutritional behaviours, resulting in the development of new, pro-health behaviour, followed by its preservation, and the prevention of relapses to previous, negative automatic behaviours. Wishful thinking that "surgery will solve the problem of obesity", and the resulting erroneous expectations of the patient regarding the effects of treatment fuel "unrealistic optimism" [22], which leads to reduced self-control, and a return to the old, pathological behaviours. Psychological instability is another aspect that should be taken into consideration when qualifying a patient to treatment. Studies demonstrate that psychopathology index in patients with morbid obesity is high, within the 20 to 60% range [23, 24].

Most common comorbidities in obesity

The most frequent mental disorders concurrent with obesity include mood disorders, anxiety disorders, personality disorders, eating disorders, distorted perception of one's body, and abnormal eating behaviours. If the patient meets the diagnostic criteria of comorbidities, intervention (psychoeducation, psychotherapy, pharmacotherapy) must be introduced in

the preparation period before the bariatric procedure to help with the difficulties. For diagnostic purposes, a psychologist can use the available tools, e.g. interview, observation, tests and standardised psychological questionnaires [21]. Below are characteristics of the most common disorders associated with obesity.

Affective disorders

Affective disorders are associated with abnormal mood and disturbances in certain physical and mental processes, reflected in the subject's functioning. Mood disorders include depression and bipolar disorder (manic-depressive). The dominant symptom in depression is lowered mood, and in bipolar disorder periods of depression alternate with periods of mania [25]. Depression or mania are associated with disturbed biological rhythm: sleep, eating, sexual drive, and acceleration or slowing down of cognitive processes and psychomotor drive. Mood disorders are significantly more frequent in patients suffering from obesity than in those with normal body weight [26]. The rate of depressive disorders in candidates for bariatric surgery is 10-30% [24, 27]. Increased incidence of depression in patients with BMI>kg/ BMI >40 kg/m^2 is observed, regardless of sex [28].

Anxiety disorders

Anxiety disorders are characterised by episodes of irrational fear of very high intensity. According to the DSM-V diagnostic criteria, anxiety disorders can be classified as specific phobias, social phobia, agoraphobia, panic disorder, and generalised anxiety [29]. It should be emphasised that patients with any of the anxiety disorders experience at the same time (or at different moments in life) another anxiety disorder, or depression [30]. Prevalence of anxiety disorders in the population of patients with obesity is 7-54%, whereas in pathologically obese patients – 15-25% [24].

Personality disorders

Personality disorders according to DSM V are constant patterns of internal experiences of a person and behaviours that differ significantly from the expectation of the environment and from the culturally accepted norms within which the subject functions. In patients with personality disorders certain behaviours are developed extensively, whereas other behavioural patterns remain underdeveloped [29].

Approximately 29% of patients with morbid obesity meet the criteria of personality disorders [24, 31, 32]. The most frequently identified ones are associated with tension and anxiety experienced by the subject. They were mostly avoidance-based personality disorders, and obsessive-compulsive disorders. Studies demonstrate that in bariatric patients with untreated personality disorders there is a risk of unsatisfactory body weight loss after the procedure, which can be associated with lack of insight and impaired impulse control mechanisms [33, 34].

Eating disorders

Binge eating disorder

It is characterised by episodes of binge eating, even without hunger, and loss of control over the amount and quality of food, as well as the speed of consumption. Eating is a compulsion to release tension, not to enjoy the flavour. The diagnostic criteria for binge eating include:

- recurring episodes of uncontrolled eating (characterised by consuming larger quantities of food than most people could eat in similar time and circumstances, loss of control over the quality and amount of food consumed);
- eating at a much greater speed than usual, eating until the unpleasant feeling of fullness, despite lack of physical hunger, eating alone, due to discomfort associated with the way one is eating, remorse after the episode of compulsive eating;
- experiencing suffering associated with episodes of binge eating [29].

To diagnose this condition, episodes of losing control over eating should occur at least once a week for three months. Binge eating disorder is observed in approximately 6% of the general population, and in 25% of obese patients [35].

Bulimia nervosa

Bulimia is a disorder characterised by temporary loss of control over the quantity of food consumed, and applying compensation mechanisms. The diagnostic criteria for bulimia include repeated episodes of overeating, until the patient feels uncomfortable fullness. To avoid gaining weight, patients use behaviours aimed at reducing the weight: provoke vomiting, use laxatives, dehydrating agents, or intensive physical exercise. Self-assessment of patients with bulimia is excessively dependent on their body weight and shape. Episodes of overeating, followed by behaviours aimed at reducing the effects of excessive eating are observed at least once a week for three months [29]. Bulimia is found in 1% of the general population, in 2% of obese patients, and in 16-52% of patients after surgical treatment of obesity [36, 37].

Night eating syndrome

This condition is observed in 1-2% of the general population, in 8-15% of obese patients, and in up to 24% of patients qualified to surgical treatment of obesity [38,

39]. Patients with night eating syndrome consume excessive amount of food in the evening or at night. Eating is compulsory, and accompanied by "morning anorexia", i.e. skipping breakfast. Meals are small, eating starts after waking up, the patient maintains full consciousness, contact and memory of the event. Night overeating cannot be explained by circadian rhythm, external factors or social norms. Night overeating is a source of considerable suffering for the subject, affects the functioning of patients, and may contribute to increased body weight [29, 40].

Negative body image

The cult of body and slim silhouette may result in dissatisfaction with one's appearance in patients with morbid obesity. Studies show that body image in patients with obesity is distorted or inadequate; in most cases it involves overestimation or underestimation of body size, which may delay the decision to start treatment [45]. A study by Sekuła et al. demonstrated that patients with morbid obesity qualified for bariatric surgery did not accept their appearance, and declared that they would like to lose weight [42].

Inappropriate eating behaviour

In the modern world, where food is easily accessible, people eat when they want, and in quantities exceeding the organism's physiological requirements, which contributes to increased body weight [41]. Eating behaviours are certain actions related to the choice of food, undertaken by individuals due to health reasons, or affecting their health. They can be classified as beneficial or harmful to the health. Harmful eating behaviour can be associated with the experienced affective condition (emotional eating), or disturbed attention processes during eating (automatic eating) [42-44]. They develop as a result of frequent repetition. As a consequence, a mental association is formed between certain behaviour and a given situation; when the situation takes place, the behaviour follows automatically. Incorrect eating behaviours result in immediate gratification, but in the longer perspective they cause health problems, including obesity [41].

Psychopathology does not exclude surgical treatment of obesity

Diagnosis of mental diseases and concurrent disorders, or identification of incorrect eating behaviours does not always disqualify the patient from surgical treatment of obesity. Therefore, the most important aspects at the qualification phase include formation of a therapeutic bond [46], an in-depth psychological evaluation, and introducing proper procedures to best prepare the patient for treatment. Studies reveal that a lack of mental problems and personality disorders was associated with greater body weight loss, and better psychosocial effects in the post-operative period [16, 24, 32-34]. As a rule, a patient diagnosed with mental disorders should start treatment prior to the bariatric surgery, and the period of disease symptoms stabilisation and pharmacotherapy should be documented. Obesity is a chronic disease, so patients considering surgical treatment should be aware of the need to co-operate with the therapeutic team in every phase. The support of a psychologist, a member of the bariatric team, is very important for effective and permanent body weight reduction.

Conclusions

This article emphasises the importance of the pre-operative psychological assessment of patients with morbid obesity. Such an assessment plays an important role in maximising the beneficial effects of body weight reduction, and the related improvement of health parameters. Psychological qualification for surgical treatment of patients with morbid obesity is aimed at diagnosing potential concurrent disorders, and initiating treatment in order to prepare the patient for the bariatric procedure. The pre-operative preparation period should include modification of eating behaviours, change of lifestyle and improvement of subject's mental functioning.

Mental disorders do not exclude the possibility of a bariatric procedure, but to ensure the optimal post-operative effect, it is important to identify all the elements contributing to excessive body weight, and treat them prior to the surgical intervention. The mental status of a patient suffering from obesity and mental disorders should be stabilised. Patients should also receive psychological support before and after the bariatric procedure, to enhance the long-term post-operative success, and reduce the risk of complications.

Literature

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2014; 384 (9945): 766–781
2. Międzynarodowa Statystyczna Klasyfikacja Chorób i Problemów Zdrowotnych ICD10 – X Rewizja, Tom I [10th revision of the International Statistical Classification of Diseases and Related Health Problems, Vol. I]. World Health Organization, Geneva 2008
3. Wąsowski M, Walicka M, Marcinowska-Suchowierska E. Otyłość – definicja, epidemiologia, patogeneza. [Obesity – definition, epidemiology and pathogenesis] Post Nauk Med, 2013; 25 (4): 301–306
4. Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg, 2014; 24 (1): 42–55
5. WHO, Word Health Organization: www.who.int/features/factfiles/obesity/en/
6. Tylka J. Psychosomatyka [Psychosomatics] Published by the Cardinal Stefan Wyszyński University in Warsaw, Warsaw 2000
7. Owecki M. Otyłość epidemią XXI wieku [Obesity - epidemic of the 21st century]. Przeg Kardiodiabet, 2009; 4 (1): 36–41

8. Buchwald H, Cowan GSM, Pories WJ, eds. Surgical management of obesity. Saunders Elsevier, Philadelphia, 2007
9. Butcher J, Hooley J, Mineka S. Psychologia zaburzeń. DSM-V. GWP, Sopot 2017
10. Sekuła M, Paśnik K. Chirurgia bariatryczna skutecznie walczy z otyłością [Bariatric surgery successful in the fight against obesity]. Mil. Phys., 2016; 94: 347–351
11. Paśnik K. Wpływ chirurgicznych metod restrykcyjnych przewodu pokarmowego na jakość życia i choroby współistniejące u chorych z otyłością olbrzymią. Rozprawa habilitacyjna. [Effect of surgical restriction of the gastrointestinal tract on the quality of life and comorbidities in patients with morbid obesity. Habilitation dissertation]. Department of General, Oncological and Thoracic Surgery, Military Institute of Medicine in Warsaw, 2004
12. Dąbrowiecki S. Zasady kwalifikacji chorych z otyłością olbrzymią do leczenia operacyjnego. [Qualification of patients with morbid obesity to surgical treatment] Post Nauk Med, 2009; 22 (7): 502-505
13. Sekuła M, Paśnik K. Ocena skuteczności rękawowej resekcji żołądka w leczeniu otyłości olbrzymiej. [Assessment of efficacy of sleeve gastroscopy in treatment of morbid obesity] Lek Wojsk, 2017; 95 (1): 64-67;
14. Brolin RE, Kenler HA, Gorman RC, et al. The dilemma of outcome assessment after operations for morbid obesity. Surgery, 1989; 105: 337–346
15. Busetto L, Segato G, De Luca M, et al. Weight loss and postoperative complications in morbidly obese patients with binge eating disorder treated by laparoscopic adjustable gastric banding. Obes Surg, 2005; 15: 195–201
16. Herpertz S, Kielmann R, Wolf AM, et al. Do psychosocial variables predict weight loss or mental health after obesity surgery? – a systematic review. Obes Res, 2004; 10: 1554–1569
17. Fred M, Hainer V, Basdevant A, et al. Wytyczne europejskie w zakresie chirurgicznego leczenia otyłości olbrzymiej. [European guidelines for surgical treatment of morbid obesity] Endokrynologia, Otyłość i Zaburzenia Przemiany Materii, 2009; 5 (3): 99–108
18. Budzyński A, Major P, Głuszek S, et al. Polskie rekomendacje w zakresie chirurgii bariatrycznej i metabolicznej. [Polish recommendations for bariatric and metabolic surgery] Med Prakt Chirurgia, 2016; 6: 13–25
19. Wyleżoł M, Paśnik K, Dąbrowiecki S, et al. Polskie rekomendacje w zakresie chirurgii bariatrycznej i metabolicznej. [Polish recommendations for bariatric surgery] Videosurgery and other miniinvasive techiques, 2009; 4 (1): 31–34
20. Będzińska B. Szczupłą być. [To be slim] Baran i Suszczyński, Kraków 1997
21. Sekuła M, Paśnik K. Rola psychologa w chirurgicznym leczeniu otyłości. [The role of a psychologist in surgical treatment of obesity] Lek Wojsk, 2017; 95 (3): 298-301;
22. Weinstein N. Unrealistic optimism about future life events. J Personal Social Psychology, 1980; 39: 806–820
23. Sarwer DB, Cohn NI, Gibbons LM, et al. Psychiatric diagnoses and psychiatric treatment among bariatric surgery candidates. Obes Surg, 2004; 14 (9): 1148–1156
24. Kalarchian M, Marcus M, Levine M, et al. Psychiatric disorders among bariatric surgery candidates: relationship to obesity and functional status. Am J Psychiatry, 2007; 164: 328–334
25. Seligman M, Walker E, Rosenhan D. Psychopatologia [Psychopathology]. Zysk i S-ka, Poznań 2003
26. Stunkard A, Faith M, Allison K. Depression and obesity. Biol Psychiatry, 2003; 54 (3): 330–337
27. Sarwer D, Wadden T, Fabricatore A. psychosocial and behavioral aspects of bariatric surgery. Obes Res, 2005; 13 (4): 639–648
28. Onyike C, Crum R, Lee H, et al. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol, 2003; 158: 1139–1147
29. Gałecki P, Pilecki M, Rymaszewska J, eds. Kryteria diagnostyczne DSM V. Amerykańskie Towarzystwo Psychiatryczne. [The DSM V diagnostic criteria. American Psychiatric Association] Edra, 2013
30. Brown T, Barlow D. A proposal for dimensional classification system based on the shared features of the DSM – IV anxiety and mood disorders: Implications for assessment and treatment. Psychol Assess, 2009: 21 (3): 256–271
31. Sarwer DB, Fabricatore AN, LaShanda RJ-C, et al. Psychologiczne następstwa chirurgicznego leczenia otyłości. [Psychological sequelae of surgical treatment of obesity] Psychiatria po Dyplomie, 2009; 6 (3): 19–24
32. Mauri M, Rucci P, Calderone A, et al. Axis I and II disorders and quality of life in bariatric surgery candidates. J Clin Psychiatry, 2008; 69 (2): 295–301
33. Herpertz S, Kielmann R, Wolf A, et al. Does obesity surgery improve psychosocial functioning? A systematic review. Int J Obes Relat Metab Disord, 2003; 27 (11): 1300–1314
34. Grothe K, Dubbert P, O'Jile J. Psychological assessment and management of the weight loss surgery patient. Am J Med Sci, 2006; 331 (4): 201–206
35. Grucza R, Przybeck T, Cloninger C. Prevalence and correlates of binge eating disorder in a community sample. Compr Psychiatr, 2007; 48: 124–131
36. Fitzgibbon M, Blackman L. Binge eating disorder and bulimia nervosa: differences in the quality and quantity of binge eating episodes. Int J Eat Dis, 2000; 27: 238–243
37. Forcano L, Fernandez-Aranda F, Alvarez-Moya E, et al. Suicide attempts in bulimia nervosa: personality and psychopathological correlates. Eur Psychiatr, 2009; 24: 91–97
38. Striegel-Moore R, Franko D, Thompson D, et al. Night eating: prevalence and demographic correlates. Obes, 2008; 4: 139–147
39. Olbrich K, Muhlhans B, Allison K, et al. Night eating, binge eating and related features in patients with obstructive sleep apnea syndrome. Eur Eat Disord Rev, 2009; 17: 120–127
40. O'Reardon J, Peshek A, Allison K. Night eating syndrome: diagnosis, epidemiology and management. CNS Drugs, 2005; 19: 997–1008
41. Kadzikowska-Wrzosek R, Szczygieł D. Samoregulacja zachowań żywieniowych: wpływ standardów oraz mechanizmów kontroli działania. [Self-regulation of eating behaviours: impact of standards and mechanisms of action control] Zeszyty Naukowe Akademii Morskiej, Gdynia 2014; 86: 43–56
42. Sekuła M, Boniecka I, Paśnik K. Ocena zachowań zdrowotnych i poczucia własnej skuteczności chorych z otyłością olbrzymią. [Assessment of health-related behaviours and sense of self-efficacy in patients with morbid obesity] Psychiatr Pol, 2018; 105: 1–13
43. Czepczor K, Brytek-Matera A. Jedzenie pod wpływem emocji. [Eating in response to emotions] Difin, Warsaw 2017
44. Oginska-Bulik N. Psychologia nadmiernego jedzenia. [Psychology of excessive eating] Wydawnictwo Uniwersytetu Łódzkiego publishing house, Łódź 2004
45. Nitsch K, Prajs E, Kurpisz J, Tryburski E. Obraz ciała i jego zaburzenia. Aspekty teoretyczne w kontekście wybranych jednostek psychopatologicznych. [Body image and its distortions. Theoretical aspects in the context of selected psychopathological conditions] Psychiatr Psychol Klin, 2012; 12 (3): 176-182
46. Stemplewska-Żakowicz K. Diagnoza psychologiczna. [Psychological diagnosis] Gdańskie Wydawnictwo Psychologiczne, Gdańsk 2011

Three different manifestations of thrombotic microangiopathy - aetiology, pathogenesis, diagnosis, treatment

Mikroangiopatie zakrzepowe. Trzy różne manifestacje zespołów zakrzepowych – etiologia, patogeneza, różnicowanie, leczenie

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Abstract. Thrombotic microangiopathy (TMA) is a clinical-pathological syndrome characterized by thrombotic changes in the vessels, thrombocytopenia and haemolytic anaemia. Haemolytic-uremic syndrome (HUS), atypical haemolytic-uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) are three different manifestations of TMA. Although the clinical courses of these syndromes are sometimes confusingly similar, they differ in aetiology. Haemolytic-uremic syndrome is caused by the action of bacterial verotoxin. Patients are mainly treated symptomatically by red cell concentrate transfusion and renal replacement therapy. The pathophysiology of atypical haemolytic-uremic syndrome involves incorrect activation of an alternative complement pathway. This process can be inhibited by targeted therapy with eculizumab, which is a monoclonal antibody directed against the C5 complement component. Thrombotic thrombocytopenic purpura is in turn characterized by inborn or acquired deficiency of plasma ADAMTS13 metalloproteinase activity. The basis for the treatment of patients with acquired TTP is a therapeutic plasma exchange, and in patients with inborn TTP an infusion of fresh frozen plasma.
Keywords: atypical haemolytic-uremic syndrome, eculizumab, haemolytic-uremic syndrome, thrombotic microangiopathies, thrombotic thrombocytopenic purpura

Streszczenie. Mikroangiopatie zakrzepowe (TMA) to zespoły kliniczno-patologiczne charakteryzujące się powstawaniem zmian zakrzepowych w naczyniach, trombocytopenią oraz niedokrwistością hemolityczną. Zespół hemolityczno-mocznicowy (HUS), atypowy zespół hemolityczno-mocznicowy (aHUS) oraz zakrzepowa plamica małopłytkowa (TTP) to trzy najczęstsze manifestacje TMA. Chociaż przebieg kliniczny tych zespołów jest niekiedy łudząco podobny, różnią się etiologią, której znajomość wpływa na proces terapeutyczny i rokowanie. HUS spowodowany jest zakażeniem bakterią wytwarzającą werotoksynę. Pacjenci leczeni są głównie objawowo, transfuzjami koncentratu krwinek czerwonych KKCz oraz nerkozastępczo. Patofizjologia aHUS wiąże się z nieprawidłową aktywacją alternatywnej drogi dopełniacza. Proces ten można zahamować poprzez zastosowanie terapii celowanej w postaci ekulizumabu - przeciwciała monoklonalnego skierowanego przeciwko składowej C5 dopełniacza. Natomiast u podstawy TTP leży wrodzony lub nabyty niedobór osoczowej metaloproteinazy ADAMTS13. Podstawą leczenia pacjentów z nabytą postacią TTP jest terapeutyczna wymiana osocza, a u pacjentów z wrodzoną postacią tej choroby - przetaczanie świeżo mrożonego osocza.
Słowa kluczowe: mikroangiopatia zakrzepowa, zespół hemolityczno-mocznicowy, atypowy zespół hemolityczno-mocznicowy, zakrzepowa plamica małopłytkowa, ekulizumab

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Haemolytic-uremic syndrome

Haemolytic-uremic syndrome (HUS) is a type of thrombotic microangiopathy characterised by severe haemolytic anaemia and thrombocytopaenia, as well as renal impairment. In most cases HUS is a result of infection with a verotoxin-producing bacteria [1].

Epidemiology

The disease affects people in all age groups, with a general frequency of 2/100,000 people. The highest incidence is observed in children under 5 years old, accounting for 50-70% of all cases [1, 2]. The number of new cases increases during the summer [5].

Aetiology, pathogenesis

In most cases HUS is caused by verotoxin-producing bacteria, typically by enterohaemorrhagic *Escherichia coli* with serotypes O157:H7 and O104:H4 [1, 5, 6], STEC *(Shiga toxin-producing Escherichia coli)* and *Shigella dysenteriae.* In approximately 8% of adult patients and in 15% of children infected with *E. coli* 0157:H7 development of HUS can be expected [5, 7]. The natural reservoir of this strain is cattle. Infection may take place after contact with an infected individual, consumption of raw or undercooked beef, unpasteurised juice or milk, fruit and vegetables contaminated with cattle faeces (e.g. Lettuce, spinach) [2, 5, 8-10]. Verotoxin-producing bacteria are transmitted through the faecal-oral route. The toxin is composed of subunits A and B. Subunit B joins with Gb3 receptor in the cellular membrane of the endothelium in afferent arterioles, renal arterioles and proximal tubules. Due to this conjunction, subunit A can penetrate inside the cell. There it inhibits protein translocation by binding with ribosomal RNA, which results in cell death [5]. By damaging the endothelium or causing antigenic variation, the toxin induces the production of antibodies. As a result, large-molecule von Willebrand factor (VWF) enters the blood circulation. VWF multimers contribute to microthrombus formation in vessels, involving large quantities of platelets. As a consequence, laboratory tests reveal thrombocytopaenia. This process is observed primarily in the renal vessels, although it may be found in many organs. Next, as a result of mechanical damage to the erythrocytes flowing through the affected vessels in the blood stream, haemolytic anaemia develops [1].

Clinical presentation

First symptoms occur within a week from infection, and they are gastrointestinal symptoms in the form of nausea, vomiting, abdominal pain and haemorrhagic diarrhoea, rarely watery diarrhoea. Haemorrhagic diarrhoea is observed in approximately 38-61% of patients following contact with STEC. The symptoms may be associated with fever. Signs of HUS develop within two weeks from the onset of first symptoms. Apart from thrombocytopaenia and non-immune haemolytic anaemia, acute renal injury is observed. Patients' general status is poor; pallor, jaundice, cutaneous and mucosal petechiae, prolonged bleeding time, and spontaneous gastrointestinal haemorrhage. Acute renal injury may manifest by high arterial pressure, increasing oedema, oliguria or anuria. Neurological symptoms are sometimes observed [1, 5]. CNS involvement may present as irritability, seizures, vomiting, headache, dementia, hemiparesis, coma or aphasia, ataxia, Huntington's disease, dystonia and visual impairment [2, 11]. Neurological disorders in HUS have a complex background; they are associated with rapidly progressing renal impairment, contributing to increased nitrogen retention parameters and water and electrolyte disorders (e.g. acidosis, hyperkalaemia, hyponatraemia), and arterial hypertension. Neurobiological symptoms may be also caused by direct effects of Shiga toxin or thrombotic microangiopathy in the CNS vessels [5, 8, 12]. Dialyses may help prevent uremic encephalopathy, or reduce its severity [2, 13]. The disease involving the cardiovascular system may cause myocardial infarction, dilated cardiomyopathy, exudative pericarditis, or cardiac tamponade [5, 14-16]. This syndrome sometimes leads to acute pancreatitis, increased concentrations of liver aminotransferases, or even cholecystitis due to cholelithiasis caused by haemolysis [5, 17]. Interestingly, the course of HUS due to *Shigella dysenteriae* infection is more severe than in the case of E *coli* infection, despite lack of differences in the structure of the toxins produced by these bacteria [5, 8].

Diagnostics

Diagnosis is based on the clinical presentation, and tests confirming infection. Laboratory tests include those identifying signs of microangiopathic haemolytic anaemia (normocytic anaemia with schistocytes, erythroblasts, reticulocytosis, increased LDH activity and elevated concentration of free bilirubin, reduced concentration of haptoglobin), vascular thrombi (thrombocytopaenia, increased concentration of fibrin degradation products [FDP] and D-dimers, renal insufficiency (elevated concentration of creatinine and urea, proteinuria, microhaematuria). Other tests include those whose positive results confirm the aetiology of HUS: tests for STEC (PCR or bacterial culture), determination of the serum concentration of IgM against *E.coli* lipopolysaccharides, and tests for the presence of toxin antigen in stools [1].

Treatment

Treatment of patients with HUS primarily involves symptomatic therapy and renal replacement therapy (RRT). Arterial pressure is controlled with calcium channel blockers. It is important to remember that using ACE-i in the initial period is contraindicated, as it may contribute to further renal insufficiency. In many cases RRT is necessary. It helps to control the arterial pressure, and maintain the water and electrolyte balance, as well as acid - base balance. Due to anaemia, patients sometimes require transfusions of red blood cell concentrate (RBC). Antibiotic therapy is recommended in *Shigella dysenteriae* infections, whereas in STEC-HUS it may be harmful, due to increased release of verotoxin [2, 9, 18, 19].

Prognosis

In up to 25% of patients with HUS the renal function cannot be fully restored, and approximately 5% die. Prognosis is worse in patients under 5 years of age, elderly patients and women [1, 2, 20].

Atypical haemolytic-uremic syndrome

Atypical haemolytic-uremic syndrome (aHUS) is another thrombotic microangiopathy, very similar to classical HUS. However, the aetiology of each of the syndromes is different. aHUS results from a genetic predisposition for uncontrollable activation of the alternative complement pathway [1, 21-23].

Epidemiology

Atypical haemolytic-uremic syndrome affects patients in all age groups. It can be familial, or occur sporadically [1, 21]. Two new cases per 100,000 population are reported annually. Approximately 5-10% of haemolytic-uremic syndromes observed in children are aHUS [22, 23].

Aetiology and aetiopathogenesis

Abnormal activation of the complement system may be due to the activation of proteins that inhibit activation (e.g. of factor H - CFH, factor I - CPI, membrane complement protein - CD46), or mutation in complement proteins that results in their activation (e.g. mutation in complement component 3 and factor B). Mutations in complement genes are detected in approximately 60% of patients with aHUS [24, 25]. The syndrome can also be induced by the presence of antibodies against the proteins inhibiting activation of the complement system, usually against CFH [1, 21, 26, 27]. Although the syndrome is caused by genetic predisposition to abnormal activation of the alternative complement pathway, most cases of aHUS are triggered by certain conditions that affect the complement. They include HELLP syndrome, pre-eclampsia, malignant arterial hypertension, infections, surgical procedures and certain medications [28-31]. Triggering factors may also include infections (e.g. caused by *Streptococcus pneumoniae*, CMV, H1N1 flu virus, HIV, parvovirus and others), and connective tissue diseases (e.g. SLE, scleroderma) [28, 32, 33]. Abnormal complement activation results in deposition of C5a and C5b-9 in the vascular endothelium, which causes its damage, followed by platelet activation and intravascular thrombosis. Finally, thrombocytopaenia and erythrocyte haemolysis are observed in the peripheral blood count [1]. Thrombi within vessels lead to organ ischaemia, which is a direct cause of organ impairment. Usually the process affects renal vessels, resulting in their insufficiency. Laboratory tests demonstrate increasing parameters of nitrogen retention, i.e. of urea and creatinine, and urinalysis reveals proteinuria and microhaematuria. In one third of patients with aHUS the disease affects the vessels in the brain, heart, lungs and pancreas.

Diagnostics

Diagnosis of aHUS is based on clinical criteria and confirmed abnormal activity of the complement system. Also important is determination of the activity of metalloproteinase ADAMTS13, which will be normal in this group of patients. Simultaneously, to differentiate between aHUS and classical HUS, tests for infection by a verotoxin-producing microorganism are conducted. Thrombocytopaenia is less frequent than in classical HUS. Characteristic features of this syndrome include impaired complement system and mutations in the genes coding its components. Routinely, the following complement components are determined: C3, C4, CFH, CFI, CD 46, and immunoglobulin anti-CFH. It should be emphasised that reduced concentration of C3, with a normal level of C4, indicates the alternative pathway of complement activation, but is not specific for aHUS. Reduced concentrations of C3 and factor H with normal concentration of C4 are observed only in one third of patients with aHUS [23, 34]. Also normal concentrations of C3 and C4 do not exclude the diagnosis. However, the analysis of gene mutations will be positive in only half of the patients, so negative results of this test do not exclude aHUS [28]. In searching for aHUS markers, researchers found that patients with this diagnosis had increased concentrations of thrombomodulin, VCAM-1, C5a and C5b-9 in the urine [28, 35].

Previously, differentiating between aHUS and thrombotic thrombocytopaenic purpura was not as important as now. Both microangiopathies used to be treated with plasmapheresis. At present, due to a deeper understanding of the aetiology of microangiopathies and a greater number of therapeutic options, the tests that

help to differentiate between these two diseases are of key importance [34, 36].

Treatment

The diagnosis of aHUS is of much consequence to treatment, as in this case a targeted therapy can be applied. The treatment of choice is eculizumab, i.e. monoclonal antibody against complement C5. When the antibody binds to C5, production of C5a and C5b is inhibited [1, 24, 37]. Early introduction of this medicine inhibits the progress of the disease, and improves the prognosis regarding renal function [22, 25]. It should be emphasised that as a result of suppression of the complement system, the risk of infection with capsid bacteria increases. Before treatment patients should be vaccinated with quadrivalent vaccine against meningococci. A two-week prophylactic antibiotic therapy with penicillin or erythromycin should also be introduced [21]. Symptomatic treatment is necessary, and RBC transfusions may be performed. Before a specific microangiopathy is diagnosed, plasmapheresis is used. Research is being conducted to identify aHUS markers whose levels decrease as the patient's clinical status improves during therapy with eculizumab. It should allow the dose to be adjusted, and help determine the duration of therapy with eculizumab, which would reduce the cost of treatment. One of such markers is C5b-9 [34, 38].

In patients with end-stage renal insufficiency in the course of aHUS, renal replacement therapy is required. Clinical studies demonstrated the effectiveness of eculizumab in prevention of disease recurrence, both before renal transplant, and long-term after the transplantation. Transplantation of liver and kidney is an alternative treatment method for patients with confirmed mutation in the complement components synthesised by the liver (factor H, factor I). Although offering a complete cure for patients with aHUS, this method is not used, as the associated risk is too high [21, 39].

Qualification for eculizumab therapy in Poland

Currently, eculizumab is available in Poland in a drug programme funded by the National Health Fund (NFZ). The inclusion criteria for patients with aHUS include signs of thrombotic microangiopathy in laboratory tests (thrombocytopaenia and haemolysis: PLT <150 x 10^9/l, or baseline value reduced by at least 25%, increased LDH concentration, or signs of red blood cell degradation: presence of schistocytes, or low concentration of haptoglobin, or haemolytic anaemia), or in tissue biopsy. Another criterion is organ injury due to thrombotic microangiopathy: renal impairment (increased serum creatinine levels or proteinuria, or albuminuria, or the necessity to start RRT), or disorders in other organs (cardiovascular, neurological, gastrointestinal or pulmonary complications). The drug programme is available to patients with aHUS who used plasmapheresis or plasma transfusion, or patients qualified to kidney transplantation. All patients must also meet two criteria: negative result of STEC test in PCR or bacterial culture, and activity of ADAMTS13 >5%. Women with childbearing potential must consent to use birth control during the treatment and 5 months after the last dose of eculizumab is necessary. Each patient must receive meningococcal vaccine. If the time from vaccination to treatment is less than 2 weeks, prophylactic antibiotic therapy must be used. The following factors disqualify patients from eculizumab therapy: pregnancy, breast-feeding, severe drug-induced adverse reactions, hypersensitivity to eculizumab, murine proteins or excipients, lack of patient compliance, and patient's withdrawal from treatment. Eculizumab is administered at body weight-dependent doses, in a slow intravenous infusion, under a strict supervision of medical personnel. If clinical remission is achieved, and normal organ function is restored, prophylactic therapy can be discontinued after 6 months of treatment. The decision is taken by the coordination team for aHUS management. The team is also responsible for the decision to reintroduce treatment, without re-qualification. It is recommended to use eculizumab as a life-long therapy. Already 4 weeks after treatment discontinuation, thrombotic microangiopathy may occur as a complication, so therapy should be stopped only in medically justified cases.

To join the drug programme, the following tests are required: assessment of the activity of ADAMTS13, test for STEC (PCR or bacterial culture), tests confirming or excluding pregnancy (in women with childbearing potential), LDH, assessment of haptoglobin concentration, or presence of schistocytes, complete blood count with smear, Coombs test, determination of aspartate aminotransferase, alanine aminotransferase, total bilirubin and its fractions, alkaline phosphatase, concentration of creatinine, urea, uric acid, and general urinalysis. In certain cases, additional tests are required. Patients with neurological symptoms will have to receive angio-MR or CT. If gastrointestinal symptoms occur, assessment of amylase and lipase activity is necessary, as well as abdominal ultrasound. In the case of cardiovascular symptoms, concentration of troponin T and I is determined, and based on the patient's condition, ECG, cardiac ECHO, or coronarography is performed. Antibodies against factor H (anti-CFH) and concentrations of complement system proteins in serum should be determined, and a test for the most common genetic mutations is required. Importantly, the treatment should not be delayed until the test results are obtained.

Patients in the drug programme require follow-up tests: in the first month - once a week, for the next two months - once in two weeks, then, until the end of the first year - once a month; after that period control tests are performed every three months [40].

Prognosis

Prognosis in this disease is poor. 67% of patients aHUS treated with TPE (therapeutic plasma exchange) or PI (plasma infusion) will develop end-stage renal insufficiency, or will die within three years [26, 41]. In addition, aHUS is associated with high mortality, and high recurrence rate [26, 43]. Studies demonstrated that use of eculizumab considerably improves the prognosis regarding improvement of renal function and reduction of TMA recurrences [25, 26]. Detection of mutations is not necessary to establish the diagnosis, but it affects the prognosis (e.g. mutation in factor H is associated with very poor prognosis. MCP mutation is associated with a mild form of aHUS [34, 43].

Thrombotic thrombocytopaenic purpura

Thrombotic thrombocytopaenic purpura (TTP) is a thrombotic microangiopathy due to reduced activity of ADAMTS13 metalloproteinase. Two forms of TTP are distinguished: congenital (Upshaw-Schulman syndrome) and acquired (Moschcowitz syndrome) [1, 44].

Epidemiology

A total of 3.7 - 11 new cases of TTP per 1,000,000 people are reported annually. In most cases the onset is observed in the fourth decade of life, and the disease affects women slightly more often than men (3:2) [45]. Congenital form of TTP is diagnosed in children under 5 years of age [46, 47].

Aetiology and aetiopathogenesis

Congenital TTP is inherited in an autosomal recessive pattern. Reduction or loss of the activity of ADAMTS13 metalloproteinase is caused by a mutation of the gene coding the enzyme [1, 46]. Acquired purpura is caused by the presence of antibodies that inhibit the activity of the metalloproteinase, or increase its renal clearance. ADAMTS13 enzyme cleaves ultralarge multimers of von Willebrand factor (ULVWF) into smaller fragments. Reduced activity of this metalloproteinase leads to accumulation of ULVWf. Complexes of von Willebrand factor activate blood platelets, resulting in their aggregation, and formation of thrombi in vessels. In the affected vessels red blood cells undergo haemolysis [1, 44, 45]. The aggregates of platelets and fibrin formed in capillaries and small arterioles cause ischaemia of organs, resulting in impaired organ function. This process typically affects vessels in the brain, kidneys, heart, pancreas, intestines and adrenal glands. The triggering factors that result in antibody production include pregnancy, infections, injuries and surgical procedures. The syndrome is characterised by spontaneous remissions and recurrences. In the asymptomatic period, the activity of metalloproteinases normalises, and antibodies disappear [1].

Clinical presentation

Five main symptoms of TTP include: thrombocytopaenia, non-immune haemolytic anaemia. Acute kidney injury, neurological symptoms and fever. Only a small percentage of patients experience all the symptoms simultaneously. Most often laboratory tests reveal thrombocytopaenia and anaemia [45].

Patients may demonstrate symptoms of thrombocytopaenic purpura, and jaundice due to the disintegration of erythrocytes. TTP may be manifested by the symptoms of CNS ischaemia, namely pain and vertigo, focal symptoms, seizures, stroke, or even coma. When coronary vessels are affected, stenocardia symptoms develop. Thrombotic lesions in the vessels providing supply to the gastrointestinal tract result in abdominal pain, diarrhoea, nausea and vomiting. Involvement of the renal vessels is associated with increased renal insufficiency [1]. In approximately 50-75% of patients with TTP neurological symptoms occur, whereas renal damage is observed less frequently than in haemolytic-uremic syndromes [46].

Diagnosis

The condition for TTP diagnosis is demonstration of the signs of thrombotic microangiopathy, and activity of ADAMTS13 <10%, or the presence of antibodies against ADAMTS13. Moreover, aetiology typical for haemolytic-uremic syndromes should be excluded [46]. In HUS and aHUS, the activity of this enzyme is normal. In secondary microangiopathies the activity of ADAMTS13 is also typically within the normal range. Only a small number of patients with malignant neoplasms, DIC and sepsis demonstrate significantly reduced activity of this metalloproteinase [34, 48, 49]. After low activity of the metalloproteinase is demonstrated, further steps include identification of mutations and anti-ADAMTS13 antibodies, to differentiate between the congenital and acquired forms [34, 50-52].

Treatment

When signs of microangiopathy are detected, a blood sample is collected to determine the activity of ADAMTS13, and treatment is applied immediately. If TTP is suspected, plasmapheresis therapy is of key importance. This procedure removes antibodies against

ADAMTS13 and ULVWf complexes, and provides normal metalloproteinase [1, 21, 45]. Routinely 1 to 1.5 of the patient's plasma is removed daily, and replaced with donor plasma. If TPE is not readily available, transfusions of fresh frozen plasma should be applied. Therapeutic plasma exchange is conducted every day, until the platelet LDH levels normalise for 2-3 consecutive days. Gradual reduction in the time of the volume of exchanged plasma is often observed; however, no prospective clinical trials support such management [1, 53]. Due to the exchange of large quantities of plasma, allergic reactions and reactions to citrates are more often observed in this group of patients. To reduce the number of citrate-induced complications, ACD-A should be used as anticoagulant. In some cases a 5% albumin solution can be added to the administered plasma (e.g. to patients with severe allergic reactions to plasma proteins, and if the amount of plasma is limited) [53].

To reduce the levels of antibodies, improve the vascular endothelial function and reduce the number of TPE required to obtain remission, oral prednisone therapy at a dose of 1 mg/kg bw/d is introduced [54]. Lack of improvement after a week of treatment, or deterioration of patient's clinical status indicate resistance, while disease recurrence is defined as recurrence of symptoms one month after the end of plasmaphereses. In both cases other diagnoses should be excluded, total plasma exchange should be performed twice a day, or the volume of the exchanged plasma should be increased [1].

If immunosuppression with glucocorticoids and rituximab does not result in improvement, introduction of other immunosuppressive drugs should be considered (e.g. cyclosporine, cyclophosphamide, mycophenolate mofetil, azathioprine, vincristine), or splenectomy. Other potential therapies are also described, e.g. Recombined ADAMTS13 (dedicated to patients with congenital TTP), or another monoclonal antibody, caplacizumab, N-acetylcysteine, and immunoadsorption protein A, which removes IgG against ADAMTS13 [21, 46, 54]. A new therapeutic approach with clinically confirmed effectiveness is caplacizumab, a nanobody against the antigen on von Willebrand factor, which prevents platelet activation and aggregation by interfering with the adhesion of VWF to platelets. Caplacizumab does not affect the binding between VWF with collagen or ADAMTS13. Studies using human plasma (containing ULVWF multimers, and without ADAMTS13) demonstrated that N-acetylcysteine, used for years as a mucolytic agent, reduced UL-VWF multimers by disrupting the disulfide bonds in the A1 domain of the factor, which leads to disturbed binding and activation of platelets by VWF [54].

Rituximab is a monoclonal antibody against CD20, found on lymphocytes B. It reduces the number of lymphocytes and limits antibody production. Rituximab was proven effective in patients with acute TTP. The mean time to remission is 10 days, regardless of the moment of therapy initiation following the diagnosis of TTP [21, 55]. The mean time to recurrence is approximately 24 months. Patients with resistant and recurrent TTP can also benefit from this therapy [21, 56]. In clinical practice, rituximab is administered together with TPE, at 18-24-hour intervals between the therapies [53]. RBC is administered as supportive treatment (in severe anaemia due to haemolysis), less often platelet concentrate is used (only in patients with a high risk of life-threatening haemorrhage due to thrombocytopaenia). Sometimes prophylactic doses of LMWH are administered. In remission, the activity of ADAMTS13 can be monitored for secondary prophylaxis with rituximab However, according to the authors, the time between reduction of enzyme activity to recurrence varies. In a small proportion of patients, despite clinical remission, the activity of the metalloproteinase does not increase. These cases should be treated with rituximab and mycophenolate mofetil [21].

Currently, treatment of congenital TTP is based on fresh frozen plasma transfusions. Patients with frequent recurrences require regular (2-3 times a week) prophylactic plasma infusions. The metalloproteinase obtained from plasma, or artificially produced can also be administered to address its deficiency [34, 50, 51].

Prognosis

Untreated thrombotic thrombocytopaenic purpura is associated with a 90% risk of death. Plasma exchange therapy reduces the risk to 10-25% [2, 45]. Patients with severe ADAMTS13 deficiency demonstrate better responses to TPE (mortality rates of 8-19%), whereas in patients demonstrating a moderate reduction of the activity of the metalloproteinase the prognosis is worse (mortality rates of 18-56%) [46, 57]. Early initiation of TPE improves the prognosis. Bad prognostics include involvement of the nervous system, heart, very low platelet levels after two days of therapy, and age of >60 years old. TTP is associated with reduced physical activity, decreased intellectual potential, and increased risk of arterial hypertension [45].

Differential diagnostics of thrombotic angiopathies

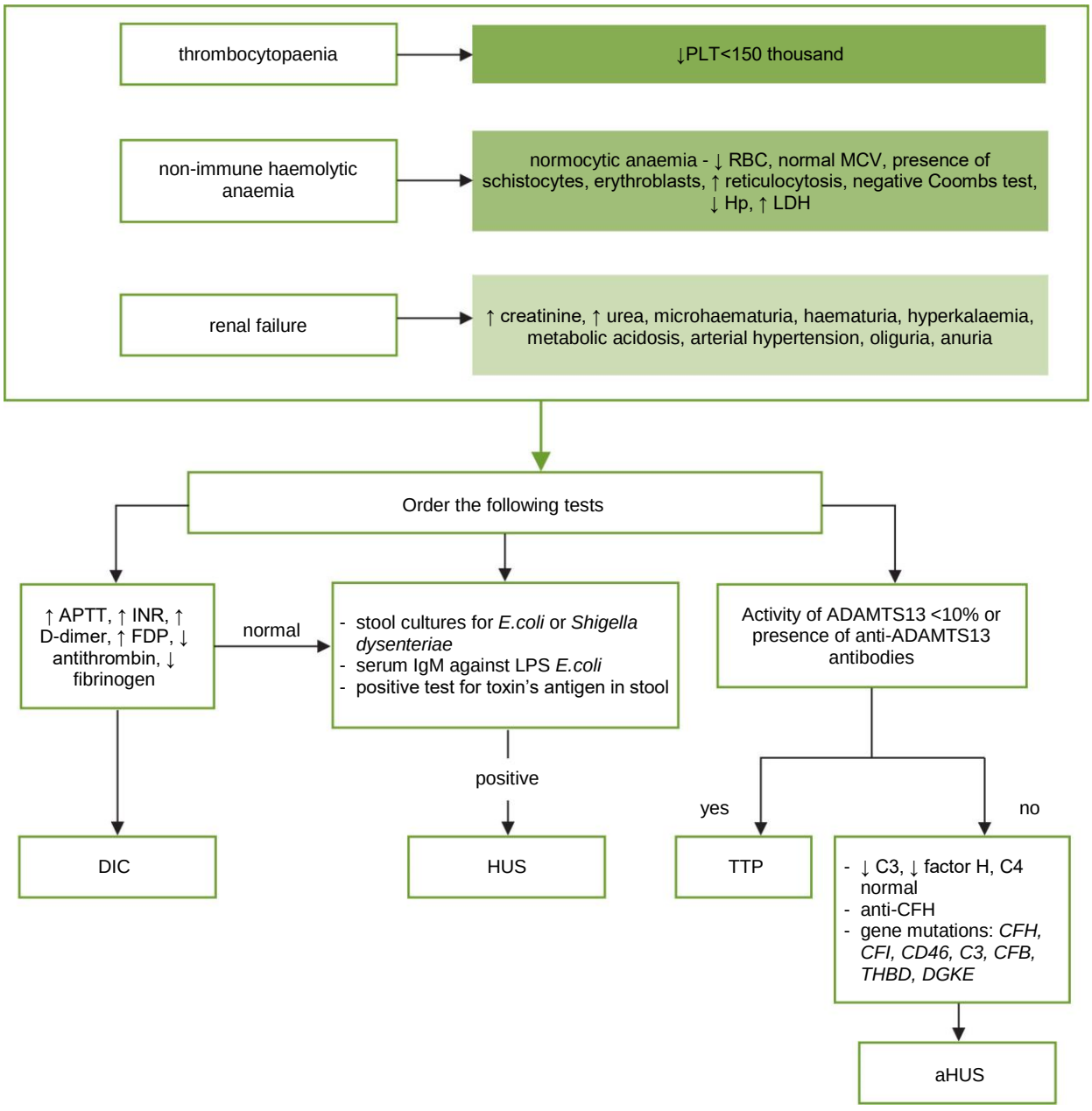
Differential diagnosis of thrombotic angiopathies is necessary, as it determines the appropriate treatment.

The key test suggesting the diagnosis of TMA is peripheral blood count with smear. Diagnostics should be extended if thrombocytopaenia, normocytic anaemia with reticulocytosis and the presence of schistocytes and

erythroblasts are demonstrated. Diagnostic tests for anaemia will reveal an increased activity of LDH and intermediate bilirubin, and negative Coombs test result, suggestive of non-immune haemolytic anaemia. Normal result of coagulation tests are important. The following laboratory parameters indicate renal injury: increased concentrations of creatinine and urea in blood, and proteinuria and microhaematuria in general urinalysis. Haemorrhagic diarrhoea is typically observed in HUS, although it may occur also in other forms of TMA, so stool cultures, tests for verotoxin antigen in the stool, and determination of IgM against LPS *E.coli* should always be performed. Positive results for *E. coli* or *S. dysenteriae* will support the diagnosis of classical HUS. Moreover, the activity of ADAMTS13 should be evaluated, as well as the levels of antibodies against metalloproteinase. Reduced activity, or the presence of antibodies, together with normal activity of the complement system, and negative results of microbiological tests, support the diagnosis of TTP. Simultaneously, the activity of the complement system should be assessed: levels of C3 and C4, factors H and I, and mutations in CFH, CFI, CD46, C3, CFB, THBD, and DGKE [21]. Abnormalities in the complement system with normal activity of metalloproteinase and negative results of the test for verotoxin-producing pathogen will justify the diagnosis of aHUS (Fig. 1). Diagnostic renal biopsy is not necessary for the diagnosis; moreover, it does not allow the determination of the exact type of TMA. It should also be emphasised, that the procedure is associated with a risk of complications, and sometimes may accelerate the disease progression [28]. Increased concentration of creatinine (>2.26 mg/dl) and blood platelets of >30 x 10^9/l indicate that the diagnosis is not TTP. However, in clinical practice these parameters are also observed in some patients with TTP [21, 28, 58-61].

Organ manifestations should not be the only diagnostic criteria. Neurological symptoms should not determine the diagnostics towards TTP, as approximately 50% of children with aHUS develop symptoms associated with CNS involvement. In addition, diarrhoea, considered to be associated mainly with STEC-HUS, is also observed in patients with aHUS and TTP [28].

As for the origin of thrombotic microangiopathy, secondary causes should be excluded, e.g. HIV infection, *Streptococcus pneumoniae* infection, SLE (dsDNA), sclerosis, antiphospholipid syndrome, cobalamin deficiency [21], and medications (quinine, cyclosporine, interferons, gemcitabine, mitomycin, clopidogrel, oestrogen, progesterone, and ticlopidine) [28, 62]. In secondary cases, the treatment should be focused on the underlying disease; if it proves ineffective, the diagnosis of aHUS should be considered and eculizumab should be introduced [28].



PLT - platelets, RBC - erythrocytes, MCV - mean corpuscular value, Hp - haptoglobin, APTT - activated partial thromboplastin time, INR - international normalised ratio, FDP - fibrin and fibrinogen degradation products, LDH - lactic dehydrogenase, *E. coli - Eschericha coli, S. dysenteriae - Shigella dysenteriae,* IgM - class M immunoglobulin, LPS - lipopolysaccharide, ADAMTS13 - metalloproteinases degrading von Willebrand factor multimers, C3 and C4 - proteins of the complement system, factor H *(CFH)* - protein activating the alternative pathway of complement activation, anti-CFH - antibody against factor H, *CFI* (factor I) - protein co-regulating the alternative pathway of complement activation, *CD46* - membrane cofactor protein, CFB - component of the alternative pathway of complement activation, *THBD* - thrombomodulin-coding gene, *DGKE* - diacylglycerol kinase epsilon, DIC - disseminated intravascular coagulation, HUS - haemolytic-uremic syndrome, aHUS - atypical haemolytic-uremic syndrome, TTP - thrombotic thrombocytopaenic purpura

Figure. Differential diagnosis of thrombotic microangiopathy
Rycina Diagnostyka różnicowa mikroangiopatii zakrzepowych

Thrombotic microangiopathy in pregnant women and in the early postpartum period

Thrombotic microangiopathies also affect women who are pregnant or in the postpartum period. Microangiopathic haemolytic anaemia, thrombocytopaenia and signs of acute renal failure should be differentiated with pre-eclampsia, HELLP syndrome, and aHUS. Conditions such as sepsis, premature placental detachment and haemorrhage may cause the above symptoms in the mechanism of disseminated intravascular coagulation (DIC) [63].

If anaemia and thrombocytopaenia are observed in a pregnant patient, pre-eclampsia and HELLP syndrome must be excluded in the first place. TTP or aHUS can be suspected if the patient does not meet the diagnostic criteria of pre-eclampsia (i.e. arterial blood pressure >140/90 mm Hg, occurring after 20 weeks of pregnancy, proteinuria) or HELLP syndrome (i.e. signs of pre-eclampsia, arterial blood pressure >160/110 mm Hg, PLT <100,000/μl, increased activity of liver enzymes or severe abdominal pain in the right upper quadrant, creatinine >1.1 mg/dl, pulmonary oedema, neurological disorders and visual disturbance), or if the clinical status does not improve, or deteriorates after the child is delivered. In this group of women, as in the general population, TTP can be hereditary (homozygous or heterozygous), or, more frequently, acquired. Diagnosis of the congenital form is associated with a considerable risk, and requires plasma transfusions throughout the pregnancy [64]. TTP can occur at any time at pregnancy, but it develops most often around the time of delivery and a few weeks after the birth. It is characterised by ADAMTS13 activity of <10%. Neurological disorders, primarily focal symptoms, as well as severe anaemia and severe thrombocytopaenia are observed more frequently. Advanced renal failure with arterial hypertension, moderate anaemia and thrombocytopaenia, without concurrent neurological disorders, without hepatic injury indicates aHUS, when all other causes of thrombotic microangiopathy are excluded. Due to a limited availability and the time required to obtain the results, genetic testing is performed primarily to assess the risk of recurrence and plan further management [63]. Differentiation between these syndromes is of key importance, as in pre-eclampsia /HELLP syndrome, depending on the condition of the mother and advancement of these syndromes, therapy consists in prompt delivery/termination of pregnancy, and control of the arterial blood pressure, whereas in TTP and aHUS the treatment is introduced immediately, efforts are made to keep the pregnancy until the required gestational age, and plasma exchange therapy is applied in TTP, and inhibitor of the complement system is administered in aHUS. No adverse effects of these therapies on foetus have been found, and no additional benefits of immediate delivery have been identified [65-68].

Drug-induced thrombotic microangiopathies

Drug-induced thrombotic microangiopathies (DITMA) are TTP and aHUS resulting from exposure to various substances, after all other causes have been excluded. The literature offers many cases of drug-induced microangiopathies, but causal relationship has not been demonstrated in all of them.

In 2015, *Blood* journal published an article reporting the results of a review of DITMA cases. The majority of 78 substances potentially associated with microangiopathy were considered to be likely causes of TMA (e.g. clopidogrel, ibuprofen, imatinib, metronidazole, oestrogens, progesterone, and tamoxifen). Only 22 substances were considered to be certainly associated with the condition: quinine (the most common cause of DITMA), quetiapine, penicillin, oxaliplatin, muromonab - CD3, trieline, cyclosporine, tacrolimus, sirolimus, interferon α, gemcitabine, interferon β, mitomycin, bevacizumab, sunitinib, pentostatin, cocaine, everolimus, interferon polycarboxylate, sulfisoxazole, vincristine, and docetaxel. Pathogenesis of DITMA involves immune reactions which result in the production of antibodies against blood platelets, as well as dose-dependent and time-dependent toxicity. The clinical feature that differentiates the two mechanisms is the time between the use of the medicine and onset of microangiopathy. It is believed that immune reactions occur earlier [62].

Immune-mediated DITMA is diagnosed when the following criteria are met:

- other causes of TMA were excluded,
- the suspected drug was the only drug taken, or other drugs were continued or restarted,
- previous or subsequent drug exposure was associated with symptoms, or drug-dependent antibodies were documented (reactive with platelets or other cells).

Symptoms should occur within 21 days, if the suspected substance was used daily, or within 24 hours if it was used occasionally.

Diagnosis of dose-dependent toxicity-mediated TMA is based on the following criteria:

- other causes of TMA were excluded,
- the suspected drug was the only drug taken, or other drugs were continued or restarted,
- TMA resolved or improved when suspected drug was stopped, or its dose reduced [69].

Thrombotic microangiopathies in neoplastic diseases

Thrombotic microangiopathies are observed in patients with neoplastic disease, usually in an advanced, metastatic stage, but also in patients who have not been diagnosed yet. The vascular thrombi may be caused directly by the neoplasm (i.e. systemic metastases, metastases to the bone marrow, or bone marrow necrosis), by chemotherapy (i.e. dose-dependent toxicity and initiation of immune reaction), or TTP, HUS or aHUS. Invasion of neoplastic cells to vessels damages the erythrocytes, which starts intravascular thrombosis, associated with increased use of blood platelets. These patients are often diagnosed with TTP, and receive ineffective treatment with plasma exchange. In the Oklahoma registry of TTP-HUS conducted in 1989-2015, 509 patients with suspected TTP were qualified to plasma exchange therapy. Eleven of these patients were finally diagnosed with disseminated neoplastic disease as the cause of the microangiopathy. The neoplasms detected in these patients included: breast cancer (two patients), non-small cell lung carcinoma (two patients), neoplasms of pancreas, kidney, prostate, Kaposi's sarcoma, non-Hodgkin lymphoma, acute lymphocytic leukaemia and refractory anaemia with excess blasts. In 90% of cases of bone marrow necrosis the cause is neoplastic diseases, mostly haematological ones (usually acute lymphocytic leukaemia), whereas the most common solid tumours are prostate cancers.

Another mechanism responsible for haemolytic anaemia and thrombocytopaenia in oncological patients is DIC. It is frequently observed in the course of promyelocyte leukaemia (due to release of procoagulatory factors) and neoplasms of the pancreas, stomach and ovary (due to activation of factor X of the coagulation system) [70]. Laboratory tests in patients with DIC reveal reduced concentrations of fibrinogen [71]. Chemotherapeutics that cause toxicity-mediated microangiopathy include: gemcitabine, mitomycin, interferon α, cisplatin, bevacizumab, pentostatin, sunitinib, oxaliplatin, docetaxel, everolimus and vincristine.

Immune-mediated toxicity, due to production of antibodies against platelets, neutrophils and other cells, is associated with the use of oxaliplatin, gemcitabine and imatinib. If symptoms of microangiopathy occur suddenly, and recur each time after administration of a chemotherapeutic, the disease may be immune-mediated. If the process is slower, and leads to progressive renal failure, drug-induced dose-dependent toxicity is a more likely cause.

In the case of drug-induced microangiopathy, the suspected substance should be discontinued. Beneficial therapeutic effects of eculizumab or rituximab are reported in the literature. When drug-induced microangiopathy is excluded, differential diagnosis of neoplasm-associated microangiopathy and TTP, HUS and aHUS should be performed [71, 72].

The tests useful in the diagnosis of neoplastic diseases include bone marrow biopsy and imaging studies. In neoplasm-associated microangiopathy bone marrow involvement may occur, and immature granulocyte and nucleated erythrocytes can be found in the peripheral blood count. In both groups the LDH concentration increases, but in neoplastic diseases it is usually higher than in TTP. In patients with neoplasms the activity of liver enzymes are increased, and coagulopathies are observed. The activity of ADAMTS13 is normal. Clinical presentation in patients with neoplastic disease is characterised by weakness, body weight loss, back pain and bone pain. In patients with TTP weakness and dyspnoea may be caused by anaemia, while weight loss or bone pain are not typically observed [73]. Atypical haemolytic-uremic syndrome is a diagnosis considered after other potential causes of microangiopathy are eliminated [71].

Prompt diagnosis is of utmost importance, as it determines further management. In TTP, therapeutic plasma exchange is required. However, in patients with neoplasm-associated microangiopathy the prognosis is very poor; the available therapeutic options include aggressive antineoplastic therapy or palliative treatment [74].

Thrombotic microangiopathies and haematopoietic cell transplantation

Patients following bone marrow transplantation are exposed to the risk of thrombotic microangiopathy. This complication develops in 0.5 to 63.3% of patients [75]. The aetiology of microangiopathy in this group of patients is probably multifactorial. It may include immunosuppressives (e.g. cyclosporine, tacrolimus), infections of various aetiology (e.g. cytomegalovirus, parvovirus, adenovirus, type A flu virus, *Aspergillus),* total body irradiation (TBI), and graft vs host disease. In these patients the pathogenesis of microangiopathy reflects that of aHUS [23].

Certain scientific communities have created their own diagnostic criteria for thrombotic microangiopathy following bone marrow transplantation. All the groups include increased LDH concentrations and presence of schistocytes in the peripheral blood, most of them also take into account thrombocytopaenia, and some mention increased concentrations of serum creatinine, negative Coombs test results, reduced haptoglobin concentration, and increased need for transfusion [76].

Cyclosporine and tacrolimus and calcineurin inhibitors have a proven potential to induce thrombotic angiopathy [77]. These substances reduce the production of prostacyclins and nitric oxide, activated protein C, and increase the concentration of thromboxane A2, resulting in damage to endothelial cells [78, 79]. Studies indicate that as a result of exposure to cyclosporine, endothelial cells release substances responsible for activation of the alternative pathway of the complement [80]. Further studies demonstrate an increase in the complement components C3, C4 and MAC in patients with cyclosporine-induced renal injury [81]. In addition, complement component C5, by binding to the receptors on neutrophils, contributes to the release of oxygen free radicals which also damage the vascular endothelium [82]. The above infections and TBI demonstrate a toxic effect on the endothelium, and initiate a cascade of reactions that result in the formation of intravascular thrombi [83, 84].

Transplant vs host disease also increases the risk of thrombotic microangiopathy due to endothelial damage, probably by increasing the concentration of cytotoxins, activation of the coagulation system, low concentration of VEGF, or cytotoxic effect of donor's T-lymphocytes [85]. Treatment of patients with thrombotic microangiopathy after transplantation of haematopoietic cells requires discontinuation of drugs with a potential microangiopathy-inducing effect, mainly calcineurin inhibitors [86]. Initially, therapeutic plasma exchange is frequently used, due to the difficulties associated with differential diagnostics of TTP and aHUS. An increasing number of studies demonstrate a positive therapeutic effect of eculizumab [87].

Conclusions

Thrombotic microangiopathies are clinical and pathological syndromes rarely observed in clinical practice. However, the subject literature offers an increasing number of reports presenting patients with this diagnosis, which raises the awareness of doctors. Nowadays, with the progress in medicine, our understanding of the aetiology, symptoms, diagnostics and treatment of the disease is more extensive and more accessible. It should be emphasised that early diagnosis and introduction of proper treatment greatly improves the patient's prognosis.

Literature

1. Zawilska K. Skazy krwotoczne płytkowe [Platelet haemorrhagic diathesis]. In: Gajewski P, ed. Interna Szczeklika [Szczeklik's Internal Medicine]. Medycyna Praktyczna, Krakow 2017: 1865-1869
2. Webster K, Schnitzler E. Hemolytic uremic syndrome. Handb Clin Neurol. 2014; 120:1113–1123
3. Moake JL. Thrombotic microangiopathies. N Engl J Med, 2002; 347: 589–600
4. Scheiring J, Rosales A, Zimmerhackl LB. Today's understanding of the haemolytic uraemic syndrome. Eur J Pediatr, 2010; 169: 7–13
5. Adamczuk D, Bieroza I, Roszkowska-Blaim M. Zespół hemolityczno-mocznicowy [Haemolytic-uraemic syndrome]. Nowa Pediatria, 2009; 2: 63-67
6. Laurence J. Atypical haemolytic uremic syndrome (aHUS): Making the diagnosis. Clin Adv Hematol Oncol, 2012; 10: 1–2
7. Myśliwiec M. Mikroangiopatie zakrzepowe – postępy w patogenezie, diagnostyce i leczeniu [Thrombotic microangiopathies – advances in pathogenesis, diagnostics and therapy]. Nefrol Dial Pol, 2008; 12: 124–127
8. Marczak E, Żurowska A. Zespół hemolityczno-mocznicowy [Haemolytic-uraemic syndrome]. In: Sieniawska M, Wyszyńska T, eds. Nefrologia dziecięca [Paediatric nephrology]. Vol. II. "Polfa" centre of Scientific Information, Warsaw 2003: 329–347
9. Safdar N, Said A, Gangnon RE, Maki DG. Risk of haemolytic – uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 enteritis – meta-analysis. JAMA, 2002; 288: 996-1001
10. Tarr PI, Gordon CA, Handler WL. Shiga – toxin-producing Escherichia coli and haemolytic uraemic syndrome. Lancet, 2005; 365: 1073–1085
11. Hahn JS, Havens PL, Higgins JJ, et al. Neurological complications of haemolytic-uremic syndrome. J Child Neurol, 1989; 4: 108–113
12. Barnett NDP, Kaplan AM, Bernes SM, Cohen ML. Haemolytic uremic syndrome with particular involvement of basal ganglia and favourable outcome. Pediatr Neurol, 1995; 12: 155–158
13. Stewart CL, Tina LU. Haemolytic uremic syndrome. Pediatr Rev, 1993; 14: 218-224
14. Thayu M, Chandler WL, Jelacic S, et al. Cardiac ischemia during haemolytic uremic syndrome. Pediatr Nephrol, 2003; 18: 286-289
15. Mohammed J, Filler G, Price A, Sharma AP. Cardiac tamponade in diarrhoea – positive haemolytic uremic syndrome. Nephrol Dial Transplant, 2009; 24 (2): 679-781
16. Thomas NJ, Messina JJ, DeBruin WJ, Carcillo JA. Cardiac failure in haemolytic uremic syndrome and rescue with extracorporeal life support. Pediatr Cardiol, 2005; 26 (1): 104–106
17. Tapper D, Tarr P, Avner E, et al. Lessons learned in the management of haemolytic uremic syndrome. J Pediatr Surg, 1995; 30 (2): 158–163
18. Banerjee S. Haemolytic uremic syndrome. Indian Pediatr, 2009; 46: 1075–1084
19. Mohsin M, Haque A, Ali A, et al. Effects of ampicillin, gentamicin, and cefotaxime on the release of Shiga toxins from Shiga toxin-producing Escherichia coli isolated during a diarrhea episode in Faisalabad, Pakistan. Foodborne Pathog Dis, 2010; 7: 85–90
20. Gould LH, Demma L, Jones TF, et al. Haemolytic uremic syndrome and death in persons with Escherichia coli O157:H7 infection, Foodborne Diseases Active Surveillance Network Sites, 2000–2006. Clin Infect Dis, 2009; 49: 1480–1485
21. Scully M, Goodship T. How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome. Br J Haematol, 2014; 164: 759–766
22. Fraga-Rodriguez GM, Brió-Sanagustin S, Turón-Viñas E, et al. Eculizumab in a child with atypical haemolytic uraemic syndrome and haemophagocytic lymphohistiocytosis triggered by cytomegalovirus infection. BMJ Case Rep, 2017; pii: bcr-2016-219065
23. Noris M, Remuzzi G. Atypical haemolytic-uremic syndrome. N Engl J Med, 2009; 361: 1676–1687
24. Kourouklaris A, Ioannou K, Athanasiou I. Postpartum thrombotic microangiopathy revealed as atypical haemolytic uremic syndrome successfully treated with eculizumab: a case report. J med. Case Rep, 2014; 8: 307
25. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical haemolytic-uremic syndrome. N Engl J Med, 2013; 368: 2169–2181
26. de Andrade LGM, Contti MM, Nga HS, et al. Long-term outcomes of the Atypical Haemolytic Uremic Syndrome after kidney

transplantation treated with eculizumab as first choice. PLoS ONE, 2017; 12 (11): e0188155
27. Noris M, Remuzzi G. Managing and preventing atypical haemolytic uremic syndrome recurrence after kidney transplantation. Curr Opin Nephrol Hypertens, 2013; 22 (6): 704–712
28. Hossain MA, Cheema A, Kalathil S, et al. Atypical haemolytic uremic syndrome: laboratory characteristics, complement-amplifying conditions, renal biopsy, and genetic mutations. Saudi J Kidney Dis Transpl, 2018; 29 (2): 276–283
29. Akimoto T, Muto S, Ito C, et al. Clinical features of malignant hypertension with thrombotic microangiopathy. Clin Exp Hypertens, 2011; 33: 77–83
30. Barbour T, Johnson S, Cohney S, Hughes P. Thrombotic microangiopathy and associated renal disorders. Nephrol Dial Transplant, 2012; 27: 2673–2685
31. Nester CM, Thomas CP. Atypical haemolytic uremic syndrome: What is it, how is it diagnosed, and how is it treated? Hematol Am Soc Hematol Educ Program, 2012; 2012: 617–625
32. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: Diagnosis and treatment. A consensus document. Nefrologia, 2015; 35: 421–447
33. Ornstein BW, Atkinson JP, Densen P. The complement system in pediatric systemic lupus erythematosus, atypical haemolytic uremic syndrome, and complocentric membranoglomerulopathies. Curr Opin Rheumatol, 2012; 24: 522–529
34. Mannucci PM, Cugno M. The complex differential diagnosis between thrombotic thrombocytopenic purpura and the atypical haemolytic uremic syndrome: Laboratory weapons and their impact on treatment choice and monitoring. Thrombosis Res, 2015; 136 (5): 851–854
35. Cofiell R, Kukreja A, Bedard K, et al. Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. Blood, 2015; 125: 3253–3262
36. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. N Engl J Med, 1991; 325: 393–397
37. Nurnberger J, Philipp T, Witzke O, et al. Eculizumab for atypical haemolytic-uremic syndrome. N Engl J Med, 2009; 360: 542–544
38. Cugno M, Tedeschi S, Ardissino G. Tailored eculizumab regimen for patients with atypical haemolytic uremic syndrome: requirement for comprehensive complement analysis: comment. J Thromb Haemost, 2015; 13: 485–486
39. Saland JM, Ruggenenti P, Remuzzi G, et al. Liver-kidney transplantation to cure atypical haemolytic uremic syndrome. J Am Soc Nephrol, 2009; 20 (5): 940–949
40. Leczenie atypowego zespołu hemolityczno-mocznicowego – program lekowy NFZ. [Treatment of atypical haemolytic-uraemic syndrome – National Health Fund drug programme] www.gov.pl/web/zdrowie/choroby-nieonkologiczne
41. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol, 2010; 5 (10): 1844–1859
42. Le Quintrec M, Zuber J, Moulin B, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical haemolytic and uremic syndrome. Am J Transplant, 2013; 13 (3): 663–675
43. Bresin E, Rurali E, Caprioli J, et al. Combined complement gene mutations in atypical haemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol, 2013; 24: 475–486
44. Kremer Hovinga JA, Coppo P, Lämmle B, et al. Thrombotic thrombocytopenic purpura. Nat Rev Dis Prim, 2017: 317 020
45. Said A, Haddad RY, Stein R, et al. Thrombotic thrombocytopenic purpura. Disease-a-Month, 2014; 60: 500-504
46. Shenkman B, Einav Y. Thrombotic thrombocytopenic purpura and other thrombotic microangiopathic haemolytic anemias: Diagnosis and classification. Autoimmunity Rev, 2014; 13: 584–586
47. Moake JL. Thrombotic thrombocytopenic purpura and the haemolytic uremic syndrome. Arch Pathol Lab Med, 2002; 126: 1430–1433
48. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura – haemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood, 2003; 102: 60–68
49. Mannucci PM, Canciani MT, Forza I, et al. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. Blood, 2001; 98: 2730–2735
50. Scully M, Gattens M, Khair K, Liesner R. The use of intermediate purity factor VIII concentrate BPL 8Y as prophylaxis and treatment in congenital thrombotic thrombocytopenic purpura. Br J Haematol, 2006; 135: 101-104
51. Peyvandi F, Mannucci PM, Valsecchi C, et al. ADAMTS13 content in plasma-derived factor VIII/von Willebrand factor concentrates. Am J Hematol, 2013; 88: 895–898
52. Hie M, Gay J, Galicier L, et al. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood, 2014; 124: 204–210
53. Journal of clinical apheresis DOI 10.1002/jca
54. Knöbl P. Thrombotic thrombocytopenic purpura. Memo, 2018; 11: 220–226
55. Westwood JP, Webster H, McGuckin S, et al. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. J Thromb Haemost, 2013; 11 (3): 481–490
56. Froissart A, Buffet M, Veyradier A, et al. Efficacy and safety of firstline rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. Crit Care Med, 2012; 40 (1): 104–111
57. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood, 2004; 103: 4043–4049
58. Zuber J, Fakhouri F, Roumenina LT. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol, 2012; 8 (11): 643–657
59. Neuhaus TJ, Calonder S, Leumann EP. Heterogeneity of atypical haemolytic uraemic syndromes. Arch Dis Child, 1997; 76: 518–521
60. Zuber J, Le Quintrec M, Sberro-Soussan R, et al. New insights into postrenal transplant haemolytic uremic syndrome. Nat Rev Nephrol, 2011; 7: 23–35
61. Noris M, Brioschi S, Caprioli J, et al. Familial haemolytic uraemic syndrome and an MCP mutation. Lancet, 2003; 362: 1542–1547
62. Al-Nouri ZL, Reese JA, Terrell DR, et al. Drug-induced thrombotic microangiopathy: A systematic review of published reports. Blood, 2015; 125: 616–618
63. George JN, Nester CM, McIntosh JJ, et al. Syndromes of thrombotic microangiopathy associated with pregnancy. Hematology, 2015; 2015: 644–648
64. Scully M, Thomas M, Underwood M, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. Blood, 2014; 124 (2): 211-219
65. Kelly R, Arnold L, Richards S, et al. The management of pregnancy in paroxysmal nocturnal hemoglobinuria on long term eculizumab. Br J Haematol, 2010; 149 (3): 446–450
66. Marasca R, Coluccio V, Santachiara R, et al. Pregnancy in PNH: another eculizumab baby. Br J Haematol, 2010; 150 (6): 707–708
67. Burwick RM, Feinberg BB. Eculizumab for the treatment of preeclampsia/ HELLP syndrome. Placenta, 2013; 34 (2): 201–203
68. Usuki K, Urabe A, Kawaguchi T, et al. Management of pregnancy in paroxysmal nocturnal hemoglobinuria (PNH): a report of 10 cases from the Working Group on Pregnancy of the Japan PNH Study Group. Blood, 2013; 122 (21): 2480
69. Reese JA, Bougie DW, Curtis BR, et al. Drug-induced thrombotic microangiopathy: experience of the Oklahoma registry and the bloodcenter of Wisconsin. Am J Hematol, 2015; 90 (5): 406–410
70. Tallman MS, Kwaan HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. Blood, 1992; 79: 543–553

71. Morton J, George JN. Microangiopathic haemolytic anaemia and thrombocytopenia in patients with cancer. J Oncol Pract, 2016; 2 (6): 523–530
72. George JN, Charania RS. Evaluation of patients with microangiopathic haemolytic anaemia and thrombocytopenia. Semin Thromb Hemost, 2013; 39: 153–160
73. Nokes T, George JN, Vesely SK, et al. Pulmonary involvement in patients with thrombotic thrombocytopenic purpura. Eur J Hematol, 2014; 92: 156–163
74. Francis KK, Kalyanam N, Terrell DR, et al. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. Oncologist, 2007; 12: 11–19
75. George JN, Li X, McMinn JR, et al. Thrombotic thrombocytopenic purpura-haemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. Transfusion, 2004; 44: 294–304
76. Obut F, Kasinath V, Abdi R. Post-bone marrow transplant thrombotic microangiopathy. Bone Marrow Transplant, 2016; 51: 891-897
77. Robson M, Côte I, Abbs I, et al. Thrombotic micro-angiopathy with sirolimus-based immunosuppression: potentiation of calcineurin inhibitor-induced endothelial damage? Am J Transplant, 2003; 3: 324–327
78. Garcia-Maldonado M, Kaufman CE, Comp PC. Decrease in endothelial celldependent protein C activation induced by thrombomodulin by treatment with cyclosporine. Transplantation, 1991; 51: 701–705
79. Brown Z, Neild GH. Cyclosporine inhibits prostacyclin production by cultured human endothelial cells. Transplant Proc, 1987; 19: 1178–1180
80. Renner B, Klawitter J, Goldberg R, et al. Cyclosporine induces endothelial cell release of complement-activating microparticles. J Am Soc Nephrol, 2013; 24: 1849–1862
81. Kim YO, Lim SW, Li C, et al. Activation of intrarenal complement system in mouse model for chronic cyclosporine nephrotoxicity. Yonsei Med J, 2007; 48: 517–525
82. Vercellotti GM, Moldow CF, Jacob HS. Complement, oxidants, and endothelial injury: how a bedside observation opened a door to vascular biology. J Clin Invest, 2012; 122: 3044–3045
83. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med, 2008; 358: 1129–1136
84. Takatsuka H, Wakae T, Mori A, et al. Effects of total body irradiation on the vascular endothelium. Clin Transplant, 2002; 16: 374–377
85. Changsirikulchai S, Myerson D, Guthrie KA, et al. Renal thrombotic microangiopathy after hematopoietic cell transplant: role of GVHD in pathogenesis. Clin J Am Soc Nephrol, 2009; 4: 345–353
86. Kim SS, Patel M, Yum K, Keyzner A. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. Transfusion, 2015; 55: 452–458
87. Mache CJ, Acham-Roschitz B, Frémeaux-Bacchi V, et al. Complement inhibitor eculizumab in atypical haemolytic uremic syndrome. Clin J Am Soc Nephrol, 2009; 4: 1312–1316

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Abstract. This article recounts the life of Col. Jan Edward Koelichen, MD, PhD (1871-1952), the first chief editor and for many years a member of the Editing Team of the "Lekarz Wojskowy" journal. He was born in Warsaw to a polonized, patriotic family of Dutch settlers. In 1899, Koelichen graduated as a physician from the Imperial University of Warsaw. As a student, he was repressed for his activity related to Poland's independence. He continued his education for two more years in renowned neurologic and psychiatric hospitals of Berlin, Heidelberg and Paris. He combined his clinical practice with scientific work and organizational activities in the Warsaw community of neurologists. During WW1, Koelichen served as a physician in a field hospital, and from 1918 in the Polish Armed Forces. Having been verified in the rank of a captain, he was appointed the head of the neurologic and psychiatric ward of the Ujazdowski Hospital in Warsaw. As the chief editor of the newly established "Lekarz Wojskowy" weekly (1920-1921), he efficiently implemented the policy of this journal, viz: "to provide military physicians with the entire state-of-the-art medical knowledge and to consolidate them into a single living entity". Having retired in 1929, Koelichen combined his medical practice with social activities in the Warsaw Neurologic Society and the editing board of the “Neurologia Polska" magazine. Mobilized in 1939, Koelichen was captured and kept as a POW by the Soviets in Dubno. After 1945, he became a nestor of Polish neurologists.
Keywords: Polish neurologists, "Lekarz Wojskowy" medical magazine. Ujazdowski Hospital

Streszczenie. Celem artykułu jest przypomnienie postaci płk. dr. med. Jana Edwarda Koelichena (1871-1952), pierwszego redaktora i długoletniego członka Komitetu Redakcyjnego „Lekarza Wojskowego". Urodził się w Warszawie, w spolonizowanej patriotycznej rodzinie osadników holenderskich. Dyplom lekarza uzyskał w 1899 r. na Cesarskim Uniwersytecie Warszawskim. Represjonowany na studiach za działalność niepodległościową. Przez 2 lata kształcił się w renomowanych klinikach neurologicznych i psychiatrycznych Berlina, Heidelbergu i Paryża. Praktykę kliniczną łączył z pracą naukową i działalnością organizacyjną w środowisku neurologów warszawskich. W czasie I wojny światowej lekarz w lazarecie dla rannych. Od 1918 r. w Wojsku Polskim. Zweryfikowany w stopniu kapitana, ordynator oddziału neurologiczno-psychiatrycznego Szpitala Ujazdowskiego. Jako redaktor (1920-1921) nowo utworzonego tygodnika „Lekarz Wojskowy" sprawnie realizował linię programową pisma: „dać lekarzom oddziałów wojskowych całokształt najnowszych postępów wiedzy lekarskiej i związać lekarzy wojskowych w jedną żywą całość". Po przejściu w 1929 r. w stan spoczynku praktykę lekarską łączył z działalnością społeczną w Warszawskim Towarzystwie Neurologicznym i redakcji „Neurologii Polskiej". Zmobilizowany w 1939 r., trafił do niewoli radzieckiej w Dubnie. Po 1945 r. nestor neurologów polskich.
Słowa kluczowe: „Lekarz Wojskowy", czasopismo medyczne. Szpital Ujazdowski, neurolodzy polscy

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On 3 January 1920, the first edition of *Military Physician* (*Lekarz Wojskowy*) was published. The weekly journal was devoted to military and general medicine. As the 100th anniversary of the magazine is approaching, we would like to present Col. Jan Koelichen MD, PhD, the co-founder, first editor, and long-term member of the Editorial Board [1]. This decision is also prompted by the 100th anniversary of the Department of Neurology and Psychiatry at the Ujazdowski Hospital, since Dr Koelichen was its founder and the first head of the department [2].

Jan Edward Koelichen was born on 14 October 1871 in Warsaw, as the son of Karol Koelichen, a descendant of Dutch settlers who came to Poland in the 18th century, and Helena Koelichen, née Krzyczewska [2, 3]. In 1892, he graduated from eight-form State Male Philological Secondary School No. 5 in Warsaw, where he participated in illegal "self-education courses", organised by organisations fighting for Polish independence. During his studies at the Medical Faculty of the Imperial University of Warsaw, he was arrested for political activity, and expelled as a "niebłogonadiożnyj" (dissident). Thanks to his family's efforts, he was allowed to return to school, and graduated in 1899 [5-7].

After leaving university, Dr Koelichen worked at the Internal Department of the Baby Jesus Hospital in Warsaw, whose head was Władysław Janowski, an internist and bacteriologist. Koelichen combined work at the hospital with scientific research at the private microscope laboratory of Edward Flatau, a 31-year-old, but already well-recognised neurologist. The laboratory was located at Herse's tenement house on Marszałkowska Street [6, 7].

In 1901, to complete his education, Koelichen went abroad, and attended the polyclinics of Hermann Oppenheim and Emanuel Mendel in Berlin, Emil Kraepelin's psychiatric clinic and W.H Erb's clinic, run by Johann Hoffmann in Heidelberg, Joseph J. Dejerine's in Salpêtrière, and Józef Babiński's in Pitie, in Paris [6, 7] After his return to Warsaw, in the years 1903-1906, he worked at Edward Flatau's Neurology Department in the Jewish Hospital in Czyste. In the years 1906-1914, Koelichen ran a clinic for patients with nervous disorders at the Evangelical Hospital at 10 Karmelicka St., and at the Karola and Maria Children's Hospital in Wola, in Warsaw. During the First World War, Koelichen worked at the Municipal Hospital for the injured, established in the barracks of the former imperial Cadet Corps (after 1918, the site of the Main Inspector of the Armed Forces, at present the Chancellery of the Prime Minister of Poland). He also conducted histopathological and experimental tests in the neurobiological laboratory of the Warsaw Scientific Society on Śniadeckich St., managed by Edward Flatau [5-7].


Rok I. Warszawa, d. 3 Stycznia 1920 r. № 1.

LEKARZ WOJSKOWY

TYGODNIK POŚWIĘCONY MEDYCYNIE WOJSKOWEJ i OGÓLNEJ

Redaktor: J. Koelichen. — *Komitet redakcyjny:* Z. Dmochowski, M. Eiger, L. Karwacki, Z. Radliński, S. Składkowski, Z. Sowiński, R. Sobański, Z. Szymanowski, L. Zembrzuski i E. Zebrowski.

Adres redakcji i administracji: *Warszawa, Szpital Ujazdowski, Wojskowa Rada Sanitarna.*

WARUNKI PRENUMERATY: (od 1 lipca 20 r.).

Dla lekarzy wojskowych z przesyłką . . rocznie 84 mk. półr. 42 mk. kwart. 21 mk.
Dla lekarzy cywilnych „ . . „ 126 „ „ 63 „ „ 31.50 „

Cena pojedyńczego numeru Mk. 4.

Figure 1. Masthead and footer of the Military Physician journal, 1920 No. 1
Rycina 1. Winieta i stopka redakcyjna „Lekarza Wojskowego" 1920 nr 1

On 13th December 1918, Dr Koelichen, 37 years old, an experienced neurologist with scientific achievements and a profitable medical practice, enlisted as a volunteer with the Polish Army.

He was verified as a captain doctor, and on the 30th December 1918 he was appointed senior head of the Department of Neuroses at the Ujazdowski Hospital. Koelichen gained the necessary military education during courses run by Col. Felicjan Sławoj Składkowski MD, at the Application School of the Medical Officers Corps. On 13th September 1919 he submitted a declaration that "he wished to remain in military service permanently as a professional military physician" [2, 3].

On 30 May – 2 June 1919, Capt. Jan Koelichen MD participated in the meetings of the Commission of the Medical Department of the Ministry of Military Affairs regarding the organisation of neurological and psychiatric service in the Polish Army [8]. Based on the regulations passed during the meeting, neurological and psychiatric departments (stations) were organised in the hospitals of General Headquarters of Military Districts (including the Headquarters of the Vilnius Fortified District) [9]. On 16th December 1920 such a department was also created at the Ujazdowski Hospital (Main Military Hospital). Doctor Jan Koelichen became the first head of the department and was promoted to Lieutenant Colonel, while the senior

head of the department, Maj. Jan Władysław Nelken MD, PhD became his deputy [2].

Together with the above work, Jan Koelichen co-edited *Military Physician*, a journal newly created by the Military Medical Board (MMB) (Fig. 1). As its editor, in the years 1920-1921, together with the Editorial Board selected from the members of the MMB, he was responsible for the choice of materials and the order of the presented articles. According to the journal's mission, the aim of *Military Physician* was to "provide the vast numbers of doctors working in military units, often in rural areas, without access to hospitals and subject literature (...) with a wide range of the most recent medical discoveries, (...) and to bind military physicians in one, live community, (...) so that they can perceive working for the army as a privilege" [10]. The list of articles published at that time in 32-page copies of *Military Physician* (initially every week, then in double and quadruple volumes) confirms that the editors followed these principles. The authors of original articles, apart from the members of the Editorial Committee, included leading figures in Polish medicine, such as (in alphabetical order): Tadeusz Bętkowski, Odo Bujwid, Zygmunt Bychowski, Edward Flatau, Antoni Gluziński, Samuel Goldflam, Adam Gruca, Wiktor Grzywo-Dąbrowski, Leon Karwacki, Władysław Melanowski, Jan Nelken, Zygmunt Radliński, Rafał Radziwiłłowicz, Jakub Rothfeld [Rostowski], Alfred Sokołowski, Bolesław Szarecki, Romuald Węgłowski, Luwik Rudolf Weigl and others [1]. Especially interesting, also for the modern reader, are the reports from the meetings of Scientific Medical Societies in military hospitals, both the regular ones and those created for the time of war. The reports contain presentations of unusual, or challenging from the diagnostic point of view, cases of diseases and combat injuries, as well as discussions – frequently argumentative – between professors and doctors working in military departments (units). Doctor Koelichen was among the most active organisers of these meetings at the Ujazdowski Hospital [11].

The contents of *Military Physician* in the years 1920-1921 also included abstracts of publications from other Polish and international journals, medical quotes, in memoriam, communications and notifications from the authorities. The following are of particular interest: the list of military physicians who die in 1920, and the associated order of the Commander in Chief, Marshall Józef Piłsudski "In praise of military physicians": "(...) The end of last year, and beginning of the second year of the war for our sacred rights and integrity of Polish borders, for which a tax of blood has been paid by the devoted officer corps, brought a deathly disease which did not spare the medical corps. (...) I trust and believe that this deadly toll will not weaken your loyalty and strength, but (...) will drive you to further work for the good of the Motherland, for which your effort and sacrifice is as important as those of the army fighting in trenches" [12].

In 1922, Jan Koelichen stood down from the position of editor of Military Physician, but he remained a member of the Editorial Committee until 1929. Without the editorial duties, he devoted all his energy to the organisation of a clinical neurological hospital (3rd Department of Neuroses) which was moved to the main building of the Ujazdowski Hospital on 16th March 1922 [5]. On 8th June 1922, Koelichen was promoted to colonel, and in October he was appointed as the scientific director of this department. In the previous location of the Department of Neurology and Psychiatry (former Psychiatric Isolation Ward) an independent psychiatric department was formed (2nd Department of Mental disorders), whose scientific director was Lieutenant Colonel Jana Nelken MD, PhD [2]. The above organisational changes were associated with the plans of the Ministry of Military Affairs to create a clinical base in the Ujazdowski Hospital (a School Hospital) for teaching army doctors. On 14th November 1922, the Military Medical School was officially opened, and its first commander was Col. Stefan Hubicki MD [13].

The Neurology Department, initially planned for 50 beds, thanks to Col. Koelichen's intervention was expanded to 70 beds, and properly equipped. Almost all military neurologists from the pre-war period worked or trained there, e.g. Tadeusz Gepner, Władysław Zienkiewicz, Czesław Bogusławski, Adam Szebesta, Mieczysław Naramowski and Stefan Bogusławski, many civilian doctors, and cadets from the Medical School for Cadets [5]. To adjust to these changes, on 25th October 1924, Col. Koelichen had his doctor's qualifications from 1899 recognised at the University of Warsaw, and he received the title of doctor of medicine (*doctor medicinae universae*). In 1924, together with Dr Stefan Pieńkowski, he edited the Polish translation of Robert Bing's classical textbook on the diagnostics and location of brain and brain stem injuries; on 25th January 1925, he received an expression of gratitude from the Minister of Military Affairs, Gen. Władysław Sikorski [2, 14]. Dr Jan Koelichen's supervisors, including Col. Stefan Rudzki MD, and Generals Ignacy Zieliński, Wojciech Rogalski and Stefan Hubicki, in their annual updates to classification reports provided uniform evaluations of his work and personality: "His character is exceptionally good, flawless, and honest. A man of unique intelligence and management skills, with a creative mind, and outstanding scientific and didactic achievements. He demonstrates extraordinary conscientiousness and devotion in his work for the benefit of soldiers". In 1928, "for the scientific and medical achievements, in particular for the dedication to work in the Polish Army", Col.

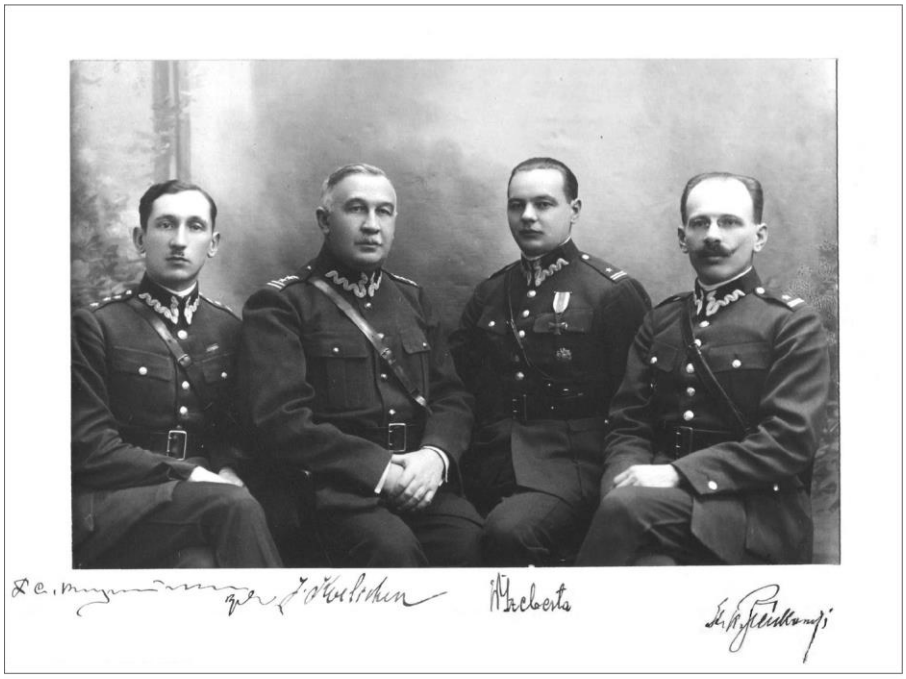

Figure 2. Col Jan Edward Koelichen, MD, PhD among collaborators of the Neurology Ward of the Ujazdowski Hospital, 1928 [17]
Rycina 2. Col. Jan Edward Koelichen wśród współpracowników Oddziału Neurologicznego Szpitala Ujazdowskiego 1928 r. [17]

Figure 3. Koelichen Family Palace in Włochy near Warsaw, post 1945, Public Library, condition as of 1958 [20]
Rycina 3. Pałac Koelichenów we Włochach, po 1945 r. biblioteka publiczna, stan 1958 r. [20]

Koelichen received the Order of Polonia Resituta Fifth Class [2].

On 1 January 1929, having reached the age limit, Col. Dr Jan Koelichen MD retired. "To honour and acknowledge the first editor and co-founder of the journal", the editorial team of *Military Physician* dedicated a special neurological edition to Dr Koelichen. It contained a eulogy written by Maj. Stefan Pieńkowski MD, the new head of the Neurology Department, and a chronological list of 94 scientific publications of Dr Koelichen, as well as articles by his excellent co-workers, e.g. Edward Flatau, Maurycy Bornsztajn and Wincenty Chodźko [15].

After his retirement from military service, Dr Jan Koelichen worked as a head of the Neurology Department at the Evangelical Hospital at 10 Karmelicka St., and ran a private practice. He also continued his work at the Neurological Society in Warsaw, which he had co-founded and also chaired briefly, in 1923. He co-operated with "Polish Neurology", a journal in which he was a member of the editorial team since 1914, and the editor in 1924 [6, 16]. In 1939, right before the Second World War, Koelichen was called up to the Polish Army,

Figure 4. Tomb of Col. Jan Edward Koelichen, MD, PhD at the Augsburg Lutheran Cemetery in Warsaw (source: Wikipedia)

Rycina 4. Grób płk. dr. med. Jana Edwarda Koelichena na Cmentarzu Ewangelicko-Augsburskim w Warszawie (źródło: Wikipedia)

and in September, in unclear circumstances, he became a prisoner of the Soviets in Dubno. Freed in October, Koelichen returned to Warsaw [3].

It is worth mentioning his co-workers from the Neurology Department, presented at the "farewell" photograph from March 1928 (Fig. 2).

Maj. Stefan Kazimierz Pieńkowski MD, PhD, received *veniam legendi* in neurology and psychiatry at the University of Warsaw, left the army, and on 4th February 1932 became a professor of the Department of Neurology and Psychiatry at the Jagiellonian University in Krakow. Called up to the army in 1939, he was taken prisoner by the Soviets, and was murdered by the NKWD in Katyń in 1940 [18].

Maj. Czesław Bogusławski MD moved to the military reserve together with Dr Koelichen, and became his assistant in the Evangelical Hospital. In 1944, he died during the Warsaw Uprising [6].

Maj. Adam Szebesta MD remained in active military service; his work as a commander and organiser of medical service during the September campaign in 1939 was admirable. In April 1943 he was a member of the Polish Red Cross delegation during the exhumation of graves in Katyń, and identification of the evidence found with the bodies. One of the deceased was Professor Stefan Pieńkowski [19].

After his return from a Soviet prison, and eviction from his flat at 2 Frascati St. by the German occupation authorities, Dr Jan Koelichen and his wife Maria (they had no children) moved to the Koelichen family palace in Włochy near Warsaw. Before the war, the palace featured not only a living area, but was also the site of the Friends of Włochy Society, the Evangelical Youth Association, and the local library. At the beginning of the war, for a few months it was turned into a hospital for the injured, run by Dr Aleksaner Stefan Śnigurowicz (after the war he was promoted to colonel, and became the head of healthcare at the Healthcare Department of the Polish Army). During the occupation it became home to many members of the Koelichen family who had lost their residences. After 1945, the palace was nationalised, and it is now a Public Library (Fig. 3) [4, 20].

After the war Dr Koelichen became one of the oldest and respected members of the Polish neurological community. He was professionally active his whole life. He worked as a consultant at the St. Elizabeth Hospital on Goszczyńskiego St., and was a member of the Disability Evaluation Board at the Social Insurance Institution. Short before his death he wrote a monograph "Diseases of the peripheral nerves" included in a neurology textbook [20].

Dr Koelichen died on 26th October 1952 in Warsaw. He was buried in his family grave at the Augsburg Lutheran Cemetery at Młynarska Street. (Fig. 4). [22, 23].

Eufemiusz Herman, a historian specialising in Polish neurology, said: "Dr Jan Koelichen combined extensive knowledge and experience with positive character traits and exceptional charm, which gained him popularity among patients and peers" [24].

Literature

1. Augustynowicz D. 90 lat „Lekarza Wojskowego" – jak zaczynaliśmy. [90 years of *Military Physician* – our beginnings] Lek Wojsk, 2011; 89 (1): 20–25
2. Centralne Archiwum Wojskowe. Akta personalne, sygn. akt Ap 822 [Central Military Archive. Personal documentation, signature Ap 822]

3. Centralne Archiwum Wojskowe. Akta personalne, sygn. akt Ap 822 [Central Military Archive. Personal documentation, signature TAP 37/52/114]
4. Koelichenowie. Stare – nowe – moje Włochy. [The Koelichens. Old - new - my Włochy] www.wlochy-pod-warszawa. pl/? koelichenowie,54; www.wlochy-pod-warszawa.pl/?koelichenowie,60
5. Pieńkowski SK. Jan Koelichen. Lek Wojsk, 1929; 14 (1/4): 3–13
6. Herman E. Neurolodzy polscy. [Polish neurologists] Państwowy Zakład Wydawnictw Lekarskich publishing house, Warsaw 1958: 51, 53, 302–306
7. Zakrzewski T. Koelichen Jan Edward. Pol Słow Biogr, 1968; 13: 252–253
8. Ilnicki S, Markowski W. Historyczne uchwały w sprawie organizacji służby neurologiczno-psychiatrycznej w Wojsku Polskim. [Historic acts on the organisation of neurological and psychiatric service in the Polish Army] Lek Wojsk, 1994; 70 (3–4): 212–218
9. Rudzki SP. Tymczasowa organizacja Wojsk i zakładów sanitarnych oraz Służby Zdrowia w broniach i służbach. M. S, Wojsk. Oddz. I szt. Nr. 3900/ org. z d. 20.VI. 1920 r. W: Zarys historii szpitalnictwa wojskowego w Polsce. [Temporary organisation of the forces, and Healthcare in military service. Ministry of Military Affairs, Department I, No. 3900/ org. from 20th April 1920. In: Short history of military hospitals in Poland] Główna Księgarnia Wojskowa publishing house, Warsaw 1927: 99
10. Dmochowski Z. Wstęp [Introduction]. Lek Wojsk, 1920; 1 (1): 1–3
11. Military Physician, 1920–1921
12. Piłsudski J. Odezwa do lekarzy WP. Rozkaz oficerski Nr. 2. № 3212/San. Pochwała lekarzy wojskowych [Address to physicians in the Polish Army. Officer's order no. 2. № 3212/San. In praise of military physicians] Lek Wojsk, 1920; 1 (12): 23
13. Felchner A. Pod znakiem Eskulapa i Marsa. Służba zdrowia Wojska Polskiego (od jesieni 1918 r. do mobilizacji w 1939 r.). [Under Aesculapius and Mars. The healthcare in the Polish Army (from autumn 1918 until the mobilisation of 1939)] Napoleon V publishing house, Oświęcim 2016: 179
14. Bing R. Zarys nauki o rozpoznawaniu umiejscowienia zmian w mózgu i rdzeniu kręgowym. Przekład z j. angielskiego Telatycki M. S. Red. Koelichen J.E. i Pieńkowski S. K. [Outline of the science of identifying the location of lesions in the brain and spinal cord. Translated from English by Telatycki M. S. Ed. Koelichen J.E. and Pieńkowski S. K.] Główna Księgarnia Wojskowa, Warsaw 1924
15. Lekarz Wojskowy, 1929; 14 (1–4)
16. Zakład Zbiorów Specjalnych GBL. Akta Warszawsko-Białostockiej Izby Lekarskiej sygn. PL\327\1\0\2533 [Institute of Special Archives, Main Medical Library. Documents of the Medical chamber of Warsaw and Białystok, signature PL\327\1\0\2533]
17. Persa J, Marek A, Wichrowski M. Warszawska uczelnia medyczna w ikonografii i fotografii. [Medical University in Warsaw in iconography and photography] Medical University of Warsaw, Warsaw 2009: 119. www.wum.edu.pl/files/uczelnia/wum_w_ikonografii_i_fotografii_pl.pdf
18. Ilnicki S, Ilnicki P. Obozowy pamiętnik mjr. rez. prof. dr. med. Stefana Pieńkowskiego znaleziony w Katyniu. [Camp diary o Reserve Maj. Prof. Stefan Pieńkowski MD, PHD found in Katyń] Lek Wojsk, 1999; 75 (5–6): 349–357
19. Brożek K. Ppłk doktor wszech nauk medycznych Adam Szebesta w 100-lecie urodzin. [Lieut. Col. Adam Szebesta MD on his 100th anniversary] Lek Wojsk, 1995; 71 (7–8): 490–494
20. Gawkowski R. Dawno, dawno temu… Kultura i sport w Dzielnicy Włochy. [Long time ago... Culture and sports in Włochy District]. www.ud-wlochy.waw.pl/data/dataPublicator/folder_kultura-sport_ 2017www.pdf
21. Koelichen J. Choroby nerwów obwodowych. W: Jakimowicz W, ed. Choroby układu nerwowego: podręcznik dla lekarzy. T. 2. [Diseases of the peripheral nerves. In: Jakimowicz W, ed. Diseases of the nervous system: textbook for physicians. Vol. 2] Państwowy Zakład Wydawnictw Lekarskich publishing house, Warsaw 1951
22. Szulc E. Cmentarz Ewangelicko-Augsburski w Warszawie: zmarli i ich rodziny. [Augsburg Lutheran Cemetery in Warsaw: the deceased and their families] Państwowy Instytut Wydawniczy publishing house, Warsaw 1989: 281
23. Jan Koelichen. www.pl.wikipedia.org/wiki/Jan_Koelichen
24. Herman E. Dr med. Jan Koelichen. Wspomnienie pośmiertne. [Dr Jan Koelichen MD. In memoriam] Neurol Neuroch Psychiatr Pol, 1953; 3 (2): 209-210

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