MILITARY PHYSICIAN

Military Physician

Quarterly

Official Organ of the Section of Military Physicians at the Polish Medical Society

Oficjalny Organ Sekcji Lekarzy Wojskowych Polskiego Towarzystwa Lekarskiego

Scientific Journal of the Military Institute of Medicine

Pismo Naukowe Wojskowego Instytutu Medycznego

Published since 3 January 1920

Number of points assigned by the Polish Ministry of Science and Higher Education (MNiSW) – 6

Indeks Copernicus 2017

ICV: 55.96

Editorial Office
The Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw 44
phone/fax: +48 261 817 380
e-mail: lekarzwojskowy@wim.mil.pl
www.lekarzwojskowy.pl

Practical Medicine Publishing House / Medycyna Praktyczna
2 Rejtana St., 30-510 Kraków
phone: +48 12 29 34 020, fax: +48 12 29 34 030
e-mail: listy@mp.pl

Managing Editor
Lidia Miczyńska

Proofreading
Dariusz Rywczak, Iwona Żurek

Cover Design
Krzysztof Gontarski

Typesetting
Łukasz Łukasiewicz

DTP
Katarzyna Opiela

Advertising
Piotr Lorens, MD
phone +48 663 430 191; e-mail: piotr.lorens@mp.pl

Print
TECHNET, Kraków

Circulation: 700 copies

For many years, "Military Physician" has been indexed in the Polish Medical Bibliography (Polska Bibliografia Lekarska), the oldest Polish bibliography database.

The original version of "Military Physician" is the electronic version (www.lekarzwojskowy.pl)

The journal is financed by the Military Medical Chamber

Translation, proofreading and DTP of the English version by Skrivanek Sp. z o.o.

GUIDELINES FOR MANUSCRIPT SUBMISSION

Background

"Military Physician" has been published continuously since 1920, currently as a quarterly of the Military Institute of Medicine in Warsaw, Poland.

1. "Military Physician" publishes original (experimental and clinical) articles, reviews, reports on military issues, deontological papers, interesting case reports, articles on the history of medicine, descriptions of rationalisation results, posthumous memoirs, letters to the editor, book reviews, article (reviews) summaries from international journals particularly on military health service, reports on meetings and scientific conferences, and announcements of events.

2. Before publication, each article is reviewed by two independent reviewers while maintaining anonymity.

3. "Military Physician" is indexed in the Polish Ministry of Science and Higher Education, number of points – 6.

4. With respect to the fact that unsolicited articles submitted to our Editorial Board are royalty-free, manuscript submission with a request for publishing will be understood as implied consent of the Author(s) not to receive any royalty and to transfer copyright to the Military Institute of Medicine.

5. A clinical article for submission should comply with the requirements of the Declaration of Helsinki. The chapter "Material and methods" should contain both the information on the approval of the Bioethical Committee and patients' informed consent to participate in a study. In the case of using results of studies conducted by other centres, such information should appear either in the text or in the acknowledgements.

6. Authors of clinical studies on medications (international name) and medical procedures should provide a description of research funding and the influence of the sponsor on the content of the publication.

7. The Author must provide the Editorial Board with the consent of the image owner to use the image in an article.

8. Please submit your article to: Editorial Board of "Military Physician", 128 Szaserów St., 04-141 Warsaw 44, Poland, or by e-mail: lekarzwojskowy@wim.mil.pl.

9. All Authors who wish to publish their papers in "Military Physician" are asked to carefully read and strictly follow the guidelines listed below. Failure to follow the requirements of the Editorial Board makes editing more difficult, increases costs and delays publication. Manuscripts not meeting the requirements will not be published, and those considered inadequately prepared will be returned to the Authors for revision.

Manuscript

1. Articles should be in MS Word and sent by e-mail.

2. The number of pages of the manuscript (including tables, figures and references) cannot exceed 30 pages for original articles, 30 for review articles, 20 for reports, 30 for articles on the history of medicine and 15 for rationalisation articles. Reports on meetings and conferences should be concise (up to 5 pages) and discuss only significant issues.

3. An original publication may also have the form of a short temporary report.

4. Materials for printing

1) Text (with references, tables and figure captions) should be uploaded as a separate file. One page of the manuscript should contain 30 lines, about 60 characters each (must be about 1,800 characters). The text must be written in Times New Roman 12 point font and double spaced (this also applies to references, tables, captions, etc.), with 2.5 cm left margin, and no right margin, i.e. with the 'flag'. Authors are asked not to format the titles, i.e. not to centre or justify them, as well as not to use the tabulator or automatic numbering (both within the text and references). A new paragraph should start from the left margin without paragraph indentation. Please do not insert blank lines between paragraphs or enumerations. From typefaces, bold (semi-bold) and italics for foreign phrases may be used.

2) Please do not insert any graphics into the Word manuscript. Figures and tables should be referenced in the body of the text as follows: "in Figure 1", "(Table 1)". The number of tables should be reduced to a minimum. Each table should be provided with captions in Polish and English in bold in the first row. Figures (including maps) and images should be saved in a separate file. Digital images should have a resolution of 300 dpi and be saved in TIFF format. Good quality traditional images should be delivered on photographic paper. The reverse side of each image delivered on paper should contain the author's last name, the title of the contribution, a consecutive number and a marking indicating the top of the image.

5. Papers should be prepared carefully, in accordance with Polish spelling and with special attention to communicativeness and Polish medical nomenclature. Abstracts, keywords and figure captions translated into English should be identical with the Polish version and show an appropriate language level. Manuscripts that do not meet the criteria will be sent back to the authors for revision.

6. Each article should include the following:

1) On the first page: main title in Polish and English, Author's or Authors' (max. 10 people) first and last names, including academic degrees, full name of the affiliated institute (institutes), head of the institute (academic degree, first and last name), below an abstract (up to 15 lines) with keywords in Polish and another abstract with keywords in English, corresponding author, his/her postal address with postal code, phone (fax) and e-mail address.

2) Main text

Original articles should be prepared according to the following structure: introduction, aim, material and methods, results, discussion, conclusions, references; case reports: introduction, case description, discussion, summary (conclusions), and references.

Abbreviations and acronyms should be defined when first mentioned in the text and consequently used in the paper.

3) References should be presented according to the order they appear in the text. If the article has no more than four authors, all of them should be named, if there are more – a maximum of the first three, followed by "et al.". References should be numbered using the keyboard, please do not use automatic numbering. Examples of citations:

Journal articles:

Calpin C, Macarthur C, Stephens D, et al. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol, 1997; 100: 452-457

Books:

Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji [Drug allergy: including anaphylactic reactions and idiosyncrasy]. Lublin, Wydawnictwo Czelej, 2002: 338-340

Chapter of a book:

Wantz GE. Groin hernia. In: Cameron JJ, ed. Current surgical therapy. St Louis, Mosby, 1998:557-561

The list of references should include only those publications that were used by the Author and should be reduced to 20. All references should be cited in the text and the numbers of references should be put in square brackets. In order to avoid errors, titles should be copied from medical databases.

7. The paper should be accompanied by: a) author's request to publish the paper with a declaration that the article has not been published before and not simultaneously submitted to any other journal b) approval of the head of the clinic, head of the department or head of the institute in which the research has been conducted, and in case of a study carried out in several centres – approval of all of them, c) Declaration of Conflict of Interest, d) acknowledgements, if applicable.

8. The Editorial Board reserves the right to correct nomenclature and stylistic errors as well as to introduce abbreviations without consultation with the Author.

9. The Author receives one free copy of the issue in which his or her article has been published. For further copies, contact the Editor.

10. If the manuscript is not accepted for publication, the Editorial Board will return the submitted article to the Author.

CONTENTS

2019, vol. 97, no 3

ORIGINAL ARTICLES

CONTENTS

CASE REPORTS

REVIEW ARTICLES

HISTORY OF MEDICINE AND MILITARY HEALTH CARE

SPIS TREŚCI

2019, tom 97, nr 3

PRACE ORYGINALNE

PRACE KAZUISTYCZNE

PRACE POGLĄDOWE

HISTORIA MEDYCYNY I WOJSKOWEJ SŁUŻY ZDROWIA

Analysis of environmental risk factors and health problems in PMC Kosovo personnel

Analiza zagrożeń środowiskowych oraz problemów zdrowotnych personelu PKW Kosovo

Robert Gregulski[1], Krzysztof Korzeniewski[2]

[1] Head of Medical and Operating Ward of Operational Command of Armed Forces in Warsaw
[2] Head of Epidemiology and Tropical Medicine Department of the Military Institute of Medicine in Warsaw

Abstract. Aim. The article presents the characteristics of environmental risk factors and health problems in the personnel of the Polish Military Contingent (PMC) on the KFOR deployment in Kosovo. Material and methods. The retrospective analysis was based on the GIDEON epidemiology database and medical records of soldiers and employees of the Polish Ministry of National Defense who had been performing mandated tasks during four, 6-month rotations of the contingents (n=250) in 2017 and 2018. Results. The morbidity intensity indexes of the PMC Kosovo were 39-49 cases/100 patients/month. The most common health problems included upper respiratory tract infections, musculoskeletal injuries/diseases and dermatoses. Conclusions. Health problems occurring in the PMC personnel were connected with the effects of environmental conditions and the failure to follow the rules on health prophylaxis.
Keywords: health problems, Kosovo, Polish Military Contingent

Streszczenie. Cel. W pracy przedstawiono charakterystykę zagrożeń środowiskowych oraz problemów zdrowotnych personelu Polskiego Kontyngentu Wojskowego (PKW) biorącego udział w operacji KFOR w Kosowie. Materiał i metody. Analiza retrospektywna została oparta na epidemiologicznej bazie danych GIDEON oraz dokumentacji medycznej żołnierzy i pracowników resortu obrony narodowej wykonujących zadania mandatowe w czterech 6-miesięcznych zmianach rotacyjnych kontyngentów (n=250) wiatach 2017-2018. Wyniki. Wskaźniki natężenia zachorowań personelu PKW Kosowo wynosiły 39-49 przypadków/100 pacjentów/miesiąc. Do najczęściej zgłaszanych problemów zdrowotnych należały stany zapalne górnych dróg oddechowych, urazy i choroby narządu ruchu oraz zmiany skórne. Wnioski. Zachorowania personelu PKW były związane z działaniem czynników środowiskowych oraz nieprzestrzeganiem zasad profilaktyki zdrowotnej.
Słowa kluczowe: Kosowo, Polski Kontyngent Wojskowy, problemy zdrowotne

Delivered: 12/02/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 193-199

Corresponding author
Col. Prof. Krzysztof Korzeniewski, MD, PhD
Epidemiology and Tropical Medicine Department of the Military Institute of Medicine
4 Grudzińskiego St., 81-103 Gdynia
Phone: +48 261 266 523
e-mail: kkorzeniewski@wim.mil.pl

Introduction

Polish Military Contingent (PMC) was formed by a decision of the President of the Republic of Poland upon the request of the Polish Prime Minister (under the Act on the principles of the use or stay of Polish armed forces outside the country) as part of the international Kosovo Force (KFOR) in the Republic of Kosovo, the former Yugoslav Republic of Macedonia, and in Bosnia and Herzegovina. The majority of KFOR PMC, i.e. approximately 250 soldiers and military employees, are located in Kosovo, where they have been performing mandatory tasks since 1999. Numerous organisational modifications were introduced in that period, and the current 39th rotation is stationed in the following bases: Novo Selo, Film City [the main KFOR headquarters in Prishtina], Bondsteel, Nothing Hill, Prizren and in Brezovica. KFOR is active mainly in the northern areas of Kosovo (Mitrovica, Leposavic, Zubin Potok, Zvecan), on the border with Serbia. As part of the Multinational Battle Group – East, PMC Kosovo performs stabilisation tasks, such as prevention of organised crime or smuggling, and supporting local authorities and security forces in the preservation of safety in the region [1].

The aim of the article is to present environmental hazards and health problems of the personnel of PMC Kosovo on the Balkan Peninsula.

Material and methods

The retrospective analysis was based on the GIDEON epidemiological database and medical records of the soldiers and employees of the Ministry of National Defence treated in the outpatient clinic of PMC Kosovo (Novo Selo military base south from the capital city, Prishtina) who were performing mandatory tasks during four 6-month rotations (n = 250) in the years 2017-2018.

The morbidity profile was assessed using the records documenting the visits to the clinic of the personnel treated in the analysed period. The calculations were based on the structure index and the intensity index per 100 patients. The main diagnoses of diseases and injuries were analysed according to the ICD-10 classification of diseases and health problems: diseases of the respiratory system, circulatory system, gastrointestinal system, musculoskeletal system, skin, nervous system, genitourinary system, eye and ear, mental and behavioural disorders, infectious and parasitic diseases, and injuries. Specific diagnoses were analysed following the same classification. The intensity index was calculated based on the number of initial visits due to certain disorders or injuries (including follow-up visits due to the same disease taking place within two weeks) used as a numerator, and the total number of patients in the analysed period (n = 250) as a denominator, multiplied by $C = 10^k$ (k = 0, 1, 2, 3...; in the statistical analysis k = 2 was used). This index was used to determine the incidence of disorders and injuries per 100 patients in a given population. The calculations were performed with STATISTICA PL software.

Environmental conditions of Kosovo

Kosovo (Figure 1), defined in the area of 10,908 km^2, is a landlocked country without access to the sea (Adriatic, the nearest sea, is approximately 130 km away), located in the centre of the Balkan Peninsula. It is bordered by Serbia (352 km), North Macedonia (159 km), Albania (112 km) and Montenegro (79 km). Its area is upland and mountainous, with the average heights of 300-600 m a.s.l., and mountain ranges of over 2000 m a.s.l. Kosovo is located in the subtropical climate zone. Average temperatures in the country's capital, Prishtina, are between 6°C in January to 26°C in July – August. Total annual precipitation is 1630 mm, primarily in the period from September to March and in May. The country has a lot of surface water. Its principal rivers include Sitnica (tributary of Ibar, Black Sea basin) and White Drin (Adriatic Sea basin). Approximately 30% of the area of Kosovo is covered by forests, especially in the mountains [2, 3].

Health threats in Kosovo

Food-borne diseases

Common conditions include diarrhoeal diseases caused by parasites (primarily giardiasis; based on the studies conducted in the Tropical Medicine Department of the Military Institute of Medicine, in southern Kosovo in a group of over 1,000 children 16.3% were diagnosed with intestinal parasitic infestation, and the dominant type was *Giardia intestinalis)* [4], bacteria (primarily salmonellosis) [5] or viruses (predominantly norovirus infections) [6]. The incidence of bacterial and viral infections increases in summer, whereas parasitic diseases occur the whole year round, mostly in the form of asymptomatic carriage. Gastrointestinal viral infections are common in most countries on the Balkan Peninsula (testing of samples from fresh water reservoirs and leafy vegetables performed in 2015 in Serbia demonstrated the presence of noroviruses in 50% and 5% of cases, respectively) [6].

Respiratory system diseases

The population of Kosovo is characterised by one of the highest rates of tuberculosis in Europe: 46 cases/100,000 citizens (to compare: 16 cases in Albania and 22 cases in Poland). Bacterial (pneumococci) and viral (flu virus) infections of the upper and lower respiratory tract are the leading diseases in children under five years of age [7-9].

Transmissible diseases

Crimean-Congo haemorrhagic fever (CCHF) is endemic to Kosovo. The disease is transmitted primarily by ticks (studies conducted in the population of ticks in Kosovo revealed that 3.6% of them were infected with CCHF virus). Endemic foci of CCHF cover 50% of Kosovo's area, especially in the central and south-western parts of the country, in the areas of meadows and pastures (using repellents and wearing appropriate clothing, i.e. covering arms and legs is absolutely required).

Seroprevalence of CCHF virus in Kosovars (due to contact with the infectious factor) is estimated at 24.3% of the population [10]. In the years 2013-2016, in the Department of Infectious Diseases of the University Hospital in Prishtina, 32 Kosovars were treated due to CCHF, and 11 patients died [11]. Another disease transmitted by ticks in Kosovo is tick-borne encephalitis. Studies by Potkonjak et al. demonstrated that the rate of the seropositive population of Kosovo that encountered tick-borne encephalitis virus (TBEV) is 37.8%, which demonstrates that infections with this virus occur in the population of Kosovars [12].

Figure 1. Physical map of Kosovo (source: Korzeniewski K. Health problems in participants of military operations and preventive medicine in modern operation theatre. Military Institute of Medicine, Warsaw 2011)

Rycina 1. Mapa fizyczna Kosowa (źródło: Korzeniewski K. Problemy zdrowotne uczestników operacji wojskowych oraz działania medycyny prewencyjnej na współczesnym teatrze działań. Wojskowy Instytut Medyczny, Warszawa 2011)

Zoonoses

Q fever is a disease endemic to Kosovo. The main source of infection is inhalation of dust contaminated with excretions and secretions of farmed animals (especially sheep, goats and cattle) left in pastures close to villages, towns and transportation routes. Infections are seasonal and occur in spring [13]. In April 2016, 32 soldiers with atypical pneumonia and diagnosed with Q fever infection were hospitalised in the KFOR hospital in the Prizren base. The highest rate of tularaemia in Europe was reported in Kosovo: 5.2 cases / 100,000 citizens (25-327 new cases per year on average). The primary sources of infections are contaminated water and food (in 50% of cases in Kosovo it is contaminated drinking water from wells). Infected ticks can also transmit the disease (studies revealed infection with the aetiological factor of the disease in 3.8% of ticks, similarly to Crimean-Congo haemorrhagic fever). In the first quarter of 2015, 206 cases of tularaemia were diagnosed in the population of Kosovo [14].

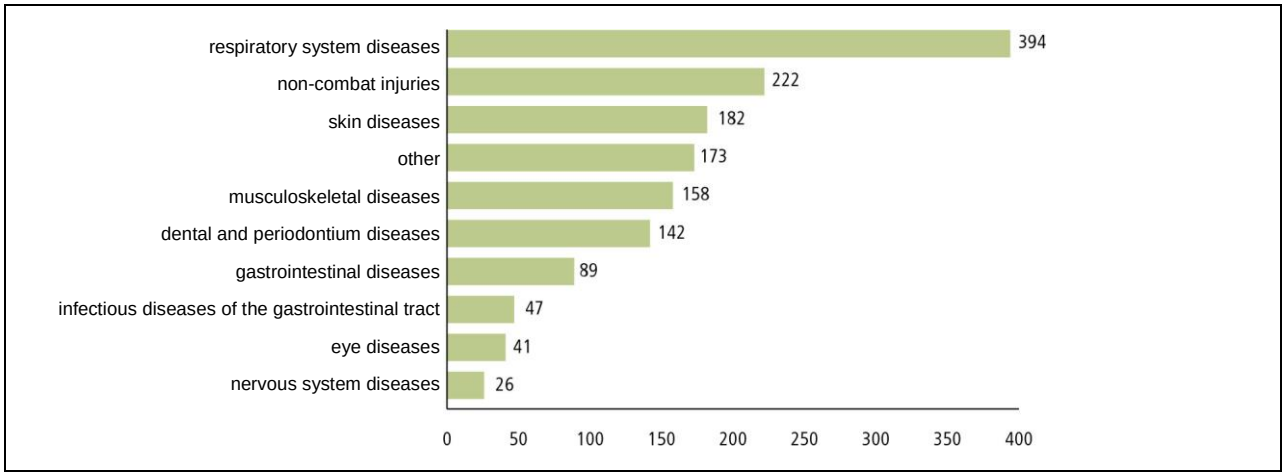


Figure 2. Morbidity in PMC Kosovo personnel in the period January-December 2017
Rycina 2. Zachorowalność personelu PKW Kosowo w okresie I-XII 2017 r.

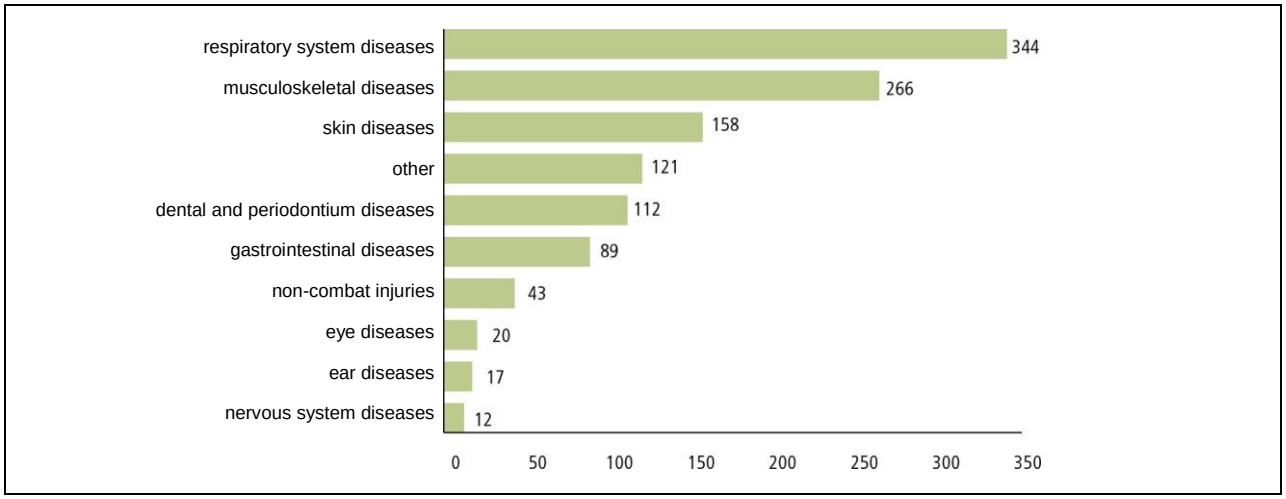


Figure 3. Morbidity in PMC Kosovo personnel in the period January-December 2018
Rycina 3. Zachorowalność personelu PKW Kosowo w okresie I-XII 2018 r.

Diseases transmitted by contact with contaminated water and soil

Soil and water tests revealed contamination with heavy metals. Soil in the Kosovska Mitrovica region is contaminated with arsenic, cadmium, copper, lead and zinc. Water in the Trepca and Sitnica rivers is contaminated with arsenic, cadmium, lead and zinc (the drinking of water other than bottled water is prohibited) [15].

Results

The diseases most frequently reported by the personnel of PMC Kosovo included: upper respiratory inflammations, injuries, musculoskeletal diseases and dermal lesions (Figure 2-3, Table 1-2).

The infection rate of the most common illnesses among the personnel of PMC Kosovo between January and December 2017 was 49 cases / 100 patients / month.

The most commonly reported health problems included:

- respiratory system diseases: 13 cases / 100 patients / month,
- non-combat injuries: 7 cases / 100 patients / month,
- skin diseases: 6 cases / 100 patients / month,
- musculoskeletal diseases: 5 cases / 100 patients / month.

Table 1. Morbidity in PMC Kosovo personnel in the period January-December 2017
Tabela 1. Zachorowalność personelu PKW Kosowo w okresie I-XII 2017 r.

Category	disease/month	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	total
A	respiratory system diseases	102	38	27	22	35	26	10	8	36	48	34	8	394
B	cardiovascular diseases	–	–	1	1	2	3	1	2	3	1	–	–	14
C	gastrointestinal diseases	6	12	4	9	11	6	3	19	4	6	5	4	89
D	dental and periodontium diseases	17	15	12	8	11	20	14	12	10	10	8	5	142
E	musculoskeletal diseases	11	10	9	29	5	8	5	–	14	18	13	36	158
F	skin diseases	17	13	7	17	15	30	17	9	15	18	13	11	182
G	nervous system diseases	2	2	5	3	9	–	1	2	1		–	–	26
H	genitourinary diseases	5	3	–	3	4	–	–	2	2	1	1	–	21
I	eye diseases	3	2	–	2	7	7	6	3	6	–	1	4	41
J	ear diseases	6	1	–	–	2	–	4	–	–	–	–	2	15
F	mental disorders	2	–	–	–	–	1	1	–	–	–	–	–	4
L 1	infectious diseases of the gastrointestinal tract	–	–	–	–	22	–	–	–	15	5	5	–	47
L 2	other infectious diseases	–	–	–	–	–	–	–	–	–		–	–	–
M 1	parasitic diseases of the gastrointestinal tract	–	–	–	8*	–	–	–	–	–	–	15*	–	23
M 2	other parasitic diseases	–	–	–	–	–	–	–	–	–		–	–	–
N	combat injuries	–	–	–	–	–	–	–	–	–		–	–	–
O	non-combat injuries	22	10	8	12	27	45	39	25	12	15	6	1	222
R	other diseases not classified above	–	–	–	–	8	20	14	26	21	1	6	–	96
	TOTAL	193	106	73	114	158	166	115	108	139	124	107	71	1474
R	other prophylactic measures, medical advice	79	44	26	32	54	94	46	118	30	45	18	32	618
S	vaccinations	7	28	27	3	67	–	4	1	7	81	46	19	290

* – intestinal parasitic infestations; studies conducted by the Military Institute of Medicine

The infection rate among the personnel of PMC Kosovo between January and December 2018 was 39 cases / 100 patients / month. The most commonly reported health problems were:

- respiratory system diseases: 11 cases / 100 patients / month,
- musculoskeletal diseases: 9 cases / 100 patients / month,
- skin diseases: 5 cases / 100 patients / month,
- dental and periodontium diseases: 4 cases / 100 patients / month.

Infectious and parasitic gastrointestinal diseases

In May and September 2017, numerous cases of acute gastroenteritis (diarrhoea, abdominal pain, vomiting) were found in soldiers of PMC Kosovo. Similar symptoms were observed in other KFOR contingents (mainly in the Hungarian contingent in the Novo Selo base). Diagnostic tests in the majority of cases demonstrated norovirus infections. They were most likely caused by contaminated food or water. Parasitological studies performed by the Military Institute of Medicine in PMC Kosovo personnel before the end of their service revealed an infestation with intestinal parasites, associated with chronic diarrhoea or asymptomatic carriage, probably caused by contaminated food and/or water.

Table 2. Morbidity in PMC Kosovo personnel in the period January-December 2018
Tabela 2. Zachorowalność personelu PKW Kosowo w okresie I-XII 2018 r.

Category	disease/month	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Total
A	respiratory system diseases	6	20	21	22	30	13	14	20	57	49	18	74	344
B	cardiovascular diseases	–	1	–	–	–	–	–	–	–	3	3	2	9
C	gastrointestinal diseases	2	4	1	15	5	6	7	17	10	10	5	7	89
D	dental and periodontium diseases	3	10	6	7	4	7	12	17	12	21	9	4	112
E	musculoskeletal diseases	18	16	21	22	21	7	22	29	11	44	31	24	266
F	skin diseases	5	9	6	21	10	9	22	17	10	15	10	24	158
G	nervous system diseases	–	–	–	–	5	2	–	2	1	1	1	–	12
H	genitourinary diseases	–	–	–	–	1	–	–	1	2	1	2	–	7
I	eye diseases	2	2	–	1	1	–	1	3	2	4	2	2	20
J	ear diseases	2	1	2	–	1	–	–	3	2	6	–	–	17
F	mental disorders	–	–	–	–	1	2	–	1	–	1	–	–	5
L 1	infectious diseases of the gastrointestinal tract	–	–	–	–	–	–	–	–	–	–	–	–	–
L 2	other infectious diseases	–	–	–	–	–	–	–	–	–	–	–	–	–
M 1	parasitic diseases of the gastrointestinal tract	–	–	–	–	8*	–	–	–	–	–	–	–	8*
M 2	other parasitic diseases	–	–	–	–	–	–	–	–	–	–	–	–	–
N	combat injuries	–	–	–	–	–	–	–	–	–	–	–	–	–
O	non-combat injuries	–	2	2	5	3	–	17	2	7	3	–	2	43
R	other diseases not classified above	–	–	28	23	11	17	4	4	–	1	–	4	92
	TOTAL	38	65	87	116	101	63	99	116	114	159	81	143	1182
R	other prophylactic measures, medical advice	52	64	53	45	27	7	15	2	7	30	34	13	349
S	vaccinations	19	31	156	33	53	23	152	243	79	83	634	307	1813

* – intestinal parasitic infestations; studies conducted by the Military Institute of Medicine

Dental and periodontium diseases

Dental and periodontium diseases are common in PMC Kosovo (mainly in the form of caries). In 2018, as many as 112 cases of dental treatment were reported in the region of this operation, which may indicate a superficial dental qualification of the candidates for foreign deployment by military medical committees.

Immunoprophylaxis

The level of preventive vaccinations of the personnel deployed abroad is low. As many as 70% of the PMC Kosovo personnel do not receive vaccinations according to the schedule. The vaccination cycles are not completed and repeated, which results in multiple immunisations against various infectious diseases. There is a legitimate concern that soldiers who were vaccinated before and during deployment do not receive re-vaccinations after their return to Poland, and the process of immunoprophylaxis is restarted during their preparation for another military operation abroad. The Central Vaccination Register for professional soldiers conducted by the Epidemiological Response Centre of the Polish Armed Forces in Warsaw contains incomplete information about the vaccinations performed in the Polish Army, which limits its analytical value. In 2018, during two rotations of the PMC in Kosovo, the personnel received 1813 vaccinations, which amounts to an average of 3-4 vaccinations performed abroad in every participant of the military operation.

Conclusions

Morbidity in the PMC Kosovo personnel is associated primarily with environmental factors and ignoring the principles of health prophylaxis. The greatest epidemiological risks in the international Kosovo force include: Crimean-Congo haemorrhagic fever in the spring and summer period (transmitted by ticks), Q fever in the spring months (air-borne, less frequently transmitted by food or ticks), year-round tularaemia (transmitted by contaminated water or food), year-round contamination of water and soil with heavy metals, gastrointestinal norovirus infections in the spring and summer period, and year-round intestinal parasitic infestations.

References

1. Dowództwo Operacyjne Rodzajów Sił Zbrojnych. PKW Kosowo. [Personnel of the Polish Military Contingent in Kosovo] www.do.wp.mil.pl/info/pkw-kosowo/ (accessed on: 09/02/2019)
2. Encyklopedia PWN. Kosowo. Warunki naturalne. www.encyklopedia.pwn.pl/haslo/Kosowo-Warunki-naturalne;4958586.html [PWN Encyclopaedia. Kosovo. Natural environmental conditions] (accessed on: 09/02/2019)
3. Wikipedia. Geografia Kosowa. [Geography of Kosovo] www.pl.wikipedia.org/wiki/Geografia_Kosowa (accessed on: 09/02/2019)
4. Korzeniewski K. Analiza porównawcza nowoczesnych metod biologii molekularnej (LAMP, Real-time PCR) oraz mikroskopii świetlnej w detekcji pierwotniaków i helmintów w materiale biologicznym populacji Kosowarów (Bałkany. Projekt badawczy MNiSW. [Comparative analysis of the advanced molecular biology methods (LAMP, Real-time PCR) and light microscopy in detection of protozoa and helminths in the biological material of Kosovars (Balkans. Research project of the Ministry of Science and Higher Education)] Military Institute of Medicine, Warsaw 2018)
5. Hoxha-Kamberi T. Causes of infectious acute diarrhea in infants treated at pediatric clinic. Med Arch., 2013; 67 (1): 17-21
6. GIDEON. Gastroenteritis viral in Serbia and Montenegro. www.web.gideononline.com/web/epidemiology/index.php?disease=11620&country=G302&view=Distribution&travel=1 (accessed on: 09/02/2019)
7. Krasnigi S, Jakupi A, Daci A, et al. Tuberculosis Treatment Adherence of Patients in Kosovo. Tuberc Res Treat, 2017; 2017: 4 850324
8. Dreshaj S, Alija AJ, Schlagenhauf P, et al. Is there a relationship between genetic factors and the incidence and severity of H1N1 in Kosova? A preliminary investigation and pointers for further research. Travel Med Infect Dis, 2017; 18: 53-56
9. Erdem H, Inan A, Guven E, et al. The burden and epidemiology of community-acquired central nervous system infections: a multinational study. Eur J Clin Microbiol Infect Dis, 2017; 36 (9): 1595-1611
10. Krüger A. Crimean-Congo hemorrhagic fever virus clades V and VI (Europe 1 and 2) in ticks in Kosovo, 2012. PLoS Negl Trop Dis, 2014; 8 (9): e3168
11. Ahmeti S, Berisha L, Halili B, et a. Crimean-Congo Hemorrhagic Fever, Kosovo, 2013-2016. Emerg Infect Dis, 2019; 25 (2): 321-324
12. Potkonjak A, Petrovic T, Ristanovic E, et al. Molecular detection and serological evidence of tick-borne encephalitis virus in Serbia. Vector Borne Zoonotoc Dis, 2017; 17 (12): 813-820
13. Faas A, Engeler A, Zimmermann A, Zöller L. Outbreak of Query fever among Argentinian special police unit officers during a United Nations mission in Prizren, South Kosovo. Mil Med, 2007; 172 (10): 1103-1106
14. ProMED-mail. Tularemia - Kosovo. www.promedmail.org (accessed on: 12/02/2015)
15. Ferati F, Kerolli-Mustafa M, Kraja-Ylli A. Assessment of heavy metal contamination in water and sediments of Trepca and Sitnica rivers, Kosovo, using pollution indicators and multivariate cluster analysis. Environ Monit Assess, 2015; 187 (6): 338

Attitudes towards disease adopted by hematologic patients before and after stem cell transplantation

Postawy wobec choroby pacjentów hematologicznych leczonych przeszczepieniem komórek macierzystych przed nim i po jego wykonaniu

Wiesław Skrzyński[1], Katarzyna Białkowska[1], Piotr Rzepecki[1], Dorota Lazar-Sito[1], Ewa Jędrzejczak[2]

[1] Department of Internal Diseases and Haematology, Military Institute of Medicine in Warsaw; Head: Prof. Piotr Rzepecki, MD, PhD
[2] Office of the Deputy Director for Science, Military Institute of Medicine in Warsaw; Head: Katarzyna Adamska, MSc

Abstract. As all chronically ill patients, hematologic patients are subject to the destructive influence of the disease over time. Their personal resources are reaching their limits. How dynamic is the process, especially when it comes to assessing one's ability to cope with constraints, assessing relationships with relatives and self-esteem? The two studies presented here are an attempt to answer these questions – one on admission to the Marrow Transplantation Centre and another prior to leaving it, after stem cell transplantation. The studies included 31 patients examined with AIS (Acceptance of Illness Scale).
Key words: assessment of relationship with close relatives and friends, self-esteem, sense of helplessness, stem cell transplantation

Streszczenie. Pacjenci hematologiczni, podobnie jak wszyscy pacjenci przewlekle chorzy, w miarę upływu czasu podlegają destrukcyjnemu wpływowi choroby. Ich zasoby osobiste ulegają ograniczeniu. Jak dynamiczny jest to proces, zwłaszcza w zakresie oceny radzenia sobie ze swoimi ograniczeniami, oceny relacji z bliskimi oraz poczucia własnej wartości? Próbę odpowiedzi na te pytania stanowią dwa prezentowane badania: przy przyjęciu do Ośrodka Przeszczepiania Szpiku oraz przed jego opuszczeniem po przeszczepieniu komórek macierzystych. W tym celu 31 pacjentów przebadano za pomocą Skali AIS (Acceptance of Illness Scale).
Słowa kluczowe: przeszczepienie komórek macierzystych, poczucie bezradności, ocena relacji z najbliższym otoczeniem, poczucie własnej wartości

Delivered: 01/04/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 200-204

Corresponding author
Wiesław Skrzyński, PhD
Department of Internal Diseases and Haematology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 818 399
e-mail: wskrzynski@wim.mil.pl

Background

Adjustment to disease, especially a chronic one, requires a number of strategies to cope with the associated difficulties. The treatment should also consider different personalities of patients, as well as the short-term and long-term consequences of a particular disorder and the length of the disease. Results of many studies suggest that patients who used varied coping strategies and changed them over time achieved a better level of adjustment than passive patients or individuals who resorted to only one coping style [1]. Other studies led to opposite conclusions: for chronically ill patients, using one coping style is the most beneficial. It appears that, at least in certain circumstances, effective coping is conditional upon the compliance between the strategies applied and the patient's individual style, rather than adjusting them to the situation [2-4]. One may assume

that the personality traits associated with activity will propel the patient to deal with the problem and change the difficult situation, whereas features such as shyness, anxiety, inhibition and neurotism, characteristic for the emotion-oriented coping, will have the opposite effect. Another group of personality traits that facilitate reactive coping with problems includes high interpersonal skills and assertiveness. They result in openness in contacts with others and authenticity, supported by the belief in one's rights and high self-esteem. They help to deal with problems in socially challenging situations [5]. The effectiveness of the coping strategies used is largely conditioned by the following: scope, access to and repertoire of the strategies available to the subject, as well as specificity of the disease. According to the interactive concept of stress, the effects of coping are determined by the actions and characteristics of the subject, as well as by the stress-inducing situation itself.

Effective coping with a chronic disease does not necessarily entail recovery, but it contributes to the individual's optimal functioning in the somatic, mental, social and spiritual dimension. Chronically ill patients must deal with the awareness that for a long time they will be forced to live with the symptoms of their disease. Moreover, their condition might deteriorate. Initially, patients do not believe that they have been affected by a severe condition. Later, they rebel and experience a sense of injustice, as they cannot find the answer to the important question: "Why me?". At the same time, they often feel resentment that people around them and doctors cannot help them. Signs of concern, especially pity, frequently trigger anger and protests. On the other hand, inconvenience, ailments and limitations that patients are forced to suffer, including rigorous diets, all types of restrictions and therapeutic procedures, result in loneliness, regret and a sense of injustice [6]. Patients understand that due to physical symptoms and limitations they depend on the assistance of the people around them and doctors, but at the same time they want to be independent, and take control over their bodies and lives.

Contact with people who adjusted successfully to life with a chronic disease may be very beneficial for patients. In the case of long-term diseases the symptoms never disappear, but persist or even exacerbate with time. This affects adversely almost every aspect of the patients' life: the organism's function is reduced, the physical and mental condition deteriorates, especially in the emotional aspect (lower mood, irritability, aggression, anxiety, indifference, emotional lability), previous lifestyle changes (it is dictated by the disease: medication, medical appointments, procedures, changing intensity of the symptoms); often the physical appearance changes (exhaustion, alopecia, effects of surgical procedures and reduced activity), the patient's activity decreases (in the physical, professional and social area, as well as in self-care), the type and intensity of contacts with other people changes (patients may express despair, seek compassion, isolate themselves; sexual activity usually decreases or disappears), the hierarchy of values and life plans change, typically the meaning of life is questioned, self-image and self-esteem are affected. The disease is often strongly associated with shame due to its visible effects (different appearance and behaviours), which prompts patients to avoid contact with other people and withdraw from social life.

Chronic disease also causes a serious crisis in family life. The daily routine, previous plans, roles and tasks are usually affected, and many aspects need to be reorganised. However, first and foremost, the family must deal with anxiety, regret, sense of helplessness, often with chronic uncertainty and overload, inherently associated with long-term difficulties [7].

The situation varies depending on who the patient is. If this is a man who is in charge of the financial aspects of life, his disease affects the financial security and affluence of the family, or even deprives them completely of resources, forcing other family members to seek work. When the patient is a woman, typically the emotional and organisational side of family life is disturbed, e.g. preparation of meals or childcare. The disease of a child also has serious consequences, although it does not pose a direct threat to the upkeep of the family. The child requires attention and time of all family members, who are actively engaged in his or her recovery, often neglecting other people or their obligations. It usually affects the siblings, who receive less attention and assistance. This may make them feel less important and encourage conflicting feelings towards the sick brother or sister: compassion, anger or jealousy.

Research questions

1. To what degree do haematological patients feel affected by the daily restrictions resulting from a long-term disease before and after stem cell transplantation?
2. To what extent are patients aware that the disease significantly reduces their independence and limits their relationships with family and friends?
3. To what extent is the patient's self-esteem reduced by the disease and its consequences?
4. To what degree can a few weeks spent in the specific conditions of the Bone Marrow Transplantation Centre and the hope related to stem cell transplantation change the image of oneself or the disease?

Material and methods

The study involved 31 patients diagnosed with plasma cell myeloma (15), testicular neoplasm (5), non-Hodgkin lymphoma (3), mantle cell lymphoma (3), acute myeloid leukaemia (3) and lymphocytic leukaemia [2]. The average age of the study subjects was 51 years old, ranging from 20 to 72 years old. Three patients received allotransplantation, and the other 28 patients received autotransplantation. The tests were performed in the years 2018-2019, individually and at two time points: at the beginning and end of the treatment at the Bone Marrow Transplantation Centre of the Department of Haematology, Military Institute of Medicine, Warsaw. The survey lasted a few minutes.

The Acceptance of Illness Scale (AIS) questionnaire was used [8]. This questionnaire contains eight statements that describe the consequences of poor health status: acceptance of the limitations imposed by the disease, lack of independence and the resulting sense of dependence on others, and reduced self-esteem [9].

Previous Polish studies demonstrated that AIS results are good predictors of the quality of life determined by the disease and the current assessment of the health status [10]. Higher scores obtained in the test signify greater acceptance of one's situation, despite the disease, better adjustment to the new conditions, and smaller discomfort. Adaptation to the disease is of great significance in the case of chronic conditions, including haematological diseases. The acceptance of the disease is often necessary for collaboration between the patient and the medical personnel and for the development of satisfactory relationships with family and friends, as well as for the ability to accept their support [11, 12].

A full version of the AIS is presented in the annex, which will facilitate interpretation of the results.

It is also worth emphasising that apart from completing the survey, the patients were under psychological observation, and many of them received continuous support, which greatly enriched the material for analysis.

Results and discussion

Any disease, especially chronic and untreatable, generates in patients a sense of restriction in everyday functioning, following their life plans and dreams, and having relationships with people important to them. Moreover, two essential needs are also affected by the limitations: self-esteem and the need to be independent and effective. In haematological patients, the awareness of the disease burden is very high; it appears to be higher than in people with organ neoplasms. The connotation of the haematological disorder with a disease present in "the entire body" intensifies the sense of helplessness and threat. As a consequence, patients tend to limit their relationships with family and people important to them, as well as demonstrate increasing difficulties with accepting support.

In this context, the AIS results obtained by patients treated with stem cell transplantation are interesting (Table 1, Figure 1).

The results should be compared with those obtained by other groups of chronically ill patients [9].

Before stem cell transplantation, patients achieve the lowest score in item 4: "Due to health problems I depend on others more than I wish". After the transplantation, this score improves slightly. The patients might hope for greater independence.

They express a similarly strong belief that their disease causes uneasiness for their family both before and after the treatment.

Unfortunately, the patients' expectations as to the possibility to do "what they like doing best" remain unchanged. In this respect, their expectations are stable and unoptimistic. A positive change regarding self-esteem is observed in the feeling of "being needed" (item 3: increase by 0.57 on a 5-point scale). However, regarding self-esteem, such improvement is not found in the sense of being "a fully valuable person" (item 6: a change by only 0.05) and "being self-sufficient" (item 7).

The sense of being a burden to the family and friends also decreases slightly (item 5). The improvement is 0.22 on a 5-point scale.

The hope associated with transplantation of stem cells, the specificity of the current course of treatment, and connotations of the term "transplantation" result in limited improvement in the area of "being needed" (item 3 [Figure 1]). Similarly, a few weeks of isolation from family and friends reduced the feeling of being dependent on them (item 4 [Figure 1]). Further enhancement of these processes may certainly increase, along with the remission and return to independent life and everyday activities.

Table 1. AIS questionnaire results (mean) prior and after transplantation of hematopoietic stem cells at the Bone Marrow Transplantation Centre of the Military Institute of Medicine
Tabela 1. Wyniki średnie uzyskane przed przeszczepieniem krwiotwórczych komórek macierzystych i po ich przeszczepieniu w Ośrodku Przeszczepiania Szpiku WIM za pomocą Kwestionariusza AIS

AIS items	Attitudes towards the disease before the stem cell transplantation		Attitudes towards the disease after the stem cell transplantation		Differences between mean scores
	M	Rank	M	Rank	
1	3.78	2	3.92	4	0.14
2	3.70	4	3.72	8	0.02
3	3.59	6	4.16	1	0.57
4	3.41	8	3.80	6	0.39
5	3.78	2	4.00	3	0.22
6	4.07	1	4.12	2	0.05
7	3.67	5	3.92	4	0.25
8	3.52	7	3.76	7	0.24
General score	29.56		31.52		1.96

Conclusions

- Among many groups of chronically ill patients, haematological patients receiving stem cell transplantation obtain the highest mean scores both before the transplantation and at their discharge from the hospital. It is possible that the support from the personnel has beneficial effects.
- After a few weeks of treatment at the Bone Marrow Transplantation Centre, the acceptance of the present situation increases visibly, and the sense of helplessness is slightly reduced.
- All the changes demonstrated in the two studies presented above are minor, as they are observed in chronically ill patients. Long-term restriction of one's potential, increasing sense of helplessness and decreasing self-esteem are elements of a fixed process.

AIS scale

Please respond to each statement by marking a number that best describes your present condition, from 1 to 5. Circle the chosen number. Every answer is correct if it is true.

	I agree completely	1	2	3	4	5	I disagree completely
1. Adapting to the restrictions imposed by the disease is difficult for me.							
2. Due to my health status, I cannot do what I like most.							
3. Sometimes my disease makes me feel that nobody needs me.							
4. Due to health problems, I depend on others more than I wish.							
5. The disease makes me a burden to my family and friends.							
6. Due to my health condition, I do not feel like a fully valuable person.							
7. I will never be self-sufficient to the extent that would satisfy me.							
8. I think that people surrounding me often feel uneasy because of my disease.							

Figure 1. AIS questionnaire results
Rycina 1. Wyniki uzyskane w kwestionariuszu AIS

Table 2. Results obtained with the same scale in other groups of chronically ill patients
Tabela 2. Wyniki uzyskiwane w tej skali przez inne grupy pacjentów przewlekłe chorych

Group	N	M
Patients on dialysis	31	25.32
Males after myocardial infarction	42	22.14
Patients with multiple sclerosis	44	24.59
Patients with chronic pain	32	18.46
Females with breast cancer and uterine cancer	60	28.13

- The analysis of the same group of patients years after the completion of the treatment might offer interesting results. Will their sense of limitation due to the disease be significantly reduced, positively affecting their self-esteem? Possibly a high correlation might be demonstrated between remission and positive changes in the patients' self-image or their perception of the world.

References

1. Heszen-Niejodek I. Psychologiczne problemy chorych somatycznie. [Psychological problems of patients with somatic diseases] In: Strelau J, ed. Psychologia. Podręcznik akademicki. [Psychology. University textbook] Vol. 3 Gdańskie Wydawnictwo Psychologiczne, Gdańsk 2000: 513-531
2. Zautra AJ, Manne SL. Coping with rheumatoid arthritis. A review of a decade of research. Ann Behav Med, 1992; 14: 31-39
3. Heszen-Niejodek I. Teoria stresu psychologicznego i radzenia sobie. [Theory of psychological stress and coping strategies] In: Strelau J (red.), Psychologia. Podręcznik akademicki, t.3, s. 465-492 [Psychology. University textbook, vol. 3, pp. 465-492], Gdańsk, 2000, Gdańskie Wydawnictwo Psychologiczne
4. Newman S. Coping with chronic illness. In: Bennet P, Weinmen J, Spurgeon P, ed. Current developments in health psychology. Harwood, London 1990
5. Sęk H, Cieślak R, ed. Wsparcie społeczne, stres i zdrowie. [Social support, stress and health] PWN, Warsaw 2004
6. Skrzyński W. Nadzieja nie umiera. [Hope does not die] Medyk, Warsaw 2016
7. Mackenthun G. Geschichte der Psychosomatik. Berlin 2002 (in German)
8. Felton BJ, Revenson TA, Hinrichsen GA. Stress and coping in the explanation of psychological adjustment among chronically ill adults. Social Sci Med, 1984;6:151-168
9. Juczyński Z. Narzędzia pomiaru w promocji i psychologii zdrowia. [Measuring tools in health promotion and psychology] Pracownia Testów Psychologicznych PTP, Warsaw 2001
10. Juczyński Z, Adamiak G. Psychologiczne i behawioralne wyznaczniki jakości życia chorych ze stwardnieniem rozsianym. [Psychological and behavioural indicators of the quality of life in patients with multiple sclerosis] Polski Mer Lek, 2000; 8:413-415
11. Wright S, Kirby A. Deconstructing conceptualisations of "adjustment" to chronic illness. J Health Psychol, 1999; 4 (2): 115-127
12. Burish T, Lyles J. Coping with adverse effects of cancer disease. Academic Press, New York 1983

Assessment of storage time and type of red blood cell concentrate impact on the release of microparticles

Ocena wpływu czasu przechowywania i rodzaju koncentratu krwinek czerwonych na uwalnianie mikrocząsteczek

Małgorzata Dorman, Agnieszka Rzeszotarska, Anna Piotrowska, Jolanta Korsak

Department of Clinical Transfusiology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Prof. Jolanta Korsak, MD, PhD

Abstract. Introduction. Microparticles (RMP) released during storage may be a potential risk factor for post-transfusion reactions. This study evaluated the impact of the type of red blood cell concentrate and storage time on the release of RMP. Material and methods. The study involved 150 RBC units of different types, including RBC units with SAGM additive solution; RBC with no buffy coat and leukocyte-depleted RBC units. RMP were tested using flow cytometry by labelling the RMP with annexin V FITC and glycophorin A. Results. The study revealed that in the RBC with SAGM additive solution there was a significant increase in RMP between day 2 and 36 of storage (1.571 *vs* 26.418, p 0.0001). In the case of RBC with the buffy coat removed, a major increase was observed on day 2 and 20 of storage (p=0.031). In the leukocyte-depleted RBC, no differences were found. When comparing the concentration of RMP depending on the RBC type, it was found that in RBC with SAGM additive fluid, RMP concentration was significantly higher than in the leukocyte-depleted RBC (9.43 ±12.34 *vs* 5.37 ±13.28). Conclusion: The concentration of red blood cell microparticles depends on the method and type of RBC obtained. Long storage (>20 days) increases the release of RMP. The use of long-storage RBC should be personalised.
Keywords: red blood cell concentrates (RBC), red blood cell microparticles (RMP), storage time, types of red blood cell concentrate

Streszczenie. Wprowadzenie. Uwalniane w czasie przechowywania mikrocząsteczki (RMP) mogą być potencjalnym czynnikiem ryzyka reakcji poprzetoczeniowych. W pracy oceniono wpływ rodzaju RBC oraz czasu przechowywania na uwalnianie mikrocząsteczek. Materiał i metody. Badaniem objęto 150 jednostek KKCz różnego rodzaju: z roztworem wzbogacającym SAGM, pozbawionym kożuszka leukocytarno-płytkowego i ubogoleukocytarne. Badania stężenia mikrocząsteczek wykonywano z użyciem cytometrii przepływowej, znakując RMPs aneksyną V FITC oraz glikoforyną A. Wyniki. W badaniach stwierdzono, że w KKCz z płynem wzbogacającym SAGM wystąpił znamienny wzrost RMP między 2. a 36. dniem przechowywania (1,571 *vs* 26,418; p 0,0001). W KKCz pozbawionym kożuszka leukocytarno-płytkowego znaczny wzrost obserwowano w 2. i 20. dniu przechowywania (p =0,031).
W ubogoleukocytarnych KKCz nie wykazano różnic. Porównując stężenie RMPs w zależności od rodzaju KKCz, stwierdzono, że KKCz z płynem wzbogacającym stężenie RMPs jest znamiennie większe niż z ubogoleukocytarnym (9,43 ±12,34 *vs* 5,37 ±13,28). Wnioski. Stężenie RMPs zależy od metody i rodzaju otrzymywanego KKCz. Czas przechowywania >20 dni wpływa na zwiększenie uwalniania RMPs. Przetaczanie KKCz o długim czasie przechowywania powinno być leczeniem spersonalizowanym.
Słowa kluczowe: mikrocząsteczki pochodzenia czerwonokrwinkowego (RMPs), koncentraty krwinek czerwonych (KKCz), czas przechowywania, rodzaje koncentratu krwinek czerwonych

Delivered: 06/12/2018
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 205-212

Corresponding author
Prof. Jolanta Korsak, MD, PhD
Department of Clinical Transfusiology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 817 206
e-mail: jkorsak@wim.mil.pl

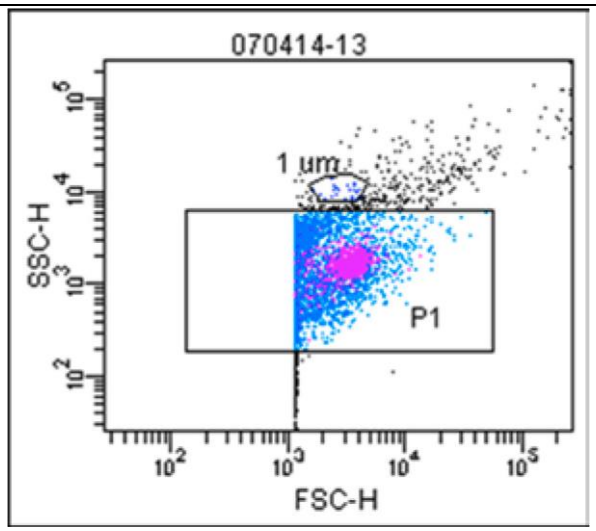
Introduction

Transfusion of red blood cell concentrate (RBC) is conducted to improve oxygen transportation in patients whose physiological compensation mechanisms are nearly or completely exhausted. Insufficient blood flow that cannot ensure proper tissue oxygenation results in physiological disorders and the death of cells. In such cases, transfusion of RBC is applied. However, when red cells are stored in a container at 2-6°C, their metabolic pathways are deregulated, and structural changes – the release of microparticles – occur in the cellular membrane. This questions the therapeutic effectiveness and safety of RBC transfusions, as the microparticles may participate in certain post-transfusion adverse reactions.

Red blood cell-derived microparticles (RMP) are membrane vesicles of <1 μm. They are released from the membrane of red blood cells with age, and probably participate in processes similar to apoptosis [1]. In the first tests on RMP, the time of storage and its effect on the concentration of microparticles were not determined, and their contribution to the pathogenesis of certain diseases and to post-transfusion reactions was not established. It was suggested that RMPs created during storage may demonstrate a pro-inflammatory potential, accelerate blood cell apoptosis and increase the incidence of post-transfusion reactions, including thrombosis, as well as contribute to the poor survival of patients following RBC transfusion [2, 3]. Therefore, the storage time and the consequences of certain changes occurring in concentrates during storage on the use of the blood component became issues to consider in clinical practice [2]. Despite the studies published on RMPs, there are few well-documented clinical trials available to adopt a clear criterion for the storage time and selection of the type of RBC for transfusion. Therefore, the aim of our study was to assess the effects of the procurement method and time of storage of RBC on the release of microparticles.

Material and methods

The analysis included 150 RBC units of 300 ml (±10%), collected from voluntary blood donors, in compliance with the principles governing the Polish Blood Service, and meeting the acceptance criteria for clinical use [4]. RBC was further prepared: 50 units were suspended in 100 ml of SAGM additive fluid; in another 50 units the buffy coat was removed, and they were suspended in 100 ml of SAGM, and the remaining 50 units were suspended in 100 ml of SAGM, and within 24 hours underwent leukoreduction with the use of MacoPharma Leucolab 2b/LCG4 filters. The studied material was divided into three groups: (1) 50 RBC units with SAGM additive solution (2) 50 buffy coat-depleted RBC units in SAGM additive solution, and (3) 50 units of leukocyte-reduced RBC in SAGM. All the analysed RBC units were stored for 42 days at 2-6°C, using an automatic system of temperature control. The concentration of red blood cell-derived microparticles was tested in each RBC unit. The tests were performed at 2, 20 and 36 days of storage. At the established time points, the RBC samples were centrifuged at 4°C for 20 minutes, at 2800 revolutions. Then, 2 ml of supernatant were collected form each RBC unit, and re-centrifuged for 13 minutes at 4°C and 2300 revolutions. The RMPs in the obtained supernatant were tested within 1 hour by flow cytometry using BD Facs Canto II cytometer at the Institute of Immunohaematology of the Postgraduate Medical Training Centre in Warsaw. In order to increase the method's specificity, it was modified so that the microparticles were labelled simultaneously with annexin V FITC, and glycophorin A. Samples of 30 μl obtained from the analysed groups were incubated for 20 minutes at room temperature in a darkroom, with 2 μl of annexin V FITC (Biosciences, San Jose, CA, USA), 3 μl of antibodies against CD 235a-APC (glycophorin A [Biosciences, San Jose, CA, USA]) and 16 μl of annexin-binding buffer. After the incubation, 250 μl of binding buffer were added to each sample, and cytometric analysis was conducted immediately. Plasma samples without specific antibodies and/or samples with CD 235a antibodies or annexin for elimination of non-specific bonds were used as controls. The test results were presented on scatter plots, and expression of the sought red blood cell-derived microparticles was determined by the measurement of fluorescence of the stained microparticles (Figure 1). The concentration of RMPs in 1 μl was calculated based on the formula presented by Grisendi et al. [5].



Colour purple signifies the microparticles derived only from red blood cells, distinguished using the modified method of double staining with glycophorin and annexin V.

Figure 1. Cytometric scatter plot of microparticles derived from red blood cells using the author's method of simultaneous glycophorin (CD235a-APC) and annexin V-FITC staining

Rycina 1. Cytometryczny wykres kropkowy mikrocząsteczek pochodzących z krwinek czerwonych z zastosowaniem własnej metody jednoczasowego znakowania glikoforyną (CD235a-APC) i aneksyną V-FITC

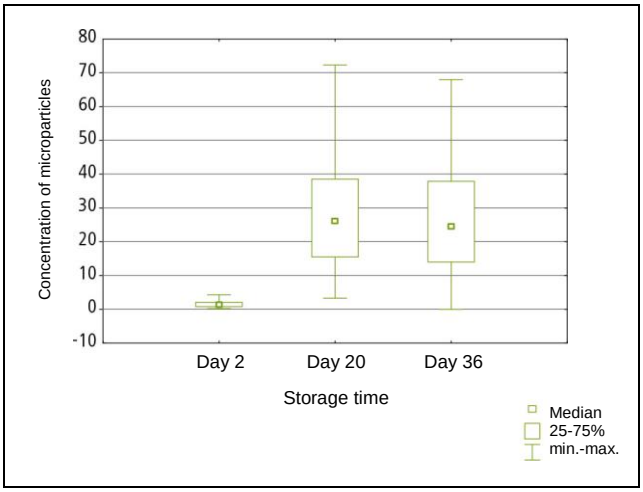


Figure 2. Relationship between the concentration of microparticles and storage time for RBC with an additive solution
Rycina 2. Zależność stężenia mikrocząsteczek w KKCz z roztworem wzbogacającym od czasu przechowywania

Statistical analysis

The statistical analysis of the results was conducted using Statistica 10 programme. Friedman's non-parametric ANOVA test was used to compare the number of microparticles in different RBC samples according to the storage time. Subsequently, *post-hoc* tests were applied to determine the statistical significance between individual storage periods. The results presented in tables include mean values and statistical deviations, as well as significance levels (p). The results are presented with a standard 95% confidence interval. The statistical significance level was set at $p<0.05$. A non-parametric Kruskal-Wallis test was used to compare microparticle concentrations in RBC according to the type of concentrate and storage time. The statistical significance level was set at $p<0.05$. The study was approved by the Bioethical Committee of the Military Institute of Medicine in Warsaw (decision no. 116/WIM/2018 of 22 August 2018). The study was funded as a statutory project no. 277 of the Military Institute of Medicine.

Tests results

In our study, we compared concentrations of red blood cell-derived microparticles in different types of RBC, according to their storage time.

Comparison of microparticle concentrations in RBC with an additive solution, according to the storage time

The study revealed a statistically significant increase of microparticle concentrations between day 2 and 36 of storage of the RBC (p 0.00001) (1.571 *vs* 26.418). A considerable increase was observed until day 20 of storage (p2-20 = 0.00001). No significant increase was revealed in the period between day 20 and day 36 of RBC storage. Figure 2 presents the relationship between the microparticle concentration in RBC with an additive solution and the storage time. The test results demonstrate that a significant increase in the concentration of microparticles in RBC with an additive solution is observed in the first two weeks of storage.

Comparison of microparticle concentrations in buffy coat-depleted RBC with an additive solution according to the storage time

Figure 3 presents the results of the analysis of microparticle concentrations in buffy coat-depleted RBC with an additive solution, according to the storage time. The analysis demonstrated a statistically significant difference of p = 0.004 in the concentration of

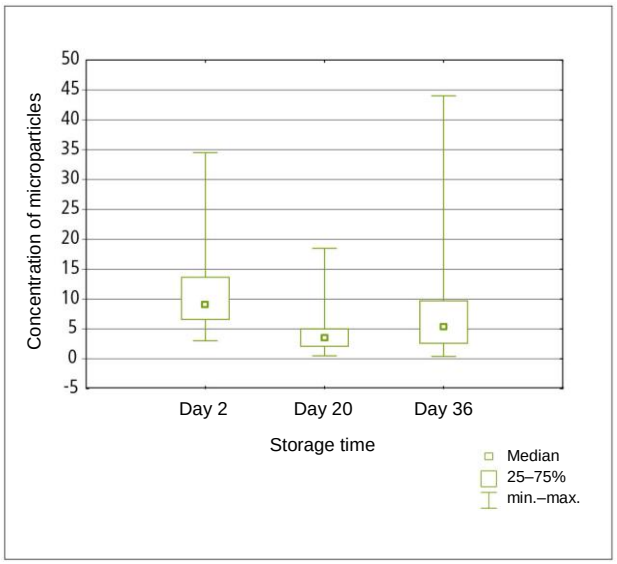


Figure 3. Relationship between the concentration of microparticles and storage time for RBC in an additive solution, devoid of the buffy coat
Rycina 3. Zależność stężenia mikrocząsteczek w KKCz w roztworze wzbogacającym pozbawionym kożuszka leukocytarno–płytkowego, od czasu przechowywania.

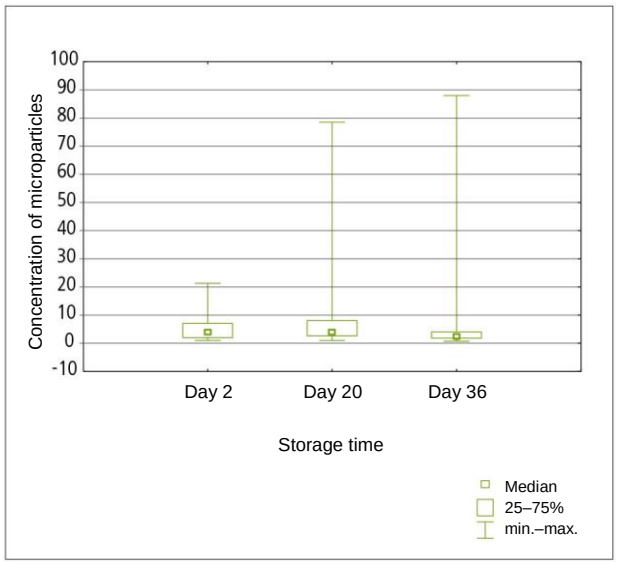


Figure 4. Relationship between the concentration of microparticles and storage time for leukocyte deficient RBC with an additive solution
Rycina 4. Zależność stężenia mikrocząsteczek w ubogoleukocytarnym KKCz z roztworem wzbogacającym od czasu przechowywania

microparticles in buffy coat-depleted RBC with an additive solution in the analysed time points. The highest microparticle concentrations (median of 9.1, mean value of 11.335) were observed on day 2 of storage of the concentrate. After 20 days of storage, a statistically significant reduction of the microparticle concentration was observed (p2-20 = 0.001), and on day 36 of storage, the concentration increased significantly to the mean value of 8.881 (p20-36 = 0.031).

Comparison of microparticle concentrations in leukocyte-reduced RBC with an additive solution, according to the storage time

The results of our study do not demonstrate statistically significant differences in microparticle concentrations in leukocyte-reduced RBC with an additive solution on days 2, 20 and 36 of storage. A minor increase in the concentration is observed on day 20, compared to day 2 (p2-20 = 0.15). The difference in microparticle concentrations between day 20 and day 36 was statistically insignificant. Moreover, no differences were observed between the concentrations of microparticles on day 2 and 36 of storage. Mean values: 5.427 on day 2 of storage, 12.078 on day 20 of storage, and 6.27 on day 36 of storage. Figure 4 presents the relationship between the concentration of microparticles and time of storage of leukocyte-reduced RBC with an additive solution.

Comparison of microparticle concentrations in the analysed RBC types according to the storage time

Concentrations of red blood cell-derived microparticles in all types of RBC were compared on days 2, 20 and 36 of storage. The comparative analysis revealed that on day 2 of storage the mean concentration of microparticles in RBC with an additive solution is 1.56 ± 0.89, and that it is statistically significantly lower than the mean value of microparticle concentration in buffy coat-depleted RBC (11.43 ± 7.43) or in the leukocyte-reduced RBC with an additive solution (LRRBC) (1.56 ± 0.89 *vs* 5.26 ± 4.23). However, a statistically significant difference was found between the mean concentration of microparticles in LRRBC and the mean concentration of microparticles in buffy coat-depleted RBC with an additive solution (5.26 ± 4.23 *vs* 11.43 ± 7.43) (p = 0.000002). Figure 5 presents the relationship between the concentrations of microparticles and the type of RBC on day 2 of storage. The test results on day 20 and 36 of storage demonstrate that mean concentration of microparticles in RBC with an additive solution on day 20 is statistically significantly higher than the mean concentration of microparticles in

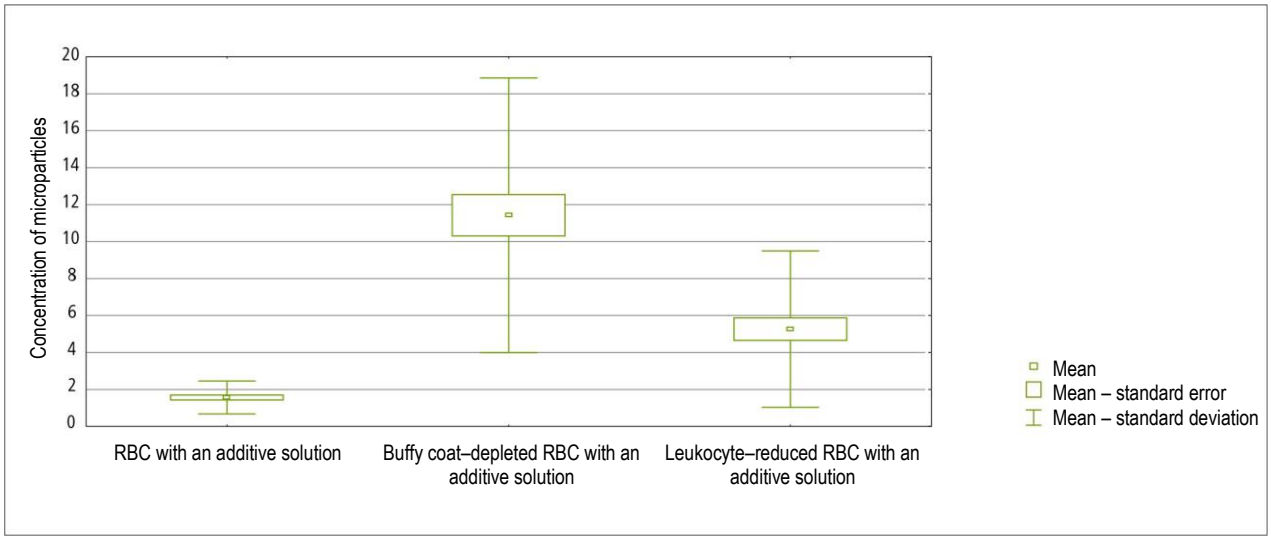


Figure 5. Relationship between concentration of microparticles and the type of RBC on day 2 of storage
Rycina 5. Zależność stężenia mikrocząsteczek i rodzaju KKCz w 2. dniu przechowywania

buffy coat-depleted RBC with an additive solution (28.54 *vs* 4.54) or the mean concentration of microparticles in LRRBC (28.54 *vs* 12.23). No statistically significant differences were observed in the mean microparticle concentrations between buffy coat-depleted RBC with an additive solution and LRRBC. On day 36 of storage, the mean concentration of microparticles in RBC with an additive solution was 26.08 ± 16.27, and it was statistically significantly higher than the mean concentration of microparticles in buffy coat-depleted RBC with an additive solution – 9.43 ±12.34 (p 0.000003). The mean concentration of microparticles in LRRBC was 5.37 ± 13.28, and it was statistically significantly lower than the mean concentration of microparticles in buffy coat-depleted RBC with an additive solution (p 0.0004). Figures 6 and 7 present the relationships between the concentrations of microparticles and type of RBC on day 20 and 36 of storage.

Interpretation of results and discussion

In the past years, the study results reported in the literature indicated that certain adverse post-transfusion reactions might be associated with transfusion of a large quantity of RBC stored for two weeks or longer [6, 7]. Goel et al. found that transfusion of RBC stored for over 35 days may be associated with adverse reactions in high-risk patients [8]. The authors examined 13,441 patients: 4491 of them received red blood cells stored for less than 21 days, 8950 received blood cells stored for over 28 days, and 3074 patients received RBC stored for over 35 days. The study results demonstrated that the red blood cells that were stored for > 35 days were an independent morbidity factor, especially in the elderly and critically ill patients. In these groups an increased number of infections, hypoxia and thrombotic episodes was observed. These correlations were not found in the comparison of patients who received RBC stored for 21 days vs 28 days. Adverse reactions were observed, but the time of storage was not an independent morbidity factor [8]. Goel et al. conclude that the results they obtained may be explained by the changes occurring in red blood cells during their storage [8]. Long storage results in deep biochemical and structural modifications in red blood cells. They include the release of microparticles from the cellular membrane [9]. Red blood cell-derived microparticles (RMPs) may contribute to pathogenesis of transfusion-related acute lung injury (TRALI), and demonstrate a pro-inflammatory and pro-coagulatory potential [10-12]. Other problems include the effect of blood drawing procedures, storage, preservation methods, and the effect of the type of RBC on the processes occurring in the container during the storage of blood cells [10].

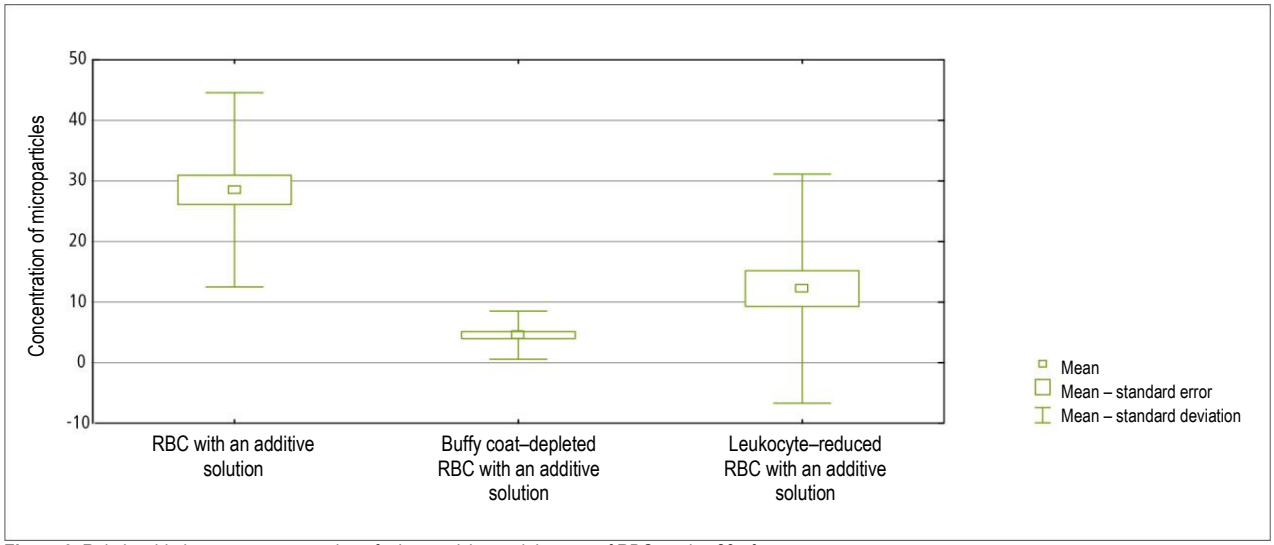


Figure 6. Relationship between concentration of microparticles and the type of RBC on day 20 of storage
Rycina 6. Zależność stężenia mikrocząsteczek i rodzaju KKCz w 20. dniu przechowywania

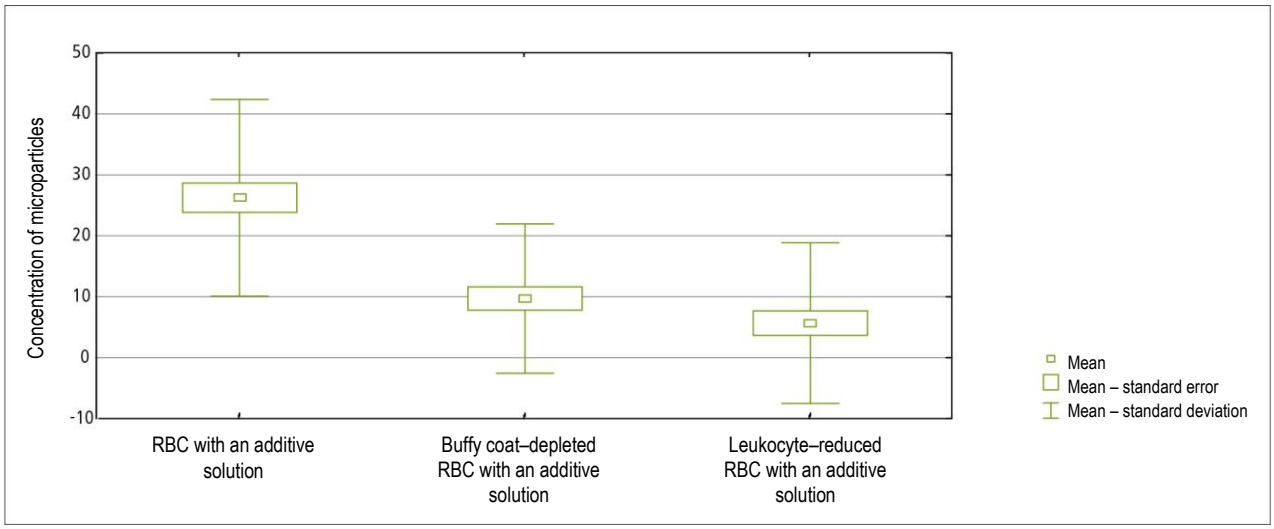


Figure 7. Relationship between concentration of microparticles and the type of RBC on day 36 of storage
Rycina 7. Zależność stężenia mikrocząsteczek i rodzaju KKCz w 36. dniu przechowywania

The presented study is the first one to assess the relationship between the concentration of red blood cell-derived microparticles and the type of red blood cell concentrate.

The study included 150 RBC units that met the approval criteria for clinical use [4]. The material was divided into three equal groups: (1) RBC with an additive solution, (2) buffy coat-depleted RBC with an additive solution, and (3) leukocyte-reduced RBC with an additive solution. The concentrations of red blood cell-derived microparticles were assessed on day 2, 20 and 36 of storage, with the use of flow cytometry. In order to increase the method's specificity, an original modification was applied, i.e. simultaneous labelling of the microparticles with annexin V FITC and glycophorin A. Rubin et al. also used flow cytometry for RMP analysis, but they labelled the microparticles with anti-CD235a antibodies (glycophorin A) and anti-CD47 antibodies [13]. Rousseau et al. labelled the isolated microparticles with annexin V [14]. Both markers are specific for red blood cells. Glycophorin A (CD 235a) is the main sialoglycoprotein of the erythrocyte cellular membrane, whereas annexin V is a marker that detects phosphatidylserine on the surface of red blood cell-derived microparticles. The double labelling of microparticles enhanced reaction, and significantly facilitated detection of RMPs and determination of their concentrations. The uniqueness of our study consisted in

the comparison of the concentrations of RMPs according to the type of RBC and its storage time. Previously published studies concentrated primarily on the assessment of RMP concentrations according to the storage time, but did not analyse the effect of the type of RBC and the production method [8, 15, 16]. The evaluation of the microparticle concentration considering the type of RBC and the storage time revealed that a significant increase of the concentration of microparticles is observed in RBC with an additive solution, compared to the buffy coat-depleted RBC with an additive solution or leukocyte-reduced RBC with an additive solution. Our study demonstrated that a statistically significant increase of microparticle concentration ($p < 0.05$) was found in RBC with an additive solution on day 20 of storage, compared to day 2. On day 36, the difference was statistically insignificant. Grisendi et al. and Gamonet et al. achieved similar results when using flow cytometry to evaluate the quantity of microparticles in RBC stored for 2 days (58/µl) *vs* 42 days (138/µl) [5, 17]. Rubin et al. compared the RMP concentration in RBC and leukocyte-reduced RBC. They demonstrated a twenty-fold increase in the quantity of microparticles released from red blood cells on day 50 of storage of RBC, compared to the day when the blood component was produced [13]. In leukocyte-reduced RBC, the concentration of microparticles increased in a statistically insignificant manner [13].

The tests conducted on buffy coat-reduced RBC with an additive solution revealed a high concentration of RMPs on the second day of storage, and it was the highest concentration of microparticles in the analysed time points (mean value of 11.335). On day 20 of storage, a statistically significant reduction of the microparticle concentration was observed ($p2\text{-}20 = 0.001$), compared to day 2, and on day 36 of storage, the concentration increased significantly to the mean value of 8.881 ($p20\text{-}36 = 0.031$). The high concentration of microparticles in the first time point of the study probably results from the manual preparation of this type of RBC. The forced pressure on the red blood cells to isolate the buffy coat might cause stress, contributing to a considerable release of microparticles from the cellular membrane of erythrocytes. The effect of blood preparation method and type of preservative solutions on the release of RMPs was emphasised by Antonelou et al. [18]. The comparison of microparticle concentrations in leukocyte-reduced RBC at different time points during the storage did not reveal any statistically significant differences. A minor increase in the concentration is observed on day 20, compared to day 2 ($p < 0.05$). The difference in microparticle concentrations between day 20 and day 36 was also statistically insignificant. Sugawa et al. conducted a study on leukocyte-reduced RBC obtained from healthy donors and stored in a refrigerator at 2-6°C, to assess concentrations of microparticles during the storage [19]. They also demonstrated that a reduction of leukocytes does not result in a significant increase in RMP concentration. A study by Tayer et al., involving an analysis of 20 units of RBC and leukocyte-reduced RBC, indicates that the preparation method may affect the release of microparticles [20]. Our study assessed concentrations of red blood cell-derived microparticles in different types of RBC, according to the storage time. The results demonstrate that mean concentration of microparticles in RBC with an additive solution after 20 days of storage is statistically significantly higher than the mean concentration of microparticles in buffy coat-depleted RBC with an additive solution (28.54 *vs* 12.23) or the mean concentration of microparticles in leukocyte-reduced RBC (28.54 *vs* 4.54). A statistically insignificant increase of RMPs in leukocyte-reduced and platelet-reduced blood components is observed, with a slight growing trend until the last day of storage. This observation supports the hypothesis that the method of production of RBC, as well as the preservative fluid and time of storage may affect the concentration of red blood cell-derived microparticles [18, 19].

Conclusions

Storage of RBC is associated with changes in erythrocytes. They include the release of microparticles from the cellular membrane. Significant changes in RMP concentrations are found in the first three weeks of storage. The methods of RBC preparation may considerably affect the release of microparticles. Due to the occurrence of adverse post-transfusion reactions attributable to red blood cell-derived microparticles, the treatment with RBC in special patient groups should be individualised.

References

1. Westerman M, Porter JB. Red blood cell-derived microparticles: an overview. Blood Cells Mol Dis, 2016; 59: 134-139
2. Rubin 0, Canellini G, Delobal J, et al. Red blood cell microparticles: clinical relevance. Transfus Med Hemother, 2012; 39: 342-347
3. Aung HH, Tung JP, Dean MM, et al. Procoagulant role of microparticles in routine storage of packed red blood cells: potential risk for prothrombotic post-transfusion complications. Pathology, 2017; 49: 62-69
4. Obwieszczenie Ministra Zdrowia z dnia 9 czerwca 2017 r. w sprawie wymagań dobrej praktyki pobierania krwi i jej składników, badania, preparatyki, przechowywania, wydawania i transportu dla jednostek organizacyjnych publicznej służby krwi. Dz. U. poz. 63 [Announcement of the Minister of Health of 9 June 2017 on Good Manufacturing Practice requirements regarding the collection of blood and its components, testing, preparation, storage, distribution and transport of blood for the organisational units of the public blood service. Official Journal of Laws item 63]
5. Grisendi G, Finetti E, Manganaro D, et al. Detection of microparticles from human red blood cells by multiparametric flow cytometry. Blood Transfus, 2015;13:274-280
6. Kriebardis A, Antonelou M, Stamoulis K, Papassideri I. Cell-derived microparticles in stored blood products: innocent-bystanders or effective mediators of post-transfusion reactions? Blood Transfus, 2012; 10: 25-38

7. Wenche JY, Ricci M, Shariatmadar S, et al. Microparticles in stored red cells as potential mediators of transfusion complications. Transfusion, 2011; 4: 886-893
8. Goel R, Johnson D J, Scott AV, et al. Red blood cells stored 35 days or more are associated with adverse outcomes in high-risk patients. Transfusion, 2016; 56: 1690-1698
9. D'Alessandro A, Kiebardis AG, Rinalducci S, et al. An update on red blood cell storage lesions, as gleaned through biochemistry and omics technologies. Transfusion, 2015; 55: 205-219
10. D'Alessandro A, Nemkov T, Kelher M, et al. Routine storage of red blood cell (RBC) units in additive solution-3: a comprehensive investigation of the RBC metabolome. Transfusion, 2015; 55: 1155-1168
11. Toy P, Gajic 0, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factor. Blood, 2012; 119: 1757-1767
12. Fisher D, Biissow J, Meybohm P. Microparticles from stored red blood cells enhance procoagulant and proinflammatory activity. Transfusion, 2017; 11: 2701-2711
13. Rubin 0, Crettaz D, Canellini G, et al. Microparticles in stored red blood cells: an approach using flow cytometry and proteomic tools. Vox Sang, 2008; 95: 288-297
14. Rousseau M, Belleannee C, Duchez AC, et al. Detection and quantification of microparticles from different cellular lineages using flow cytometry. Evaluation of the impact of secreted phospholipase A2 on microparticle assessment. PLoS ONE, 2015; 10 (1): e0116812.2015:1-27
15. Kaukonen KM, Bailey M, Ady B, et al. A randomized controlled trial of standard transfusion versus fresher red blood cell use in intensive care (TRANSFUSE): protocol and statistical analysis plan. Crit Care Resusc., 2014; 16: 255-261
16. Eikelboom JW, Cook RJ, Barty R, et al. Rationale and design of the Informing Fresh versus Old Red Cell Management (INFORM) Trial: an international pragmatic randomized trial. Transfus Med Rev, 2016; 30: 25-29
17. Gamonet C, Mourey G, Aupet S, et al. How to quantify microparticles in RBCs? A validated flow cytometry method allows the detection of an increase in microparticles during storage. Transfusion, 2017; 57: 504-516
18. Antonelou MH, Kriebardis AG, Stamoulis KE, et al. Red blood cell aging markers during storage in citraphosphate-dextrose-saline-glucose-mannitol. Transfusion, 2010; 50: 376-389
19. Sugawa A, Nollet KE, Yajima K, et al. Preventing platelet-derived microparticle formation-and possible side effects-with prestorage leukofiltration of whole blood. Arch Pathol Lab Med, 2010; 134: 771-775
20. 20.Tayer AH, Amirizadeh N, Ahmadinejad M, et al. Procoagulant Activity of Red Blood Cell-Derived Microvesicles during Red Cell Storage. Transfus Med Hemother, 2018

Hemodynamic disturbances in patients with hormone-secreting pituitary tumours – what unites and what divides patients with acromegaly and prolactinoma?

Zaburzenia hemodynamiczne u chorych z hormonalnie czynnymi guzami przysadki – co łączy, a co dzieli chorych z akromegalią i prolaktynoma?

Agnieszka Jurek[1], Grzegorz Gielerak[1], Paweł Krzesiński[1], Beata Uziębło-Życzkowska[1], Przemysław Witek[2], Grzegorz Zieliński[3], Anna Kazimierczak[1], Robert Wierzbowski[1], Małgorzata Banak[1]

Department of Cardiology and Internal Diseases, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw;
Head: Lt. Col. Prof. Paweł Krzesiński, MD, PhD
[2] Department of Gastroenterology, Endocrinology and Internal Diseases, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw;
Head: Prof. Przemysław Witek, MD, PhD
[3] Department of Neurosurgery, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine, Warsaw; Head: Assoc. Prof. Andrzej Koziarski, MD, PhD

Abstract. Prolonged exposure of tissues to abnormal hormone levels in hormone-secreting pituitary tumours can contribute to significant cardiovascular remodelling. The aim of this study was to assess the hemodynamic profile in patients with acromegaly and prolactinoma compared with healthy subjects. 19 patients with acromegaly (AC) (mean age 47 years, 8 males, 47% of subjects with controlled AH-mean BP 119/75 mm Hg), 19 patients with prolactinoma (PR) (mean age 43 years, 18 males, 36% of subjects with controlled AH-mean BP 114/75 mm Hg) were subject to comparative analysis against 35 healthy volunteers (HV). Impedance cardiography (ICG) was performed to evaluate the cardiac output index (CI), stroke volume index (SI), systemic vascular resistance index (SVRI) and thoracic fluid content (TFC). The patients from AC group showed a higher HR (73.8 *vs* 66.6 1/min.; p =0.04), while PR group patients showed a higher BMI (30.5 *vs* 25.7 kg/m^2; p=0.0006). In the cardioimpedance assessment, patients with pituitary diseases presented: AC group a higher TFC (38.0 *vs* 29.0 1/kOhm; p <0.00001), and PR group a higher SVRI (2149 *vs* 1908 dyn*s*m^2/cm^5; p=0.031). Hormonal disorders accompanying acromegaly and prolactinomas, even with well-controlled blood pressure, are associated with intensified vasoconstriction, increased volaemia in the thorax and left ventricular hemodynamic dysfunction, carrying substantial diagnostic and therapeutic implications.
Keywords: acromegaly, cardiovascular diseases, impedance cardiography

Streszczenie. Długotrwała ekspozycja tkanek na nieprawidłowe stężenia hormonów w hormonalnie czynnych guzach przysadki może się przyczynić do istotnego remodelingu sercowo-naczyniowego. Celem pracy była analiza profilu hemodynamicznego chorych z akromegalią i prolaktynoma w porównaniu z osobami zdrowymi. Analizie porównawczej wobec referencyjnej grupy 35 zdrowych ochotników (HV) poddano 19 chorych z akromegalią (AC) (średni wiek 47 lat, 8 mężczyzn, 47% osób z AH kontrolowanym – średnie BP 119/75 mm Hg); 19 chorych z prolaktynoma (PR) (średni wiek 43 lata, 18 mężczyzn, 36% osób z kontrolowanym nadciśnieniem tętniczym [AH] – średnie BP 114/75 mm Hg). W ocenie hemodynamicznej metodą kardiografii impedancyjnej (ICG) przeanalizowano wartości wskaźników: rzutu serca (CI), objętości wyrzutowej (SI), systemowego oporu naczyniowego (SVRI) oraz zawartości płynu w klatce piersiowej (TFC). Pacjenci z grupy AC charakteryzowali się wyższym HR (73,8 *vs* 66,6 1/min; p =0,04), a z grupy PR wyższym BMI (30,5 *vs* 25,7 kg/m^2; p =0,0006). W ocenie kardioimpedancyjnej prezentowali: w AC wyższy TFC (38,0 *vs* 29,0 1/kOhm; p <0,00001), a w PR wyższy SVRI (2149 *vs* 1908 dyn*s*m^2/cm^5; p =0,031). Zaburzenia hormonalne towarzyszące AC i PR nawet w przypadku dobrej

kontroli BP wiążą się z nasiloną wazokonstrykcją, zwiększoną wolemią w obrębie klatki piersiowej oraz upośledzeniem funkcji hemodynamicznej lewej komory, co niesie za sobą istotne implikacje diagnostyczno-terapeutyczne
Słowa kluczowe: akromegalia, choroby układu sercowo-naczyniowego, kardiografia impedancyjna

Delivered: 14/01/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 214-220

Corresponding author
Agnieszka Jurek, MD
Department of Cardiology and Internal Diseases,
Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 817 285
e-mail: ajurek1@wim.mil.pl

Introduction

Acromegaly (AC) and prolactinoma (PR) are relatively rare disorders of the pituitary gland. Their clinical presentation is associated with oversecretion of the frontal lobe hormones (GH and PRL), resulting in a number of general systemic disturbances that increase morbidity and mortality, as well as adversely affect the quality of life. Hormonal disorders in AC and PR have significant effects on the cardiovascular function, changing the haemodynamic profile and increasing the cardiovascular risk [1-4]. The mortality rates in patients with AC and male patients with PR are a few times higher than in the general population, primarily due to cardiovascular complications [4-7]. The cardiovascular abnormalities most frequently observed in AC and PR patients include: left ventricular dysfunction, arterial hypertension (AH), arrhythmias, valvular defects, vascular endothelial dysfunction, hyperinsulinaemia and disturbed lipid metabolism [8, 9]. AH is a particularly common problem in this population. Its pathogenesis is multifactorial. This secondary arterial hypertension in the case of acromegaly results from oversecretion of growth hormone (GH), and in prolactinoma it may be associated with various metabolic disorders [4, 10]. The clinical course of AH may be varied. The disease develops early and may persist even for several years following the clinical and hormonal remission of the underlying disorder [10-13]. Control of AH in this group of patients may be difficult, and current guidelines emphasise the need for personalised hypotensive therapy [14]. Due to a multidirectional pathomechanism of the changes occurring due to excessive hormone production in AC and PR patients, the majority of standard diagnostic methods used to control AH, such as control of arterial pressure with automatic meter or 24-hour pressure monitoring may be of limited use because of their selectivity and incomplete presentation of the processes taking place [8, 10-13]. Therefore, new diagnostic methods are required for patients with AC and PR to enable early detection of abnormalities, and to increase the chances of targeted, optimal therapy and reduction of the cardiovascular risk. Impedance cardiography (ICG) is a novel, non-invasive method that offers an assessment of the haemodynamic function of the circulatory system, e.g. vascular stiffness, volaemia and heart's pumping function [15], and can be useful in the clinical evaluation of patients with AC and PR, especially with concurrent AH. Using ICG in diagnostics and treatment of patients with AC and PR may enhance the individual assessment of the haemodynamic status of patients, and provide a better insight into the pathophysiology of the disease, thus improving the control of arterial pressure and preventing cardiovascular remodelling.

Aim of the study

The aim of the study is to analyse the haemodynamic profile of patients with AC and PR, and compare it with that of healthy individuals.

Material and methods

Study population

The comparative analysis in this observational, prospective clinical study involved two age-matched groups of patients:

- 19 patients with AC - mean age of 47 years, 8 men, 47% of the group with controlled AH (mean arterial pressure of 119/75 mm Hg),
- 19 patients with PR - mean age of 43 years, 18 men, 36% of the group with controlled AH (mean arterial pressure of 114/75 mm Hg),
- 35 non-smoking, healthy volunteers.

Inclusion criteria for the AC group

The AC group included patients of both sexes, diagnosed with active acromegaly, defined on the basis of standard hormone and imaging tests, according to the European Society of Endocrinology (ESE) guidelines: occurrence of

characteristic somatic symptoms of AC together with abnormal laboratory test results (increased IGF-1, above the normal sex and age-matched range, lack of suppression of GH to <46 pmol/l [1,0 µg/l] during an oral glucose tolerance test (OGTT) with 75 g of glucose), and a focal lesion in the pituitary visible in an MRI scan.

Inclusion criteria for the PR group

The PR group comprised patients of both sexes diagnosed with prolactinoma pituitary tumour, defined on the basis of standard hormone and imaging tests, following the ESE guidelines: occurrence of clinical symptoms of hyperprolactinaemia, together with increased serum prolactin concentrations above the laboratory normal range, and radiological evidence of pituitary tumour. Functional hyperprolactinaemia and using medications affecting the dopaminergic system had to be excluded in each case.

All patients from the AC and PR groups also underwent a standard assessment of adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinising hormone (LH) and thyroid-stimulating hormone (TSH). In addition, concurrent disorders in the metabolism of carbohydrates (previously diagnosed or detected during the first diagnostic visit) were reported. Patients in the AC and PR group did not use medications that modify the function of the hypothalamus-pituitary-adrenal axis, so pharmacotherapy did not affect their haemodynamic assessment by impedance cardiography. Patients in both groups are still under clinical observation in this observational study.

Exclusion criteria for AC and PR groups

- Coronary disease, including a history of myocardial infarction
- Chronic heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFrEF) (left ventricular ejection fraction < 50%)
- History of pulmonary embolism
- Documented history of cerebral stroke or transient ischaemic attack (TIA)
- Severe chronic obstructive pulmonary disease (COPD) (FEV_1 <50% pred.)
- Respiratory failure (partial pressure of O_2 in the arterial blood reduced to PaO_2 <60 mm Hg and/or partial pressure of CO_2 in the arterial blood increased to $PaCO_2$ >45 mm Hg)
- Status post head trauma
- Pregnancy
- Lack of patient's consent
- Circumstances that prevent patient's compliance to the study protocol

HV group

The HV group comprised healthy volunteers of both sexes with normal arterial pressure, non-smoking, non-obese, with undisturbed metabolism of carbohydrates, who gave their consent to participate in the clinical study.

Bioethics

The study was conducted in compliance with the Declaration of Helsinki and the principles of Good Clinical Practice (GCP). The study protocol was approved by the Bioethical Committee of the Military Institute of Medicine in Warsaw. All patients provided written consent to participate in the study.

Clinical study

The clinical assessment was focused on the cardiovascular risk factors (e.g. family history of cardiovascular diseases, symptoms from the cardiovascular system, disorders in the metabolism of carbohydrates, lifestyle, abuse of alcohol, psychoactive agents, nicotinism), on-site measurement of blood pressure: systolic (SBP) and diastolic (DBP), as well as on the constitutional factors (height, body weight, body mass index [BMI]).

Impedance cardiography

Haemodynamic parameters were examined with the ICG method during a 10-minute resting test in a supine position, using a Niccomo™ device (Medis, Ilmenau, Germany). Based on the 10-minute ICG records, mean haemodynamic indicators, including heart rate (HR), SBP, DBP, stroke volume index (SI) (ml/m^2), cardiac output index (CI) ($ml*m^{-2}*min^{-1}$), systemic vascular resistance index (SVRI) ($dyn*s*cm^{-5}*m^2$) and thoracic fluid content (TFC) (1/kOhm) were analysed in detail (Niccomo Software).

Statistical analysis

The statistical analysis of the results was performed using MS Office Excel 2016 and Statistica 12.0 (StatSoft Inc., Tulsa, USA).

The results were presented as mean values ± standard deviation (SD). The distribution of variables was assessed visually and using the Kolmogorov-Smirnov test. To compare the results between groups, the Student's t-test and Mann-Whitney U-test were used. Statistical significance was set at $p < 0.05$.

Basic characteristics

The basic group characteristics are presented in Tables 1 and 2.

In the group of patients with AC, mean BP was 119/75 mm Hg (in 95% of subjects it was <140/90 mm Hg), in patients with PR, mean BP was 115/72 mm Hg (in 100% of subjects BP was <140/90 mm Hg). AH was found in 47% of AC patients and in 36% of PR patients. In all cases, it was treated pharmacologically, usually with one or two hypotensive agents. Significant differences with regard to the basic parameters were observed in HR and BMI. Patients in the AC group demonstrated a significantly higher HR (73.8 *vs* 66.6 1/min, p = 0.04) compared to the HV group. Patients in the PR group demonstrated a significantly higher BMI (30.5 *vs* 25.7 kg/m^2, p = 0.0006) compared to the HV group. Diabetes was observed in 10% of AC patients and in 10% of PR patients, and abnormal fasting glycaemia and abnormal glucose tolerance were found in 37% of AC patients and in 21% patients in the PR group. In the group of patients with AC, one patient received treatment with insulin and metformin, and one patient was treated with insulin, whereas in the PR group one patient received treatment with metformin, and one with metformin and insulin. Transsphenoidal pituitary tumour resection was performed in 53% of AC patients and in 5% of PR patients.

Cardioimpedance variables

Despite minor differences in the assessed basic parameters (HR, SBP, DBP, BMI), the comparative analysis of cardioimpedance variables demonstrated a number of differences between the groups (Tables 3-4, Figure 1). In cardioimpedance assessment, patients with pituitary disorders were characterised by:

- a significantly higher TFC in the AC group (38.0 *vs* 29.0 1/kOhm; p < 0.00001),
- a significantly higher SVRI in the PR group (2149 *vs* 1908 dyn*s*m^2/cm^5; p = 0.031),
- lower SI in the AC and PR groups (45.1 *vs* 46.2 *vs* 49.9 ml/m^2; p = 0.160; p = 0.132), although the differences were not statistically significant.

Table 1. Comparative analysis between healthy volunteers group (HV) and acromegaly group (AC) (baseline characteristics)
Tabela 1. Analiza porównawcza danych ogólnych pomiędzy grupą osób zdrowych (HV) a grupą pacjentów z akromegalią (AC)

	HV	AC	P
Age, mean [±SD]	43.7 [±9.12]	47.7 [±15.4]	0.253
SBP (mmHg), mean [±SD]	114.5 [±10.0]	118.6 [± 12.7]	0.216
DBP (mmHg), mean [±SD]	72.3 [±7.97]	74.9 [± 11.1]	0.338
HR (bpm), mean [±SD]	66.6 [±11.7]	73.8 [± 12.0]	0.043
BMI (kg/m^2), mean [±SD]	25.7 [±3.22]	27.7 [± 4.21]	0.073

SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, BMI – body mass index

Discussion

The study group comprised patients newly diagnosed with AC and PR, without any comorbidities that could significantly impair the cardiovascular function. Arterial hypertension was found in 47% of AC patients and in 36% of PR patients, and in both groups it was successfully controlled. Cardioimpedance assessment demonstrated a significantly elevated thoracic fluid content (TFC) in AC patients, and a significantly increased systemic vascular resistance index (SVRI) in PR patients, compared to healthy volunteers. The indicators of the cardiac pumping function (SI, CI) were similar in both groups, although a trend towards lower SI values was observed in the AC and PR groups, compared with healthy volunteers.

The results of our study indicate that patients with acromegaly and prolactinoma, despite similar basic clinical characteristics, demonstrated a poorer haemodynamic profile than healthy individuals, which was associated with a significantly pronounced vasoconstriction (PR) or higher thoracic volaemia (AC). The observed subclinical haemodynamic changes might confirm the additive effect of long-term exposure to abnormal pituitary hormone levels on the cardiovascular function in patients with AC and PR [1-4, 16]. These findings may be explained by complex pathomechanisms that may contribute to the development of cardiovascular complications in patients with AC and PR, including increased heart rate, ejection fraction and cardiac output, increased left ventricular afterload, reduced perfusion pressure in the coronary arteries and disturbed vascular endothelial function with modification of the peripheral vascular resistance [17-19], concurrent metabolic disorders [20, 21], insulin resistance syndrome [22-24] and disturbed metabolism of lipids 8, 19, 25, 26].

Table 2. Comparative analysis between healthy volunteers group (HV) and prolactinoma group (PR) (baseline characteristics)
Tabela 2. Analiza porównawcza danych ogólnych pomiędzy grupą osób zdrowych (HV) a grupą pacjentów z prolaktynoma (PR)

	HV	PR	P
Age, mean [±SD]	43.7 [±9.12]	43.4 [±13.6]	0.923
SBP (mmHg), mean [±SD]	114.5 [±10.0]	113.8 [±15.1]	0.831
DBP (mmHg), mean [±SD]	72.3 [±7.97]	74.7 [±9.39]	0.327
HR (bpm), mean [±SD]	66.6 [± 11.7]	66.2 [±10.0]	0.896
BMI (kg/m^2), mean [± SD]	25.7 [±3.22]	30.5 [± 6.34]	0.0006

SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, BMI – body mass index

Table 3. Hemodynamic parameter comparison between healthy volunteers group (HV) and acromegaly group (AC) (impedance cardiography characteristics)
Tabela 3. Porównanie parametrów hemodynamicznych ocenianych metodą kardiografii impedancyjnej pomiędzy grupą osób zdrowych (HV) a grupą pacjentów z akromegalią (AC)

	HV	AC	p
SI (ml/m^2), mean [±SD]	49.9 [±8.4]	45.1 [± 10.6]	0.160
CI (ml*m^{-2}*min^{-1}), mean [±SD]	3.26 [±0.53]	3.27 [±0.73]	0.965
TFC (1/kOhm), mean [±SD]	28.9 [±3.40]	37.9 [± 6.64]	<0.0001
SVRI (dyn*s*cm^{-5}*m^2), mean [±SD]	1907 [±368.4]	2065 [± 659.9]	0.273

SI – stroke volume index, CI – cardiac output index, TFC – thoracic fluid content, SVRI – systemic vascular resistance index

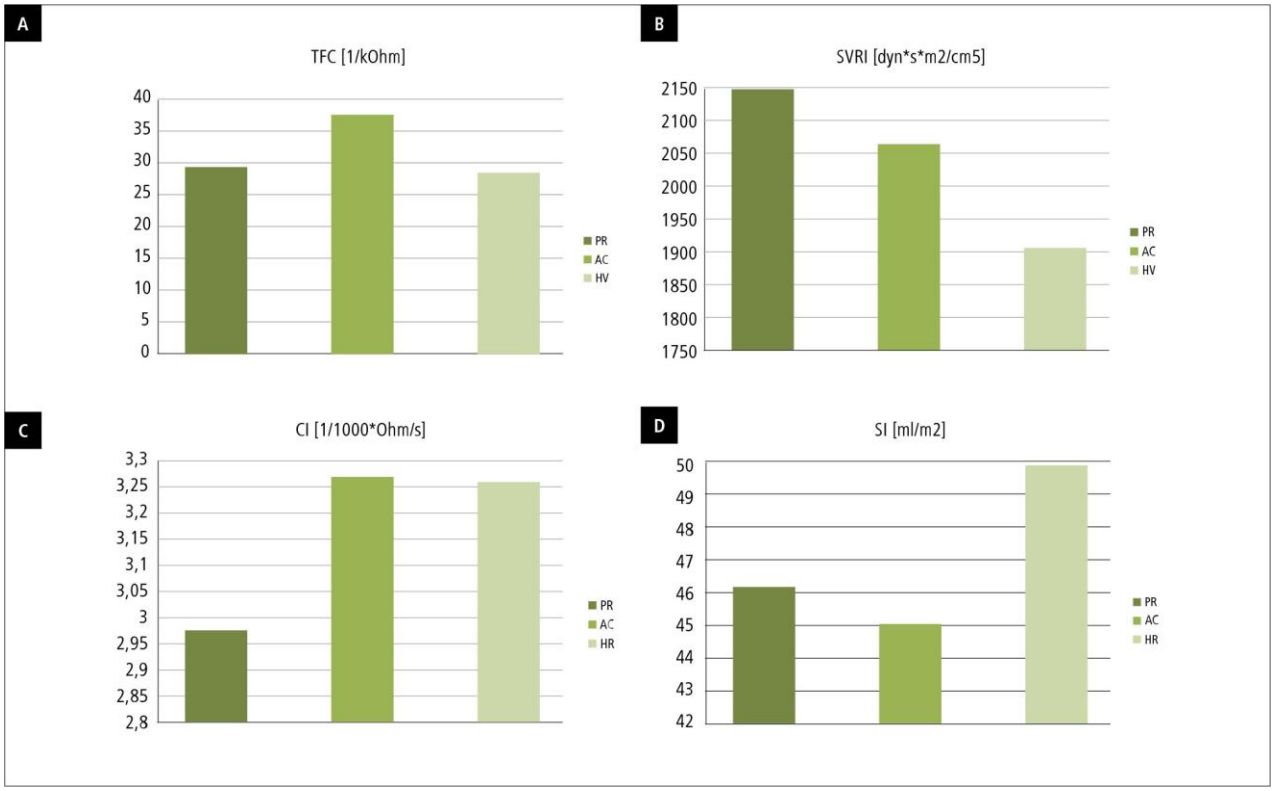


Figure 1. Hemodynamic profile of study groups including parameters
Rycina 1. Profil hemodynamiczny badanych grup z uwzględnieniem parametrów

Table 4. Hemodynamic parameter comparison between healthy volunteers group (HV) and prolactinoma group (PR) (impedance cardiography characteristics)
Tabela 4. Porównanie parametrów hemodynamicznych ocenianych metodą kardiografii impedancyjnej pomiędzy grupą osób zdrowych (HV) a grupą pacjentów z prolaktynoma (PR)

	HV	PR	p
SI (ml/m^2), mean [±SD]	49.9 [± 8.4]	46.2 [± 10.7]	0.132
CI (ml*m^{-2}*min^{-1}), mean [±SD]	3.26 [±0.53]	2.98 [± 0.52]	0.070
TFC (1/kOhm), mean [±SD]	28.9 [±3.40]	29.9 [±4.37]	0.355
SVRI (dyn*s*cm^{-5}*m^2), mean [±SD]	1907 [±368.4]	2148 [± 409.1]	0.031

SI – stroke volume index, CI – cardiac output index, TFC – thoracic fluid content, SVRI – systemic vascular resistance index

Our findings may have important clinical implications, as cardiovascular complications due to prolonged exposure to abnormal pituitary hormone levels (GH, prolactin) greatly worsen the prognosis in patients with AC and PR, already at the early stages of the disease. Observational studies confirm that AC is associated with higher mortality compared to the general population, due to the structural and functional changes in the cardiovascular system, resulting in a significant cardiovascular remodelling and increasing the risk of death, already elevated a few years before the diagnosis, which provides evidence of the unfavourable role of GH [1-3, 8, 27, 28]. The data regarding the incidence of cardiovascular diseases in PR patients are limited, but they also indicate an increased risk of cardiovascular diseases and death in this group, primarily due to metabolic comorbidities and premature development of atherosclerosis [4, 7, 20, 21, 24-26]. It is not associated with oversecretion of prolactin, but rather with its adverse effect on the function of the hypothalamus-pituitary-gonadal axis. In women, it is manifested by disturbed menstruation and abnormal estradiol concentrations, and in men – by testosterone deficits and metabolic complications of hypogonadism [29]. Therefore, it appears that early diagnosis of cardiovascular complications, prior to the clinical manifestation of symptoms, followed by prompt treatment, may be of considerable clinical significance, and it could help to reduce the mortality due to cardiovascular causes in patients with AC and PR [1, 8, 21].

Our study results revealed that, compared to healthy individuals, patients with PR demonstrate greater afterload in cardiographic impedance tests (higher SVRI). It indicates that other pathomechanisms than the widely recognised metabolic disorders and insulin resistance may contribute to the development of AH in the course of PR [4, 21, 30, 31]. Secondary endothelial dysfunction, resulting in increased vasoconstriction, probably plays an important role in the process. Therefore, the use of angiotensin convertase inhibitors as first-line hypotensives appears to be justified in this group of patients. It should be emphasised that increased vascular resistance is an important prognostic factor of cardiovascular diseases, and its complex haemodynamic consequences adversely affect not only blood vessels, but also the heart's pumping function [32].

The studied patients with AC presented a slightly different haemodynamic profile. The pathophysiological mechanisms responsible for AH in AC have not been completely understood. Increased stroke volume and cardiac output, increased left ventricular afterload and vascular endothelial dysfunction with changes in the peripheral vascular resistance are considered to be important factors in the process [10, 11, 12]. In our study, patients with AC demonstrated a tendency for thoracic hyperhydration (higher TFC). TFC is a good detector of the intra- and extracellular fluid in the thorax; its increase by 10% may already indicate fluid retention and hyperhydration [15]. The tendency for fluid retention is explained by pathophysiology. Both GH and insulin-like growth factor (IGF) demonstrate an antidiuretic effect. In acromegaly, their excessive concentrations may indirectly cause increased renal sodium absorption, and, as a result, water absorption, resulting in increased plasma volume. Coupled with other disorders induced by GH and IGF-1 (excessive stimulation of the smooth muscles in small vessels and their fibrosis, vasoconstriction, insulin resistance syndrome and hyperinsulinaemia, hyperactivation of the sympathetic system), the risk of insufficient BP control is significantly elevated [10, 34, 35]. The presented pathomechanisms support the use of polytherapy based on vasodilators (angiotensin convertase inhibitors, calcium blockers) in combination with diuretics in the treatment of AH in this group of patients.

Our study also revealed that patients with AC demonstrated a significantly higher HR and slightly higher CI than subjects in the HV group. These abnormalities may constitute an early, subclinical stage of cardiomyopathy associated with acromegaly. These findings would be consistent with previous reports; in the first, subclinical phase of cardiomyopathy, which is still reversible, concentric hypertrophy of the cardiac muscle and its increased contractility are observed, as well as elevated heart rate and cardiac output [3, 19, 36]. Primarily, hyperkinetic circulation may develop, followed by dysfunction of the left ventricle as a pump in the next phases [19, 37].

The trend towards impaired heart pumping function (lower SI), observed in both groups, AC and PR, may also be important from the clinical point of view. Many studies emphasise that patients with AC and PR often demonstrate structural remodelling of the cardiac muscle,

due to the hypertrophy and concentric restructuring of the left ventricle muscle. It results in impaired haemodynamic function of the left ventricle, manifested by diastolic dysfunction, followed by systolic dysfunction and the development of symptomatic heart failure [3, 4, 9, 19, 33, 38]. Various reports indicate that impedance cardiography may be an effective method of assessment of the left ventricular dysfunction in patients with AH [39]. Our study revealed that selected cardioimpedance parameters (including lower SI and increased SVRI) demonstrate a significant relationship with left ventricular dysfunction [40]. A study conducted in patients with heart failure presented a significant correlation between the change in the cardiac index (CI), determined by ICG, and the left ventricular ejection fraction assessed by echocardiography [41, 42].

Considering numerous reports illustrating the usefulness of ICG in the diagnostics and treatment of patients with AH and heart failure [43-46], our study results encourage the use of this method in AC and PR patients. It appears that patients with acromegaly and prolactinoma, characterised by increased cardiovascular risk, could profit from treatment optimisation based on an individual haemodynamic assessment.

Limitations

Our study was mainly limited by a relatively small size of groups, due to low incidence of AC and PR. Moreover, many patients with AC and PR demonstrate signs of significant cardiovascular dysfunction already at the diagnosis, which was one of the exclusion criteria in this study, and further reduced the number of its subjects. In addition, the study involved patients with pituitary diseases without clinically symptomatic cardiovascular dysfunctions, which excluded patients with serious comorbidities. Interpretation of the results should also consider potential effects of AH (despite its sufficient control) and the hypotensive therapy used. In the group of patients with prolactinoma, male subjects were more numerous (18 males vs 1 female); however, in none of the patients did the haemodynamic tests reveal distinctive values that would require exclusion or use of resistant statistical methods. The effect of sex on the haemodynamic disorders in hormonally functioning prolactin-secreting pituitary tumours requires further research.

Conclusions

Hormonal disorders in the course of AC and PR, even in the case of good control of the arterial pressure, are associated with pronounced vasoconstriction, increased thoracic volaemia and impaired haemodynamic function of the left ventricle. These abnormalities vary, depending on the endocrine pituitary tumour: in AC the thoracic volaemia is increased, in PR vasoconstriction is observed, and they both have diagnostic and therapeutic implications. Haemodynamic changes in these patients may be detected with the use of advanced, non-invasive diagnostic tools. Individualised assessment by impedance cardiography may be useful in the assessment of early complications, facilitate early pharmacological treatment, and optimise therapy in this group of patients.

The study was supported by the Military Institute of Medicine (grant no. 335/WIM).

Acknowledgements

We would like to thank the medical personnel of the Department of Cardiology and Internal Diseases, the Department of Gastroenterology, Endocrinology and Internal Diseases, and the Department of Neurosurgery of the Military Institute of Medicine for their assistance in providing care to our patients.

References

1. Melmed S, Bronstein, MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol, 2018; 14 (9): 552-561
2. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest, 2009; 119:3189-3202
3. Melmed S. Medical progress: Acromegaly. N Engl J Med, 2006; 355: 2558-2573
4. Toulis KA, Robbins T, Reddy N, et al. Males with prolactinoma are at increased risk of incident cardiovascular disease. Clin Endocrinol, 2018; 88 (1): 71-76
5. Dekkers OM, Biermasz NR, Pereira AM, et al. Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab, 2008; 93: 61-67
6. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab, 2004; 89: 667-674
7. Krogh J, Selmer C, Torp-Pedersen C, et al. Hyperprolactinemia and the Association with All-Cause Mortality and Cardiovascular Mortality. Horm Metab Res, 2017;49:411-417
8. Pivonello R, Auriemma RS, Grasso L, et al. Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary, 2017; 20: 46-62
9. Jiang XB, Zhang J, Li CL, et al. Subclinical impairment of left ventricular longitudinal function in patients with prolactinomas. Endocr Pract, 2017; 23 (12): 1379-1386
10. Bondanelli M, Ambrosio MR, degli Uberti EC. Pathogenesis and prevalence of hypertension in acromegaly. Pituitary, 2001; 4 (4): 239-249
11. Fazio S, Cittadini A, Biondi B, et al. Cardiovascular effects of short-term growth hormone hypersecretion. J Clin Endocrinol Metab, 2000; 85:179-182
12. Maison P, Demolis P, Young J, et al. Vascular reactivity in acromegalic patients: preliminary evidence for regional endothelial dysfunction and increased sympathetic vasoconstriction. Clin Endocrinol, 2000; 53 (4): 445-451
13. Reuwer AQ, Sondermeijer BM, Battjes S, et al. Microcirculation and atherothrombotic parameters in prolactinoma patients: a pilot study. Pituitary, 2012;15:472-481
14. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J, 2018; 39 (33): 3021-3104
15. Krzesiński P, Gielerak G, Kowal J. Kardiografia impedancyjna -nowoczesne narzędzie terapii monitorowanej chorób układu krążenia. [Impendance cardiography – an advanced tool for monitoring cardiovascular diseases] Kardiol Pol, 2009; 67: 65-71
16. Haring R, Friedrich N, Volzke H, et al. Positive association of serum prolactin concentrations with all-cause and cardiovascular mortality. Eur Heart J, 2014; 35:1215-1221
17. Maison P, Demolis P, Young J, et al. Vascular reactivity in acromegalic patients: preliminary evidence for regional endothelial dysfunction and increased sympathetic vasoconstriction. Clin Endocrinol, 2000; 53 (4): 445-451
18. Fazio S, Cittadini A, Biondi B, et al. Cardiovascular effects of short-term growth hormone hypersecretion. J Clin Endocrinol Metab, 2000; 85:179-182
19. Colao, A, Ferone, D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev, 2004; 25:102-152
20. Pala NA, Laway BA, Misgar RA, Dar RA. Metabolic abnormalities in patients with prolactinoma: response to treatment with cabergoline. Diabetol Metab Syndr, 2015; 7: 99

21. dos Santos Silva CM, Barbosa FR, Lima GA, et al. BMI and metabolic profile in patients with prolactinoma before and after treatment with dopamine agonists. Obesity, 2011; 19: 800-805
22. Punjabi NM, Shahar E, Redline S, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance. The Sleep Heart Health Study Investigators, 2004; 160 (6): 521-530
23. Jaffrain-Rea ML, Moroni C, Baldelli R, et al. Relationship between blood pressure and glucose tolerance in acromegaly. Clin Endocrinol, 2001; 54 (2): 189-195
24. Berinder K, Nystrom T, Hoybye C, et al. Insulin sensitivity and lipid profile in prolactinoma patients before and after normalization of prolactin by dopamine agonist therapy. Pituitary, 2011; 14: 199-207
25. Arslan MS, Topaloglu 0, Sahin M, et al. Preclinical atherosclerosis in patients with prolactinoma. Endocr Pract, 2014; 20: 447-451
26. Erem C, Kocak M, Nuhoglu I, et al. Blood coagulation, fibrinolysis and lipid profile in patients with prolactinoma. Clin Endocrinol (Oxf), 2010; 73: 502-507
27. Holdaway IM, Rajasoorya RC, Gamble GD, et al. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab, 2004; 89: 667-674
28. Ritvonen E, Loyttyniemi E, Jaatinen P, et al. Mortality in acromegaly: a 20-year follow-up study. Endocr Relat Cancer, 2015; 23 (6): 469-48
29. Krogh J, Selmer C, Torp-Pedersen C, et al. Hyperprolactinemia and the Association with All-Cause Mortality and Cardiovascular Mortality. Horm Metab Res, 2017;49:411-417
30. Haring R, Friedrich N, Volzke H, et al. Positive association of serum prolactin concentrations with all-cause and cardiovascular mortality. Eur Heart J, 2014; 35:1215-1221
31. Reuwer AQ, Twickler MT, Hutten BA, et al. Prolactin levels and the risk of future coronary artery disease in apparently healthy men and women. Circ Cardiovasc Genet, 2009; 2: 389-395
32. Abdelhammed Al, Smith RD, Levy P, et al. Noninvasive hemodynamic profiles in hypertensive subjects. Am J Hypertens, 2005; 18: 51S-59S
33. Clayton RN. Cardiovascular function in acromegaly. Endocr Rev, 2003; 24: 272-274
34. Feld S, Hirschgerg R. Growth hormone, the insulin-like growth factor system, and the kidney. J Clin Endocrinol Metab, 1996; 5: 423-480
35. Hansen TK, Muller J, Thomsen K, et al. Effects of growth hormone on renal tubular handling of sodium in healthy humans. Am J Physiol Endocrinol Metab, 2001; 281 (6): E1326-E1332
36. Matta MP, Caron P. Acromegalic cardiomyopathy: a review of the literature. Pituitary, 2003; 6 (4): 203-207
37. Thuesen L, Christensen SE, Weeke J, et al. A hyperkinetic heart in uncomplicated active acromegaly. Explanation of hypertension in acromegalic patients? Acta Med Scand, 1988; 223: 337-343
38. Melmed S, Colao A, Barkan A, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab, 2009; 94: 1509-1517
39. Bhalla V, Isakson S, Bhalla MA, et al. Diagnostic ability of B-type natriuretic peptide and impedance cardiography: testing to identify left ventricular dysfunction in hypertensive patients. Am J Hypertens, 2005; 18: 73S-81S
40. Krzesiński P, Gielerak G, Stańczyk A, et al. What does impedance cardiography add more to the assessment of left ventricular diastolic function in essential hypertension? Pol Merkur Lekarski, 2015; 39: 352-358
41. Parrott CW, Burnham KM, Quale C, et al. Comparison of changes in ejection fraction to changes in impedance cardiography cardiac index and systolic time ratio. Congest Heart Fail, 2004; 10: 11-13
42. Cianci P, Lonergan-Thomas H, Brennan S, et al. Bedside use of impedance cardiography to document and monitor heart failure with preserved systolic function: delineation of impaired stroke volume reserve. J Card Fail, 2003; 9:S95
43. Krzesiński P, Gielerak GG, Kowal JJ. A "patient-tailored" treatment of hypertension with use of impedance cardiography: a randomized, prospective and controlled trial. Med Sci Monit, 2013; 19: 242-250
44. Yancy C, Abraham WT. Noninvasive hemodynamic monitoring in heart failure: utilization of impedance cardiography. Congest Heart Fail, 2003; 9 (5): 241-50
45. Gielerak G, Krzesiński P, Piotrowicz E, Piotrowicz R. The usefulness of impedance cardiography for predicting beneficial effects of cardiac rehabilitation in patients with heart failure. Biomed Res Int, 2013; 2013: 595369
46. Parrott CW, Quale C, Lewis DL, et al. Systolic blood pressure does not reliably identify vasoactive status in chronic heart failure. Am J Hypertens, 2005; 18: 82S-86S

Surgical treatment of pituitary tumour apoplexy – own experience

Leczenie operacyjne udaru gruczolaka przysadki – doświadczenia własne

Andrzej Styk, Grzegorz Zieliński, Łukasz Robak, Andrzej Koziarski

Department of Neurosurgery, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Assoc. Prof. Andrzej Koziarski, MD, PhD

Abstract. Pituitary apoplexy is a life-threatening condition caused by ischemic or hemorrhagic necrosis of the pituitary gland. Main symptoms include a sudden severe headache, nausea and emesis, as well as decreased consciousness, visual impairment and pituitary hormonal dysfunction. To date, there are no guidelines for the treatment of pituitary tumour apoplexy resulting in a better outcome. The aim of the study was to assess the neurosurgical treatment of patients with pituitary tumour apoplexy. Surgical treatment of seven pituitary tumour apoplexy patients was analysed. The most common symptoms are deterioration of visual field (7/7,100%), accompanied by cranial nerves III. IV, VI palsy (7/7, 100%), intense headache with nausea and vomiting (6/7, 85.6%). All patients (7/7, 100%) showed adrenocortical insufficiency pre-op, four of them (57.1%) – hypothyroidism and six – hypogonadism. All patients underwent surgery which resulted in the improvement of the visual field and cranial nerve function. Hypopituitarism was reported in all cases (100%) post-treatment. All tumours were confirmed nonsecretory adenomas in histopathological examination. After the surgery, each patient was provided with hormone replacement therapy and long-term follow-up.
Keywords: pituitary apoplexy, pituitary adenoma, transsphenoidal surgery, visual disturbances

Streszczenie. Udar przysadki jest stanem zagrażającym życiu spowodowanym martwicą niedokrwienną lub krwotoczną przysadki. Główne objawy to nagły, silny ból głowy, nudności, wymioty, pogorszenie stanu świadomości oraz zaburzenia widzenia i funkcji hormonalnej przysadki. Dotychczas nie opracowano zaleceń wpływających na poprawę skuteczności leczenia udaru przysadki. Celem pracy była ocena wyników leczenia neurochirurgicznego chorych z udarem guza przysadki. Analizowano wyniki leczenia operacyjnego 7 chorych z udarem gruczolaka przysadki. Najczęstszym objawem udaru przysadki jest ograniczenie pola widzenia (7/7,100%) z towarzyszącymi niedowładami nerwów gałkoruchowych (7/7,100%), silny ból głowy oraz nudności i wymioty (6/7, 85,7%). U wszystkich pacjentów (7/7,100%) stwierdzono przed operacją niedoczynność kory nadnerczy, u 4 (57,1%) niedoczynność tarczycy, a u 6 (85,7%) niedoczynność gonad. Chorych leczono operacyjnie, co doprowadziło do poprawy pola widzenia i ruchomości gałek ocznych. Niedoczynność przysadki stwierdzono u wszystkich chorych (100%) po zastosowanym leczeniu. Diagnostyka histopatologiczna wykazała nieczynny hormonalnie charakter guzów. Wszyscy pacjenci po operacji otrzymują substytucję hormonalną i pozostają w obserwacji klinicznej.
Słowa kluczowe: udar przysadki, gruczolak przysadki, operacja przezklinowa, zaburzenia widzenia

Delivered: 16/01/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 221-226

Corresponding author
Andrzej Styk, MD
Department of Neurosurgery,
Clinical Hospital of the Ministry of National Defence,
Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
e-mail: astyk@wim.mil.pl

Introduction

Pituitary apoplexy is a rare, potentially life-threatening condition caused by ischaemic or haemorrhagic necrosis of the pituitary gland [1]. The main clinical symptoms include a sudden severe headache, nausea and emesis, as well as decreased consciousness, visual impairment and pituitary hormonal dysfunction [2]. Accurate and early diagnosis is of crucial importance for the proper treatment [3]. No randomised studies have been conducted so far, and there are no guidelines available to improve the management of pituitary apoplexy.

The condition was presented for the first time in 1898 by Percival Bailey [4]. Another presentation of a lethal,

massive haemorrhage to a somatotropic pituitary tumour was published in 1905 by Bleibtreu [5]. Brougham et al. provided a broad description of five patients with the symptoms of pituitary necrosis, and in 1950 introduced the term "pituitary apoplexy" [6]. Recently, a number of case reports and few original articles have been published discussing the factors predisposing for pituitary apoplexy and evaluating treatment outcomes.

Aim of the study

The aim of the study was to assess the effects of life-saving surgical treatment in a group of patients hospitalised due to a pituitary tumour, diagnosed based on medical interviews and diagnostic tests.

Material and methods

The material included seven subsequent patients with the symptoms of pituitary apoplexy from the group of 689 patients diagnosed with pituitary adenoma, hospitalised at the Department of Neurosurgery of the Military Institute of Medicine in Warsaw from 2016 to June 2018. The analysed patients with haemorrhagic apoplexy of the pituitary tumour, diagnosed based on medical interviews and diagnostic tests, were admitted to the hospital for life-saving treatment.

All the analysed patients received pre-operative and post-operative endocrinological diagnostics, MR imaging examination of the central nervous system, and neurological tests focusing on the assessment of the field of vision and eye mobility. Pituitary apoplexy was diagnosed based on the typical clinical symptoms and the results of brain CT and MRI examinations. The radiological evaluation of the size of the pituitary tumour was performed using magnetic resonance examination of the hypothalamus-pituitary system, with a 1.5T or 3T scanner in T2-weighted frontal projections, and in T1-weighted sagittal and frontal projections, before and after the administration of contrast medium. Based on the measurements, the tumours were classified as: macroadenoma if the diameter was >10 mm, or microadenoma if the largest dimension was ≤10 mm. The assessment included intrasellar expansion (distortion/damage of the sellar floor, with tumour penetration to the sphenoid sinus), extrasellar expansion to the cavernous sinuses, according to Knosp classification, and suprasellar expansion (compression and deformation of the optic chiasm) of the adenomas.

Serum cortisol, PRL and fT_4 levels were determined at the admission. Normal range was set at:

- 6.2 – 19.4 µg/dl for cortisol, measured at 8.00 a.m.,
- 23 ng/ml for prolactin in females, and 16 ng/ml in males,
- 12 – 22 pmol/l for fT_4.

Three months following the surgery, the pituitary function was assessed, including the function of the adrenal cortex, thyroid and gonads. The occurrence of the symptoms of diabetes insipidus was also examined, both in the pre-operative and post-operative period.

The ophthalmological assessment included a general examination of the field of vision and eye mobility, as well as concurrent 3rd, 4th and 6th cranial nerve palsy.

Therapeutic management

After the diagnosis of pituitary apoplexy, all patients received 50 mg of intravenous hydrocortisone every 6 hours, with proton pump inhibitor, and intravenous crystalloid infusions. Following the surgical treatment, the substitution therapy with hydrocortisone was continued, initially at a dose of 4 x 50 mg/d, then at 30 mg/d orally. All patients received transsphenoidal surgery under general anaesthesia, with the use of the microsurgical technique. The biological material for histopathological tests obtained intraoperatively was preserved in 4% formaldehyde solution for 3 days, then transferred to the Institute of Pathology of the Oncology Centre in Warsaw, where it was histologically examined based on the WHO 2004 classification.

Results

The study group included 5 males and 2 females (M:F 5:2), whose mean age was 44.29 ±13.29 years old (median: 59.29 years; scope: 24-64 years). Until the disease onset (admission to the hospital), none of the analysed patients was diagnosed or treated due to a pituitary tumour or adrenal cortical insufficiency. Based on physical examination, symptoms of acromegaly and Cushing's disease were excluded in all the patients. The analysis of medical history allowed to identify the risk factors of pituitary apoplexy in five patients. Two patients (cases no. 1 and no. 7) used hypotensive drugs due to arterial hypertension together with acetylsalicylic acid. One male patient (case no. 24) abused anabolic steroids, and the symptoms of apoplexy occurred during a gym workout (in the Trendelenburg position, when the patient was lifting his own weight on a slanting bench). In another patient (case no. 2), the symptoms were observed after the administration of interferon due to hepatitis C infection, without any signs of concurrent coagulation disorders in standard laboratory tests. In patient no. 4, the symptoms were observed during prostate cancer surgery, after he was in the Trendelenburg position for about an hour.

Table 1. Clinical characteristics of 7 patients with pituitary apoplexy
Tabela 1. Charakterystyka kliniczna 7 chorych z udarem przysadki

№	Age	Sex	Symptoms of pituitary apoplexy							
			Sudden headache	Nausea and vomiting	Consciousness disorders	Loss of consciousness	Field of vision	Eye mobility	Adrenal cortex insufficiency (cortisol <5 µg/dl)	PRL concentration (ng/ml)
1	55	F	Yes	Yes	Yes	Yes	↓	Nerve VI	Yes	43
2	36	M	Yes	Yes			↓ left eye blindness	Nerve III	Yes	112
3	49	F	Yes	Yes			↓	Nerve III	Yes	39
4	64	M	Onset during anaesthesia / surgery				↓	Right eye ophthalmoplegia	Yes	51
5	37	M	Yes	Yes			↓	Nerve III	Yes	37
6	24	M	Yes	Yes	Yes	Yes	↓ left eye blindness	Right eye ophthalmoplegia	Yes	80
7	45	M	Yes	Yes			↓	Nerve III	Yes	31

Table 1 presents epidemiological data and symptoms of pituitary tumour apoplexy in the analysed group.

Sudden, severe headache with nausea and vomiting was the dominant clinical symptom associated with the disease onset. The symptoms were found in 6 patients. Two patients experienced consciousness disorders and lost consciousness for several minutes immediately after the onset. They both suffered from severe memory disorders and psychotic symptoms (delusions) during hospitalisation, before and after the surgery. Field of vision disorders were observed in all the patients. In five cases, they consisted in temporal visual deficits of various intensity in both eyes. One patient suffered from blindness in the left eye, with ipsilateral 3rd cranial nerve palsy. The last patient experienced blindness and ophthalmoplegia of the right eye, and light sensation in the left eye; the symptoms occurred 5 days following an incident of a severe headache during a gym workout. All the patients demonstrated impaired function of the 3rd, 4th and 6th cranial nerves. 3rd cranial nerve palsy was found in 4 patients, and isolated impairment of the abducens nerve function was observed in one patient. Two patients (no. 4 and no. 6) presented right-sided ophthalmoplegia at the admission (impaired function of all the eye movement nerves).

In two cases, patients reported increased thirst, associated with frequent passage of non-concentrated urine (cases no. 1 and no. 4). The symptoms suggested diabetes insipidus in the course of pituitary apoplexy. Laboratory tests revealed hypernatraemia in these patients. Their serum sodium concentrations were 149 mmol/l and 152 mmol/l, respectively.

Cerebral MRI examinations demonstrated pituitary macroadenoma in all the patients. The revealed tumours were characterised by suprasellar location, compression and dislocation of the optic chiasm, resulting in a reduced field of vision. The assessment of the parasellar proliferation according to Knosp classification revealed expanding tumour growth and deformation of the walls of the cavernous sinuses, which cased impairment of the eye movement nerves. In all the patients, the outline of the sellar floor was enlarged and deformed. Four patients also demonstrated penetration of the tumour through the distorted sellar floor to the sphenoid sinus. The MR image of the tumours revealed signs of haemorrhagic necrosis. Table 2 presents detailed information regarding the size and parasellar growth of the tumours.

Table 2. Detailed data of operated tumours and the scope of their parasellar growth and histopathological examination results
Tabela 2. Szczegółowe dane dotyczące wielkości operowanych guzów i zakresu ich wzrostu okołosiodłowego oraz wyników badań histopatologicznych

№	Age	Sex	Size of adenoma [mm]	Pituitary tumour growth			Histopathological diagnosis
				parasellar acc. to Knosp	suprasellar	intrasellar	
1	55	F	28 x 26 x 22	2	Yes	Yes	Gonadotropic adenoma LH (+)
2	36	M	21 x 28 x 25	2	Yes	Yes	Lactotropic adenoma PRL (+)
3	49	F	23 x 24 x 29	2	Yes	Yes	Gonadotropic adenoma LH (+), alphaSU (+)
4	64	M	39 x 31 x 24	2/3	Yes	Yes	Gonadotropic adenoma FSH (+)
5	37	M	21 x 19 x 32	2	Yes	Yes	Null cell adenoma
6	24	M	42 x 29 x 28	2/3	Yes	Yes	Lactotropic adenoma PRL (+)
7	45	M	29 x 23 x 34	2	Yes	Yes	Gonadotropic adenoma FSH (+), LH (+/-)

Due to the field of vision disorders, the patients underwent transsphenoidal surgery. During the procedure, necrotic haemorrhagic masses were found in all the patients in the pituitary adenoma diagnosed in MRI. The histopathological diagnostics confirmed the presence of necrotic haemorrhagic masses in the removed pituitary adenomas. The histopathological diagnostics revealed gonadotropic adenomas in 4 cases (57.1%), lactotropic adenoma in 2 cases (28.6%) and in one case (14.3%) a null cell adenoma. Table 2 presents a histopathological diagnosis of the removed tumours.

After the surgical treatment, all the patients received intravenous hydrocortisone (hormonal substitution), followed by oral therapy with 30 mg of cortisone daily. The symptoms of diabetes insipidus recognised in two patients disappeared after a few days following the surgery. After the operation, two patients (no. 4 and no. 7) developed symptomatic hyponatraemia which was addressed by pharmacological treatment. At the discharge, none of the patients demonstrated electrolyte imbalance.

The first signs of an improved function of the eye movement nerves were observed already at day 7 after the surgery. In five patients, the normal function was restored 3 months following the surgical treatment. In two patients, the eye movement dysfunction persists after 12 months of follow-up. The field of vision improved in all the patients, but in two of them, demonstrating the most pronounced defects before the surgery, the improvement in the blind eye has been insignificant, as it is limited to the sensation of light in the affected eye. Hormonal tests conducted 3 months after the surgical treatment revealed multi-hormone insufficiency of the anterior pituitary lobe in all the patients treated due to pituitary apoplexy. In three patients, hormonal tests conducted 12 months after the operation demonstrated normal corticotropic function of the pituitary. However, the thyreotropic and gonadotropic function is still impaired. Other patients require constant substitution therapy with adrenal cortex hormones and levothyroxine.

Post-operative MRI of the pituitary revealed complete resection of the adenomas in all the patients.

Discussion

Pituitary apoplexy, also referred to as pituitary tumour apoplexy, is a rare, life-threatening condition caused by ischaemic or haemorrhagic necrosis of the pituitary gland, with concurrent secondary insufficiency of the adrenal cortex [5]. In the analysed period, the problem affected 1% of patients treated surgically due to pituitary tumour. Rajasekaran et al. estimate the incidence of pituitary apoplexy with the typical violent clinical course at 2-7% of patients treated for pituitary tumour [7]. Cardoso and Petersen emphasise that in approximately 25% of patients with pituitary tumour MRI examination reveals signs of haemorrhagic necrosis in the tumour [8]. In most cases, the radiological image does not correlate with the clinical symptoms. The typical clinical course, involving a sudden, severe headache, nausea and vomiting, was observed in 85.7% of patients in the study. In one of the patients, the disease onset was different, as the pituitary apoplexy occurred during general anaesthesia for a urological procedure. The cited authors emphasise that the presented symptoms should suggest pituitary apoplexy and this condition should always be considered in differential diagnostics of subarachnoid haemorrhage, cerebral stroke, meningitis, acute hydrocephalus and brain tumour or abscess [3, 9]. In two patients, the disease onset was associated with decreased awareness and loss of consciousness. Randewa et al. claim that these symptoms usually indicate a large-sized tumour [10]. Pituitary adenomas are more frequently found in women, but pituitary adenoma affects men more often [11]. It is estimated that their incidence is over twice as high in men than in women. In the study material, pituitary

apoplexy was found 2.5 times more often in men, and the mean age of the analysed population was 44 years. According to the literature data, the mean age of patients suffering from pituitary apoplexy is similar: 51 years.

Pathophysiology of the disease has not been understood [1, 2, 5]. The most commonly mentioned factors predisposing for pituitary tumour necrosis include arterial hypertension, the sudden reduction of arterial pressure during cardiac, orthopaedic, urological and gynaecological surgeries, head trauma, coagulation disorders, dynamic endocrinological tests, pregnancy and intensive physical exercise [12]. These factors were found in five patients in this study. Particularly interesting is the case of apoplexy that occurred in a patient during urological surgery conducted in the Trendelenburg position (venous blood retention in cerebral circulation), associated with blood loss and arterial hypotonia.

Verres et al. believe that the clinical symptoms of pituitary apoplexy result from a sudden expansion of the existing pituitary tumour, which increases intracranial pressure and causes acute insufficiency of the adrenal cortex [5]. Jho et al. present a similar view [2]. Our study, based on the serum cortisol assays in all the patients, demonstrated adrenal cortex insufficiency. This is a life-threatening condition that always requires intravenous substitution treatment with hydrocortisone. At the Department of Neurosurgery, hydrocortisone is administered in an intravenous dose of 4 x 50 mg, together with intravenous infusions of crystalloids, until the patient's clinical status stabilises (normotension, stabilisation of consciousness). It is a management of choice in acute adrenal cortex insufficiency [3]. A sudden increase of the size of pituitary adenoma during apoplexy results in compression of the visual pathway, and damage of the cranial nerves responsible for eye movement [5, 7]. It is assumed to be an indication for urgent neurosurgical intervention that increases the chances for prompt improvement of vision [9, 11]. All the analysed patients received surgical therapy. Field of vision improved in seven of them (100%), but in two cases of severe visual impairment the improvement was insignificant, and the post-operative vision could be considered "useless" (two patients have only sensation of light in one eye). Impaired function of the cranial nerves responsible for eye movement leads to severe disability in the form of double vision or "turning off" the eye function as a result of upper eyelid dropping [13]. In the presented study palsy of the nerves responsible for eye movement was observed in all the patients. After the surgical treatment, improvement was observed in 71.4% of them. The cited authors present similar outcomes regarding functional improvement of the 3rd, 4th and 6th cranial nerve [3, 7, 13]. A sudden increase of the intrasellar volume causes direct compression and necrosis of the pituitary, exacerbated by ischaemia of the gland [5, 14]. In our study, early post-operative multi-hormone pituitary insufficiency was found in all the patients. Two patients were diagnosed with temporary diabetes insipidus. In three patients, 12 months after the neurosurgical procedure, the corticotropic pituitary function normalised: the adrenal cortex insufficiency resolved, although the thyreotropic and gonadotropic insufficiency persisted. Both Randeva et al. and Rajasekaran et al. found that constant therapy with glucocorticosteroids is necessary in 60% of patients treated for pituitary apoplexy [7, 10]. According to these authors, gonadotropic insufficiency occurred in 80% of patients, thyreotropic insufficiency was found in 60% of patients, and symptoms of diabetes insipidus were observed in 10-15% of patients, who were thus with treated desmopressin products. Bujawansa et al. demonstrate that the time of surgical intervention from the disease onset does not affect the post-operative pituitary function [15]. However, this factor is crucial for the improvement of vision, as emphasised also by other authors [3, 7, 13].

In our study, all tumours were adenomas. In four cases, they were gonadotropic adenomas (57.1%), classified as non-functional tumours; one lesion was null cell adenoma (14.3%), and two tumours were lactotropic adenomas (28.6%), found in male patients. All the cited authors find non-functional tumours to be dominant among the adenomas presenting with apoplexy [3, 10, 11]. In the study by Rutkowski et al., non-functional adenomas constituted 70% of the treated neoplasms, while lactotropic tumours accounted for 15% [13]. Wand et al. also present a significant dominance of non-functional tumours (86%) among those presenting with apoplexy [16]. The cited authors emphasise the need for long-term follow-up of patients treated for pituitary tumour apoplexy, in order to understand the pathophysiology of the process, and explore its relationships with the pathology of the treated tumours [3, 9, 16]. They underline the importance of a long-term assessment of the effectiveness of surgical treatment in the following aspects: (1) frequency of recurrence of adenoma after the apoplexy, (2) restoration of the function of the anterior and posterior pituitary lobe or recurrence of metabolic disorders, (3) resolution of visual disorders and (4) restoration of the function of the cranial nerves responsible for eye movement [10, 14].

Conclusions

Our previous experience indicates that pituitary apoplexy should be considered in every case of severe headache with vomiting and visual impairment. Contrast-enhanced MRI examination should be the basic imaging test in the diagnostics of the presented condition. The therapy of

choice in patients with pituitary tumour apoplexy with visual impairment is surgical treatment. Patients after a pituitary tumour apoplexy require endocrinological supervision, due to concurrent hormonal disorders.

References

1. Dubuisson AS, Beckers A, Stevenaert A. Classical pituitary tumour apoplexy: clinical features, management, and outcomes in a series of 24 patients. Clin Neurol Neurosurg, 2007; 109: 64-70
2. Jho DH, Biller BM, Agarwalla PK, et al. Pituitary apoplexy: large surgical series with grading system. World Neurosurg, 2014; 82: 781-790
3. Ajuk J, McGregor EJ, Mitchell RD, et al. Acute management of pituitary apoplexy – surgery or conservative management? Clin Endocrinol, 2004; 61: 747-752
4. Bailey P. Pathological report of a case of acromegaly with especial reference to the lesions in the hypophysis cerebri and in the thyroid gland and of a case of hemorrhage into the pituitary. Philadelphia Med J, 1898; 1: 789-792
5. Verrees M, Arafah BM, Selman WR. Pituitary tumor apoplexy: characteristics, treatment and outcomes. Neurosurg Focus, 2004; 16: E6
6. Brougham M, Heusner AP, Adams RD. Acute degenerative changes in adenomas of the pituitary body – with special reference to pituitary apoplexy. J Neurosurg, 1950;7:421-439
7. Rajasekaran S, Vanderpump M, Baldeweg S,et al. UK guidelines for the management of pituitary apoplexy. Clin Endocrinol (Oxf), 2011; 74: 9-20
8. Cardoso ER, Peterson EW. Pituitary apoplexy: a review. Neurosurgery, 1984; 14 (3): 363-373
9. Nawar RN, AbdelMannan D, Selma WR,et al. Pituitary tumor apoplexy: a review. J Intensive Care Med., 2008; 23: 75-90
10. Randeva HS, Schoebel J, Byrne J, et al. Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol (Oxf), 1999; 51:181-188
11. Johnston PC, Hamrahian AH, Weil RJ, et al. Pituitary tumor apoplexy. J Clin Neurosci, 2015; 22 (6): 939-944.
12. Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. J Neurol Neurosurg Psychiatry, 2001; 71: 542-545
13. Rutkowski MJ, Kunwar S, Blevins L, et al. Surgical intervention for pituitary apoplexy: an analysis of functional outcomes. J Neurosurg, 2018; 129 (2): 417-424
14. Arafah BM, Ybarra J, Tarr RW, et al. Pituitary tumor apoplexy: pathophysiology, clinical manifestations and management. J Intensive Care Med., 1997; 12: 123-134
15. Bujawansa S, Thondam SK, Steele C, et al. Presentation, management and outcomes in acute pituitary apoplexy: a large single center experience from the United Kingdom. Clin Endocrinol (Oxf), 2014; 80: 419-424
16. Wang Z, Gao L, Wang W, et al. Coagulative necrotic pituitary adenoma apoplexy: A retrospective study of 21 cases from a large center in China. Pituitary, 2018; 2

Correlation between the Ankle Brachial Index and the results of revascularisation in ischemia of lower limbs in a selected group of patients

Korelacja wskaźnika kostka-ramię i wyniku zabiegów rewaskularyzacyjnych w niedokrwieniu kończyn dolnych na wyselekcjonowanej grupie chorych

Piotr Florczuk-Dąbek,[1,2] Marcin Malka,[2] Arkadiusz Krakowiecki,[2] Łukasz Drelicharz,[3] Wojciech Jasek[1]

[1] Clinical Department of Plastic Surgery, Reconstruction Surgery and Burn Treatment, Dialysis Therapy, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Wojciech Witkowski, MD, PhD
[2] PODOS Wound Treatment Hospital in Warsaw; Medical Director: Marcin Malka, MD
[3] Clinical Department of Angiology and Cardiology, University Hospital in Krakow; Acting Head: Assoc. Prof. Paweł Maga, MD, PhD

Abstract. The number of lower-limb amputations in Poland exceeds 10,000 per year, which is one of the highest rate of amputations in Europe. This brings serious financial and social consequences. Most amputations are performed in patients with diabetic foot syndrome and critical ischemia of lower limbs. The Ankle Brachial Index evaluates blood supply in lower limbs. Patients with critical ischemia of lower limbs who did not undergo endovascular treatment are fraught with almost 100% risk of amputation of the lower limb within 6-12 months. The paper shows that even in the group of patients over 70 years old and with undetectable ABI, it is possible to perform effective revascularisation and avoid amputation.
Keywords: ABI, amputation of a lower limb, ankle-brachial index, critical ischemia of lower limb, revascularisation

Streszczenie. Liczba amputacji kończyn dolnych w Polsce przekracza 10 000 w skali roku, co stawia nas na jednym z pierwszych miejsc wśród krajów wykonujących największą ilość tych zabiegów w Europie. Niesie to za sobą poważne konsekwencje zarówno społeczne, jak i ekonomiczne. Najwięcej takich zabiegów przeprowadza się u chorych z zespołem stopy cukrzycowej oraz niedokrwieniem kończyn dolnych. Wskaźnikiem oceniającym ukrwienie w obrębie kończyny dolnej jest wskaźnik kostka ramię (ABI). W przypadku braku interwencji naczyniowej chorzy z krytycznym niedokrwieniem kończyn dolnych obarczeni są praktycznie 100% ryzykiem amputacji kończyny wciągu 6-12 miesięcy. Praca wykazuje, że nawet u chorych z nieoznaczalnym ABI oraz powyżej 70. roku życia możliwe jest wykonanie skutecznego zabiegu rewaskularyzacji oraz uniknięcie amputacji kończyny.
Słowa kluczowe: krytyczne niedokrwienie kończyny dolnej, wskaźnik kostka-ramię, ABI, amputacja kończyny dolnej, rewaskularyzacja

Delivered: 15/01/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 227-230

Corresponding author
Piotr Florczuk-Dąbek, MD
Clinical Department of Plastic Surgery,
Reconstruction Surgery and Burn Treatment,
Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 817818
e-mail: pflorczuk-dabek@wim.mil.pl

Introduction

The ankle brachial index (ABI) is the ratio of the blood pressure at the dorsalis pedis artery to the higher blood pressure in the right or left upper arm. The index value helps to assess the blood perfusion of the lower limb. To calculate ABI, the measurement presenting a higher value is used (the pressure is measured on the dorsalis pedis and on the posterior tibial artery). The normal range covers the values of 0.8 to 1.4. To determine ABI, a blood pressure cuff is fitted above the ankle on the lower limb, and a blind Doppler is used to measure the blood flow in the above arteries. One should bear in mind that in diabetics, whose blood vessels are more resistant to pressure, and in patients with a history of atherosclerosis, the ABI values within or above the normal range cannot be considered an indicator of proper blood perfusion in the limb. It also needs to be emphasised that the described test is technically impossible or very difficult to perform in patients with ulceration at the site where the cuff should be placed. Alternative tests include the toe brachial index, which is measured by fitting a special cuff connected to a Doppler device around the big toe. However, these values are lower by approximately 10 mm Hg from those measured at the ankle level [1-3]. The ABI values < 0.8 indicate limb ischaemia. If a patient reports rest pain persisting for at least two weeks and requiring the use of analgesics, and if a radiological examination (Doppler ultrasound or computed tomography angiogram) reveals concurrent venous necrosis or obstruction, this supports the diagnosis of critical ischaemia of the lower limb. Without a surgical intervention (endovascular therapy or traditional treatment involving implantation of vascular prostheses), the risk of limb loss after 6 to 12 months is 100% [4].

In Poland, over 10,000 amputations of lower limbs are conducted annually ("major" amputations, at the knee level, and "small" amputations, at the forefoot or midfoot level) [5]. The majority of these procedures are conducted in patients with diabetic foot syndrome, which may be also be accompanied by limb ischaemia, often critical. Amputation is an operation associated with numerous adverse psychosocial and economic consequences. It has always induced many negative emotions, both among the patients and doctors, as it is irreversible. Moreover, the 5-year survival following a major amputation (above the knee) is approximately 20%, which can be compared to the 5-year survival in certain oncological diseases, not to mention the quality of life of patients after amputation [6, 7].

Material and methods

The study involved 77 patients receiving outpatient treatment in the PODOS Wound Treatment Centre in Warsaw. Its aim was to determine the correlation between ABI values and radiological and haemodynamic results of revascularisation procedures (clinical outcomes, assessed in physical examination), and whether its value may be used as a prognostic factor before these procedures.

A retrospective analysis of medical records of patients treated in the years 2014-2016 was performed. They all presented symptoms of lower limb ischaemia, confirmed in a Doppler ultrasound examination. The revascularisation procedures were conducted at the Department of Angiogram of the University Hospital in Krakow, 6 Skawińska Street. The study group comprised 45 males (n = 45, mean age – 73.00 years old, standard deviation – 11.12) and 32 females (n = 32, mean age – 73.97, standard deviation – 10.86). The following were considered positive haemodynamic outcomes: improved limb temperature after the procedure (palpation test), palpable blood pressure at the peripheral arteries (dorsalis pedis artery), and active bleeding during the removal of necrotic tissue or wound debridement in the limb. A positive radiological effect was assessed intraoperatively, based on angiographic examination. The effectiveness of the procedure was assessed through a physical examination at the first outpatient visit following the surgery, usually 7 days after the operation. Non-parametric Mann-Whitney U-test and Friedman's ANOVA were used as statistical tools to compare the obtained values, due to limited group sizes and lack of normality of distribution of the variables. For the parametric variables, typical measures of dispersion and location were applied (standard deviation, means, median if applicable).

Study results and discussion

The mean ABI value in male patients was 0.59 (standard deviation SD = 0.43, $p > 0.05$, which did not reveal statistical significance), while in female patients the mean ABI value was 0.58 (SD = 0.46, $p > 0.05$, which also was not statistically significant). In the group of patients with positive radiological outcomes (n = 51), the mean age was 75.11 (SD = 11.25, $p = 0.03$ [Table 1]), and the mean ABI value was 0.60 (SD = 0.44, $p > 0.05$ [Table 2]). All the patients in this group were soon qualified for re-revascularisation, but the results of the new procedure are not considered in this study.

Table 1. Age in the group with positive radiological effect
Tabela 1. Zestawienie wieku w grupie z pozytywnym efektem radiologicznym

	Mean	Standard deviation	N-valid	P
Age	75.11	11.25	51	> 0.05

Table 2. Average value of ankle brachial index in the group of patients with positive radiological effect
Tabela 2. Średnia wartość ABI w grupie chorych z pozytywnym efektem radiologicznym

	Mean	Standard deviation	N-valid	P
ABI	0.60	0.44	68	> 0.05

Table 3. Average value of age in the group of patients with positive hemodynamic effect
Tabela 3. Średnia wieku w grupie pacjentów z pozytywnym efektem hemodynamicznym

	Mean	Standard deviation	N-valid	P
Age	72.88	11.31	68	> 0.05

Table 4. Average value of ABI in the group of patients with positive hemodynamic effect
Tabela 4. Średnia wartość ABI w grupie pacjentów z pozytywnym efektem hemodynamicznym

	Mean	Standard deviation	N-valid	P
ABI	0.61	0.45	68	> 0.05

Table 5. Average value of age in the group of patients with negative radiological effect
Tabela 5. Średni wiek pacjentów w grupie z negatywnym efektem radiologicznym

	Mean	Standard deviation	N-valid	P
Age	70.03	9.70	26	<0.05

Table 6. Average value of ABI in the group of patients with negative radiological effect
Tabela 6. Średnia wartość ABI w grupie pacjentów z negatywnym efektem radiologicznym

	Mean	Standard deviation	N-valid	P
ABI	0.55	0.46	26	> 0.05

Table 7. Average value of age in the group of patients with negative hemodynamic effect
Tabela 7. Średnia wartość wieku w grupie pacjentów z negatywnym efektem hemodynamicznym

	Mean	Standard deviation	N-valid	P
Age	77.33	6.49	9	> 0.05

Table 8. Average value of ABI in the group of patients with negative hemodynamic effect
Tabela 8. Średnia wartość ABI w grupie pacjentów z negatywnym efektem hemodynamicznym

	Mean	Standard deviation	N-valid	P
ABI	0.42	0.29	9	> 0.05

In the group of patients with positive haemodynamic outcomes (n = 68), the mean age was 72.89 years (SD = 11.31, p > 0.05 [Table 3]), and the mean ABI value was 0.61 (SD = 0.45, p > 0.05 [Table 4]). In the group of patients with negative radiological outcomes (n = 68), the mean age was 70.03 years (SD = 9.70, p < 0.05 [Table 5]), and the mean ABI value was 0.55 (SD = 0.46, p > 0.05 [Table 6]). The mean age of patients with negative haemodynamic outcomes was 77.33 years (SD = 6.49, p > 0.05 [Table 7]), and the mean ABI value was 0.42 (SD = 0.29, p > 0.05 [Table 8]). It is worth noting that the group of patients with negative haemodynamic effects also included patients with positive haemodynamic outcomes, which was probably due to a well-developed collateral circulation. In 14 study subjects, ABI was impossible to determine, in 8 of them a positive haemodynamic outcome was achieved, and 10 of them achieved positive radiological effects. In 4 patients, revascularisation did not result in a positive radiological or haemodynamic effect. With adequate radiological diagnostics and limited reliance on isolated risk factors (age, ABI), it is possible to obtain positive outcomes of revascularisation and to avoid limb amputation (only two major amputations and 3 amputations at the level of phalanges or forefoot were performed in study subjects, 7 deaths were reported, primarily due to other general medical causes). It is associated with immense benefits, both in the social and economic dimension. High perioperative mortality in patients over 70 years old who undergo amputations above the knee level should also be taken into consideration [8].

Conclusions

The ABI value should not be treated as a prognostic factor while assessing the effectiveness of endovascular therapy. As demonstrated in this study, positive treatment outcomes can be achieved in patients with indeterminable ABI, and in patients over 70 years of age. Moreover, the ABI value in the above groups did not differ significantly. In addition, ABI should not be used as the sole qualifying criterion for limb amputation. A positive radiological outcome does not always correlate with the haemodynamic outcome. Patients with a well-developed collateral circulation probably achieve a good haemodynamic effect despite the lack of a positive radiological outcome.

References

1. Szmidt J, Kużdżal J. Podstawy chirurgii. Podręcznik dla specjalizujących się w chirurgii ogólnej. [Basic surgery. Textbook for physicians specialising in general surgery] Medycyna Praktyczna, Krakow 2009: 1126-1246
2. Krzesiński K, Niedolaz K, Piotrowicz K, Gielerak G. Forum Medycyny Rodzinnej [Familily Medicine Forum], 2014; 8 (3): 117-126
3. Szczeklik A. Choroby wewnętrzne. [Internal diseases] Medycyna Praktyczna, Krakow 2006: 102-103
4. Nazarewski S. Krytyczne niedokrwienie kończyn dolnych. [Critical ischaemia of lower limbs] Chir Dypl, 2016; 01 (electronic version)
5. Raport w sprawie ustalenia taryfy świadczeń Agencji Ochrony Technologii Medycznych i Taryfikacji WT.521.17.2016 [Report of the Agency for Health Technology Assessment and Tariff System on the development of tariffs for services WT.521.17.2016]
6. Alvarsson A, Snadgren B, Wencel C, et al. A retrospective analysis of amputation rates in diabetic patients: can lower extremity amputations be further prevented? Cardiovasc Diabetol, 2012; 2 (11): 18
7. Morawiecki M, Wilemska-Kucharzewska K, Zielonka W. Amputacje kończyn na przestrzeni wieków. [Limb amputations through ages] Leczenie Ran 2015; 12 (4): 197-200
8. Uccioli L, Meloni M, Izzo V, et at. Critical limb ischaemia: current challenges and future prospects. Vasc Health Risk Manag, 2018; 14: 63-74

Role of mindfulness practice while using the adaptive fight strategy in coping with stress

Rola praktyki uważności w stosowaniu adaptacyjnej strategii walki w radzeniu sobie ze stresem

Magdalena Mazurkiewicz,[1] Kamilla Bargiel-Matusiewicz[2]

[1] Psychology Department, Chair of Social Psychology, SWPS University of Social Sciences and Humanities in Poznań; Head: Assoc. Prof. Wojciech Kulesza
[2] Psychology Department, Chair of Health and Rehabilitation Psychology, University of Warsaw; Head: Prof. Ewa Pisula, PhD

Abstract. The ability to use effective strategies in dealing with stress plays a vital role in the prevention of negative effects of stress, such as depression and even PTSD. Soldiers comprise a group particularly susceptible to chronic, intense exposure to stress. One of the latest techniques being used to develop this ability is a mindfulness practice. The aim of the study was to analyse the relationship between mindfulness practice and the adaptive strategy, i.e. fight, and the non-adaptive strategy, i.e. avoidance. The study involved 90 civilians, both practising and not practising mindfulness. The results showed that mindfulness practice provides for a more frequent adoption of the fight strategy and less frequent adoption of the avoidance strategy, and at the same time this relationship is mediated by a higher level of mindfulness. The fight strategy is associated with determination and motivation to act; thus, it seems to be particularly useful for soldiers. Future research will focus on verifying the effectiveness of mindfulness practice in a population of soldiers.
Keywords: coping with stress strategies, mindfulness, stress

Streszczenie. Umiejętność stosowania skutecznych strategii radzenia sobie ze stresem jest kluczowa w zapobieganiu jego negatywnym skutkom (np. depresji, a nawet PTSD). Żołnierze są jedną z grup szczególnie narażonych na długotrwałe intensywne doświadczanie stresu. Jedną z ostatnio badanych technik rozwijających tę umiejętność jest praktyka uważności. Celem przedstawionego badania była analiza relacji pomiędzy praktyką uważności a strategią adaptacyjną – walki, i strategią nieadaptacyjną – unikania. W badaniu uczestniczyło 90 cywilów praktykujących uważność i jej niepraktykujących. Wyniki wykazały, że praktyka uważności przewiduje częstsze stosowanie strategii walki, a rzadsze unikania, jednocześnie związek ten jest mediowany przez wyższy poziom uważności. Strategia walki związana jest z determinacją i motywacją do działania, wydaje się więc szczególnie przydatna dla żołnierzy. Dalsze badania zostaną poświęcone sprawdzeniu skuteczności praktyki uważności w grupie żołnierzy.
Słowa kluczowe: uważność, stres, strategie radzenia sobie ze stresem

Delivered: 30/01/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 231-237

Corresponding author
Magdalena Mazurkiewicz, MA
SWPS University of Social Sciences and Humanities
Interdisciplinary Doctoral Programme
19/31 Chodakowska St., 03-815 Warsaw
Phone: +48 603 375 160
e-mail: mmazurkiewicz@st.swps.edu.pl

Introduction

In military service soldiers experience long-term stress, particularly pronounced during military actions and missions. As a result, many of them suffer from PTSD and depression. These disorders, especially PTSD, are very difficult to treat and can lead to suicide [1]. According to the report from studies performed in NATO armies [2], the suicide rates in the army are higher than in the general population. In order to reduce the consequences of that stress, it is crucial to understand how the ability to cope with it can be developed.

Mindfulness is one of the recently studied techniques of dealing with stress. Since it proved to be an effective

preventive method reducing the stress levels, it raised the interest of the American Army. As a result, the Mindfulness-Based Mind Fitness Training (MMFT) was developed [3], and it became an integral element of preparation for deployment.

The effectiveness of dealing with stress is associated with the method applied, i.e. with the coping strategies. The mechanism of choice and types of strategies were described by Lazarus and Folkman in their relational theory of stress, considering stress as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" [4]. The mechanism involves a two-stage cognitive appraisal of the situation. First, a general evaluation is conducted to establish if the situation is neutral or threatening (primary appraisal). Next, one's own resources to deal with the situation are evaluated (secondary appraisal). A positive result (situation perceived as a challenge) leads to the selection of an adaptive/effective strategy. A negative result (situation perceived as a threat) leads to the selection of a non-adaptive strategy. Folkman and Lazarus classified the strategies of coping with stress, and they developed a tool for their measurement: the Ways of Coping Questionnaire (WCQ) [4].

During the Polish adaptation of the questionnaire, a fight strategy, specific for Poles, was identified [5]. A study conducted by Bargiel et al. [5] demonstrated that this strategy correlates positively with the cognitive appraisal of the situation as a challenge. Moreover, it obtained the highest score among other adaptive scales, and is the only one negatively correlated with the avoidance strategy. One may also consider the fight strategy the most useful one for soldiers, due to its active character. Therefore, we wanted to verify if mindfulness training may predict a more frequent use of the fight strategy and less frequent use of the avoidance strategy.

Mindfulness, complete awareness, is part of the 2.5 thousand years old Buddhist tradition. Despite a variety of schools and differences in texts and rituals, mindfulness remains the foundation of the Buddhist meditation practice [6]. The concept gained the interest of western researchers in the 1970s. Mindfulness is usually defined as intentional, non-judgemental and accepting attention directed towards the experience taking place in a given moment [6].

Mindfulness is developed by special mental training. Although the practice was derived from the Buddhist tradition, the basic form of meditation – practising mindfulness – is not associated with any religion, and can be applied by anyone, regardless of their religious beliefs or the culture in which they live or were raised [6]. The training consists in the observation of thoughts, emotions and physical sensations occurring in the body, with complete openness and acceptance, without the need to remove or avoid them. Practising mindfulness starts with concentration on breathing. It is important to focus on one thing, usually on one's breathing. When attention is distracted, and thoughts or feelings occur, one simply notices them and calmly concentrates on breathing again. The process is repeated whenever distractions appear. This practice emphasises the simple acknowledgement of the objects (thoughts, emotions) occurring in one's mind, and accepting them without any judgement, interpretation or reaction [7]. The practising person is asked to assume the same role of an observer when dealing with stressors and automatic reactions to them in daily life. This position of an observer creates a gap between perception and reaction, which helps to react to a stimulus in a more thoughtful, not automatic way [8]. This allows to develop the ability to be more aware of oneself and of the present moment, as well as to react in a more adaptive way to future stressors.

Numerous studies demonstrate that mindfulness training, both in the Buddhist practice and as non-religious training, increases the level of mindfulness [9, 10]. This relationship is linear: the longer one practices, the higher their level of mindfulness [10]. The minimum time of practice necessary to observe a significant increase in mindfulness is two weeks. After four weeks of regular training, the level of perceived stress is reduced considerably [10].

The best researched and most frequently used lay training system is the 8-week Mindfulness-Based Stress Reduction (MBSR) training created by Jon Kabat Zinn [6]. Studies conducted since its introduction demonstrate that the system successfully reduces stress, depression and anxiety levels [9]. Due to its universal character, it became the basis for other training addressing certain problems or needs: prevention of depression episodes or dependency relapse. The mindfulness-based prevention training for the army, MMFT, was created in a similar way. Studies on MMFT revealed [3] that after the completion of the training its participants demonstrated higher levels of mindfulness than the control group, lower levels of stress (they experienced stress less often), as well as they were able to regain their initial balance faster. The results were measured with self-description scales and physiological indicators, such as variability of the sinus rhythm or galvanic skin response.

In order to understand/identify the mechanism behind the correlation between mindfulness and stress, the types of strategies applied by people with a high level of mindfulness and practising mindfulness were examined. The results demonstrated that people with a higher degree of mindfulness more often use adaptive strategies, and less often the non-adaptive ones, which results in a higher level of mental well-being [11].

Adaptive strategies are described as focused on facing or confronting the problem directly in the mental, emotional or behavioural dimension. Non-adaptive strategies are defined as avoidance strategies, e.g. denial, mental dissociation or abandoning any action [12]. As mentioned before, in the Polish adaptation of the Folkman and Lazarus's scale a new strategy was developed, the so-called fight strategy. Its name may resemble the confrontational strategy described by Lazarus, but they differ significantly in structure and adaptive style. The Lazarus' scale is classified as a non-adaptive strategy, and it comprises aspects of aggressive behaviours: "I expressed anger towards the person who caused the problem". In the Polish version of the scale, only one item from the confrontational scale was preserved: "I stood by my beliefs, and I fought for what I wanted", which reveals no aspects of aggression. Other items are derived from different scales. For instance, the following item: "I knew what had to be done, so I doubled my efforts to make sure everything was right" was moved from the "following the plan" scale; whereas "I preserved my dignity, I didn't give up" is a new item, absent in the original version by Lazarus. Simultaneously, as mentioned before, studies demonstrated [5] that this is an adaptive strategy, positively correlated with the cognitive appraisal of the situation as a challenge and negatively correlated with the non-adaptive avoidance strategy. This scale is characterised by motivation and determination to face the challenge. Therefore, considering its active and adaptive specificity, we decided to examine if it is positively correlated with mindfulness and practice of mindfulness, as well as whether the avoidance strategy is negatively correlated with them.

Following the design of a study by Baer et al. [10], which showed that increased mindfulness as a result of training mediates the effect of mindfulness practice on the mental and physical health, we adopted a similar/analogous research strategy in our study.

Moreover, as intention is the fundamental element of the concept of mindfulness ("intentional focusing on the present moment"), we decided to control this variable by analysing two groups of people who do not meditate: (1) people who are planning to practice mindfulness and (2) people who are not planning to do it.

Research questions

1. Do meditating people present a higher level of mindfulness than those who do not meditate or those who are planning to start meditating?
2. Does the higher level of mindfulness in meditating people intervene in the relationship between practising mindfulness and more frequent use of the fight strategy, as well as less frequent use of the disengagement strategy in comparison to people who do not meditate or are planning to start meditating?

Method

Subjects

Study subjects (N = 90) were recruited via the Internet (announcement on Facebook). Those who were interested were directed to the website where the study was published. The study involved 54 females and 34 males, two people did not state their sex, but this variable was not considered in the analysis, as previous studies on mindfulness and coping strategies did not demonstrate that sex is a differentiating variable [9]. The mean age of the subjects was 34 years (M = 34.73; SD = 9.09). The lower age limit was 18 years, and the upper limit was not set, as studies did not demonstrate that this variable affects the level of mindfulness or the strategies of coping with stress.

The subjects were asked about their meditation experience and intention to start practising meditation.

Based on this information, they were assigned to three groups:

- (1) group of people practising meditation (N = 30),
- (2) group of people who do not practise and do not intend to practise meditation (N = 30),
- (3) group of people who do not practise, but intend to start practising meditation (N = 30).

Procedure and materials

The study was conducted in a quasi-experimental form, where the independent variable was meditation practice, the dependent variable were the strategies of coping with stress, and where mindfulness was the intervening variable between the practice of meditation and the strategies of coping with stress.

The independent variable was measured using the Meditation Practice Questionnaire created for this study. The questionnaire comprised questions regarding (1) meditation practice or lack thereof, (2) the intention to start meditation, if the subject did not meditate before.

The dependent variable – the strategy of coping with stress – was measured using the Behaviour Questionnaire I, which is a Polish version of the WCQ questionnaire by Folkman and Lazarus, adapted by Łosiak, and modified by Heszen-Niejodek, Januszek and Gruszczyńska [13]. It was developed to determine what type of activities people undertake in stressful situations. These activities include problem-solving strategies, as well as those applied to reduce emotional tension. The questionnaire comprises 67 test items regarding various behaviours in stressful situations. As a result of the exploratory factor analysis and the analysis of item

content, some items were transferred between scales. Finally, 10 scales presented in Table 1 were developed (charge > 0.3). As mentioned before, in the original version of the Lazarus and Folkman's questionnaire the number of strategies was lower (8), and the confrontational strategy (4 items) retained only one original item: "I stood by my beliefs and fought for what I wanted", which modified the content of the scale. For instance, the item: "I felt motivated to do something creative" was moved from the original positive reappraisals scale to the Polish fight scale.

The disengagement strategy (7 test items) preserved most of the original items, and its content did not change (example: "I acted as if nothing had happened", "I tried to forget about everything").

All the responses are marked on a 4-point Likert scale, where 1 means "definitely no", and 4 means "definitely yes". Our study subjects were asked to respond to all the questions, but the analysis included only the fight scale and the disengagement scale.

The following modifications were introduced to the study: (1) past tense was introduced in the instructions, (2) a final item was added to control if the stressful situation occurred at the time when the respondent already practised meditation.

Intervening variable – mindfulness, mediating the relationship between meditation and the applied strategies of coping with stress, was measured using the Mindfulness Attention Awareness Scale (MAAS), translated by Tomasz Jankowski [14]. The questionnaire was developed by Brown and Ryan [15] to measure individual differences, manifested in the occurrence frequency of the state of mindfulness, in other words, in the disposition towards mindfulness.

The MAAS questionnaire contains 15 test items. The respondents are asked to respond to the questions about how often they experience a given situation or state in their everyday life. The responses are marked on a 6-point Likert scale, where 1 means "almost always" and 6 means "almost never". Higher scores correspond to a greater disposition to mindfulness. The mean in the presented study was M = 4.23, SD = 0.67.

Example statements include: "I catch myself on being absorbed by the past or the future", "I perform work and tasks automatically, without being aware of what I'm doing", "I do not notice physical tension or discomfort until they really attract my attention".

Table 2 presents Cronbach's alpha, a measure of internal consistency, obtained in Brown and Ryan's study [15], in the Polish adaptation, and in our study.

The time for the completion of all three questionnaires was unlimited, but it took approximately 15 minutes on average.

Table 1. Reliability of scale (Cronbach's alpha) of Polish WCQ adaptation
Tabela 1. Rzetelności skali (alfa Cronbacha) polskiej adaptacji WCQ

Name of the scale	Adaptation by Heszen-Niejodek	Own study
Wishful thinking	0.67	0.79
Personal development	0.65	0.72
Fight	0.69	0.54
Reduction of tension	0.71	0.65
Disengagement	0.66	0.69
Minimising the problem	0.62	0.61
Solving the problem	0.52	0.36
Change of perspective	0.62	0.38
Self-consoling	0.58	0.63
Acting according to the plan	0.26	0.14

Statistical analysis

SPSS version 25 was used to analyse the results. To verify question 1, whether mindfulness practice predicts a higher level of mindfulness, analysis of variance for independent groups was performed. PROCESS version 3.2 (Model 4) was applied to analyse question 2, whether a higher level of mindfulness will mediate the relationship between the mindfulness practice and more frequent use of the fight strategy and less frequent use of the avoidance strategy [16]. The analysis included 10,000 bootstraps with adjusted confidence intervals of 95%.

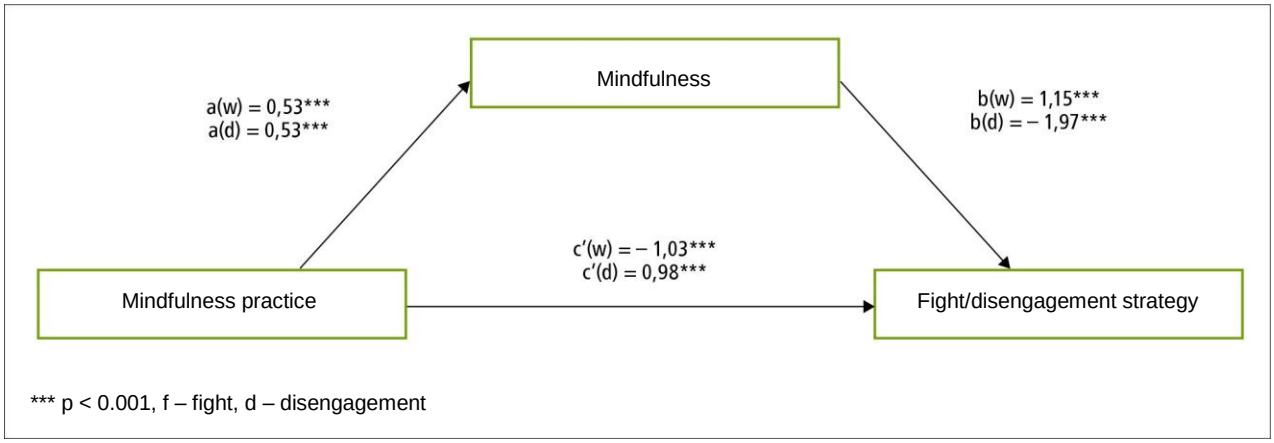


Figure 1. Relationship between mindfulness practice and fight/avoiding strategies mediated by mindfulness
Rycina 1. Relacja między praktyką uważności a strategią walki/unikania mediowana przez uważność

Table 2. Reliability of MAAS scale (Cronbach's alpha)
Tabela 2. Rzetelności skal (alfa Cronbacha) MAAS

Variable	Brown and Ryan – students	Brown and Ryan – adults	Adaptation by Jankowski	Own study
Mindfulness	0.82	0.87	0.80	0.85

Table 3. Results of Indirect Effect (IE)
Tabela 3. Wyniki efektu pośredniego (IE)

Dependent variable	IE	SE	95% CI (lower and upper confidence interval
Fight strategy	0.61	0.22	(0.25; 1.10)
Disengagement strategy	1.05	3.90	(-1.90: -0.39.)

Results

The analysis of variance for independent groups was used to answer the first question: whether the meditating subjects (Md) demonstrate a higher level of mindfulness than non-meditating subjects (NMd) or people who are planning to start meditation (PMd). The analysis revealed that meditation is associated with significant differences in the level of mindfulness ($F [2, 87] = 7.68$; $p < 0.01$). The *post hoc* comparisons with the use of Bonferroni's test demonstrated a significant difference ($p < 0.001$) between the group of meditating subjects ($M = 4.6$; $SD = 0.53$) and non-meditating subjects ($M = 4.0$; $SD = 0.73$), as well as between the group of meditating respondents and those who intend to start meditating ($M = 4.1$; $SD = 0.6$). The difference between the groups of non-meditating subjects and individuals planning to start meditating was statistically insignificant. As there were no significant differences in the level of mindfulness between the non-meditating group and individuals who intended to start meditating, further in the analysis both groups were considered as one, non-meditating group.

To verify the second hypothesis that a higher level of mindfulness in meditating individuals affects/predicts a more frequent use of the fight strategy and a less frequent use of the disengagement strategy compared to non-meditating people (NMd + PMd), two mediation analyses were conducted: one for the fight strategy and one for the disengagement strategy. Meditation was the predictor in both cases, mindfulness was the intervening factor, the dependent variable was the fight strategy (first analysis) and disengagement strategy (second analysis) (Figure 1). In the analysis of the fight strategy, the total model was significant: $F (1, 88) = 14.67$, $p < 0.001$, $R^2 = 0.14$. The indirect effect was significant and positive (Table 3), whereas the direct effect was significant and negative (Figure 1). In the analysis of the disengagement strategy, the total model was significant $F(1, 88) = 14.67$, $p < 0.001$, $R^2 = 0.14$. The indirect effect was significant and negative (Table 3). The direct effect was significant and positive (Figure 1).

Discussion

The study confirmed that meditating individuals demonstrate a higher level of mindfulness than those who do not meditate. This outcome is consistent with previous studies by Brown and Ryan [15], in which individuals who practice mindfulness, both in the Buddhist tradition and as part of the MBSR programme, obtained higher MAAS scores compared to the control group. However, although the difference of means in our study is statistically significant, it is not large. It may be due to the fact that many subjects practised meditation for less than a year. As mentioned previously, the level of mindfulness increases linearly along the time spent on practising meditation.

Our study also demonstrated that the sole intention to meditate is not associated with a higher level of

mindfulness. It may be assumed that people who intend to start meditation are interested in the subject and try to be more mindful. However, the intention alone is not sufficient to increase mindfulness, and training is a necessary condition.

In compliance with our assumptions, the study revealed that individuals with a higher level of mindfulness more often use the fight strategy and less frequently resort to disengagement. As mentioned before, the fight strategy is defined as decisive actions focused on problem-solving, characterised by high determination and motivation. This result clearly demonstrates that acceptance, which is characteristic of mindfulness, cannot be mistaken for resignation. Acceptance is direct, undisturbed contact with experience [17]. It is the opposite of avoidance, denial or distortion of the experience. These outcomes are consistent with the theoretical mechanism in which mindfulness affects a person's behaviour. The appraisal of a situation as changeable, together with an accepting attitude are sources of strong motivation for action, and willingness to accept risk. Therefore, the higher the level of mindfulness, the greater the engagement in action. The disengagement strategy is the opposite of action-oriented strategies. The subject does not engage in solving the problem, gives up and expects the situation to improve on its own. This strategy is usually adopted by subjects who perceive the situation as an unchangeable threat. This result is also consistent with the expected theoretical mechanism of action in which a person with a high level of mindfulness perceives the situation and reacts to it in a manner opposite to the one presented above.

Palmer and Rodger [18] obtained similar results. Their study revealed a positive relationship between mindfulness and rational coping with stress, as well as a negative correlation between mindfulness and emotional and avoidance-oriented coping with stress.

Limitations and further studies

The study group comprised individuals who did not practice meditation for long (less than a year), which certainly reduced the difference in the mean levels of mindfulness between meditating and non-meditating subjects. This is probably also associated with the principal effect being the opposite of the indirect effect. Further studies should be far more restrictive regarding the time of practice: at least one year of practice, and systematic training at least 5 times a week should be required. In addition, the study group should be larger. However, the control of mindfulness practice is still based solely on the declaration of participants. Therefore, to be certain of the effectiveness of the mindfulness practice, an experimental study should be conducted in which one group of subjects participates in mindfulness training, and the other group is, for example, on the waiting list. Such a study, using the MMFT training, would be particularly interesting when conducted among Polish soldiers. Previous studies involving veterans in Israel demonstrated that active problem-solving strategies (appraisal of the situation as a challenge) are positively correlated with more effective coping with stress and with less pronounced consequences of long-term combat stress [19], contrary to the passive strategies, concentrated on the alleviation of unpleasant emotions. However, the levels of mindfulness or particular strategies were not examined in this study. Considering the fact that stressors in the army are significantly different than those experienced in everyday civilian life (especially with regard to the threat to life), a questionnaire of coping with stress addressing the specificity of military service should be developed and examined.

Importantly, using a certain strategy in response to a situation is not a single reaction, but a process repeated multiple times throughout the duration of the event, and the type of strategy used may change. This process involves the primary appraisal (of the situation), secondary appraisal (threat vs challenge), and the choice of the strategy [4]. Elasticity in the use of strategies according to the changing conditions in a given situation and between different situations is presently deemed to be the key element in adaptive coping with stress, and it provides a new area for stress research [20]. A recent study conducted by Kenga et al. [20] demonstrated that a higher level of mindfulness predicts greater elasticity in the use of adaptive strategies. Adaptive strategies can be active (fight) or passive (e.g. re-evaluation of the problem). The choice of the strategy depends on the context and the resources available to the individual at the given moment. Our study concentrated on the average frequency of the use of a strategy, but it disregarded the aspect of elasticity in the adaptation of the type of the strategy to the changing situational context. A study including this aspect in the context of everyday functioning in the army would be very interesting.

Conclusions

- It has been demonstrated that mindfulness practice is associated with a higher level of mindfulness and, importantly, a higher level of mindfulness predicts a more frequent use of the adaptive strategy of coping with stress: fight.
- Adaptive strategies are associated with lower levels of stress, and as a consequence, with a lower risk of negative emotional disorders such as PTSD or depression.
- Due to the specificity of the fight strategy, characterised by determination and motivation for problem-solving, it is particularly useful for soldiers participating in military missions.
- It has also been demonstrated that higher levels of mindfulness predict a less frequent use of disengagement, a non-adaptive strategy.
- Non-adaptive strategies are associated with more frequent experiencing of stress, and as a result, with an increased risk of emotional disorders, such as depression, anxiety or PTSD.
- The disengagement strategy involves an appraisal of the situation as a threat which cannot be changed. Such a distorted perception of the situation leads to the avoidance of decision-making, resulting in the lack of any action. In a situation of increased risk, such as a military mission, the effects can be negative not only for the individual, but for an entire group of soldiers.

References

1. Ramsawh HJ, Fullerton CS, Mash HBH, et al. Risk for suicidal behaviors associated with PTSD, depression, and their comorbidity in the U.S. Army. J Affect Dis, 2014;161:116-122
2. Unicki P, Unicki St. Samobójstwa w armiach NATO i państw partnerskich w pierwszej dekadzie XXI wieku. [Suicides in the Armed Forces of NATO and partner states in the first decade of the 21st century] Mil. Phys., 2018; 96 (2): 105-111
3. Johnson DC, Thorn NJ, Stanley EA, et al. Modifying resilience mechanisms in at-risk individuals: a controlled study of mindfulness training in marines preparing for deployment. Psychiatry, 2014; 171: 844-853
4. Lazarus RS, Folkman S. Stress, appraisal and coping. New York, Springer-Verlag 1984
5. Bargiel-Matusiewicz K, Trzciniecka-Green A, Kielan K. Ocena poznawcza a strategie zaradzcze podejmowane w obliczu egzaminu. [Cognitive assessment and coping strategies applied during exams] Psychoterapia, 2003; 3 (130): 55-61
6. Kabat-Zinn J. Full catastrophe living. New York, Delta 1990
7. Segal ZV, Williams JGM, Teasdale JD. Mindfulness-based cognitive therapy for depression: A new approach for preventing relapse. New York, Guilford Press 2002
8. Bishop SR, Lau M, Shapiro S. Mindfulness: A proposed operational definition. Clin Psychol Sci Pract, 2004; 11: 230-241
9. Creswell JD. Mindfulness interventions. Ann Rev Psychol, 2017;68:491-516
10. Baer RA, Carmody J, Hunsinger M. Weekly change in mindfulness and perceived stress in a mindfulness-based stress reduction program. J Clin Psychol, 2012; 68 (7): 755-765
11. Weinstein N, Brown KW, Ryan RM. A multi-method examination of the effects of mindfulness on stress attribution, coping, and emotional well-being. J Res Pers, 2009; 43 (3): 374-385
12. Roth S, Cohen LJ. Approach, avoidance, and coping with stress. Am Psychol, 1986; 41 (7): 813-819
13. Heszen-Niejodek I, Januszek M, Gruszczyńska E. Sprawozdanie końcowe z wyników uzyskanych w ramach projektu: Styl radzenia sobie ze stresem, rodzaj sytuacji stresowej a przebieg i efektywność radzenia sobie. Grant KBN NR 1 H01F 014 15,2001 [Final report of the outcomes of the project: Style of coping with stress, types of stresfull situations and the course and effectiveness of coping. Grant no. 1 H01F 014 15,2001 of the State Committee for Scientific Research]
14. Jankowski T. Struktura koncepcji siebie i procesy przetwarzania informacji o sobie u osób o różnym stopniu uważności. Praca doktorska [The structure of the self-concept and self-information processing in people with varying levels of mindfulness. Doctoral thesis] Instytut Psychologii KUL, Lublin 2006
15. Brown K, Ryan RM. The benefits of being present: Mindfulness and its role in psychological well-being. J Pers Soc Psychol, 2003; 84: 822-848
16. Hayes AF. Introduction to meditation, moderation, and conditional processes analysis. Guilford Press, New York 2013
17. Crane R, Elias D. Being with what it is – mindfulness practice for counsellors and psychotherapists. Therapy Today, 2006; 17 (10): 31
18. Palmer A, Rodger S. Mindfulness, stress, and coping among university students. Can J Counsel, 2009; 43: 198-212
19. Gilbar 0, Ben-Zur H, Lubin G. Coping, mastery, stress appraisals, mental preparation, and unit cohesion predicting distress and performance: a longitudinal study of soldiers undertaking evaluation tasks. Anxiety Stress Coping, 2010; 23 (5): 547-562
20. Keng S-L, Choo X, Tong. Association between Trait Mindfulness and Variability of Coping Strategies: a Diary Study. Mindfulness, 2018; 9 (5): 1423-1432

Carotid intima-media thickness does not correlate with the activity of plasma PAF acetylhydrolase in patients with anaphylaxis

Grubość kompleksu intima-media tętnic szyjnych wspólnych nie koreluje z aktywnością osoczowej acetylohydrolazy PAF u chorych z anafilaksją

Krzysztof Łukasz Piwowarek,[1] Aleksandra Juszkiewicz,[2] Agnieszka Rzeszotarska,[3] Jerzy Kruszewski[1]

[1] Department of Infectious Diseases and Allergology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Prof. Jerzy Kruszewski, MD, PhD
[2]Department of Internal Diseases and Rheumatology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw;
Head: Prof. Witold Tłustochowicz, MD, PhD
[3]Department of Clinical Transfusiology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Assoc. Prof. Jolanta Korsak, MD, PhD

Abstract. Background. The activity of plasma PAF acetylhydrolase has in recent years aroused interest as a potential biomarker of the atherosclerotic process. This parameter is also assessed as a risk factor for severe anaphylaxis. The aim of the study. Comparison of the stage of subclinical atherosclerosis depending on the history of severity of anaphylaxis and analysis of correlation with the activity of plasma PAF acetylhydrolase. Material and methods. A cross-sectional study was conducted from December 2018 to December 2019 with the participation of anaphylactic patients and a control group with negative atopic history. The severity of the reaction was assessed using the Muller classification. Ultrasound measurement of carotid intima-media was performed using manual and semi-automatic methods. Plasma PAF acetylhydrolase activity was measured using the colorimetric method. Results. The thickness of intima-media was statistically slightly lower in the subgroup of patients with grade III and IV anaphylaxis compared to the subgroup of patients after grade I and II reactions; however, this difference was significant only with manual measurement (0.672 mm *vs* 0.582 mm, p = 0.0126). No correlation was found between the thickness of intima-media and the plasma PAF acetylhydrolase activity regardless of the measurement method used. Conclusions. The CIMT value does not correlate with the activity of PAF plasma acetylhydrolase in the population of patients after anaphylactic reactions.
Keywords: atherosclerosis, anaphylaxis, PAF acetylhydrolase (PAF-AH), platelet-activating factor

Streszczenie. Wstęp. Aktywność osoczowej acetylohydrolazy PAF wzbudza w ostatnich latach zainteresowanie jako potencjalny biomarker procesu aterosklerotycznego. Parametr ten oceniany jest także jako czynnik ryzyka ciężkiego przebiegu anafilaksji. Cel pracy. Porównanie stopnia zaawansowania subklinicznej miażdżycy w zależności od stopnia nasilenia anafilaksji w wywiadzie oraz analiza korelacji z aktywnością osoczowej acetylohydrolazy PAF. Materiał i metody. Badanie przekrojowe prowadzono w okresie od grudnia 2018 r. do grudnia 2019 r. z udziałem pacjentów po anafilaksji oraz grupy kontrolnej z ujemnym wywiadem atopowym. Ciężkość reakcji oceniano z wykorzystaniem klasyfikacji Mullera. Wykonywano ultrasonograficzny pomiar grubości kompleksu intima-media tętnic szyjnych wspólnych metodą manualną i półautomatyczną. Aktywność osoczowej acetylohydrolazy PAF oznaczano metodą kolorymetryczną. Wyniki. Grubość kompleksu intima-media statystycznie była nieznacznie mniejsza w podgrupie chorych po anafilaksji III i IV stopnia niż w podgrupie chorych po reakcjach I i II stopnia, ale różnica ta była istotna tylko w przypadku pomiaru manualnego (0,672 mm *vs* 0,582 mm, p =0,0126). Nie stwierdzono korelacji pomiędzy grubością kompleksu a aktywnością osoczowej acetylohydrolazy PAF, niezależnie od stosowanej metody pomiaru. Wnioski. Wartość CIMT nie koreluje z aktywnością osoczowej acetylohydrolazy PAF w populacji chorych po reakcjach anafilaktycznych.
Słowa kluczowe: acetylohydrolaza PAF (PAF-AH), anafilaksją, czynnik aktywujący płytki, miażdżyca

Delivered: 08/03/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 238-243

Corresponding author
Krzysztof Łukasz Piwowarek, MD
Department of Infectious Diseases and Allergology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 817 519, fax 261 818544
e-mail: kpiwowarek@wim.mil.pl

Introduction

Plasma platelet-activating factor acetylhydrolase (PAF-AH), also referred to as lipoprotein-associated phospholipase A2 (Lp-PLA2, EC no. 3.1.1.47), is an enzyme whose relationship with the activity of the atherosclerotic process has been suggested in many publications. The broadest exploration of this subject was presented in the Lp-PLA2 Studies Collaboration, a meta-analysis from 2010 comprising 32 prospective studies, involving a total of 79,036 participants [1]. It demonstrated that concentration and activity of PAF-AH are associated with the risk of coronary disease, ischaemic stroke and death due to cardiovascular causes. Moreover, plasma PAF-AH appeared to be a predictor of cardiovascular incidents comparable to systolic blood pressure and non-HDL cholesterol levels [1]. A few theories explain the pathophysiology of the relationship between PAF-AH and the development of atherosclerosis. The following mechanisms were suggested:

- degradation of PAF and related compounds, so-called PA-mimetics, reduces their pro-inflammatory effect;
- free oxidised phospholipids created with the participation of PAF-AH can increase the immunogenicity of oxidised low-density lipoproteins (oxLDL),
- another product of the enzyme, lysophosphatidylcholine (LPC), induces synthesis of cytokines, and increases the migration of smooth muscle cells and monocytes,
- PAF-AH is produced by macrophages, especially in the regions of their increased migration, e.g. in unstable atherosclerotic plaque.

Despite the above facts, the results of previous studies exploring the relationship between the activity of PAF-AH and morphological markers of atherosclerosis, such as intima-media thickness (IMT) were inconsistent. First studies on patients with disturbed metabolism of lipids and with metabolic syndrome did not reveal any correlation between the above parameters [2-4]. Similar conclusions were reached in studies involving children with familial hypercholesterolaemia, as well as by the American Multi-Ethnic Study of Atherosclerosis project, which comprised approximately six thousand participants [5, 6]. On the other hand, a statistically significant relationship was observed in studies involving subjects with low cardiovascular risk, a population of Japanese males aged 50-70 years old, HIV-positive patients, patients with β-thalassemia, chronic ischaemic heart disease and rheumatoid arthritis [7-12]. Findings from these studies indicated that higher PAF-AH activity is associated with higher IMT values. However, the relationship between IMT and PAF-AH activity in the population of anaphylactic patients was not previously examined. It is worth noting that Italian and American studies demonstrate a significantly reduced activity of plasma PAF-AH in patients with a history of severe anaphylaxis [13-16]. This mechanism is clear: PAF is one of the key mediators of anaphylaxis; therefore, deficiency of the enzyme degrading this mediator should be associated with a more severe course of the disease. On the other hand, referring to the previously mentioned outcomes of studies on the role of PAF-AH in the atherosclerotic process, low activity of PAF-AH in anaphylactic patients could potentially be a protective factor against atherosclerosis.

Aim of the study

The aim of the study was to analyse the correlation between plasma PAF-AH activity and the carotid intima-media thickness (CIMT) in patients with a history of anaphylaxis. CIMT, determined in ultrasound examination, was adopted as a morphological indicator of the subclinical atherosclerotic process.

Material and methods

Subjects of the study were recruited among the patients of the Department of Infectious Diseases and Allergology, and its outpatient allergology clinic. The study group comprised 62 patients with a history of an anaphylactic reaction. Control group included ten patients with a negative atopic history. Patients in the study group were divided into two subgroups, according to the severity of anaphylaxis, assessed according to the Muller scale (Table 1) [17]. The first group comprised patients with a history of reactions of grade two maximum intensity (28 patients). The second group comprised patients with a

Table 1. Müller's grading system of anaphylaxis according to severity [17]
Tabela 1. Klasyfikacja ciężkości przebiegu anafilaksji wg H.L. Mullera [17]

Stage I	Generalised urticaria Pruritus Malaise Anxiety
Stage II	Any of the above and at least two of the following: Angioedema Chest discomfort Nausea Vomiting Diarrhoea Abdominal pain Dizziness
Stage III	Any of the above and at least two of the following: Dyspnea Wheezing Stridor Dysarthria Hoarseness Helplessness Confusion Feeling of imminent death
Stage IV	Any of the above and at least two of the following: Hypotension Collapse Loss of consciousness Cyanosis

history of at least one reaction of grade three or four (34 patients). The activity of plasma PAF-AH was determined using colorimetric method and PAF Acetylhydrolase Assay Kit Item No. 760901 by Cayman Chemical Company. Following the recommendations of the manufacturer, the absorbance of radiation of 412 nm was measured six times, at one-minute intervals. As plasma was collected to two vials from each participant, the measurements were also performed twice. CIMT was determined in an ultrasound examination of the common carotid artery (CCA), with the use of LOGIQ S7 Expert with MLG-15 transducer by GE Healthcare. Each study started with B (brightness) presentation imaging in order to detect CCA in transverse projection.

Next, the longitudinal projection was applied, and the frequency of the transducer was optimised to the depth of the analysed structure. The CIMT was measured on the posterior carotid wall, following the protocol described by Kisiel et al. [18]. It defines atherosclerotic plaque as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT or demonstrates a thickness of ≥1.5 mm as measured from the media-adventitia interface to the intima-arterial lumen interface. CIMT was defined as a mean value of 6 measurements: 1, 2, and 3 cm proximal to the bifurcation, bilaterally [18]. In addition, alternative CIMT measurements were conducted by a semi-automatic method, with the use of ultrasound device software. The ultrasonographist marked the measured area of 1 2 cm from the bifurcation, and the measurement was done by the default programme installed in the device. All statistical analyses were performed with the use of STATISTICA 13.0 by StateSoft Inc. Kolmogorov-Smirnov test, Lilliefors test and Shapiro-Wilk test were used to determine the normality of distribution of variables. Next, according to the results, parametric or non-parametric tests were applied to compare the study subgroups: t-test or Mann-Whitney U-test. To compare multiple groups, Bonferroni correction for t-test and ANOVA analysis of variance or Kruskal-Wallis test by ranks were applied.

Table 2. CIMT assessment results – manual technique
Tabela 2. Wyniki pomiarów CIMT – technika manualna

Subgroup	n	Average	SD	Median	p
Grade I and II anaphylaxis	28	0.0672	0.0151	0.0642	0.0339
Grade III and IV anaphylaxis	34	0.0583	0.0122	0.0560	
Control group	10	0.0594	0.0129	0.0572	

Results

The CIMT value in the manual assessment using the method by Kisiel et al. was significantly lower in the subgroup of patients with a severe anaphylactic reaction (0.672 *vs* 0.582 mm, p = 0.0126 in Student's t-test), and no differences compared to the control group were observed (Table 2). Considering in this case multiple comparisons with the control group and Bonferroni correction, the result was still statistically significant (a ≈ 0.0167). Also, ANOVA analysis of variance provided a statistically significant difference for the comparison of multiple groups (p = 0.0339). It is worth noting that mean values of arterial pressure, age, sex, body weight, BMI, concentrations of lipid fractions, hs CRP (high-sensitivity c-reactive protein), rate of smokers and patients with arterial hypertension were statistically similar in both groups. These are the typical factors affecting the development of atherosclerosis, and thus the CIMT value. Their similar distribution in both subgroups suggests the effect of another factor on the CIMT of the common carotid artery in study subjects (Figure 1). Also in semi-automatic assessment, CIMT was lower in the second subgroup (Figure 2, Table 3), although in this case the difference was not statistically significant (0.634 *vs* 0.564 mm, p = 0.0618 in the Mann-Whitney U-test), despite the fact that both methods demonstrated a considerable correlation of measurement results (Spearman's rank correlation coefficient r_S = 0.933, with preserved statistical significance [Figure 3]). This was probably due to the limited size of the study group, which prevented a normal distribution of the variable. The

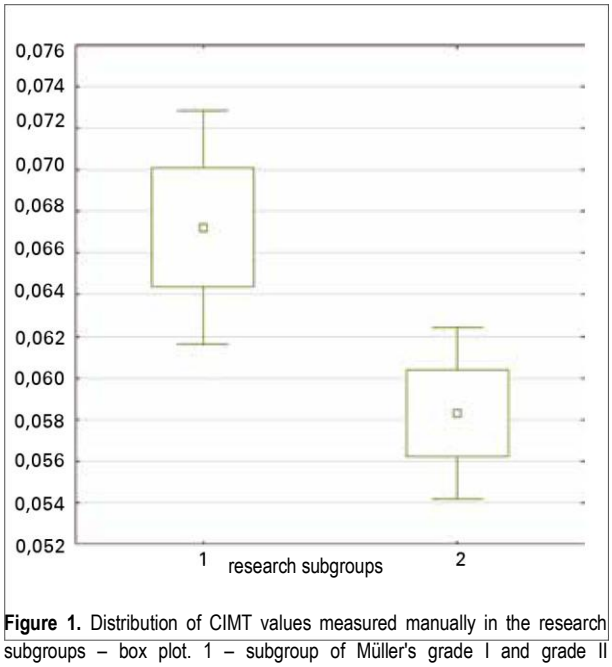


Figure 1. Distribution of CIMT values measured manually in the research subgroups – box plot. 1 – subgroup of Müller's grade I and grade II anaphylaxis, 2 – subgroup of Müller's grade III and grade IV anaphylaxis.
Rycina 1. Rozkład wartości CIMT mierzonego manualnie w podgrupach badawczych–wykres ramka–wąsy. 1 –podgrupa anafilaksji I i II stopnia wg Mullera, 2 – podgrupa anafilaksji III i IV stopnia wg Mullera.

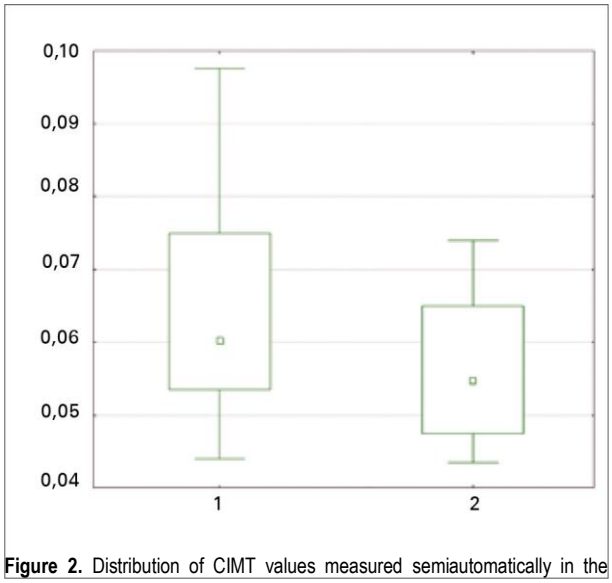


Figure 2. Distribution of CIMT values measured semiautomatically in the research subgroups – box plot. 1 – subgroup of Müller's grade I and grade II anaphylaxis, 2 – subgroup of Müller's grade III and grade IV anaphylaxis.
Rycina 2. Rozkład wartości CIMT mierzonego półautomatycznie w podgrupach badanych – wykres ramka–wąsy. 1 – podgrupa anafilaksji I i II stopnia wg Mullera, 2 – podgrupa anafilaksji III i IV stopnia wg Mullera.

presented differences did not result from the plasma activity of PAF-AH, as in the study groups there was no significant correlation between the enzyme's activity and CIMT value, neither in the manual nor in the semi-automatic test. The Spearman's rank correlation coefficients were 0.056 and 0.117, respectively (Table 4-5).

Table 3. CIMT assessment results – semiautomatic technique
Tabela 3. Wyniki pomiarów CIMT – technika półautomatyczna

Subgroup	n	Mean	SD	Median	p
Grade I and II anaphylaxis	28	0.0634	0.0146	0.0603	0.0618
Grade III and IV anaphylaxis	34	0.0564	0.0101	0.0548	
Control group	10	0.0594	0.0129	0.0572	

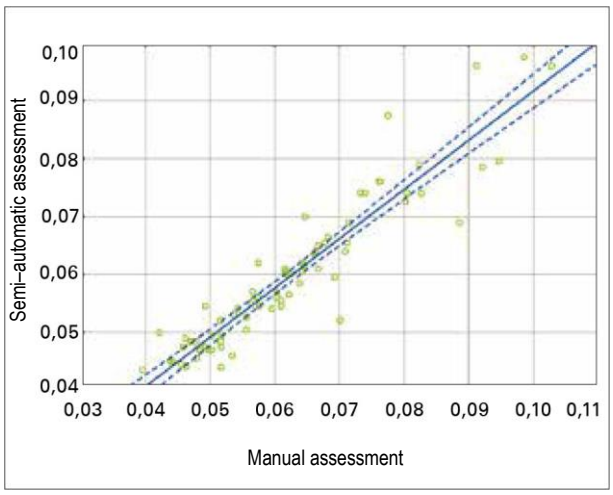


Figure 3. Correlation between semi-automatic and manual CIMT measurement results
Rycina 3. Korelacja pomiędzy wynikami pomiarów CIMT – półautomatycznego i manualnego

Table 4. Results of plasma PAF acetylhydrolase activity assays
Tabela 4. Wyniki oznaczeń aktywności osoczowej acetylohydrolazy PAF

Subgroup	n	Mean	SD	Median	p
Grade I and II anaphylaxis	28	9.014	1.676	8.970	0.3353
Grade III and IV anaphylaxis	34	9.446	1.796	9.586	

Table 5. Correlations for the research group – Spearman's rank correlation coefficients
Tabela 5. Korelacje dla grupy badawczej – współczynniki porządku rang Spearmana

	Mean	SD	PAF-AH	mCIMT	saCIMT
PAF-AH	9.2513	1.7420	1	0.056	0.117
mCIMT	0.06234	0.0142	0.056	1	0.933 p <0.001
saCIMT	0.059613	0.0128	0.117	0.933 p <0.001	1

mCIMT – manual assessment of CIMT, saCIMT – semi-automatic assessment of CIMT

Conclusions

Assuming the PAF-AH demonstrates an actual effect on the development of atherosclerosis, in the subgroup of patients with severe anaphylaxis, due to a limited plasma activity of PAH-AH, CIMT should reach lower mean values. It appears that the results of the manual assessment of CIMT in the presented study initially confirm this hypothesis. Reduced activity of plasma PAH-AH in the studied population would be a risk factor for severe anaphylaxis, but on the other hand, a protective factor against subclinical atherosclerosis of the common carotid artery.

Unfortunately, the analysis of correlations presented further in the study contradicts this view. The findings support the hypothesis that PAF-AH plasma activity is not correlated with the development of atherosclerosis in the population of patients with anaphylaxis. The shortcomings of this study include the relatively small number of participants, and disregard for the CIMT changes in time, due to the cross-sectional character of the study. However, the created database allows performing a new assessment of CIMT in the same group of patients in a follow-up. It would complete this study with valuable information regarding the effect of PAF-AH activity on the increase of CIMT, and progression of the atherosclerotic process. Presently, it is difficult to assess if PAF-AH is a common pathophysiological factor in atherosclerosis and anaphylactic reactions. New studies exploring correlations between these diseases are required. The available literature on the subject concentrates on case reports describing anaphylaxis overlapping with atherosclerosis of the coronary arteries. This is referred to as allergic myocardial infarction type II or III (or Kounis syndrome). A similar phenomenon is reported in other vascular locations, such as mesenteric or cerebral arteries [19]. These are case reports of acute reaction, and not analyses of long-term pathophysiological relationships between anaphylaxis and atherosclerosis, but this subject may provide an interesting field for future research.

References

1. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet, 2010; 375 (9725): 1536-1544
2. Campo S, Sardo MA, Bitto A, et al. Platelet-activating factor acetylhydrolase is not associated with carotid intima-media thickness in hypercholesterolemic Sicilian individuals. Clin Chem, 2004; 50 (11): 2077-2082
3. Mattsson N, Magnussen CG, Ronnemaa T, et al. Metabolic syndrome and carotid intima-media thickness in young adults: roles of apolipoprotein B, apolipoprotein A-I, C-reactive protein, and secretory phospholipase A2: the cardiovascular risk in young Finns study. Arterioscler Thromb Vasc Biol, 2010; 30 (9): 1861 -1866
4. Kiortsis DN, Tsouli S, Lourida ES, et al. Lack of association between carotid intima-media thickness and PAF-acetylhydrolase mass and activity in patients with primary hyperlipidemia. Angiology, 2005; 56 (4): 451-458
5. Braamskamp MJ, Tsimikas S, Wiegman A, et al. Statin therapy and secretory phospholipase A_2 in children with heterozygous familial hypercholesterolemia. Atherosclerosis, 2013; 229 (2): 404-407
6. Garg PK, McClelland RL, Jenny NS, et al. Association of lipoprotein-associated phospholipase A(2) and endothelial function in the Multi-Ethnic Study of Atherosclerosis (MESA). Vasc Med, 2011; 16 (4): 247-252
7. Hargens TA, Rhodes PG, VanReenen J, et al. Lipoprotein-associated phospholipase A2 and carotid intima-media thickness in individuals classified as low-risk according to Framingham. Cardiovasc Diagn Ther, 2014; 4 (6): 487-494
8. Mangili, A, Ahmad R, Wolfert RL, et al. Lipoprotein-associated phospholipase A2, a novel cardiovascular inflammatory marker, in HIV-infected patients. Clin Infect Dis, 2014; 58 (6): 893-900
9. Ragab SM, Safan MA, Obeid OM, et al. Lipoprotein-associated phospholipase A2 (Lp-PLA2) and tumor necrosis factor-alpha (TNF-α) and their relation to premature atherosclerosis in β-thalassemia children. Hematology, 2015; 20 (4): 228-238
10. Ikonomidis I, Kadoglou NN, Tritakis V, et al. Association of Lp-PLA2 with digital reactive hyperemia, coronary flow reserve, carotid atherosclerosis and arterial stiffness in coronary artery disease. Atherosclerosis, 2014; 234 (1): 34-41
11. Södergren A, Karp K, Bengtsson C, et al. Is lipoprotein-associated phospholipase A2 a link between inflammation and subclinical atherosclerosis in rheumatoid arthritis? Biomed Res Int, 2015; 2015: 673,018
12. Ueshima H, Kadowaki T, Hisamatsu T, et al. Lipoprotein-associated phospholipase A2 is related to risk of subclinical atherosclerosis but is not supported by Mendelian randomization analysis in a general Japanese population. Atherosclerosis, 2016; 246: 141-147
13. Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med, 2008; 358 (1): 28-35
14. Vadas P, Perelman B, Liss G. Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis. J Allergy Clin Immunol, 2013; 131 (1): 144-149
15. Perelman B, Adil A, Vadas P. Relationship between platelet activating factor acetylhydrolase activity and apolipoprotein B levels in patients with peanut allergy. Allergy Asthma Clin Immunol, 2014; 10 (1): 20
16. Pravettoni V, Piantanida N, Primavesi L, et al. Basal platelet-activating factor acetylhydrolase: prognostic marker of severe Hymenoptera venom anaphylaxis. J Allergy Clin Immunol, 2014; 133 (4): 1218-1220
17. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res, 1966; 3 (4): 331-333
18. Kisiel B, Kruszewski R, Juszkiewicz A, et al. Methotrexate, cyclosporine A, and biologics protect against atherosclerosis in rheumatoid arthritis. J Immunol Res, 2015; 2015: 759,610
19. Pietraszek N, Bil J. Zespół Kounisa. Wprowadzenie. Epidemiologia. [Kounis syndrome. Introduction. Epidemiology] Kardiol Inwazyjna, 2016; 11 (4): 1-5

Non-functioning pituitary adenomas: pathogenesis, symptoms, diagnosis and treatment

Nieczynne hormonalnie gruczolaki przysadki: patogeneza, objawy, diagnostyka, leczenie

Miłosz Chwiałkowski, Andrzej Koziarski, Grzegorz Zieliński

Department of Neurosurgery, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Assoc. Prof. Andrzej Koziarski, MD, PhD

Abstract. Pituitary adenomas derive from gland cells of the anterior lobe of the pituitary gland, and they are the third most common neoplasm of the central nervous system after gliomas and meningiomas. Their pathogenesis remains unknown. The symptoms depend first of all on the tumour size and include visual disturbances, endocrine function disorders and intracranial hypertension. Preoperative diagnostics include the assessment of the pituitary hormone level, ophthalmological examinations and neuroradiological scanning using MR imaging. Neurosurgical resection is a treatment of choice in patients with symptomatic non-functioning pituitary adenomas.
Key words: pituitary adenoma, pituitary gland, sella turcica

Streszczenie. Gruczolaki przysadki mózgowej wywodzą się z komórek gruczołowych przedniego ptata przysadki i są trzecim (po glejakach i oponiakach) pod względem częstości występowania nowotworem ośrodkowego układu nerwowego. Patogeneza tych guzów pozostaje niejasna. Objawy kliniczne zależą przede wszystkim od wielkości guza i są to: zaburzenia widzenia, upośledzenie czynności hormonalnej przysadki oraz nadciśnienie wewnątrzczaszkowe. Diagnostyka przedoperacyjna obejmuje badania hormonalne przysadki i obwodowych gruczołów dokrewnych, badania okulistyczne oraz ocenę radiologiczną z wykorzystaniem rezonansu magnetycznego. Leczeniem z wyboru u pacjentów z objawowym, nieczynnym hormonalnie guzem przysadki jest operacja neurochirurgiczna.
Słowa kluczowe: przysadka mózgowa, gruczolak przysadki, siodło tureckie

Delivered: 12/03/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 244-250

Corresponding author
Second Lt. Miłosz Chwiałkowski
Department of Neurosurgery, Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 816 427
e-mail: mchwialkowski@wim.mil.pl

Introduction

Pituitary adenomas constitute, according to various statistics, between 10 and 25% of all intracranial tumours, and are the third most common (following gliomas and meningiomas) neoplasm of the central nervous system. Pituitary adenomas arise from the gland cells of the anterior lobe of the pituitary gland, and usually are functioning neoplasms (they synthesise and secrete to the peripheral blood hormones typical for the anterior pituitary lobe). It is estimated that approximately 70% of adenomas are functioning tumours, while approximately 30% of adenomas do not demonstrate hormonal activity. They are non-functioning pituitary adenomas, which usually do not produce characteristic endocrine symptoms [1, 2, 6, 9, 12].

The incidence in patients with non-functioning pituitary adenoma is estimated at 7 to 22 cases / 100,000 population, and the standard morbidity ratio is 1.02/100,000 population. The mean age of a patient at diagnosis is 52 years. Epidemiological studies revealed that non-functioning tumours are the second most common pituitary adenoma, following prolactinoma, and they are the most frequently diagnosed tumour in the macroadenoma stage. They affect men and women equally often. Many are detected by accident, during imaging diagnostics of the brain after trauma or traffic accidents. Approximately 50% of accidentally detected

macroadenomas grow during the observation. Tumours found at the microadenoma stage usually do not grow, even in many years of follow-up [1]. These neoplasms are most often classified according to size: microadenomas of under 10 mm in diameter, and macroadenomas of > 10 mm in diameter. Sometimes adenomas whose growth is limited to the sella turcica are distinguished as a separate category. They are referred to as mesoadenomas [2]. Recent epidemiological studies estimate the incidence of clinically silent pituitary adenomas at 14.4% in post-mortem examination, and at approximately 22.5% in radiological tests. Moreover, non-functioning pituitary macroadenomas are considered to affect 0.16 to 0.2% of the population. Pituitary adenomas are believed to be characterised by a benign, slow, and often long-lasting development, and their clinical picture depends on the size and associated hormonal disorders. In some cases, however, they demonstrate an aggressive, invasive progression, accompanied by intracranial growth, compression of the optic chiasm and the floor of the third brain ventricle, and invasion of the adjacent structures, in particular the cavernous sinuses. This limits the effectiveness of treatment, contributing to increased morbidity and mortality among the patients [4, 6]. Non-functioning pituitary adenomas include tumours that do not demonstrate any hormonal expression, null cell adenomas, which constitute approximately 3% of all pituitary adenomas, as well as tumours that do not reveal hormonal oversecretion, but in histopathological examinations express certain hormones, e.g. growth hormone (GH), prolactin (PRL), gonatotropins (lutropin – LH or follitropin – FSH), thyreotropin (TSH) or corticotropin (ACTH). They are referred to as clinically silent adenomas [7, 8, 11].

The most commonly recognised non-functioning pituitary adenoma is a tumour arising from gonadotropic cells. Its incidence is estimated at approximately 30% of all glandular pituitary tumours. In the majority of cases, it is a macroadenoma, frequently infiltrating the adjacent structures, especially the cavernous sinuses, and penetrating into the cranial cavity. Other non-functioning pituitary tumours are less frequent [4, 8].

Pathogenesis

The aetiology of these tumours has not been completely understood. It is suggested that their pathogenesis involves epigenetic factors, posttranscriptional modification of histones, and DNA methylation of the CpG islands, resulting in somatic mutations in the progenitor pituitary cells. Recent studies demonstrated that disturbed miRNA expression and changes in the mitogen-activated protein kinases (MAPKs) or in the β growth factor contribute to the development of pituitary adenomas through cellular proliferation, differentiation and apoptosis. Other factors in the aetiopathogenesis of non-functioning pituitary adenomas include abnormalities in the signalling pathways associated with p53 and Wnt proteins, regulating life processes in cells. Another example is disturbed expression of the epidermal growth factor receptor (EGFR), which contributes to the activation of processes engaged in the neoplastic transformation in numerous tissues, including the pituitary gland. It has been demonstrated that binding of the epidermal growth factor (EGF) is stronger in invasive adenomas, especially if the cavernous sinus is infiltrated. Increased expression of the vascular endothelial growth factor (VEGF), together with its receptor-1 (VEGFR-1) also contributes to the development of non-functioning pituitary tumours, which suggests the role of increased angiogenesis in the development of adenoma, resulting in tumour growth. Increased expression of the programmed cell death protein 1 (PD-1) in T-cells, B-cells and macrophages could also play a role in the pathogenesis of these tumours, which results in the suppression of the activation of the immune system, and reduced accumulation of lymphocytes. Patients with multiple endocrine neoplasia type 1 (MEN1), with McCune-Albright syndrome and with Carney's syndrome demonstrate an increased predisposition for the disease [7, 18, 19].

To date, few studies have been conducted to indicate the potential risk factors of pituitary tumours. It has been established that high concentrations of oestrogens may promote the growth of adenomas, especially prolactin-producing tumours. This is associated with an increased expression of ER1 receptors and the oestrogen level. In addition, chronic testosterone deficiency results in pituitary enlargement, and may be a secondary cause of the gonadotropic tumour, as demonstrated in patients with Klinefelter syndrome. One of studies revealed increased susceptibility to the tumours in individuals who consume spicy food and use mobile phones excessively, but these findings require further analysis [18, 19].

Classification

The current classification of pituitary tumours and neoplasms of the central nervous system (WHO 2016/2017) is based on the cell line from which the tumour originates. There are five types of adenomas with uncertain prognosis [1]: lactotropic adenomas in men, silent corticotropic adenomas, Crooke's cell pituitary adenomas, multihormonal pituitary adenomas from Pit1 cell line, and sparsely granulated somatotropic pituitary adenomas.

In addition, according to the WHO guidelines, a group of non-functioning pituitary tumours derived from the cells

of the posterior pituitary lobe is distinguished. They express TTF-1 (thyroid-transforming factor-1) and induce similar symptoms [12]. They include pituicytoma, spindle cell oncocytoma, granular cell tumour and sellar ependymoma.

Symptomatology

Clinical manifestations of these tumours are varied. Some of them are asymptomatic for many years, or their symptoms are non-specific, e.g. headache, dizziness, weakness or drowsiness. The symptoms typical for tumour growth usually occur late, when the neoplasm has already grown to a large size. The most important ones include visual disorders (field of vision deficits with typical location, e.g. bitemporal hemianopsia, and blurred vision), insufficiency of the anterior pituitary lobe, ad symptoms of intracranial hypertension [20]. Occasionally, symptoms of diabetes insipidus occur. Visual disorders (blurred vision and reduced field of vision) are found in approximately 70% of patients with non-functioning pituitary adenomas. They result from compression of the visual pathway and its impaired blood supply (optic nerve, optic chiasm and/or optic tract). In the case of symmetrical suprasellar growth of the tumour, and compression of the crossed fibres of the visual pathway, bitemporal hemianopsia occurs. Asymmetrical suprasellar growth of the tumour leads to an injury of the optic nerve, lateral part of the optic chiasm, or the optic tract, and causes corresponding disorders in the field of vision: unilateral loss of vision, nasal loss of vision or ipsilateral, contralateral hemianopsia. Prolonged compression of the nerve by the tumour may cause atrophy of the optic nerve, and blindness [2, 4, 10]. Rare symptoms include palsy/paresis of the nerves responsible for eye movement (3rd, 4th and 6th cranial nerve), manifested by double vision [20]. Headache is a non-specific symptom of pituitary tumour. It is believed that it results from the growth of the intrasellar mass, which causes compression of the dura lining the sellar floor and cavernous sinuses. With large tumours, the headache may result from the increase in intracranial pressure. Sudden, severe headaches with nausea, vomiting and decreased consciousness suggest pituitary apoplexy due to necrosis or haemorrhage to the tumour [1, 4, 14]. The decreased hormonal function of the anterior pituitary lobe develops as a result of increasing intrasellar pressure, and, secondarily, as a result of ischaemia of the anterior pituitary lobe. Most patients at the moment of diagnosis of non-functioning pituitary tumour present symptoms of gonadotropic and somatotropic axes insufficiency. Thyreotropic or corticotropic insufficiency occurs less frequently, but a full assessment of the pituitary is always required. Diabetes insipidus is a rare symptom. Hyperprolactinaemia is observed in most pituitary tumours, especially in macroadenomas, and it is a consequence of the displacement of the pituitary stalk, or compression on the floor of the 3rd brain ventricle. In non-functioning pituitary tumours, the prolactin levels are slightly elevated, usually not more than to 150 ng/ml [2, 10].

Intracranial tumour growth and compression of the floor of the 3rd brain ventricle may cause hypothalamic damage, manifested by quantitative and qualitative consciousness disorders, memory disorders and disturbed biological rhythm, thermal regulation and nutrition, with a tendency for significant weight gain. Large tumours penetrating into the cerebral ventricles, especially to the 3rd ventricle, impair the patency of the fluid tracts, and cause hydrocephalus, due to the obstruction of the foramen of Monro [6].

Diagnostics

Endocrinological diagnostics

In every case of pituitary adenoma, hormonal diagnostic include the assessment of blood prolactin concentration, and the evaluation of clinical and biochemical symptoms observed in acromegaly and Cushing's disease. Further, the function of the anterior pituitary lobe is assessed regarding the secretion of GH (somatotropic insufficiency), ACTH and cortisol (corticotropic insufficiency), TSH and fT_4 (thyrotropic insufficiency), as well as FSH, LH, testosterone and estradiol, depending on the patient's sex. Diagnosis of pituitary insufficiency together with clinically non-functioning tumour always requires hormone replacement therapy [2, 10]

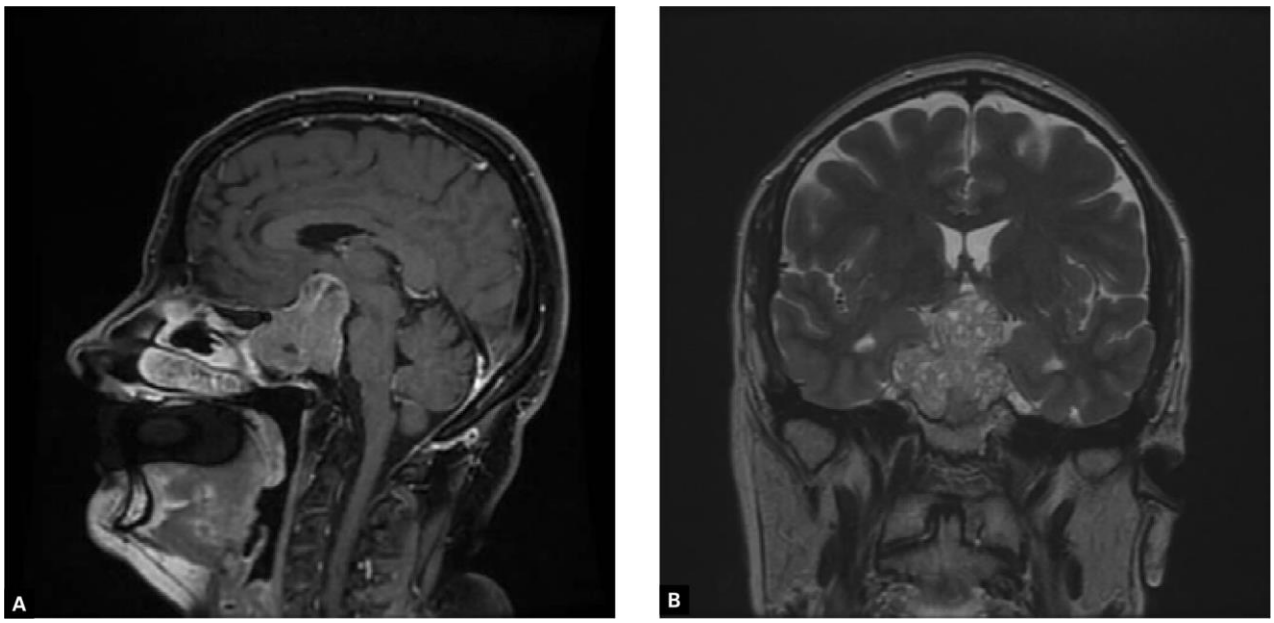


Figure 1. Invasive pituitary adenoma with optic chiasm compression. **A**. Sagittal. **B**. Coronal.
Rycina 1. Inwazyjny gruczolak przysadki uciskający skrzyżowanie wzrokowe. **A**. Przekrój strzałkowy. **B**. Przekrój czołowy.

Ophthalmological diagnostics

Ophthalmological diagnostics include the assessment of visual acuity with Snellen charts, evaluation of eye mobility, assessment of the field of vision using confrontational method, Goldmann perimetry or Donders' test, as well as fundoscopy to assess oedema of the optic nerve disc, filling of the retinal venous vessels, or potential atrophy of the optic nerve. Sometimes, the assessment of visual evoked potentials and optical coherence tomography are used for diagnostic purposes [20].

Radiological diagnostics

Magnetic resonance is a method of choice in the diagnostic of abnormalities in the sella turcica region. If the study is contraindicated, computed tomography may be used, although its sensitivity and specificity are lower than in MRI. The basic advantage of the MR examination is the possibility to obtain multiplanar images with high linear resolution and good contrast, which allows differentiating between the anatomical structures of the pituitary and the adjacent area, especially the hypothalamus and vessels of the cranial base. MRI demonstrates high effectiveness in the assessment of the pituitary tumour growth. Particularly important is the evaluation of the infiltration of the cavernous sinuses. The obtained information is of great importance in the diagnosis of the type of the analysed pathology, the scope of its growth, and the assessment of the processes taking place around the tumour (in its vicinity). It also helps to monitor the dynamics of the tumour growth and the effectiveness of treatment, as well as to plan a potential surgical intervention. The imperfection of MRI consists in a relatively low specificity regarding the presentation of calcifications and bone tissue, as well as in the impossibility to differentiate between the types of pituitary tumours [8, 11, 13].

Differential diagnostics

Pituitary adenomas are the most common tumours found in the optic chiasm area. The differential diagnosis should always consider other pathological processes observed in this location. The most common cystic lesions are craniopharyngiomas, Crooke's pouch cysts, and epidermal or arachnoid cysts. Non-glandular solid tumours include meningiomas, Chlamydomonas, germinal neoplasms, gliomas and hamartomas. Very rare pathologies include giant aneurysms, inflammatory processes (lymphocytic hypophysitis, sarcoidosis, amyloidosis, Wegener's granulomatosis), and neoplastic metastases from distant organs (lung, kidney, colon, ovary, prostate or melanoma) [2, 10, 20].

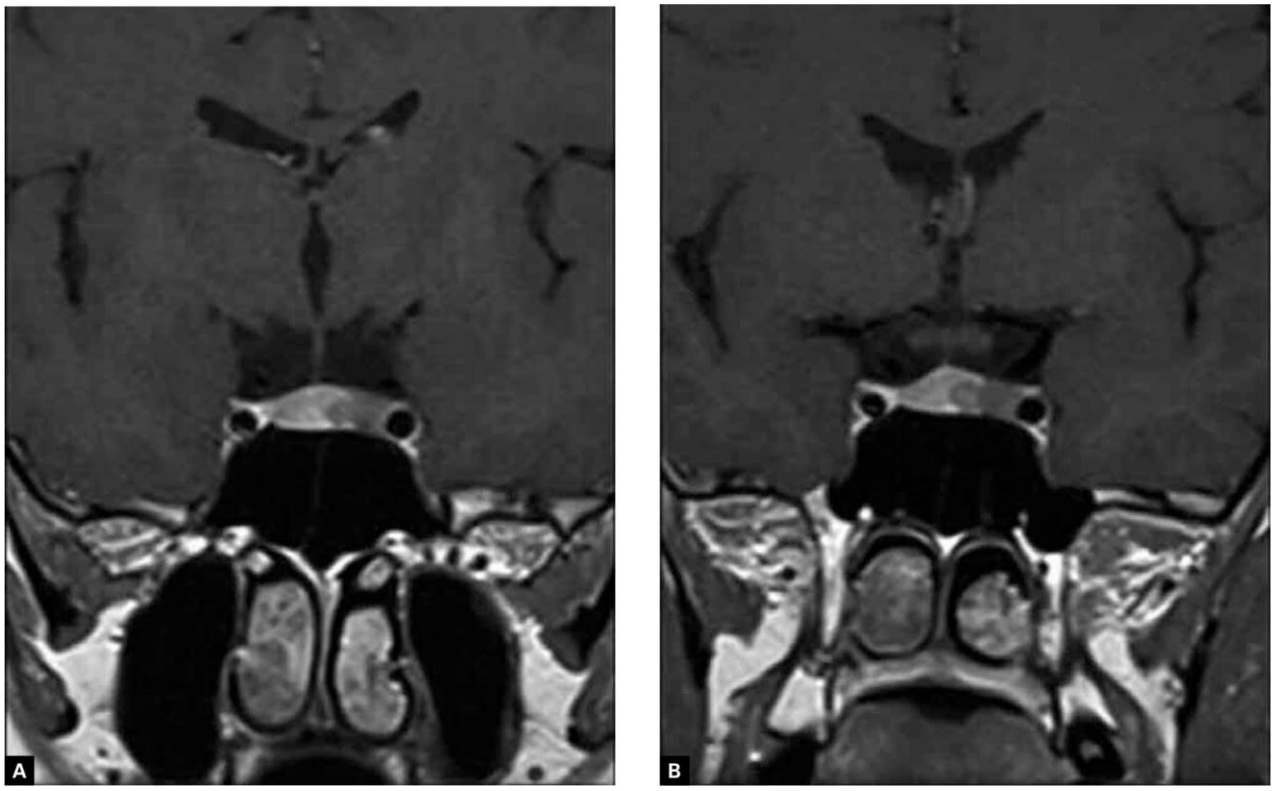


Figure 2. Intrasellar adenoma with infiltration of the left cavernous sinus in two-year observation – without progression. **A**. Sagittal – first test. **B**. Coronal – control after two years.
Rycina 2. Śródsiodłowy gruczolak naciekający lewą zatokę jamistą w okresie dwuletnej obserwacji – bez progresji. **A**. Przekrój strzałkowy– pierwsze badanie. **B**. Przekrój czołowy – kontrola po 2 latach.

Treatment

In patients with symptomatic non-functioning pituitary macroadenoma, neurosurgery is the treatment of choice. In most cases, transsphenoidal access is used. This method is minimally invasive. It offers good visualisation of the lesion, and anatomical, oncologically safe removal, resulting in faster recovery and few complications. In the case of advanced, asymmetrical intracranial growth, craniotomy is required. Both transsphenoidal and transcranial procedure may be supported by neuronavigation and intraoperative MR examination to enhance its effectiveness and safety [2, 5, 6, 9, 15, 16].

The effectiveness of surgical therapy depends on the size of the tumour, the scope of its parasellar growth, and experience of the surgical team. The most common complications of the surgical treatment include insufficiency of the anterior pituitary lobe, diabetes insipidus, hyponatraemia, fistulas of the cerebrospinal fluid, meningitis, injury of the internal carotid artery, and injury of the visual pathway or the eye movement apparatus [2, 3]. The complementary treatment is radiotherapy.

This method is used in incomplete resection of a tumour infiltrating the adjacent tissues. Presently, conventional and stereotactic radiotherapy is used.

Radiotherapy is also used in certain cases of tumour recurrence. It involves doses of 40-50 Gy, and lasts for 4 to 6 weeks. Such a treatment strategy is considered when the recurrence is difficult to remove, and the tumour continues to grow.

Radiotherapy should not be used as a routine treatment, due to the risk of complications such as damage to the optic nerves, other cranial nerves, memory disorders or pituitary apoplexy [2, 4, 8, 10]. Asymptomatic adenomas or tumours detected accidentally are usually subject to observation. In microadenomas, conservative strategy is recommended, involving follow-up MR examinations in 1, 2, 5 years of the disease, and if the tumour does not grow, the tests can be abandoned. In tumours of > 1 cm, the recommended assessments include the evaluation of the field of vision, monitoring of the pituitary function, and MR examination within 0.5, 1, 2 and 5 years of the disease, as well as every time the symptoms occur [2, 4, 11].

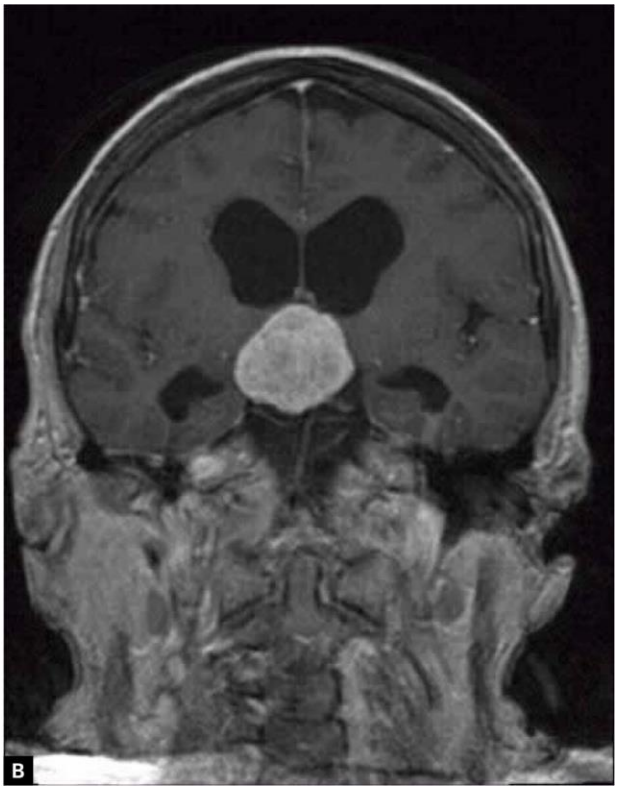


Figure 3. Giant pituitary adenoma filling the third ventricle with hydrocephalus and visual impairment. A. Sagittal. B. Coronal.
Rycina 3. Olbrzymi guz przysadki wypełniający komorą trzecią, powodujący wodogłowie i zaburzenia widzenia. A. Przekrój strzałkowy. B. Przekrój czołowy.

Prognosis

In some patients treated for a non-functioning pituitary tumour, the quality of life deteriorates. They complain about chronic fatigue, reduced activity, and lack of motivation to act, compared to the healthy population. However, these symptoms are even more pronounced in patients following treatment of functioning pituitary adenomas. The main factor that may contribute the above post-treatment problems is hormonal insufficiency of the pituitary. Even the best hormone replacement therapy cannot provide the same concentration of hormones as those in healthy individuals. It has not been confirmed unambiguously, but according to some researchers, even a minimal pituitary insufficiency may contribute to increased mortality. It is also worth noting that the recurrence rate following pituitary adenoma surgery is approximately 12% (mostly within 4-8 years after the surgery) [15-17].

References

1. Chung Thong L, Korbonitis M. Update on the clinicopathology of pituitary adenomas. Endocrine Pract, 2018: 1-24
2. Mark S. Greenberg handbook of neurosurgery. Thieme Medical Publishers Inc. 2016: 718-755
3. Chen L, White WL, Spetzler RF, Xu B. A prospective study of nonfunctioning pituitary adenomas: presentation, management and clinical outcome. J Neurooncol, 2011; 102: 129-138
4. Dekkers OM, Pereira AM, Romijin JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab, 2008; 93 (10): 3717-3726
5. Zhan R, Zhenshen M, Wang D, et al. Pure endoscopic endonasal transsphenoidal approach for nonfunctioning pituitary adenomas in the elderly; surgical outcomes and complications in 158 patients. World Neurosurg, 2015; 84: 1572-1578
6. Zhang D, Chen J, Li Z, et al. Clinical features and management of nonfunctioning giant pituitary adenomas causing hydrocephalus. Oncotarget, 2018; 9 (20): 15409-15417
7. Kober P, Boresowicz J, Rusetzka N, et al. DNA methylation profiling in nonfunctioning pituitary adenomas. Mol Cell Endocrinol, 2018; 473: 194-204
8. Mayson SE, Synder PJ. Silent (clinically nonfunctioning) pituitary adenomas, J Neurooncol. 2014; 117: 429-436
9. Colao A, Di Somma C, Pivonello R, et al. Medical therapy for clinically non-functioning pituitary adenomas. Endocr Relat Cancer, 2008; 15: 905-915
10. Kinoshita Y, Kuriusu K, Arita K. Nonfunctioning pituitary adenomas in elderly patients. J Clin Neurosci, 2018; 53: 127-131
11. Greenman Y, Stern N. Non-functioning pituitary adenomas. Best Pract Res Clin Endocrinol Metab, 2009; 23: 625-638
12. Shibuya M. Welcoming in the new WHO classification of pituitary tumors 2017: revolution in TTF-1-positive posterior pituitary tumors. Brain Tumor Pathol, 2018; 35: 62-70
13. Davies BM, Carr E, Soh C, et al. Assessing size of pituitary adenomas: a comparison of qualitative and quantitative methods on MR. Acta Neurochir, 2016; 158: 677-683
14. Wildemberg LE, Glezer A, Bronstein, MD, et al. Apoplexy in nonfunctioning pituitary adenomas. Pituitary, 2018; 21: 138-144
15. Tanemaura E, Nagatani T, Aimi Y, et al. Quality of life in nonfunctioning pituitary macroadenoma patients before and after surgical treatment. Acta Neurochir, 2012; 154: 1895-1902

16. Dekkers OM, van der Klaauw AA, Pereira AM, et al. Quality of life is decreased after treatment for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metabol, 2012; 91 (9): 3364-3369
17. Bulow B, Hagmar L, Mikoczy Z, et al. Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf), 2006; 46: 75-81
18. Leng L, Zhang Y. Etiology of pituitary tumors: a case control study. Turk Neurosurg, 2016; 26 (2): 195-199
19. Zatelli MCh. Pathogenesis of non-functioning pituitary adenomas. Pituitary, 2018; 21: 130-137
20. Ntali G, Wass JA. Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. Pituitary, 2018; 21: 111-118

Intervention helpline in psychiatric and psychological support for war mission veterans and their families – a case study

Linia interwencyjna w pomocy psychiatryczno-psychologicznej weteranom misji i ich rodzinom – opis przypadku

Anna Nycz, Radosław Tworus, Piotr Ilnicki

Department of Psychiatry, Combat Stress and Psychotraumatology of the Central Clinical Hospital of the National Ministry of Defence the Military Institute in Warsaw;
Head: Col. Radosław Tworus, MD, PhD.

Abstract. Both Polish and global data confirm the complexity of mental health conditions which afflict war mission veterans after they complete their military service. Their problems eventually affect all aspects of their lives, i.e. professional, social and family life. Stigma on people treated for their mental illnesses can enhance their reluctance to use the available psychiatric and psychological help and prevent specialists from reaching such inconspicuous veterans. This study describes a case of a 44-year-old soldier who decided on an inpatient treatment after using an anonymous intervention helpline intended for war mission veterans and their families. Thanks to an efficient telepsychiatry intervention, the patient was hospitalised twice, which resulted in symptoms reduction and improvement of his mental health. The patient's partner was also provided with psychological support. This paper discusses a potential cooperation range of a telepsychiatry remote tool and conventional therapy in clinical conditions.
Keywords: case study, intervention helpline, online help, telepsychiatry, veteran

Streszczenie. Zarówno dane światowe, jak i polskie potwierdzają złożoność problemów zdrowia psychicznego, z którymi zmagają się weterani misji wojennych po zakończeniu działań bojowych. Problemy te przekładają się na funkcjonowanie we wszystkich sferach życia – zawodowej, społecznej i rodzinnej. Stygmatyzacja osób leczonych z powodu problemów zdrowia psychicznego może nasilać niechęć do korzystania z pomocy psychiatryczno-psychologicznej i utrudniać dotarcie do „ukrywającej się" grupy weteranów. W publikacji przedstawiono opis 44-letniego żołnierza, który na stacjonarne leczenie psychiatryczne zdecydował się po skorzystaniu z anonimowej linii interwencyjnej dla weteranów misji i ich rodzin (LI). Dzięki sprawnej interwencji telepsychiatrycznej pacjent odbył 2 hospitalizacje, dzięki którym udało się uzyskać poprawę stanu zdrowia psychicznego i redukcję objawów. Wsparciem psychicznym objęto również osobę bliską – partnerkę weterana. W artykule zaprezentowano możliwy zakres współdziałania zdalnego narzędzia telepsychiatrycznego i leczenia tradycyjnego w warunkach klinicznych.
Słowa kluczowe: linia interwencyjna, telepsychiatria, pomoc on-line, weteran, opis przypadku

Delivered: 19/02/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 251-253

Corresponding author
Anna Nycz, MSc
Department of Psychiatry, Combat Stress and Psychotraumatology of the Central Clinical Hospital of the National Ministry of Defence the Military Institute
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 816 450
e-mail: anycz@wim.mil.pl

Introduction

Approximately 40-60% of American veterans of missions in Iraq and Afghanistan suffer from various mental disorders, and 30% of them developed post-traumatic stress disorder (PTSD). Data provided by the Department of Psychiatry, Combat Stress and Psychotraumatology of the Central Clinical Hospital of the National Ministry of Defence – Military Institute of Medicine indicate that approximately 70% of veterans hospitalised there suffer from mental disorders associated with their service on a military mission; approximately 15% of them were diagnosed with PTSD.

The prevalence of mental disorders associated with deployment abroad among Polish veterans in the general

population is unknown. Based on different information sources, approximately 7-10% of veterans in Poland have PTSD [1]. The data support the assumption that there is a group of veterans in our society who hide their mental problems and do not seek psychiatric or psychological assistance. This is probably mainly due to a fear of stigmatisation, admitting one's weakness, and professional or social rejection. Considering the above statistics and the fact that resorting to specialist psychiatric help is still very problematic for most of the population, motivating the person who needs assistance to start therapy poses a great challenge. This article presents the role and usefulness of a remote telepsychiatric tool, a helpline for military mission veterans and their families, in the diagnostic and therapeutic process [2].

Case report

A 44-year-old professional soldier in the rank of a captain, veteran of the 1st and 9th rotation of the Polish Military Contingent in Afghanistan, a widower, presently in an informal relationship, father of one child, received outpatient psychiatric treatment for nine months. The patient had never been hospitalised before due to psychiatric causes. In January 2014, he called the helpline for military mission veterans and their families operated by the Department of Psychiatry, Combat Stress and Psychotraumatology of the Central Clinical Hospital of the National Ministry of Defence, Military Institute of Medicine. During the intervention, he described his symptoms in the following manner: "I decided to go on a mission due to financial reasons. My wife was treated oncologically at that time, the treatment was expensive, and I had to make money to pay for it. During the mission in Afghanistan, my wife died. I came back for the funeral, but I preferred to run away from problems on another mission. I left my 17-year-old son at home. Now he has mental problems, isolates himself from people, has a sleeping disorder. After I returned from the mission, I tried to come back to work in the unit, but I couldn't cope. Presently, I've been on medical leave for seven months. I'm receiving psychiatric treatment. At first, the drugs helped me, but then headaches started, so I stopped medication. I also go to therapy with a psychologist, but it isn't helping. Both the psychologist and the psychiatrist are far from where I live. I cannot make it to the appointments. I feel that I can't control my emotions and recurring memories from the mission any more, I worry about my son. I hit him once. I'm temperamental, especially after alcohol".

A few days later, the soldier's partner called and completed the interview with her account.

Intervention no. 1: "I'm calling to talk it out. I'm tired of my partner's cheating. I know he cheated on his ex-wife, even when she was very ill. Once he hit me, he has problems with alcohol. He is overbearing and aggressive. I want to separate from him. I gave him an ultimatum: he starts therapy or I will report him to his superiors.

Intervention no. 2: "A few days ago my partner hit me again. I don't know what to do. For a few months, things were good, but recently I've noticed that something is happening to him again. He also noticed it. I think he stopped taking his drugs because he has problems with erection. I feel like I'm all alone".

As a result of the interventions, the soldier was offered hospitalisation at the Daily Ward of the Department of Psychiatry, Combat Stress and Psychotraumatology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine. Due to the spectrum of the reported problems and the patient's address outside the Mazovian province, few weeks-long observation at a day ward was considered to be more beneficial for the patient (currently on medical leave) than outpatient consultations. The hospital admission was planned, in line with the patient's request, for April, i.e. approximately three months after the first helpline intervention. The patient claimed that earlier hospitalisation would have been impossible, as he needed to take care of his 17-year-old son.

At the admission to the hospital, the patient was fully oriented and verbally responsive, in a slightly lowered mood and expressing pronounced tension. Affect was present. The patient complained about irritability, increasing tension and sleeplessness. He reported problems with family and professional relationships. According to the patient, the problems started after his return from a military mission. He became temperamental, sometimes aggressive. To address these problems, he started therapy with the psychologist at the unit. Since January 2014, he experienced increasing tension, problems with sleep and with performing professional duties. Despite pharmacotherapy received on an outpatient basis, his condition did not improve. At the ward, the patient was subordinated, adjusted, quickly adapted to new circumstances. Active in therapeutic meetings in the rehabilitation section of the department. Had good relations with other patients and personnel. At the ward, the patient did not report any complaints or problems, apart from persisting problems with sleep. Laboratory test results did not reveal any significant abnormalities, computed tomography of the head did not demonstrate focal lesions. As a result of the applied biological treatment, i.e. 100 mg/d of sertraline and 100 mg/d of chlorprothixene, the tension was reduced, and sleeping pattern improved. After eight weeks of treatment, the patient was discharged, demonstrating

symptomatic improvement. The diagnostic and therapeutic process revealed a picture consistent with adaptive disorders (F43.2) and emotionally unstable personality disorder, the impulsive type (F60.3), without signs supporting the diagnosis of post-traumatic stress disorder [3].

In November 2014, five months after the end of hospitalisation, the patient reported to the hospital again, with a referral from the Mental Health Outpatient Clinic, due to identical symptoms as previously. According to the patient, he functioned well after the discharge. In July, his condition worsened, which presented as sleeplessness, irritability and impulsive behaviour. During the hospitalisation, he reported aggressive behaviour towards the people around him and problems with emotional control. He was critical about his behaviour. The patient declared willingness to undertake actions that would help to improve his personal and family life. During seven weeks of hospitalisation, his pharmacological treatment was modified to include 400 mg of carbamazepine daily, 300 mg of perazine daily and 40 mg of propranolol daily. The patient was discharged in an improved condition, with recommendations of continued treatment at an outpatient mental health centre.

Discussion

This case report presents one of many stories of veterans hospitalised at the Department of Psychiatry, Combat Stress and Psychotraumatology of the Central Clinical Hospital of the Ministry of National Defence – Military Institute of Medicine. A classic case of a patient diagnosed with adaptive disorder is interesting not because of the course of the disease, but because of the way the patient came from the onset of symptoms to receiving professional help. It should be emphasised that it took almost a year. Initially, the patient sought consultation with a psychologist in the military unit, then was referred to a psychiatrist at his local outpatient mental health centre. Nine months of therapy did not bring the expected results, as the soldier sought another treatment centre. Based on over five years of experience with the helpline, nearly half (50%) of those calling the helpline received psychiatric or psychological assistance near the place of residence. During the outpatient therapy, the veteran in question called the helpline for military mission veterans and their families where adequate intervention was implemented.

After three months (the admission date was appointed according to the patient's wishes) the patient started diagnostic and therapeutic hospitalisation at a daily psychiatric ward. This intervention might have motivated the soldier to start hospitalisation, although he had not been willing to do it during the few months of outpatient treatment. Since the second hospitalisation, which ended in December 2014, the patient did not return to the hospital. This suggests that his mental status stabilised.

The patient's family, i.e. his son and partner, should also be mentioned, as the problem affected them to a great degree, as demonstrated by the above moving account of the soldier's partner, in which she expressed her care about him, and reported the physical and mental abuse she had been suffering. This supports the observation that when veterans struggle with mental problems, it affects their families [4-6]. Family members are often the first ones to notice subtle changes in veterans' behaviour, even when soldiers fail to see them. Wives and partners of veterans frequently not only seek help for their husbands/partners, but also psychological support for themselves. In the presented situation, the therapy offered to the veteran helped to improve his family life. It also reduced the anxiety and tension in people closest to the patient.

Conclusion

Prompt diagnosis of a mental health problem and motivating the person who needs help to start psychiatric treatment is essential for effective intervention. A remote telepsychiatric tool such as a helpline for military mission veterans can be a useful form of psychiatric and psychological assistance for initial problem assessment, emotional support and sustained motivation to start treatment, as well as to continue therapy.

References

1. www.news.wim/aktualnoci-topmenu-19/medycyna-w-mundurze/2434-e kspert-z-wim-o-ptsd-i-samobojstwach-weteranow, accessed on 22.11.2018
2. Nycz A, Tworus R, Dziuk M. Telefony zaufania dla osób z problemami zdrowia psychicznego i ich rodzin – prymitywna forma telemedycyny czy skuteczna forma pomocy? [Helplines for people with mental problems and their families – a primitive form of telemedicine or effective assistance?] Mil Phys. 2015; 93: 185-189
3. Międzynarodowa Statystyczna Klasyfikacja Chorób i Problemów Zdrowotnych. Rewizja dziesiąta. Tom I. [International Statistical Classification of Diseases and Related Health Problems. 10th revision. Volume 1] WHO 2008: 207-228
4. Pępkowska B. Życie w stresie. Trudności jakich mogą doświadczać żołnierze przed, w czasie działań zbrojnych i po ich zakończeniu. [Life in stress. Difficulties faced by soldiers before, during and after military actions] Colloquium of the Faculty of Humane and Social Sciences, 2016; 3: 111-132
5. Rybak J. Zakamarki żołnierskiego umysłu. [Nooks and crannies of the soldier's mind] Polska Zbrojna 2014; 5: 22-24
6. Szymańska S, ed. Tułaczka Odyseusza. Powrót z wojny do domu. [Odyssey's journey. Returning home from war] Military Institute of Medicine, Warsaw 2017: 17-42, 74-87

Burnout syndrome in medical professionals

Wypalenie zawodowe pracowników medycznych

Agnieszka Dancewicz, Dorota Lazar-Sito

1 Department of Oncology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Assoc. Prof. Renata Duchnowska, MD, PhD

Abstract. Burnout syndrome has become a major area of scientific research conducted since the 1970s in hopes of finding, by thorough knowledge of the subject, an effective method of prevention of the syndrome or at least mitigation of its consequences, both in terms of daily lives of the affected persons, their physical and psychological symptoms, and their relationship with other people. In the case of medical professionals, the burnout syndrome may adversely affect the quality of interaction with a patient and, in consequence, affect the effectiveness of treatment. This work discusses the results of research conducted to-date on the nature of the phenomenon, its consequences and possible means of prevention.
Key words: burnout, burnout syndrome, medical professionals, nurses, physicians, stress

Streszczenie. Wypalenie zawodowe stało się istotnym obszarem zainteresowań naukowców, którzy od lat 70. XX w. podejmują się szeregu badań w nadziei, że wnikliwe poznanie tematu pozwoli na znalezienie skutecznego sposobu na zapobieganie występowaniu tego zjawiska lub przynajmniej minimalizowanie jego konsekwencji – zarówno w zakresie codziennego funkcjonowania, objawów fizycznych czy psychicznych, jak i relacji z innymi ludźmi. W przypadku pracowników medycznych wypalenie zawodowe może wpływać negatywnie na jakość kontaktu z pacjentem, a co za tym idzie – oddziaływać na skuteczność leczenia. Niniejsza praca stanowi omówienie wyników dotychczasowych badań nad zjawiskiem, jego następstwami i możliwą profilaktyką.
Słowa kluczowe: wypalenie zawodowe, zespół wypalenia, stres, lekarze, pielęgniarki, pracownicy medyczni

Delivered: 25/02/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 254-257

Corresponding author
Agnieszka Dancewicz, MA
Department of Oncology, Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
e-mail: a.dancewicz@poczta.onet.pl

Introduction

Burnout syndrome has been observed and discussed since the 1970s. The term was introduced by Freudenberger to denote exhaustion due to excessive demands of the environment or a given individual [1]. It quickly gained popularity, as researchers started to realise its consequences for the people affected, as well as those who experience its indirect effects.

Among the professions particularly exposed to the risk of burnout syndrome are so-called social services, i.e. people whose work consists in providing assistance to others (doctors, nurses, teachers, policemen, social workers and psychologists) [2]. Especially doctors and nurses have been in the centre of the research on burnout syndrome, as their professional role requires a close, engaged contact with human suffering and dissatisfaction, is associated with risks and difficulties with ensuring therapeutic success, and is often burdened with organisational imperfections in medical care, difficult working conditions, low income and low professional status [3].

With time, as the interest in the problem of burnout increases, this area is being extended to other professional groups: fire-fighters, soldiers, prison personnel, priests and customer service employees.

People working in the environment at risk of burnout syndrome are also exposed to the negative effects of this process. The consequences may affect daily functioning, physical or mental symptoms, as well as relationships with other people. Indirectly, the effects of burnout syndrome in employees may adversely affect the quality of services they provide, as well as their interpersonal relations in the professional and private environment. In the case of medical professionals, burnout syndrome may have negative effects on the quality of contact with patients, thus affecting the effectiveness of treatment.

Researchers often emphasise that better communication between a doctor and a patient and higher quality of contact between them translates to

better patient compliance. Furthermore, doctors suffering from burnout syndrome are less efficient for the institution, as their work will probably be less effective, slower, and at times fraught with errors. If the burnout progresses to the fully symptomatic phase, the health-related effects could be so significant that the affected person may become incapable of performing everyday work, and be forced to take medical leave and rely on other benefits to restore balance [4]. The most popular and frequently mentioned concept of burnout syndrome, proposed by Christine Maslach, describes burnout syndrome as a three-dimensional phenomenon: emotional exhaustion, depersonalisation and a reduced sense of personal accomplishment. Emotional exhaustion refers to the feeling of being overwhelmed emotionally, and having significantly depleted emotional resources. Depersonalisation refers to negative, callous or indifferent reactions to other people who are usually either recipients of services offered by a given person, or are under their care. Reduced sense of personal accomplishment refers to a decreased sense of one's competence and professional success [5]. Fengler distinguished ten stages of burnout: politeness and idealism; overwork; decreasing politeness, resulting in the sense of guilt; increasing effort to be polite and reliable; lack of success; helplessness; loss of hope; exhaustion, aversion towards clients; anger and burnout. These phases do not need to be consecutive; characteristics of a few phases may be concurrent, and return to previous stages is also possible. However, as the author posits, the more advanced the burnout process, the more difficult it is to reverse it [6].

Consequences of professional burnout

As the consequences of professional burnout, especially among social service workers, may be very severe, many researchers across the world conduct studies to demonstrate the scale of the problem, and to find relationships between this phenomenon and other factors. This research is driven by the hope that exploration of the subject will result in effective preventive measures to eliminate or at least minimise the consequences of burnout. Studies have been conducted across the world for a few decades. In the field of health service, they include various groups of medical employees: doctors of different specialisations, medical students, nurses, other medical employees who are in direct contact with patients – physiotherapists, psychologists, caretakers, therapists and tutors in health centres. All these professional groups are at high risk of burnout.

Special attention is paid to people working with chronically and terminally ill patients. The factors associated with work at psychiatric wards, notably a long-term, often emotion-loaded relationship with patients, also increase the risk of burnout in doctors or nurses working at these departments. The constant development in medicine provides patients with chances for longer survival despite a chronic illness, but also has negative consequences for medical personnel. As the patient remains longer under the care of a physician, their relationship deepens, which may be a burden for the doctor.

Studies on burnout syndrome

Professional burnout, defined as a result of long-term stress at work, for several decades has been attributed to many factors which can be divided into three groups: individual, interpersonal and organisational.

The individual characteristics contributing to the development of burnout include the following: personality traits, cognitive schemata, sense of self-effectiveness, level of empathy and sense of coherence, as well as the level of experienced stress and methods of coping with it. The interpersonal factors include all elements related to contact with co-workers and supervisors. The organisational factors are associated with the environment and organisation of work in a given institution: management, remuneration, workflow, but also with the general system (e.g. healthcare system in the country). Many studies conducted in different countries demonstrate that professional stress and burnout are increasing problems.

In the USA, the cost of medical help and reimbursements for employees covered by the state is growing. Based on the analysis of studies from North America, Maslach et al. demonstrated that over 20% of healthcare professionals experience advanced burnout, while the data from Eastern Europe and Asia reveal that in these areas the rate is nearly 30% [7]. In order to better understand burnout syndrome, a number of factors potentially contributing to its occurrence, development and prevention are examined, including demographic characteristics such as sex, age and marital status. Although the majority of studies do not report any relationship between sex and the level of burnout, most authors agree that women generally demonstrate a higher level of burnout. Usually a higher level of emotional exhaustion and lower sense of personal accomplishment are observed, whereas men demonstrate more pronounced depersonalisation. The data regarding the relationship between professional burnout and age or marital status are inconclusive. In some studies, age and burnout correlate positively, in others the level of burnout decreases with age. Regarding marital status, conclusions are also inconsistent [8].

Researchers agree that professional burnout is associated with high stress levels, and individual methods of coping with stressful situations may demonstrate a protective effect (e.g. planning the problem-solving process, avoidance of impulsive behaviours). European studies conducted in 2013 and 2014, including young oncologists (under 40 years of age), demonstrated that 71% of them show symptoms of professional burnout. The often mentioned factors contributing to this phenomenon were confirmed: a similar general level of burnout in women and in men, more pronounced emotional exhaustion in women and depersonalisation in men. Researchers emphasised the importance of access to professional support, appropriate amount of time free from work/holidays, maintaining work-life balance, living alone and residing in Eastern or Southern Europe [9].

The problem seems to be escalating. Reports based on ESMO studies reveal that in 2013 less than 40% of doctors demonstrated burnout, and in 2015 the number increased to 46%. Another study estimated the rate of doctors suffering from burnout in 2011 at 46%, and in 2015 the percentage was 54%. In a Medscape report from 2011, 79% of oncologists declared they would choose the same specialisation again, whereas in 2015 only 51% would repeat the choice [9].

In Poland, this unsettling trend of growing stress and burnout levels is also observed and confirmed by studies involving doctors and nurses of various specialisations [7]. A study on professional stress conducted in 2009 among the employees of Scotland Cancer Centre demonstrated that one-third of employees experience a significant emotional burden, compared to a mean of 18% in the age-matched and sex-matched control group. The study confirmed a trend described in the subject literature regarding greater emotional burden in physicians and nurses compared to radiotherapist and physicists working in oncology, which proves the importance of a relationship with patient and frequency of contacts, i.e. the intensity of interpersonal relationships. Doctors and nurses more often than representatives of the other mentioned professions reported the need to take medical leave due to emotional burden at work. Only 62% were convinced that they wanted to stay in the current place of work, and did not intend to change it within the following year [10].

Many studies on professional burnout syndrome focus on the effect of communicative skills on burnout in physicians. A doctor in a better relationship with the patient can achieve better cooperation, which sometimes translates into greater effectiveness of treatment, but also an objective reduction of burnout [11]. A Turkish study from 2012-2013 assessed the relationship between burnout syndrome and professional satisfaction in general practitioners. It demonstrated that higher emotional exhaustion corresponded to an increased level of anxiety and depression, and a higher level of burnout correlated with decreased satisfaction with work. In this study, the phenomenon was not correlated with age or sex of the subjects [12]. Many studies indicate a similar degree of professional burnout among doctors and nurses. The difference is observed between various specialisations: surgical and non-surgical. The group of nurses demonstrating the highest level of burnout included paediatric, oncological and psychiatric nurses, whereas the lowest degree of burnout was found among general nurses [13].

A study by Kulik indicates that in a group of neurologists, cardiologists, orthopaedists and endocrinologists, the neurologists present the highest level of burnout, whereas orthopaedists – the lowest. The study confirmed the correlation between a high sense of self-effectiveness and lower burnout [14]. Numerous studies concentrate on the role of personality traits of employees; they suggest that people characterised by a higher degree of introversion and neuroticism are at a higher risk of burnout [15]. For instance, a study by Muszalska confirmed the correlations between personality traits and the previously mentioned variations in the probability of burnout between surgical doctors (surgeons) and non-surgical physicians (general practitioners) [16]. A study by Tabała also presents a relationship between personality traits such as extraversion, amicability and conscientiousness and the level of professional burnout in medical caretakers [17]. Also, a Spanish study conducted in a group of oncological nurses confirms the correlation between a high degree of neuroticism or low degree of conscientiousness and the level of burnout [18].

Conclusion

The problem of professional burnout has not been fully explored, despite several decades of research. The limitations resulting from the organisation of studies and a great number of factors associated with this phenomenon might prevent the formation of one reliable theory regarding the causes and mechanisms of development of professional burnout. However, it appears that years of work of different authors allowed to identify potential prophylactic or corrective actions, both on the systemic level, including education and training of students and medical personnel, and in the organisation of work in individual institutions. In education, the main task consists in providing information about burnout, its predictors, stages and consequences, in order to enable the next step in the planning of actions of various levels of education, from students to experienced healthcare professionals. It included workshops addressing the

problems of stress, methods of coping with it, time management at work, communication skills, empathy, but also the ability to release emotions or to rest, as well as workshops on group collaboration or effective personnel/team management [19]. It is important to introduce activities focused on releasing emotions, sharing experience with other people in a similar situation, and paying particular attention to the work-life balance, so that one can find satisfaction outside the work environment.

References

1. Freudenberger HJ. Staff burnout. J Soc Issues, 1974; 30: 159-165
2. Maslach C. Wypalenie w perspektywie wielowymiarowej. [Burnout in a multidimensional perspective] In: Sęk H, ed. Wypalenie zawodowe. Przyczyny, mechanizmy, zapobieganie. [Professional burnout, Causes, mechanisms, prevention] Wydawnictwo Naukowe PWN, Warsaw 2000: 13-31
3. Sęk H. Poznawcze i kompetencyjne uwarunkowania wypalenia w pracy z chorymi. [Cognitive and competence-related aspects of burnout at work with patients] Post Psych Neurol, 2005; 14 (2): 93-98
4. De Walden-Gałuszko K. Psychoonkologia w praktyce klinicznej. [Psychooncology in clinical practice] Wydawnictwo Lekarskie PZWL, Warsaw 2001
5. Sęk H, ed. Wypalenie zawodowe. Przyczyny, mechanizmy, zapobieganie. [Professional burnout. Causes, mechanisms, prevention] Wydawnictwo naukowe PWN, Warsaw 2000
6. Fengler J. Pomaganie męczy. Wypalenie w pracy zawodowej. [Helping is tiring: Burnout syndrome in professional work] Gdańskie Wydawnictwo Psychologiczne, Gdańsk 2001
7. Wilczek-Rużyczka E. Wypalenie zawodowe pracowników medycznych. [Professional burnout syndrome in medical professionals] Wolters Kluwer SA, Warsaw 2014
8. Walkiewicz M. Wypalenie wśród personelu medycznego – przegląd literatury. [Burnout syndrome in medical personnel – a literature review] Przegl Lek, 2014; 71 (5): 263-269
9. Banerjee S, Califano R, Corral J, et al. Professional burnout in European young oncologists; results of the European Society for Medical Oncology (ESMO) Young Oncologists Committee Burnout Survey. Ann Oncol, 2017; 28 (7): 1590-1596
10. Jones MC, Wells M, Gao C, et al. Work stress and well-being in oncology settings: a multidisciplinary study of health care professionals. Psycho-Oncol, 2013; 22: 46-53
11. Travado L. Physician-patient communication among southern European cancer physicians; the influence of psychosocial orientation and burnout. Psycho-Oncol, 2005; 14: 661-670
12. Yilmaz A. Burnout, job satisfaction, and anxiety-depression among family physicians; A cross-sectional study. J Family Med Primary Care, 2018; 7: 952-956
13. Beisert M. Przejawy, mechanizmy i przyczyny wypalania się pielęgniarek. [Signs, mechanisms and causes of burnout in nurses] In: Sęk H, ed. Wypalenie zawodowe. Przyczyny, mechanizmy, zapobieganie. [Professional burnout. Causes, mechanisms, prevention] Wydawnictwo Naukowe PWN, Warsaw 2000: 182-215
14. Kulik M. Cierpienie, które przerasta, czyli o wypaleniu lekarzy pracujących z przewlekle chorymi. [Suffering that overwhelms. Burnout in doctors working with chronically ill patients] Studia z Psychologii w KUL, 2008; 15: 81-112
15. Mańkowska B. Wypalenie zawodowe. Źródła, mechanizmy, zapobieganie. [Professional burnout. Sources, mechanisms, prevention] Harmonia Universalis, Gdańsk 2017
16. Muszalska M. Cechy osobowości lekarzy a indywidualne wzorce zachowań i przeżyć związanych z pracą zawodową u chirurgów i lekarzy rodzinnych. (Nieopublikowana praca magisterska). [Personality traits of doctors and individual patterns of behaviour and emotional reactions related to professional work in surgeons and general practitioners. (Unpublished MA thesis) Kazimierz Wielki University in Bydgoszcz, Bydgoszcz 2003
17. Tabała K, Stecz P, Kocur J. Profil osobowości, style radzenia sobie ze stresem a wypalenie zawodowe wśród szkolących się opiekunów medycznych. [Personality profile, styles of coping with stress and professional burnout in medical caretakers in training] Medycyna Ogólna i Nauki o Zdrowiu, 2014; 20 (3): 270-275
18. De la Fuente-Solana EI. An explanatory model of potential changes in burnout diagnosis according to personality factors in oncology nurses. Int J Environ Res Public Health, 2019; 16 (3): 312
19. Stawiarska P. Wypalenie zawodowe w perspektywie wyzwań współczesnego świata. [Professional burnout and challenges of the modern world] Difin, Warsaw 2016

Microparticles in red cell concentrates – can they be responsible for post-transfusion reactions?

Mikrocząsteczki w koncentratach krwinek czerwonych – czy mogą odpowiadać za reakcje poprzetoczeniowe

Małgorzata Dorman, Jolanta Korsak

Department of Clinical Transfusiology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; Head: Jolanta Korsak, MD, PhD, Professor of the Military Institute of Medicine

Abstract. Red blood cells release membrane vesicles of size not exceeding one urn, called microparticles (RMPs). The basis for creating RMPs is the loss of plasma membrane asymmetry due to cell activation or apoptosis. Microparticles have surface antigens typical for the cells they were derived from. The paper presents the mechanism of RMP formation in red blood cell concentrates and describes their surface antigens. Various types of microparticle activity are described, namely procoagulant and anticoagulation activity, immunomodulatory effect, the ability to induce inflammatory processes and participation in apoptosis. These are analysed in the context of transfusion medicine and their participation in triggering post-transfusion reactions, especially TRALI.
Keywords: physiopathology of microparticles, post-transfusion reactions, red blood cell concentrate, red blood cell-derived microparticles, TRALI

Streszczenie. Krwinki czerwone uwalniają pęcherzyki błonowe wielkości nieprzekraczającej 1 μm, które noszą nazwę mikrocząstek (RMPs). Podstawą tworzenia RMPs jest utrata asymetrii błony plazmatycznej w wyniku aktywacji komórek lub procesu apoptozy. Mikrocząsteczki mają antygeny powierzchniowe charakterystyczne dla komórek, z których powstały. W pracy przedstawiono mechanizm powstawania RMPs w koncentratach krwinek czerwonych i scharakteryzowano ich antygeny powierzchniowe. Opisano różne rodzaje aktywności mikrocząsteczek: prokoagulacyjną i antykoagulacyjną, efekt immunomodulacyjny, zdolność do indukowania procesów zapalnych oraz udział w apoptozie w kontekście medycyny transfuzyjnej i udział w powstawaniu reakcji poprzetoczeniowych, zwłaszcza TRALI.
Słowa kluczowe: mikrocząsteczki pochodzenia czerwonokrwinkowego, koncentrat krwinek czerwonych, fizjopatologia mikrocząsteczek, niepożądane reakcje poprzetoczeniowe, TRALI

Delivered: 06/12/2018
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 258-264

Corresponding author
Prof. Jolanta Korsak, MD, PhD
Department of Clinical Transfusiology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine
128 Szaserów St., 04-141 Warsaw
Phone: +48 261 817 206
e-mail: jkorsak@wim.mil.pl

Transfusion of blood and blood components is an essentially safe and effective method of correcting haematological deficits, but it is not free from the risk of post-transfusion reactions. The risk associated with haemotherapy is difficult to assess, as it depends on numerous factors, such as the type of transfused blood component, its storage time, volume and transfusion rate, as well as the health status of the recipient. In addition, the variety of post-transfusion reactions indicates that they are caused by multiple factors. Adverse post-transfusion reactions are observed in approximately 10% of blood and blood product recipients. It is also estimated that post-transfusion reactions [1, 2] may occur after the transfusion of 0.5-3% of all blood components. The classification of adverse post-transfusion reactions is based on their immunological or non-immunological character, i.e. interaction between antigen and antibody, and the presence or absence of haemolysis. However,

many factors causing post-transfusion reactions are still to be understood. In the context of post-transfusion complications, researchers started studying the biochemical, metabolic ad structural changes occurring in red blood cell concentrates (RBC) during their storage. The therapeutic effectiveness of red blood cells with long storage time and their role in post-transfusion reactions have been examined, and factors that could be responsible for certain post-transfusion reactions have been sought.

Potential factors include microparticles from the cellular membrane of erythrocytes [2, 3]. Microparticles (MPs) were described for the first time by Wolf in 1967 [4]. He noticed very small, rich in lipid particles originating from the cellular membrane of blood platelets, and he referred to them as "platelet dust". Wolf also found that they demonstrate the activity of tissue factor (RF, CD142), also known as thromboplastin or platelet factor 3. The microparticles forming the "dust" were elements of pseudopodia released form platelet plasma membrane, and they also presented pro-coagulatory properties [4]. Studies published in the last decade revealed that microparticles are membrane vesicles released to blood circulation not only by platelets but also by red cells, white cells and endothelial cells, as well as neoplastic cells. Their size is 0.2-2.0 μm. They are heterogeneous and contain phospholipids, surface antigens and proteins. They can participate in processes associated with cellular apoptosis and reaction to oxidative stress. Microparticles are commonly present in the blood of healthy individuals, and their elevated concentrations are found in the plasma of patients with thrombotic disease, diabetes, meningococcal sepsis, cardiovascular diseases and congenital sickle cell anaemia [5-7]. Their role in the pathogenesis of certain clinical syndromes is presented in Table 1.

Red blood cell-derived microparticles (RMPs) are similar to those originating from other blood cells. They are not bigger than 1 μm; they account for approximately 4-8% of all microparticles in blood [8].

Glycophorin A (CD235a), the main RMPs marker, is present on their surface. Group antigens A, B, H, as well as P_1, D, c, e, and Fya were found on the microparticles isolated from stored red cells. Weak expression of antigens M and N was also detected [9]. The physiological role of red blood cell-derived microparticles has not been explained. In the context of transfusion medicine, they are perceived as changes in red blood cells occurring during storage, and possibly are responsible for certain adverse reactions in patients following the transfusion of RBC stored for over 21 (or 30) days. Rubin et al. demonstrated that during the storage of RBC at 4°C, a constant increase of RMPs is observed. On day 50 of storage of red blood cells, the increase of microparticles was 20 times higher than on the day on which the blood compound was obtained [10]. A model of formation of microparticles from the cell membrane, including translocation, changes in lipid layers, various protein modifications and irreversible fragmentation of membranes, was developed in the study [11]. Red blood cell membrane is a plasma membrane created by a mosaic of lipids in the form of a lipid bilayer with proteins nestled into it. The lipid monolayers have different composition: (1) the external one contains mostly phospholipids, cholesterol and glycolipids, and (2) the internal, cytoplasmatic layer is composed mainly of aminophospholipids: phosphatidylethanolamine (PE) and phosphatidylserine (PS). Membrane asymmetry is preserved in resting cells, which is expressed by constant localisation of membrane proteins, and very precise orientation of the proteins of the cytoskeleton, composed of specific structural proteins: spectrin and ankyrin. Spectrin molecules form cytoskeletal structures together with another protein, actin. The main protein binding cytoskeleton with the surface of the erythrocyte membrane is band 3 protein and glycophorin C [12]. Another enzyme, aminophospholipid translocase (flippase), preserves the asymmetry of the cell membrane phospholipids [13]. It is suppressed during cell activation by increased concentrations of intracellular calcium, which result in the displacement of PC and PE phospholipids from the internal to the external layer of the cell membrane, and disturb their asymmetry. As a consequence, erythrocytes lose their ability to change shape during passage through narrow blood vessels [12, 13]. Elevated calcium concentrations also activate proteases, e.g. calpain, which degrades the links between membrane proteins and cytoskeletal proteins. Figure 1 presents the model of formation of erythrocyte-derived microparticles [8]. They are released from the membrane of red blood cells as they age, and appear to participate in processes similar to apoptosis [14]. During 120 days of life, erythrocytes lose approximately 20% of their volume due to the release of microparticles, while the haemoglobin concentration increases by 14% [15]. Blood cell ageing is a physiological process resulting in apoptosis. The basic mechanism of apoptosis is an increase in intracellular Ca+, and activation of enzymes, which results in the degradation of protein DNA and the release of microparticles. The release of RMPs from the erythrocyte cell membrane may also be a mechanism eliminating reactive compounds that form during the storage of blood cells, e.g. denatured haemoglobin, C5b-9 membrane attack complex of complement, bond 3 proteins or immunoglobulins G (IgG) [15, 16].

Table 1. Contribution of microparticles in the pathogenesis of some clinical syndromes
Tabela 1. Udział mikrocząsteczek w patogenezie wybranych zespołów klinicznych

Name of disease	Origin of microparticles
Scott syndrome and Castaman syndrome	Platelets
Wiskott-Aldrich syndrome	Platelets
Congenital sickle cell anaemia (haemoglobinopathy S)	Endothelial cells, platelets, erythrocytes, monocytes
Heparin-induced thrombocytopenia	Platelets
Sepsis	Monocytes, platelets, endothelial cells
Thrombotic thrombocytopenic purpura	Platelets
Paroxysmal nocturnal haemoglobinuria	Platelets, granulocytes, endothelial cells
Diabetes	Platelets, endothelial cells, monocytes
Cardiovascular diseases	Endothelial cells, platelets
Deep vein thrombosis and pulmonary thrombosis	Endothelial cells, platelets

The products of cellular metabolism are removed, and cell viability is preserved. However, the release of microparticles may also contribute to the elimination of erythrocytes from circulation. Integrin associated protein (IAP, CD47) is a surface protein integral to the cell membrane. It is believed that its presence on the membrane prevents the phagocytosis of blood cells by macrophages [17]. As erythrocytes age, and CD47 expression on their surface is gradually reduced due to the release of microparticles, the phagocytosis of red blood cells by macrophages increases [7, 17]. Föller et al. suggested two main models of microparticle release: (1) erythroptosis and (2) structural model of band 3 protein [18]. In the erythroptosis model, a mechanism similar to apoptosis in nuclear cells was adapted for erythrocytes. This mechanism is activated by blood cells in response to triggering factors, e.g. Calcium ions, free radicals and changes in the structure of the cell membrane (Figure 1) [18]. The increased intracellular concentration of calcium ions activates enzymes that disorganise the erythrocyte membrane.

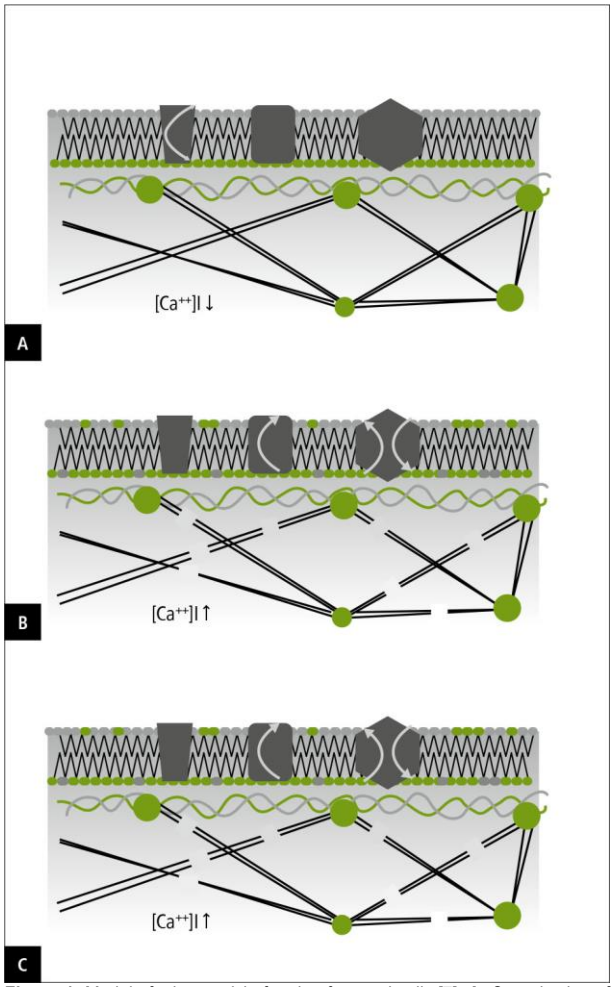


Figure 1. Model of microparticle forming from red cells [7]. **A.** Organisation of phospholipids in the cell membrane of the red blood cell is controlled by three enzymes: flippase, floppase and scramblase. Under physiological conditions, flippase maintains the asymmetry of the phospholipid bilayer structure. Floppase and scramblase are inactive enzymes; the calcium ion concentration in the cytoplasm is low. **B.** The activation of red blood cells leads to an increase in the intracellular calcium concentration, which inhibits the activity of flippase. The activation of floppase and scramblase, which are responsible for the disruption of the cell membrane by loss of phospholipid asymmetry. **C.** Elevated concentration of intracellular calcium also activates proteases. This causes the cytoskeleton to become unsealed; the cell membrane becomes more elastic and can form a released micromolecule.

Rycina 1. Model tworzenia się mikrocząsteczek z krwinek czerwonych [7]. **A**. Organizacja fosfolipidów w błonie komórkowej krwinki czerwonej kontrolowana jest przez trzy enzymy: flipazę, flopazę i skramblazę. W warunkach fizjologicznych flipaza utrzymuje asymetrię dwuwarstwowej struktury fosfolipidów. Flopaza i skramblaza są enzymami nieaktywnymi; stężenie jonów wapnia w cytoplazmie jest na niskim poziomie. **B**. Aktywacja krwinek czerwonych prowadzi do zwiększenia wewnątrzkomórkowego stężenia wapnia, co hamuje aktywność flipazy. Aktywacja flopazy i skramblazy, odpowiadających za dezorganizację błony komórkowej poprzez utratę asymetrii fosfolipidów. C. Zwiększone stężenie wewnątrzkomórkowego wapnia aktywizuje także proteazy. Powoduje to rozszczelnienie cytoszkieletu, błona komórkowa staje się bardziej elastyczna i może utworzyć uwalnianą mikrocząsteczkę.

Factors that change intracellular calcium ion concentrations are not fully understood, although authors of other studies attribute them to the effect of non-specific cation channels [19]. The structural model of band 3 protein combines the process of haemoglobin oxidisation and formation of haemichrome with dimerisation of band 3 protein in the cell membrane by the creation of a disulfide bond. Dimerisation results in the structural modification of the extracellular area of band 3 protein and the formation of neoantigen. Natural antibodies of this neoantigen combine with it, thus removing ageing erythrocytes [18]. Although it has not been demonstrated directly that the presence of neoantigens of band 3 protein can result in the formation of microparticles by erythrocytes, their presence, as well as the presence of band 3 protein dimers in RMPs, suggests the role of the latter in the elimination of neoantigens. Both presented models of formation of erythrocyte-derived microparticles have the same effect, i.e. conformational changes in band 3 protein and in the degree of phosphorylation of membrane skeletal proteins [18]. This process provides sufficient elasticity of the membrane to enable the formation and release of RMPs. The described changes take place in the cell membrane of an erythrocyte circulating in the vascular system, but similar mechanisms of microparticle release are also found in red blood cells collected from a donor and stored for transfusion, i.e. in RBC. During storage, the cellular concentrations of compounds participating in metabolism naturally decrease, or the compounds are transformed into end-products. This process is referred to as storage lesion [20]. The most important metabolic process occurring in stored blood cells is anaerobic glycolysis. The lack of external sources of energy results in a gradual depletion of energy-providing compounds in blood cells, and in reduced antioxidative defence. Concentrations of energy-carrying compounds, adenosine triphosphate (ATP) and 2,3-diphosphatidylglycerol acid (2,3-DPG), decrease. ATP is responsible for the metabolic activity of erythrocytes, and it determines the cell's flexibility and ability to retain its shape after repeated deformations. ATP preserves the activity of aminophospholipid translocase, an enzyme responsible for intracellular sequestration of phosphatidylserine, whose presence on the surface of the erythrocyte provides a signal for phagocytosis by macrophages [20]. On the day of blood collection from the donor, ATP concentration in the blood cell is usually approximately 4 ±1 μm/g Hb. This value increases to 5 ±1 μm/g Hb in the first week of storage, as a result of a significant reduction in 2,3-DPG concentration, and then decreases. Approximately 30 days after the collection, ATP concentration is only 1-3 μm/g Hb. As a consequence, the content of products of the proteolytic degradation of band 3 protein in the erythrocytic membrane increases, resulting in changes in the structure of the cell membrane [14, 20]. Similarly to the circulating blood cells, also the stored erythrocytes produce ad release microparticles containing harmful substances that accumulate during storage [15]. Interestingly, it has been demonstrated that the release of microparticles by red blood cells during storage is accompanied by the elimination of oxidised proteins. Spontaneously released microparticles contain proteins rich in carbonyl groups [21]. This confirms the hypothesis that the formation of microparticles is a mechanism that promotes the "cleansing" of blood cells from harmful molecules. Iy et al. observed the rate of the release of microparticles from the cell membrane of stored erythrocytes [2]. Their study demonstrated that in the first 10 days of RBC storage microparticles were not released, and between day 10 and 15 of storage their concentrations increased considerably. A constant increase in microparticle concentrations was observed until day 42 of blood product storage. This process was significantly suppressed or reversed by adding an additive fluid with glucose, pyruvate, inosine, adenine and phosphates to RBC [2].

Two types of erythrocyte-derived microparticles, characterised by a different size and physicochemical properties, are formed in stored RBC [22]. The first one, of 0.1-1.1 μm, contains synectin, band 3 protein, aquaporin, CD47, caspase, Fas particles, DAF (decay-accelerating factor; CD55) and high concentrations of immunoglobulin G (IgG). Kriebardis et al. analysed in detail the concentrations of substances in microparticles, comparing them to the concentrations of the same substances detected in stored erythrocytes [23]. The authors demonstrated that concentrations of enzymes and proteins in RMPs, compared to red blood cells, increase in proportion to the time of storage [23]. They also noticed that some proteins detected in microparticles are membrane skeleton proteins, e.g. CD47 or band 3 protein, and others are associated with cell apoptosis, for instance, caspase, Fas particles, DAF. It prompted the authors to conclude that the red blood cells stored in RBC undergo a kind of apoptosis [23]. Moreover, they confirmed a significant increase in the concentration of lipid peroxidation products in these microparticles, visible especially on day 15 of storage. These results supported the conclusion that the main function of microparticles released from erythrocytes is the elimination of harmful substances produced through anaerobic transformation [23]. The presented study outcomes and conclusions confirm the hypotheses from previous studies, published by other authors, but they still do not explain if this is the only or principal function of the erythrocyte-derived microparticles, or what clinical

implications may be expected in patients after transfusion of products containing RMPs [15, 21, 22].

Salzer et al. used a 3 D atomic force microscope to analyse red blood cell-derived microparticles in products stored for 50 days [24]. The authors demonstrated the existence of the second type of microparticles, sized 0.5-2 μm, and found that they contained thrombin and phosphatidylserine. They also demonstrated that small erythrocyte-derived microparticles may also contain acetylcholinesterase, band 3 protein, stomatin, CD55 and Duffy system antigens [24]. Bosman et al. conducted a proteomic analysis of these particles and identified 257 additional proteins in them [16]. Concentrations of some proteins were comparable with large microparticles and blood cells in RBC. The studies demonstrated that, for instance, the concentration of semaphorin 7A (a glycoprotein) and the concentration of peroxiredoxin decrease in erythrocytes proportionally to longer storage, but the concentrations of these proteins also increase in microparticles of both sizes [16]. Using proteomic analysis, complement components C1, C3, C4 and C9 were also found in microparticles. Higher concentrations of the components were observed in small microparticles. Based on these findings, Pasini et al. hypothesised that red blood cell-derived microparticles formed during storage may demonstrate pro-inflammatory potential [25].

CR1 receptor (CD35) for complement component is found on the surface of the erythrocyte membrane. It participates in inflammatory processes involving complement system, also in adverse reactions following transfusion of blood products [26]. Its concentration increases progressively over the time of erythrocyte storage and correlates with decreasing ATP concentrations in the blood cell. The principal role of CR1 consists in the elimination of immune complexes. The complement system is activated in the case of post-transfusion haemolytic reaction, anaphylactic reaction, and transfusion-related acute lung injury (TRALI). TRALI accounts for 7% of all post-transfusion reactions, and it is one of the leading causes of death related to blood transfusion [26]. The aetiopathological factors of this syndrome include inflammatory reaction initiated by microparticles. Following blood transfusion, RMPs activate endothelium of the pulmonary capillaries, neutrophils and platelets of the recipient, initiating complex reactions that result in the release of pro-inflammatory factors, whose role is to attract and activate immune cells [27]. This supports the hypothesis that TRALI is strongly associated with inflammatory response of the patient to transfused blood components, and that it is triggered by the activation of neutrophils, resulting in damage to the lungs. Land et al. suggest that TRALI is an acute autoinflammatory condition that may be activated, for instance, by the donor's erythrocyte-derived microparticles transfused with blood components [28]. The factors activating neutrophils in transfused blood components include biologically active lipids, e.g. lipophosphatidylcholine (L-PC) or cytokines accumulated during storage of blood components [29]. A study by Berda-Haddad et al. demonstrated that microparticles participate in the modulation of sterile inflammatory response, carrying pro-inflammatory cytokines (IL-1a), or acting as a specific "autoadjuvant" and stimulating response of B cells to organism's own antigens [30]. Isobe et al. hypothesised that red cell-derived microparticles may demonstrate pro-coagulatory activity, and significantly increase the risk of post-transfusion thrombosis [31]. This characteristic probably depends on the expression of phospholipids on the membrane of microparticles, as they create the environment in which the coagulation process may be initiated. The authors used an animal model to examine the formation of thrombin-antithrombin complex by measuring the prothrombotic activity in mice following the administration of erythrocyte-derived microparticles. No correlations were observed in the group of normal mice. The mice receiving high-fat diet revealed a significantly reduced rate of thrombin inactivation by antithrombin, and thrombotic readiness [31]. These findings confirm the hypothesis that microparticles present in transfused erythrocytes can induce adverse post-transfusion reactions, but only in certain groups of patients. It also appears that microparticles originating from different blood cells may cooperate in the pathogenesis of thrombotic post-transfusion reactions. Spinela et al. revealed that in the group of post-trauma patients who received erythrocytes stored for over 28 days, incidents of deep vein thrombosis were observed significantly more often (34%) than in patients who received red blood cells that had been stored for less than 28 days (16%; $p < 0.02$) [32]. The study involved analysis of platelet-derived and red blood cell-derived microparticles, and it demonstrated a significant increase in their concentrations during storage. The pro-coagulatory activity of platelet-derived microparticles (PMPs) is 50-100 times higher than that of thrombocytes [8]. *In vitro* thrombin activates more effectively via a thrombin receptor on the surface of a microparticle than platelets. It may indicate a greater effect of PMP on haemostasis. Red blood cell-derived microparticles may demonstrate similar pro-coagulatory properties [8]. Isolated from RBC and added to plasma samples, they significantly reduce prothrombin time (PT). Typically, platelet-rich plasma contains 2×10^9/l erythrocyte-derived microparticles [33]. When red blood cell concentrate is stored for over 35 days, the quantity of RMPs may be up to $20 \pm 10 \times 10^9$/l, which significantly increases the risk of post-transfusion thrombotic reactions [10]. The role of RMPs in transfusion-related

immunomodulation could also be explored. This phenomenon, observed after transfusion of blood components, is probably associated with reduced cellular immunity, with concurrent increased humoral immunity. Effects of transfusion include reduced antibody-dependent cell-mediated cytotoxicity (ADCC), and disturbed interleukin production. Alloimmunisation and immunosuppression are two basic processes behind post-transfusion immune changes, although their exact mechanism has not been understood. It is believed that leukocytes in the transfused blood components play a fundamental role in transfusion-related immunomodulation. Sadallah et al. emphasised a significant contribution of red blood cell-derived microparticles to post-transfusion immunomodulation [34]. During storage of red blood cell, concentrations of CR1 and DAF decrease, as they cumulate on microparticles. These factors, similarly to CD 59, probably do not participate in the elimination of immune complexes containing complement. Microparticles activate complement components C1q and C_3, stimulating immunosuppression. The authors also demonstrated that RMPs significantly reduce the release of cytokines, i.e. TNF-α, IL-8 and IL-10 [34].

Many studies published recently indicate the possibility of frequent post-transfusion reactions and worse survival of patients following transfusion of red blood cells stored longer than for 35 days. It has been demonstrated that this results from changes in blood cell membrane and formation of microparticles [35, 36]. However, the mechanisms of changes taking place during storage have not been fully explained. Contrary results were obtained in TRANSFUSE, a randomised, multi-centre study conducted by an Australian research team, and in TRIBE, a study conducted by American researchers [37, 38]. These studies compared the effects of transfusing red blood cell concentrate stored for 42 days, and under 35 days in groups of critically ill patients. The results did not correlate with increased mortality or occurrence of adverse post-transfusion reactions, and they did not justify clinical use of RBCs with a short storage time [37, 38]. RMPs in red blood cell concentrates are structurally and functionally varied biological particles. Their prothrombotic, fibrinolytic, pro-inflammatory and immunomodulatory character may affect the clinical outcomes of transfusions in certain groups of patients (e.g. people after trauma, patients with sepsis or repeated recipients). Planning future studies that would involve the determination of storage profiles for red blood cell concentrates, as well as analysis of the clinical implications associated with different storage profiles should introduce more personalised transfusion medicine.

References

1. Alvarado-Ramy F, Kuchnert MJ, Alonso-Echanove J, et al. A multistate cluster of red blood cell transfusion reactions associated with use of a leukocyte reduction filter. Transf Med, 2006; 16: 41-48
2. Iy W, Ricci M, Shariatmadar S, et al. Microparticles in stored red blood cells as potential mediators of transfusion complications. Transfusion, 2011; 51: 886-893
3. Glynn SA. The red blood storage lesion: a method to the madness. Transfusion, 2010; 50: 1164-1169
4. Wolf P. The nature and significance of platelet products of platelet products in human plasma. Br J Haematol, 1967; 13: 269-288
5. Diamont M, Tushnizen ME, Sturk A, Nieuwland R. Cellular microparticles: new players in the field of vascular disease? Eur J Clin Inves, 2004; 34: 392-401
6. Van Wijk MJ, VanBavel E, Sturk A, Nieuwland R. Microparticles in cardiovascular diseases. Cardiovase Res, 2003; 59: 277-287
7. Van Beers EJ, Schaap MC, Berckmans RJ, et al. Circulating erythrocyte – derived microparticles are associated with coagulation activation in sickle cell disease. Haematologica, 2009; 94: 1513-1519
8. Rubin O, Canellini G, Delobal J, et al. Red blood cell microparticles: clinical relevance. Transf Med Hemother, 2012; 39: 342-347
9. Greenwalt TJ. The know and why of exocytic vesicles. Transfusion, 2005; 46: 143-152
10. Rubin O, Crettaz D, Canellini G, et al. Microparticles in stored red blood cells: an approach using flow cytometry and proteome tools. Vox Sang, 2008; 95: 288-297
11. Arnaud N, Linares R, Tan S, et al. Extracellular vesicles from blood plasma: determination of their morphology, size, phenotype, and concentration. J Thromb Haemost, 2014; 12: 614-627
12. Balasubramanian K, Schroit AJ. Aminophospholipid asymmetry: a matter of life and death. Ann Rev Physiol, 2003; 65: 701-734
13. An XL, Guo XH, Sum H, et al. Phosphatidylserine binding sites in erythroid spectrin: location and implications for membrane stability. Biochemistry, 2004; 43: 310-315
14. Westerman M, Porter JB. Red blood cell-derived microparticles: An overview. Blood Cells Mol Dis, 2016; 59: 134-139
15. Willekens FLA, Werre JM, Groenen-Döpp YAM, et al. Erythrocyte vesiculation a self-protective mechanism. Br J Haematol, 2008; 141: 549-556
16. Bosman G, Lasonder E, Luten M, et al. The proteome of red cell membranes and vesicles during storage in blood bank conditions. Transfusion, 2008; 48: 827-835
17. Stewart A, Urbaniak S, Turnei M, Bessos H. The application, of a new quantitative assay for the monitoring of integrin-associated protein CD47 on red blood cells during storage and comparison with the expression of CD47 and phosphatidylserine with flow cytometry. Transfusion, 2005; 45: 1496-1503
18. Föller M, Huber SM, Lang F. Erythrocyte programmed cell death. IUBMB Life 2008; 60: 661-668
19. Lang F, Gulbins L, Lerche H, et al. Eryptosis a window in systemic disease. Cell Physiol Biochem, 2008; 22: 373-380
20. Hess JR. Red cell storage. J Proteomic, 2010; 73: 368-373
21. Delobel J, Prudent M, Rubin O, et al. Subcellular fractionation of stored red blood cells reveals a compartment-based protein carborylation evolution. J Proteomics, 2012; 76: 181-193
22. Iy W, Horstman LH, Ahn YS. Microparticle size and its relation to composition, functional activity, and clinical significance. Semin Thromb Hemost, 2010; 36: 876-880
23. Kriebardis AG, Autonelon MH, Stamoulis KE, et al. RBC-derived vesicles during storage: ultrastructure, protein composition, oxidation and signalling components. Transfusion, 2008; 48: 1943-1953
24. Salzer V, Zhu R, Luten M, et al. Vesicles generated during storage of red cells are rich in the lipid raft marker stomatin. Transfusion, 2008; 48: 451-462
25. Pasini EM, Kirkegaard M, Mortensen P, et al. In-depth analysis of the membrane and cytosolic proteome of red blood cells. Blood, 2006; 108: 791-801
26. Korsak J, Łata A. Ostre poprzetoczeniowe uszkodzenie płuc – często nierozpoznawana reakcja po przetoczeniu składników krwi. [Acute post-transfusion pulmonary damage – a frequently undiagnosed reaction following blood product transfusions] Pediatr Med Rodz, 2015; 11: 250-258
27. Kent MW, Kelher MR, West FB, Silliman CC. The proinflammatory potential of microparticles in red blood cell units. Transf Med, 2014; 24: 175-181
28. Land WG. Transfusion-related acute lung injury: the work of DAMPs. Transf Med Hemother, 2013; 40: 3-13
29. Peters AL, von Hezel ME, Juffermans NP, et al. Pathogenesis of non-antibody mediated transfusion-related acute lung injury from bench to bedside. Blood Rev, 2015; 29: 51-61
30. Berda-Haddad Y, Robert S, Salers P, et al. Sterile inflammation of endothelial cell-derived apoptotic bodies is mediated by interleukin-1α. Proc Natl Acad Sci USA, 2011; 108: 20684-20689
31. Isobe H, Perkmann T, Breuss JM, et al. Red blood cell derived microparticles are thrombogenic in mouse models of atherosclerosis. Blood, 2007; 110; 1060A, Ab#3624
32. Spinella PC, Carroll CL, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in-hospital mortality in patients with traumatic injuries. Crit Care, 2009; 13: R 151
33. Lacroix R, Robert S, Poncelet P, et al. Standardization of platelet-derived microparticle enumeration by flow cytometry with calibrated beads: results of the

Society on Thrombosis and Haemostasis SSC Collaborative workshop. J Thromb Haemost, 2010; 8: 2571-2574
34. Sadallah S, Eken C, Schifferli JA. Ectosomes as modulators of inflammation and immunity Clin Exp Immunol, 2011; 163: 26-32
35. Sanders J, Patel S, Cooper J, et al. Red blood cell storage is associated with length of stay and renal complications after cardiac surgery. Transfusion, 2011; 51: 2286-2294
36. Van de Watering L, Lorinser J, Versteegh M, et al. Effects of storage time of red blood cell transfusion on the prognosis of coronary artery bypass graft patients. Transfusion, 2006; 46: 1712-1718
37. Cooper DJ, Mc Quilten ZK, Nickol A, et al. TRANSFUSE Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Age of red cells for transfusion and outcomes in critically ill adults. N Engl J Med, 2017; 377: 1858-1867
38. Cartotto R, Taylor SL, Holmes JH, et al. The effects of storage age of blood in massively transfused burn patients: a secondary analysis of the randomized transfusion requirement in Burn Care Evaluation Study. Crit Care Med, 2018; XX: 1-8

Extreme travel medicine

Ekstremalna medycyna podróży

Dagmara Pokorna-Kałwak,[1] Krzysztof Korzeniewski[2]

[1] Chair and Department of Family Medicine of the Medical University in Wrocław; Head: Assoc. Prof. Agnieszka Mastalerz-Migas, MD, PhD
[2] Head of Epidemiology and Tropical Medicine Department of the Military Institute of Medicine in Warsaw

Abstract. Extreme sports, i.e. diverse physical activities with a variable level of safety, which often expose their participants to risks to health and life, are becoming popular among travelling tourists. They include backcountry skiing, scuba diving, sailing, spelunking and mountaineering. Extreme activities are often carried out in destinations characterised by harsh environmental conditions or limited access to specialist healthcare facilities. This makes the suitable preparation of extreme travellers highly significant. Preventive measures are as important as general health assessment, paying special attention to cardiovascular and other chronic diseases, among others. The article provides information on prophylactic measures and health risk factors that the travellers intending to do extreme sports may face.
Keywords: extreme sports, health hazards, preventive healthcare

Streszczenie. Wśród turystów podróżujących po świecie coraz większą popularność zyskują tzw. sporty ekstremalne, czyli uprawianie różnego rodzaju aktywności fizycznej o zróżnicowanym poziomie bezpieczeństwa, często obciążonej występowaniem zagrożeń dla zdrowia i życia. Należą do nich narciarstwo poza wyznaczonymi trasami, nurkowanie i żeglarstwo morskie, eksploracja jaskiń oraz wspinaczka wysokogórska. Ekstremalne aktywności często realizowane są w krajach i rejonach charakteryzujących się ciężkimi warunkami środowiskowymi oraz ograniczonym dostępem do specjalistycznych placówek służby zdrowia. W tym kontekście dużego znaczenia nabiera odpowiednie przygotowanie ekstremalnych podróżnych przed wyjazdem. Istotne są zarówno działania profilaktyczne, jak i ocena ogólnego stanu zdrowia, m.in. pod kątem chorób układu sercowo-naczyniowego i innych chorób przewlekłych. W pracy przedstawiono informacje na temat działań profilaktycznych oraz zagrożeń zdrowotnych występujących podczas wyjazdów podróżnych planujących uprawianie sportów ekstremalnych.
Słowa kluczowe: sporty ekstremalne, zagrożenia zdrowotne, profilaktyka zdrowotna

Delivered: 11/02/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 265-269

Corresponding author
Col. Prof. Krzysztof Korzeniewski, MD, PhD
Epidemiology and Tropical Medicine Department of the Military Institute of Medicine
4 Grudzińskiego St. 81-103 Gdynia
Phone: +48 261 266 523
e-mail: kkorzeniewski@wim.mil.pl

Introduction

Extreme tourism refers to travel involving physical activities associated with a significant threat to health or life, often off the beaten track. Destinations include Third World countries, as well as regions with limited access in developed countries. Types of activities undertaken vary. In the mountains, it is usually skiing outside the designated ski routes or high-altitude mountain climbing; in the aquatic environment, it is diving and open sea sailing, or white-water rafting; in the air, it is ski diving or paragliding. Cave exploring, abseiling and bungee jumping are also popular.

The health problems associated with extreme tourism belong to the area of travel medicine, as well as expedition medicine. Types of activities generally considered extreme are best illustrated by exclusions from the travel insurance coverage, which require insurance extension to cover the cost of treatment of bodily injuries sustained as a result of extreme sports and the cost of emergency services (not covered by accident insurance) [1]:

- professional sport, amateur contact sport,
- amateur athletic activities used for purposes other than recreation,
- mountaineering with the use of equipment (rope) or over 4500 m a.s.l.,
- aviation sports (except as a passenger in a commercial aircraft),
- hang gliding, parachuting or bungee jumping,

- snow skiing or snowboarding, except for recreational downhill or cross-country (no cover provided while skiing away from designated areas or against the advice of the local ski school or authoritative body)
- racing by any animal or motorised vehicle,
- caving,
- scuba diving,
- jet skiing,
- any other sport or athletic activity that is undertaken for thrill-seeking and exposes one to abnormal or extraordinary risk of injury.

The traveller should be aware that the above insurance exclusions are common, so in the case of extreme travel, an additional insurance agreement for the time of travel is required. Insurance companies offer such coverage for an extra fee [2].

Healthcare professionals providing advice to extreme travellers before expedition should demonstrate an adequate understanding of the prophylaxis and health threats typical for the planned destinations, both considering the environmental risk factors, and the intended athletic activities [3]. The demographic profile of the extreme traveller should also be taken into account. Studies involving American tourists revealed that the mean age of extreme travellers is lower than that of the general population of tourists going abroad (32 vs 44 years) [4, 5]. Although most extreme travellers are approximately 30 years old, there are also elderly tourists.

Two major causes of death among travellers are cardiovascular diseases in elderly individuals, and body trauma in young people [6]. Therefore, it is important to undergo a medical examination before the journey, especially in the case of senior citizens. The increased burden and stress associated with the travel on their organism may result in the presentation or exacerbation of cardiovascular disorders [7]. Myocardial infarction in tourists usually occurs within the first two days of travel [8]. In travellers over 50 years of age with cardiovascular risk factors (e.g. obesity, arterial hypertension, hypercholesterolaemia), at least an ECG examination should be performed before the departure. Other specialist consultations are also recommended for all tourists: stomatological, in order to exclude dental and periodontal diseases and gynaecological (women), as well as preparation of a first-aid kit, which contains medications which are used long-term [9,10].

Health risks during extreme travel

The task of a physician specialising in extreme tourism is not only to provide advice regarding the management of potential health problems, but also to discuss risk factors that may occur during the travel. The two most common risk factors are the long duration of travel and destinations with a different climate and sanitary conditions. Other health risks during extreme travel include:

- activity conducive to bodily injuries,
- increased risk of drowning (unknown water reservoirs, poorly marked swimming areas, water currents),
- crime / unstable political situation,
- using local means of transport (overcrowded vehicles, bad roads, lack of traffic regulations).

Extreme travellers usually experience bodily injuries as a result of athletic activities or using local transport. In developing countries, most injuries are consequences of road traffic accidents [11]. The risk of an accident increases by 6 times when the driver is not a local carrier, but the traveller. In addition, the risk of a road accident increases by 2.5 times if the traffic in the destination country uses the opposite side of the road than the traffic in the country of origin [12, 13]. Travelling after dark, under the influence of alcohol, or without seatbelts is also dangerous [2, 11].

Types of extreme sports

When travelling, people often practise traditional sports on land, in water or in the air. However, extreme sports, i.e. various physical activities with different levels of safety, often associated with health and life risks, are becoming popular among tourists. The most common mistakes made by tourists choosing this type of entertainment is lack of health insurance covering extreme sports, lack of properly equipped first-aid kit, lack of assistance from qualified guides/instructors, and lack of diligence while planning the journey.

Snow skiing outside the designated areas

Lack of supervision, unprepared routes and a high likelihood of an avalanche increase the risk of an accident. They also significantly extend the time of waiting for medical help in the case of bodily injury. The probability of an avalanche is particularly high in winter. The risk cannot be eliminated, even with adequate experience and good preparation. In approximately 90% of cases, an avalanche occurs on the slopes of 30-45°, usually after intensive snowfall, i.e. in perfect conditions for skiing enthusiasts.

Skiers are recommended to travel in organised groups and to prepare the equipment that can save lives (avalanche detector, shovel, CO_2 scrubber) [14]. A study conducted by Radwin et al. [15] demonstrated that when trapped by an avalanche, most victims suffer from necrosis due to carbon dioxide intoxication earlier than from hypoxia or hypothermia, which means that CO_2 scrubbers are first-aid devices.

Scuba diving, snorkelling

Diving trips are organised by countless travel agencies across the world. In countries where tourism is well organised (e.g. Belize, Australia, Thailand), participation in a diving expedition is conditional upon hiring a licensed instructor, but in developing countries it is not always required.

Decompression sickness and the risk of drowning are the greatest hazards for divers. Divers Alert Network is an organisation that offers assistance in critical situations. This association helps to choose the right insurance, find the nearest hyperbaric chamber, and organise hyperbaric therapy.

However, if travellers decide to dive in sites far from a health centre with a decompression chamber, they need to be aware of other safety measures. One of them is in-water recompression, i.e. going back underwater to the level where the symptoms resolve and then slowly resurfacing; the time of decompression should be doubled. Such situations require experience, an adequate amount of air in the bottle, favourable weather conditions and sufficient time [1].

Caving

Recently, visiting closed caves with difficult access has become popular. The greatest hazards for cavers include bodily injuries and the risk of drowning if the cave is flooded. In developing countries, an evacuation from a cave in a dangerous situation is often impossible. To ensure safety during caving, local authorities should be informed about the planned expedition, and the support of medical and rescue services should be secured.

Cavers are also exposed to the risk of infectious diseases, e.g. rabies, if they come in contact with infected bats (in the USA approximately 17% of all animals with rabies are bats) [16]. It is important to remember that rabies is transmitted not only by direct contact with an animal, but also indirectly, by contact with its excretions (e.g. saliva), or even through droplet spread. This is possible when encountering a large group of bats, in poorly ventilated caves with high humidity and temperature [17].

Mountaineering

For mountaineers, their own experience and using the services of licences guides are of greatest importance. Staying at high altitudes is associated with a risk of bodily injuries and altitude sickness. Bodily injuries usually occur as a result of a fall, an avalanche, or falling into a crevice. Conditions associated with low temperatures (frostbites, hypothermia, pernio, trench foot) or solar radiation (sunburns, photophthalmia) are also frequent [18].

Health problems manifesting as altitude sickness are found in people who ascend to high altitudes above the sea level. Three types are distinguished: acute mountain sickness (AMS), high altitude pulmonary oedema (HAPE) and high altitude cerebral oedema (HACE). While ACE typically is not a condition of a direct threat to life, HAPE and HACE are life-threatening in the absence of preventive or therapeutic actions. The symptoms are caused by the low partial pressure of oxygen, resulting in the disturbed functioning of the central nervous system, cardiovascular system and respiratory system. The rate of symptom development and exacerbation depends on the altitude, as well as on age, psychophysical condition, level of hydration, medications, rate of ascent and time of exposure to high altitude [19].

Table 1. Selected types of extreme sports, risks and preventive actions [1]
Tabela 1. Wybrane rodzaje sportów ekstremalnych, ryzyka i działań zapobiegawczych [1]

Type of extreme sport	Risk	Preventive measures
Snow skiing outside designated areas	Avalanches	Understanding the risk of an avalanche, avalanche detector, CO_2 scrubber
Scuba diving, snorkelling	Decompression sickness, drowning	Recompression in a hyperbaric chamber or in water (if the chamber is not available)
Caving	Bodily injury, drowning	Experienced guides, refraining from exploration during rainfall, avoiding bat faeces, vaccination against rabies
Mountaineering	Altitude sickness, bodily injury	Experienced guides, expedition supervised by healthcare professionals, avoiding fast climbing, acclimatisation
Rock climbing	Bodily injury	Local guides, experience in climbing
Parachuting, bungee jumping	Bodily injury	Services of a licensed agency
Rafting	Drowning	Services of a licensed agency

Symptoms of altitude sickness are observed in 10-20% of people who ascended to 1800-2400 m a.s.l. in less than 24 hours. A rapid ascent to 3400-4300 m a.s.l. induces mild symptoms in most mountaineers, while moderate symptoms occur in 50%, and severe symptoms in 12-18% of people. An excessively rapid ascent to over 5300 m a.s.l. results in serious pathological changes in nearly all mountaineers. Symptoms of acute mountain disease should be considered in all unacclimatised individuals who ascended to over 1800 m a.s.l. within 24 hours and stayed at that altitude for several hours. The symptoms may occur in people who moved suddenly from a low to a high altitude, or in those who ascended still higher from a high altitude [18]. The disease is therefore caused not by the altitude itself, but by a significant altitude difference covered in a short time [20].

The basic preventive measures in altitude sickness include slow acclimatisation, stopping a further ascent or a descent if symptoms occur, the administration of oxygen and medications and, when it is available and a quick descent is impossible, the use of a portable hyperbaric chamber (e.g. Gamow bag producing pressure that simulates the conditions of a lower altitude) [19].

However, even the best insurance and the highest quality equipment cannot substitute common sense. An insurance policy covering the costs of emergency services gives an illusion of safety, but in practice, it is of little use in emergency situations resulting in death. For people without proper experience, it is crucial to adjust one's behaviour to the circumstances.

References

1. Boulware DR. Travel medicine for the extreme traveller. Dis Mon, 2006; 52: 309-325
2. Korzeniewski K. Medycyna podróży. [Travel medicine] Kompendium. [Travel medicine. A compendium] Wydawnictwo Lekarskie PZWL, Warsaw 2016
3. Goodyer L, Gibbs J. Medical supplies for travelers to developing countries. J Travel Med., 2004; 11: 208-211
4. Chen LH, Hochberg NS, Magill AJ. The pretravel consultation. In: Brunette GW, ed. CDC yellow book 2018. Health information for international travel. Oxford University Press, New York 2017: 16-32
5. U. S. Department of Commerce, Office of Travel & Tourism Industries. 2003 profile of US resident traveler visiting overseas destinations. Reported from: survey of international air travelers. www.ti-dev.eainet.com/ view/f-2003-101-001/index.html (accessed on: 24/03/2005)
6. Jong EC. Approach to travel medicine and contents of a personal travel medicine kit. In: Sanford CA, Pottinger PS, Jong EC, eds. The travel and tropical medicine manual. Elsevier, Marickville 2017
7. Christenfeld N, Glynn LM, Phillips DP, et al. Exposure to New York City as a risk factor for heart attack mortality. Psychosom Med, 1999; 61: 740-743
8. Kop WJ, Vingerhoets A, Kruithof GJ, et al. Risk factors for myocardial infarction during vacation travel. Psychosom Med, 2003; 65: 396-401
9. Wilder-Smith A, Khairullah NS, Song JH, et al. Travel health knowledge, attitudes and practices among Australasian travelers. J Travel Med, 2004; 11: 9-15
10. Cabada M, Maldonado F, Mozo K, et al. Travel-related health issues: a comparison between North American and European travelers visiting Cuzco, Peru. J Travel Med, 2005; 12: 61-65
11. Odero W, Garner P, Zwi A. Road traffic injuries in developing countries: a comprehensive review of epidemiological studies. Trop Med Int Health, 1997; 2: 445-460
12. Carey MJ, Aitken ME. Motorbike injuries in Bermuda: a risk for tourists. Ann Emerg Med. 1996; 28: 424-429
13. Petridou E, Askitopoulou H, Vourvahakis D, et al. Epidemiology of road traffic accidents during pleasure travelling: the evidence from the Island of Crete. Accid Anal Prev, 1997; 29: 687-693
14. Radwin MI, Grissom CK. Technological advances in avalanche survival. Wilderness Environ Med, 2002; 13: 143-152
15. Radwin MI, Grissom CK, Scholand MB, et al. Normal oxygenation and ventilation during snow burial by the exclusion of exhaled carbon dioxide. Wilderness Environ Med, 2001; 12: 256-262
16. Krebs JW, Noll HR, Rupprecht CE, et al. Rabies surveillance in the United States during 2001. J Am Vet Med Assoc, 2002; 221: 1690-1701
17. Messenger SL, Smith JS, Rupprecht CE. Emerging epidemiology of bat-associated cryptic cases of rabies in humans in the United States. Clin Infect Dis, 2002; 35: 738-747
18. Korzeniewski K. Problemy zdrowotne w warunkach wysokogórskich. [Health problems at high altitudes] Pol Merk Lek, 2008; 146: 161-165
19. Hartman-Ksycińska A, Kluz-Zawadzka J, Lewandowski B. High altitude illness. Przegl Epidemiol, 2016; 70: 490-499
20. Huey RB, Eguskitza X. Limits to human performance: elevated risks on high mountains. J Exp Biol, 2001; 204: 3115-3119

Impact of "Military Physician" on the development of haemotherapy and blood donation in Poland, 1920-1939. Part 2

Wpływ czasopisma „Lekarz Wojskowy" na rozwój krwiolecznictwa i dawstwa krwi w Polsce w latach 1920-1939. Część 2

Renata Elżbieta Paliga

Institute of History of Medicine and Medical Ethics at the Pomeranian Medical University; Head: Aleksandra Kładna, MD, PhD

Abstract. The interwar period saw an increased interest in blood transfusion. "Military Physician" published articles on the topic. Initially, blood transfusion was promoted, quoting data from international sources, and information about transfusions carried out by Polish physicians was publicised. Over time, expertise in blood treatment increased among Polish physicians. They willingly published their observations and comments in scientific magazines. The awareness of the need to introduce a law on blood donation and haemotherapy was growing. "Military Physician" played a significant role in the advancement of works and spreading knowledge on blood transfusion among physicians in interwar Poland.
Keywords: blood, method, physicians, tools, transfusion

Streszczenie. W dwudziestoleciu międzywojennym wzrosło zainteresowanie transfuzją krwi. W „Lekarzu Wojskowym" zamieszczano artykuły dotyczące tego tematu. Początkowo propagowano przetaczanie krwi, powołując się na dane z ośrodków światowych, i informowano o transfuzjach wykonanych przez polskich lekarzy. W miarę upływu czasu i pozyskiwania praktycznego doświadczenia wzrastała wśród polskich medyków umiejętność leczenia krwią. Lekarze chętnie publikowali swoje spostrzeżenia i uwagi na łamach periodyków naukowych. Dojrzewała świadomość o konieczności stworzenia w Polsce regulacji prawnych dotyczących krwiodawstwa i krwiolecznictwa. Czasopismo „Lekarz Wojskowy" odegrało znaczącą rolę w postępie prac i propagowaniu wiedzy o transfuzji krwi wśród medyków w dwudziestoleciu międzywojennym w Polsce.
Słowa kluczowe: krew, transfuzja, metoda, narzędzia, lekarze

Delivered: 07/01/2019.
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97 (3): 270-275;

Corresponding address:
Renata Elżbieta Paliga, MD, PhD
Institute of History of Medicine and Medical Ethics
1 Rybacka St., 70-204 Szczecin
e-mail: rpaliga@pum.edu.pl

Introduction

The global development of transfusion medicine in the 1920s and 1930s was a consequence of the gaining of skills in blood maintenance during World War I and the increase in the number of procedures performed. In the 1930s, "Military Physician" began to publish articles on the preparation of the medical service for the next armed conflict. Among the articles on military sanitary tactics, a discussion on the issues related to transfusion and its application in a future war was unavoidable. In 1933 and 1934, a number of articles on the methodology and organisation of the blood service were published in the periodical. Bolesław Szarecki, Tadeusz Sokołowski, Julian Henryk Levittoux and Jan Antoni Korczakowski, were among those who took up the subject. The discussion between experienced doctors covered the organisation of blood donation during a potential war, the unification of the procedure methodology and the need to create legal regulations that did not exist in Poland at that time.

Views on blood transfusion based on the articles published in "Military Physician" in 1930-1939

Discussions in "Military Physician" concerning the methods and organisation of blood transfusion

At the beginning of the 1930s, military doctors often mentioned the fact that treatment with blood is not popular in Poland (Sokołowski, Szarecki, Korczakowski, Neyman, Zalewski et al.). There were ongoing discussions about the usefulness of particular methods. There was no shortage of supporters of both the direct method (blood transfused directly from the donor without preservation) and of transfusion with preserved blood (so-called citrate-stabilised blood). In the years 1933-1934, "Military Physician" hosted a discussion on numerous aspects related to blood transfusion.

The discussion was initiated by Captain Henry Levittoux, who in 1933 published an article on the organisation of transfusions during a war [1]. He argued that during an armed conflict, blood must be given by women and that medical transport should be done by air. These were bold and modern statements that differed from the reality and possibilities of interwar Poland. He wrote about the value of fresh and preserved blood: "I base all my dreams of blood transfusion on the ability to preserve blood (...). All this may be in the realm of dreams, but it seems to me that it would be worthwhile to consider this idea and put it into practice." His project of blood treatment in the event of a war in 1933 was based on the existence of haematological units placed on the front line. They were to consist of a haematologist, an internist, auxiliary personnel and the representatives of women's organisations involved in the recruitment of women willing to donate blood. The front-line haematological units were to examine the general health status of donors and the test the Wassermann reaction, to determine the blood type, to perform morphology tests, blood collection, and to pack blood in 500 ml ampoules, etc. When J.H. Levittoux wrote these words in 1933, he could not suppose that the transfusion units would be created in the American and British armies and that a system similar to the one he proposed would already be in use during World War II.

From the early 1930s, Bolesław Szarecki defended the thesis of the superiority of transfusion with preserved blood, seeing it as the future of military transfusion medicine. He referred to his experiences from medical centres abroad, including Soviet ones. Large Soviet cities had their own haematological institutes which studied the process of preservation and storage of blood. In 1933, Szarecki published two articles in "Military Physician" concerning various aspects of blood transfusion, which were the result of lectures given during a session of the Sanitary Section of the Military Knowledge Society in 1932 and 1933 [2, 3]. He promoted blood treatment and sought to popularise the procedure among military doctors "because blood transfusion in Poland is not widespread enough and encounters difficulties due to the lack of paid donors. We should use all our strength and energy to make proper use of this healing method, at least in the broad military strata. To this end, skilfully organised propaganda must be launched immediately, emphasising the special importance of blood transfusion in the military during wartime."

He also raised organisational issues: "today I again appeal to the accountable factors to speed up the organisation of blood transfusion in the military. A central institution should be set up which, with scientific authority, would carry out research into blood transfusion, blood storage and transport methods, organise courses for military doctors in order to familiarise them with the theoretical foundations of this therapeutic method and its practical application during wartime."

Tadeusz Sokołowski, who willingly used blood transfusion in his medical practice, was another military doctor who joined in the discussion on haemotherapy in "Military Physician" in the interwar period. In 1933, he wrote: "So what difficulty can there be in transfusing blood under field conditions? Only lack of blood donors! After all, the question of technology and quick determination of group membership is long solved, and there is no need to talk about it. Which method of blood transfusion should be used in field conditions? The best, safest and simplest, i.e. direct transfusion with a syringe (...). In my opinion, the issue of transfusing preserved blood, raised by Colonel Szarecki in ''Military Physician'', remains a laboratory issue. If we manage to preserve blood in such a way that neither temperature nor time will change its vital properties, we will arrive at a perfect method of transfusing blood" [4].

Initially, Sokołowski was performing direct transfusions. We can assume that he did that with a syringe of his own making. In 1933, he wrote: "in the surgical ward of the 8th Regional Hospital, transfusion has been an ordinary procedure for the past six years and, if necessary, is usually used in the same way as any other rescue procedure. This procedure can be quickly arranged and performed by any of the department's assistants. During this period, more than 100 blood transfusions were performed always using the direct method." Two years later, most likely after taking up employment in Warsaw, Sokołowski became an advocate of treatment with preserved blood.

In 1933, Jan Korczakowski, Senior Head of the Surgical Ward of the 8th Regional Hospital, also

discussed the organisation of the blood service during the war: "The issue of transfusion of citrate-stabilised and transported blood (preserved blood – author's note) is still in the trial period. Direct blood transfusion will always be superior to indirect blood transfusion. I propose the creation of a group of voluntary blood donors from men belonging to cat. D, possibly E, who would be assigned to field hospitals in surgical front line units [5].

The analysis of the articles published in "Military Physician" shows that each blood transfusion method had its own supporters. Over time, the indirect transfusion method became more widespread due to the simplicity of the procedure. In the search for practical solutions, the previously announced methods of transfusion were being modified. In 1933, Kazimierz Neyman from the Department of Internal Medicine of the 7th Regional Hospital in Poznań discussed blood transfusion with trisodium citrate in "Military Physician": "in our ward, for blood transfusion we use uncoagulated blood, made so by adding trisodium citrate, and 20 cm Record syringes". The syringes and needles were rinsed with trisodium citrate solution, two cubic centimetres of citrate were drawn into each syringe, blood was collected from the donor, mixed slightly in the syringe, the needle was changed, and the mixture was administered to the patient's vein [6]. Transfusions of small blood volumes collected from the donor and immediately administered to the recipient's bloodstream with syringes were performed as early as in the 19th century. The only modification made by Neyman was the mixing of donor blood with trisodium citrate and the use of type-compatible blood. The use of trisodium citrate was not to store blood, but to prevent clotting during the procedure.

Tools for direct transfusion designed by Poles in the interwar period

Doctors performing blood transfusions often designed tools for this purpose. They tried to popularise methods and tools for commercial purposes. In Poland of the interwar period, direct transfusion devices were the first to be created. These were syringes that changed the direction of the blood flow. The first device worth mentioning was a syringe created by Tadeusz Sokołowski (Figure 1). It was probably created in the 1920s, when Sokołowski was the Head of the Surgical Ward of the 8th Military Regional Hospital [7]. Sokołowski's syringe was produced by the "Alfred Mann i Syn" [Alfred Mann and Son] manufacturing workshop of surgical instruments in Warsaw and was registered in the Patent Office [8]. The device with a capacity of 5 cubic centimetres had a cylinder made of Polish glass. The valve had three channels and two drains for blood. The valve settings determined the flow direction. The drains were connected to rubber tubes terminating in needles for puncturing the veins of the donor and the recipient.

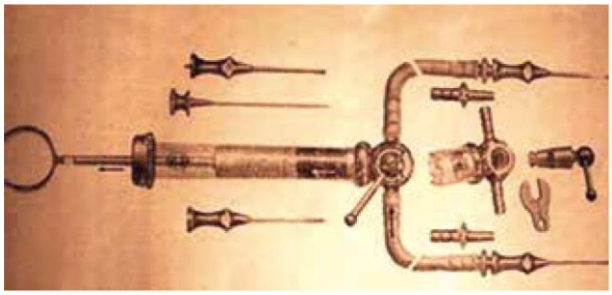


Figure 1. Sokołowski's syringe (in: Hirszfeld L. Grupy krwi. Warsaw 1934:164)
Rycina 1. Strzykawka Sokołowskiego (w: Hirszfeld L. Grupy krwi. Warszawa 1934:164)

Another device for direct transfusion, which was created in Poland in the 1930s, was a syringe by Jerzy Rutkowski (Figure 2), a well-known surgeon who repeatedly published his works in "Military Physician" in the interwar period [9].

The war in Spain and its impact on the development of global transfusion medicine

During the Spanish Civil War (1936-1938), blood duty was organised for the first time. Donor frameworks were created, methodology and preservation procedures were developed. Blood transfusion was used on a massive and unprecedented scale. In 1938, "Military Physician" published T. Sokołowski's article on the use of blood transfusion on the front line. The report was created thanks to the author's acquaintance with Frederik Duran-Jord, MD, the creator of the blood service on the frontlines in Spain [10]. The service was organised by order of the Department of Health during the Red Terror in Spain. "On the side of the Spanish national army, there is an extensive organisation for the transfusion of preserved blood. In the cities occupied by the national army, 20 volunteer blood donation centres were established. The number of blood donors in S. Sebastian is 843. Each Spanish and Legionnaire's (Italian) brigade has its own blood transfusion service organisation". Initially, blood types A and 0 were collected, but due to technical difficulties, type A blood was no longer determined and until the end of the war only type 0 was collected, preserved and sent to the front.

Figure 2. Rutkowski's syringe (from the author's collection, in: Paliga R. Haemotherapy and blood donation in Polish medicine of the XIX and XX century [1830-1951]. Oficyna Wydawnicza Uniwersytetu Zielonogórskiego, Zielona Góra 2014: 243-244)
Rycina 2. Strzykawka Rutkowskiego (własność autorki; w: Paliga R. Krwiolecznictwo i krwiodawstwo w medycynie polskiej XIX i XX wieku [1830-1951]. Oficyna Wydawnicza Uniwersytetu Zielonogórskiego, Zielona Góra 2014: 243-244)

The blood donor gave 300-400 cm^3 of blood at one sitting, which was preserved with 4% trisodium citrate at a ratio of 1:10 and maintained at 1-2°C. The blood was stored for up to 3 weeks. Bacteriological tests were carried out using agar cultures. The growth of bacteria was evaluated after 24 hours. The donated blood, which complied with the sterility norms of the time, was filtered and poured into a bottle. Blood from six donors was poured into a 2 L container. It was mixed and filtered again, then divided into ampoules for storage, transport and transfusion. In the 1930s, it was believed that the mixing of blood from several donors resulted in fewer unexplained complications in recipients.

The 300 cm^3 ampoules filled with blood and pressurised gas were supplied with a rubber tube with a glass insert. The ampoules were marked with the blood type symbol and expiration date (18 days – author's note). Transfusion with such a device was simple because the compressed gas caused blood to be pushed out, and the flow rate was controlled by a clamp. One end of the ampoule was to be broken off for air, and the other end was to be inserted with a needle into the recipient's vein. The ampoules were packed individually. Blood was transported to the frontline in special refrigerated vehicles and usually transfused 8-16 days after collection. It is known that in autumn 1937, during military operations, about 5000 transfusions with preserved blood type 0 were performed.

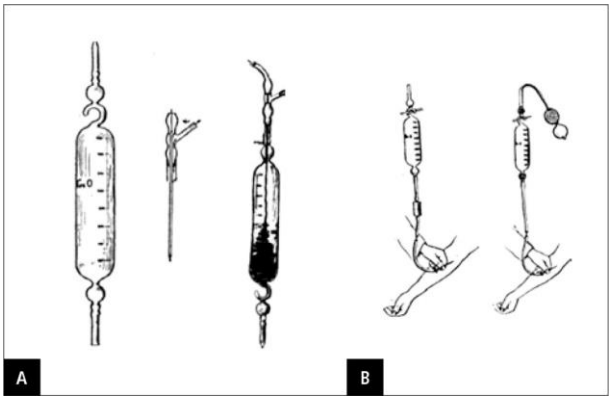


Figure 3.A-B. Blood drawing, storage and transfusion tool made at the Warsaw Traumatology Institute (in: Marat W. Ampoule for collecting, storing, transporting and transfusing preserved blood. Chir Pol, 1937; 2 [5]: 256.)
Rycina 3.A-B. Przyrząd do pobierania, przechowywania i przetaczania krwi stworzony w Instytucie Chirurgii Urazowej w Warszawie (w: Marat W. Ampułka do pobierania przechowywania transportu i przetaczania krwi konserwowanej. Chir Pol, 1937; 2 [5]: 256.)

Research on preserved blood in Poland

In Poland, in the 1930s, in line with the global trend, intensive work on blood preservation was being carried out. In Warsaw at that time, two centres for blood preservation and transfusion were established. In 1935, the Blood Transfusion Institute was established at the Main Hospital of the Polish Red Cross in Warsaw. It was created thanks to the efforts of Bolesław Szarecki, while its head was Henryk Gnoiński, whose scientific research concerned the processes taking place in red blood cells during preservation. Another place where blood preservation was tested was the Trauma Institute of the 1st Regional Hospital in Warsaw, also established in 1935. The head of the institution was Tadeusz Sokołowski. At the Trauma Institute, 500 ml glass containers were used to collect and preserve blood and were typically used to store sterile physiological saline (Figure 3).

During direct bleeding, 5% glucose solution was poured into an ampoule of 200 cm^3 and sterilised in an autoclave. It was believed that taking blood with a syringe would cause blood cell trauma. After filling the container with blood, glucose and 5% sodium citrate solution, the glass tube of the ampoule was placed above the gas burner to close it, and after cooling the contents were mixed. In order to perform the transfusion, the ampoule was turned upside down, and blood flowed through a rubber tube containing a muslin filter designed to stop potential clots [11].

At this point, it is worth mentioning another pioneer of Polish haematology of the interwar period, Julian Aleksandrowicz. In 1937, he published an article in

"Military Physician" about the use of preserved blood in military health care and demonstrated his own device for collecting, preserving, storing and administering blood (Figure 4). He also presented his research on blood preservation and compared it with the reports of other scientists from Poland and abroad. He determined the indications for transfusions in war medicine: posthemorrhagic anaemia, intoxication with combat gases, burn, trauma shock, etc.

The described container was registered in the Patent Office of the Republic of Poland under no. 27514 on 23 December 1938 as an instrument for collecting, storing and transfusing blood. Aleksandrowicz wrote: "My instrument has the form of a 1-litre ampoule made of Jena glass. At the top of the ampoule, there is a glass tube "h" bent at a right angle and closed with a rubber cap "b". Next to it, there is a shorter tube terminating in an "l" bubble, filled with a cotton wool filter and also closed with a rubber cap. At the bottom, there is a neck closed with a rubber "k" plug. Before collecting blood, pour a preserving fluid into the vessel" [12].

Legislation on blood donors

The dispute between physicians, which took place in "Military Physician" in 1933 and 1934, also concerned the need to create legal regulations related to transfusion and blood donation. In the interwar period in Poland, blood was donated for a fee and was expensive. The patient's family usually made a direct payment to the doctor who performed the procedure. Some donors donated blood "professionally", and due to the lack of adequate legislation there were cases of fraud and numerous irregularities. There were also differences between military and civil medicine. Tadeusz Sokołowski described blood donation in the military health service in the early 1930s, which can be compared to modern times: "...military hospitals are in a better position; they usually have no difficulty in finding blood donors because, on the one hand, military doctors have special official authority that facilitates the recruitment of donors and, on the other hand, a sense of camaraderie is a strong moral stimulus that encourages our soldier to donation. Here, however, the customary and differing rules of blood donation centres should take the form of uniform regulations as soon as possible" [13].

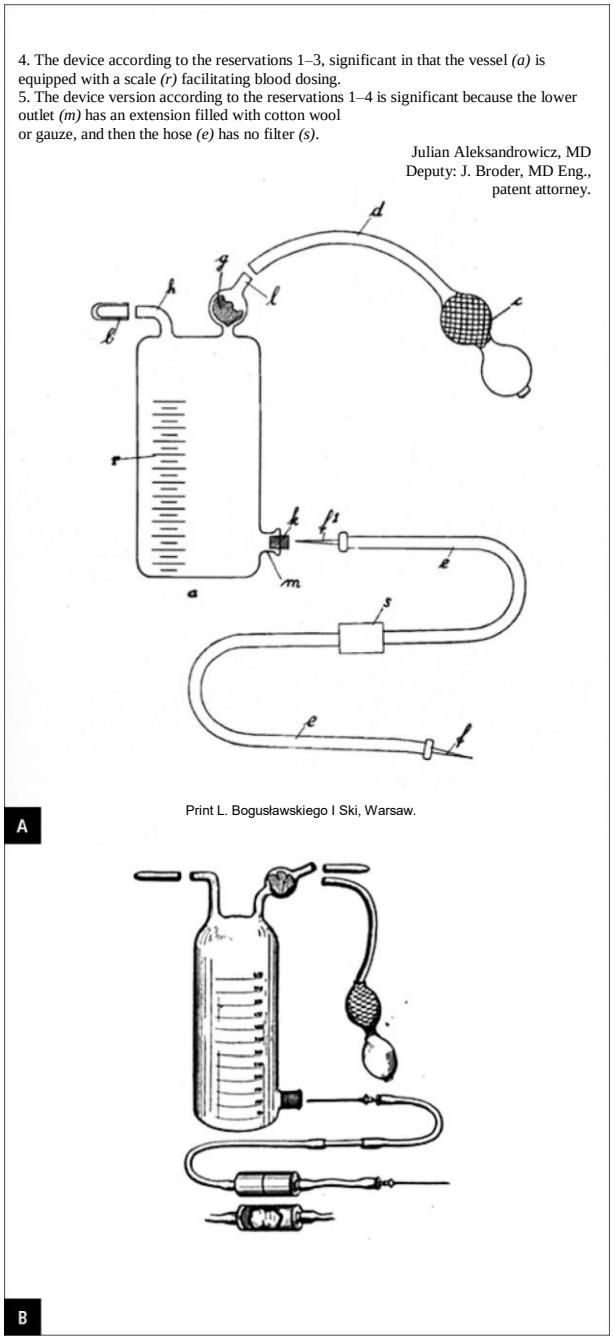


Figure 4.A-B. Drawing showing Aleksandrowicz's apparatus for banked blood storage and transfusion (in: Aleksandrowicz J. Preserved blood and its use for transfusion in military health care. Mil. Phys., 1937; 29 [7]: 405.)

Rycina 4.A-B. Rysunki przedstawiające aparat Aleksandrowicza do przechowywania i przetaczania krwi konserwowanej (w: Aleksandrowicz J. Krew konserwowana i jej zastosowanie do przetaczania w wojskowej służbie zdrowia. Lek Wojsk, 1937; 29 [7]: 405.)

The draft of the first regulation concerning blood donation and blood healing in Poland was drawn up in 1932. It was most likely created on the initiative of Ludwik Hirszfeld with the participation of civil and military surgeons. Despite votes on the need for legislation on blood donation, division of competencies and the need to supervise the transfusion, the first regulation saw the light only in 1937. It concerned the supervision of donors and the safety of the donated blood. The annexes to the regulation include templates of identity cards (with minor adjustments still functioning today) and determine the colours of group designations [14].

Before World War II, within the framework of the activity of the Polish Red Cross, blood typing campaigns for potential donors began, and blood collection campaigns for the army were organised.

International conferences and symposia on transfusion medicine

In the 1930s, Poles were very successful in transfusion medicine and were considered Europe's scientific leaders in this field. They shared their experiences and knowledge at international congresses and symposia. Ludwik Hirszfeld, a world-famous scientist, opened the First International Congress on Blood Transfusion, which took place in Rome in 1935. The second section was headed by Tadeusz Sokołowski, who gave a lecture on problems related to blood transfusion in the military sanitary service. This lecture aroused a great deal of interest. Its content was a report from the discussion on the method and organisation of the military blood service, which took place in "Military Physician" in the years 1933-1934. The next International Congress on Blood Transfusion in Paris in 1937 was attended by a large delegation of Polish doctors, including military doctors. They gave lectures on their own work on blood preservation, and a great deal of comment was made with respect to the achievements of Henryk Gnoiński, who was invited to the Blood Preservation Commission.

Conclusion

In the interwar period, "Military Physician" was a popular medical journal in Poland. It shaped views and promoted modern medical knowledge. Articles dealing with issues related to blood transfusion shaped attitudes and promoted blood donation. Theoretical papers and reports on transfusions encouraged the use of blood transfusion in medical practice. Analysing the literature from this period, we can observe a huge progress in transfusion medicine. From a primitive and rarely used method in 1920, it transformed into a modern and organised blood service within a dozen or so years.

During the war in Spain in 1936-1938, projects of organisational solutions were tested. A well-functioning blood service was developed. Military doctors were particularly interested in haemotherapy and blood donation. In their view, the transfusion procedure could save many wounded during warfare.

The achievements of Poles in the field of transfusion medicine gained recognition in the international arena. Numerous papers published in medical journals of international reach and participation in conferences presenting Polish scientific achievements placed our fellow countrymen among the top scientists dealing with transfusion medicine in Europe. Publications in the periodical "Military Physician", whose editorial staff willingly published articles on blood transfusion, contributed to the successes.

References

1. Levittoux H. Organizacja przetaczania krwi podczas wojny [Organisation of blood transfusion during the war]. Mil. Phys., 1933; 21 (5): 385-391;
2. Szarecki B. O przetaczaniu krwi konserwowanej i transportowanej w warunkach wojny [About the transfusion of preserved and transported blood in war conditions]. Mil. Phys., 1933; 21 (6): 494-503;
3. Szarecki B. W sprawie przetaczania krwi w wojsku w czasie wojny i w czasie pokoju [About blood transfusions in the military during war and peacetime]. Mil. Phys., 1933; 22 (10): 687-699;
4. Sokołowski T. W kwestii przetaczania krwi na wojnie [About the blood transfusion during the war]. Mil. Phys., 1933; 22 (4): 178-182;
5. Korczakowski J. O organizacji przetaczania krwi na froncie [About the blood transfusion organisation on the front]. Mil. Phys., 1933; 22 (7): 335-338;
6. Neyman K. Przetaczanie krwi w klinice schorzeń wewnętrznych [Blood transfusions at the Internal Medicine Teaching Hospital]. Mil. Phys., 1933; 21 (1): 11-24;
7. Brzeziński W. Tadeusz Sokołowski i jego szkoła chirurgiczna [Tadeusz Sokołowski and his surgical school]. Szczecin 1995: 131.
8. Hirszfeld L. Grupy krwi [Blood Types]. Warsaw 1934: 164.
9. Augustynowicz D, Karolak A, Grodzka H, Kosater A. Oni tworzyli „Lekarza Wojskowego" w okresie dwudziestolecia międzywojennego. Wykładowcy Uniwersytetu Warszawskiego w pierwszym dziesięcioleciu jego istnienia. Część II [It was them who created "Military Physician" during the interwar period. Lecturers of the University of Warsaw in the first decade of activity of the journal. Part II]. Mil. Phys., 2016; 94 (1): 101-110;
10. Sokołowski T. Przetaczanie krwi na froncie wojny domowej w Hiszpanii [Blood transfusions on the front line of the Spanish Civil War]. Mil. Phys., 1938; 31 (2): 154-165;
11. Marat W. Ampoule for collecting, storing, transporting and transfusing preserved blood. Chir Pol, 1937; 2 (5): 254-258;
12. Aleksandrowicz J. Preserved blood and its use for transfusion in military health care. Mil. Phys., 1937; 29 (7): 399-408;
13. Sokołowski T. Organizacja przetaczania krwi. Rozwój metody [Blood transfusion organisation. Development of the method]. Mil. Phys., 1934; 23 (8): 393-406;
14. Paliga R. Krwiolecznictwo i krwiodawstwo w medycynie polskiej XIX i XX(1830-1951) [Haemotherapy and blood donation in Polish medicine of the XIX and XX century (1830-1951)]. Oficyna Wydawnicza Uniwersytetu Zielonogórskiego, Zielona Góra 2014

Wars and occupation as seen by Colonel Kazimierz Jan Płoński, MD (1901-1970) Senior Head of the Dermatological and Venereal Department of 9th Regional Hospital in Brest-on-the-Bug

Wojny i okupacje z perspektywy płk. dr. Kazimierza Jana Płońskiego (1901-1970), starszego ordynatora oddziału skórno-wenerycznego 9. Szpitala Okręgowego w Brześciu nad Bugiem

Krzysztof Kopociński, Zbigniew Kopociński

Subdepartment of Ophthalmology of the 105th Borderline Military Hospital with Clinic in Żary: Head Krzysztof Kopociński, MD, PhD

Abstract. Brest-on-the-Bug is a city where in the interwar period the 9th Regional Hospital, one of the ten most important military hospitals in Poland, was stationed. The last Head of its Dermatological Department was Captain Kazimierz Jan Płoński (1901-1970), a military physician, a graduate of the Faculty of Medicine at the University of Warsaw and the Medical Cadet School in Warsaw. In 1920, he took part in the Polish-Soviet War as a soldier of the 211th Volunteer Regiment of Niemen Uhlans. During the 1939 Defensive War, he commanded the 902nd Field Hospital. After 17 September 1939, he became a captive of the Soviet army. He managed to escape from the transport to the East, when Polish officers were being taken to POW camps. Most of them were killed by the NKVD in 1940. During the German occupation, he was a soldier of the Home Army in Biała Podlaska District, where he took on the pseudonym "Bożena". In 1944, he joined the 2nd Polish Army, with which he took part in the crossing of the Lusatian Neisse in April 1945. For many years, Colonel Kazimierz Jan Płoński served as the Head Dermatologist of the Polish Army. He died on 1 May 1970 and was buried in Tomaszów Lubelski.
Keywords: 2nd Polish Army, 9th Regional Hospital, Brest-on-the-Bug, dermatologist, Home Army, Kazimierz Płoński, military physician

Streszczenie. Brześć nad Bugiem to miasto, w którym w okresie międzywojennym stacjonował 9. Szpital Okręgowy, jeden z dziesięciu najważniejszych szpitali wojskowych w Polsce. Ostatnim szefem oddziału dermatologicznego tej placówki był kpt. Kazimierz Jan Płoński (1901-1970), lekarz wojskowy, absolwent Wydziału Lekarskiego Uniwersytetu Warszawskiego i Szkoły Podchorążych Sanitarnych w Warszawie. W 1920 r. brał udział w wojnie Polski z Rosją jako żołnierz 211. Ochotniczego Pułku Ułanów Nadniemeńskich. Podczas wojny obronnej 1939 r. dowodził 902. Szpitalem Polowym, po 17 września dostał się do sowieckiej niewoli. Zdołał uciec z transportu na wschód, którym wieziono polskich oficerów do obozów jenieckich; większość z nich zginęła w 1940 r. zabita przez NKWD. W czasie okupacji niemieckiej był żołnierzem Armii Krajowej Obwodu Biała Podlaska, gdzie posługiwał się pseudonimem „Bożena". W 1944 r. wstąpił do II Armii Wojska Polskiego, z którą brał udział w forsowaniu Nysy Łużyckiej w kwietniu 1945 r. Przez wiele lat płk. Kazimierz Jan Płoński pełnił funkcję Naczelnego Dermatologa Wojska Polskiego. Zmarł 1 maja 1970 r., został pochowany w Tomaszowie Lubelskim.
Słowa kluczowe: Kazimierz Płoński, lekarz wojskowy, 9. Szpital Okręgowy, Brześć nad Bugiem, dermatolog, II Armia Wojska Polskiego, Armia Krajowa

Delivered: 29/01/2019
Accepted for print: 09/04/2019
No conflicts of interest were declared.
Mil. Phys., 2019; 97(3): 276-283;

Corresponding author
Zbigniew Kopociński, MD, PhD
Ophthalmologic Subdivision
Borderlands Military Hospital with Outpatient Clinic
2 Domańskiego St., 68-200 Żary

Phone: +48 684 707 862
e-mail: zkopocinski@wp.pl

Introduction

The 20th century was an extremely dramatic time for the Polish nation, something no one would have expected at the century's outset. Poles living under the occupation of three partitioners – Russia, Austria-Hungary and Prussia – despite more than one hundred years in captivity, never came to terms with the loss of their independence. The great calamity, which was the outbreak of World War I in 1914, gave Poles the opportunity to restore their Polish state, as a result of the Treaty of Versailles in 1919. In the following year, the Republic of Poland had to fight for its existence during the Bolshevik invasion. Thanks to the extraordinary generosity of the entire Polish society, the bravery of Polish soldiers and the brilliant plan of General Tadeusz Rozwadowski (1866-1928), the Bolsheviks were repelled and the Polish Army celebrated one of the greatest victories in its history. After less than twenty years, in September 1939, the attack of the Third Reich and the USSR (with the participation of Slovakia) put an end to the existence of the reborn homeland and, at the same time, became the source of a global conflict. Poland once again become occupied by its aggressive neighbours. In 1945, the victory over Hitler had a bittersweet taste, as under the disgraceful treaties of Yalta and Potsdam, Poland lost a large part of its territory, and the country ceased to be a fully sovereign state. The generation of Poles born at the beginning of the 20th century witnessed all these dramatic events. Their fate was marked by numerous wars, changes in successive ruling parties and socio-economic systems. Families have suffered the death of relatives, famine, feelings of contempt and hatred, sudden deprivations of security and stability, the pillaging of all their possessions, brutal and intrusive political indoctrination and the worst of all – betrayal. This generation also included representatives of the medical world, who, despite all these dramatically unfavourable circumstances, never lost hope and tried to remain faithful to the principles proclaimed by Hippocrates. They helped those in need, but at the same time they often suffered the brutal consequences of their choices. Colonel Kazimierz Jan Płoński, MD, the last Senior Head of the Dermatological and Venereal Department of the 9th Regional Hospital in Brest-on-the-Bug, personally experienced all these tragic events of the first half of the 20th century.

Figure 1. Kazimierz Jan Płoński (1901–1970) as a student of the Faculty of Medicine at the University of Warsaw (courtesy of Nikodem Butrymowicz)

Rycina 1. Kazimierz Jan Płoński (1901–1970) jako student Wydziału Lekarskiego Uniwersytetu Warszawskiego, 1922 (dzięki uprzejmości Nikodema Butrymowicza)

Youth and participation in the war of 1920

Kazimierz Jan Płoński was born on 5 August 1901 in the village of Honiatycze (the then Russian partition), in the region of Tomaszów Lubelski, to the family of Michał and Stanisława Płoński. His father was a gamekeeper, so the financial situation of the family was not too bad. Kazimierz was the oldest child and had three younger brothers. He started his education at the four-class Common School in Tomaszów Lubelski. After the outbreak of World War I, the area was occupied by the Austro-Hungarian Empire, so he continued his education at the Imperial-Royal Male Realgymnasium in Zamość, which in 1918 changed its name to the Royal-Polish Gymnasium, and one year later became the Jan Zamoyski State Male Gymnasium [1-3]. The patriotic upbringing received at home, additionally consolidated and enhanced by excellent teachers from the Zamość school, meant that he did not remain passive in the face of social and political changes. The independent Republic of Poland was reborn before his very eyes, which was what several generations of Poles had prayed for. He belonged to the youngest of these generations, and although he was born a subject of Tsar Nicholas II (1868-1918), he still lived to see the restitution of the Polish state.

In the summer of 1920, when the Red Army invaded Poland and threatened to annihilate it, thousands of young Poles volunteered to defend their homeland. More than fifty students of the Gymnasium in Zamość joined the ranks of the Polish Army. One of them was a sixth-grade student Kazimierz Płoński, who on 16 July 1920 enrolled in the 211th Volunteer Regiment of Niemen Uhlans under the command of Major Władysław Dąbrowski (1891-1927); his deputy was Captain Jerzy Dąbrowski (1889-1940). The Dąbrowski brothers were legendary raiders, who became famous in the battles of the Samoobrona [Self-defence] units in the Vilnius and Grodno regions. In 1919, they formed a partisan unit, which sowed fear among the Bolsheviks stationed in the area. The first squadron of the 211th Volunteer Regiment of Niemen Uhlans was formed by experienced soldiers from the times of partisan fighting, while the second and fourth squadrons were formed by volunteers.

Płoński was in one of the squadrons. The unit set off to the front on 12 August 1920 and fought numerous battles with the Bolsheviks, including those at Płock, Góra and Chorzele. The squadron became famous for its daring charge that ended with conquering a bridge over the Niemen River and the town of Druskininkai. In October 1920, the regiment took part in the operation of General Lucjan Żeligowski and fights against the Lithuanians.

After the winning campaign on 21 November 1920, Płoński was demobilised in order to for him to complete his education in the gymnasium, and his unit became a part of the Central Lithuanian Army. Radiant with the war fame of the legendary Major Dąbrowski voluntary unit, he returned to the gymnasium, which in no way provided him with favourable treatment during his school education and promotion to the next class. In 1922, he passed his secondary school final exam and began to apply for medical studies [1-5].

Alma Mater of military doctors of the Second Republic of Poland

It should be stressed that the state authorities tried to reward and recognise the sacrifices made by the soldiers defending their homeland in 1920. The militant past of the young graduate from Zamość was probably one of the circumstances that determined his admission to the elite group of students of the Military Medical School (WSS, *Wojskowa Szkoła Sanitarna*).

The school was established under the Regulation of the Minister of Military Affairs of 1 November 1922 as a result of the transformation of the Application School of Medical Officers, and its main objective was to provide trained officers for the needs of the military health service. In order to be admitted, one had to be a Polish citizen, unmarried, up to 24 years of age, in very good health (category A), and with a secondary school final exam certificate. Medical classes were held at the Faculty of Medicine (in the case of physicians) of the University of Warsaw, while military training was organised at the WSS base. Each graduate, after obtaining a diploma and promotion to the first officer rank, was obliged to serve in the professional military service for two months for each month of the studies. The conditions provided by the WSS were very attractive, especially for the less wealthy graduates, so the number of candidates was very high. Only 40 people were admitted to the first year, but Płoński succeeded. His participation in the battles during the war in 1920 was to a large extent a contributing factor.

Immatriculation at the Faculty of Medicine of the University of Warsaw took place on 1 October 1922, and the official opening of the WSS happened on 14 November 1922. This day became a holiday for this military university, celebrated also after its transformation in 1924 into the Officer Medical School, and then in 1928 into the Medical Cadet School. The studies took six years, and at the same time a military training program was conducted at the WSS headquarters, i.e. at the Ujazdowski Castle, as well as during summer camps. The students also performed duties resulting from the requirements of military life, for example, they did military service in the place of their accommodation. In the years 1922-1925, they also completed obligatory monthly practices in infantry and cavalry regiments.

Płoński was assigned to a cavalry training course organised by the 1st Riding Brigade at the base of the 7th Uhlan Regiment in Mińsk Mazowiecki. Interestingly, the former uhlan of the 211th Volunteer Regiment of Niemen Uhlans received a 'sufficient' grade in horse riding skills, but it should be remembered that the evaluation criteria of the time were very high and could only be met by professional cavalrymen. Thanks to his persistent work and complete commitment, Płoński successfully completed his medical studies at the Faculty of Medicine of the University of Warsaw, obtaining in 1929 the diploma of doctor of all medical sciences. At the same time, he was promoted to the rank of second lieutenant [1, 6-8].

In military health service in the Eastern Borderlands of the Second Republic of Poland

In 1929, Second lieutenant Płoński received his first assignment as a physician in the Romuald Traugutt 83rd Riflemen Regiment of Polesia in Kobryn, in the 9th Corps District bordering the USSR. For a young physician who wanted to broaden his knowledge and skills in the field of dermatological and venereal diseases, serving in a remote borderland garrison was a big challenge, which every military doctor is well aware of. At that time, his great hope for professional development was the 9th Regional Hospital in Brest-on-the-Bug. It was one of the ten most important military medical facilities in Poland, and it was stationed in the famous fortress on Wyspa Szpitalna [Hospital Island], in former Bernardine monastery buildings. The facility had 400 beds in eight wards: internal, surgical, infectious, gynaecological and obstetrical, ophthalmic, otological, dermatological and venereal, and nervous. Psychiatric patients, due to the lack of a proper ward, were referred to the Vilnius Fortified Area Hospital or to the 1st Regional Hospital in Warsaw. In the years 1935-1938, the facility also had a branch, i.e. the Seasonal Military Hospital in Domaczew.

When Second Lieutenant Płoński arrived in Kobryn, the commanding officer of the hospital was Lieutenant Colonel Leonard Szmurło, MD (1876-1940), an extremely experienced military surgeon, who tried to help his younger colleagues in their professional development, so he did not make any problems for Płoński in taking up his specialisation. The Senior Head of the Dermatological and Venereal Department, Lieutenant Colonel Robert Funk, MD, an excellent dermatologist, under whose watchful eye Płoński gained experience and perfected his skills, also had no objections. From 3 November 1930 to 31 January 1931, thanks to the unit commander's consent to a temporary secondment, he was able to complete a specialisation internship in his home unit. However, commuting from Kobryn to Brest proved problematic for the young doctor. This could have put his specialisation in his dream medical field into question, so he decided to obtain a transfer to the place where he was stationed. In 1931, Płoński was promoted to the rank of lieutenant, and in August of the following year he was transferred from Kobryn to the position of a physician of the Support Team of the 9th Regional Hospital. The task of the Support Team (KZ, *Kadra Zapasowa*) was to conduct all mobilisation and training matters concerning the military health service reserves of the 9th Corps District; its commander was simultaneously the deputy commander of the hospital. At the moment of Płoński's arrival, the commander of KZ was Major Wiaczesław Michałowski, MD (1891-1940), who was replaced in 1935 by Major Faustyn Derecki, MD (1894-1971). The work there was well organised, and the superiors did not make it difficult for the young physician to specialise at the local Dermatological and Venereal Department. Lieutenant Colonel Robert Funk, MD, Senior Head, was also pleased that he gained a doctor for a 120-bed ward, which was not easy to run.

Figure 2. Lt. Kazimierz Jan Płoński, MD (1901–1970), Brest–on–the–Bug, 1930 (courtesy of Andrzej Płoński)
Rycina 2. Ppor. dr Kazimierz Jan Płoński (1901–1970), Brześć nad Bugiem, 1930 r. (udostępnione dzięki uprzejmości Andrzeja Płońskiego)

These were ideal conditions for a young physician who was no longer burdened with countless duties in the so-called green garrison or the need to commute to the hospital, but instead could devote himself to working at the Dermatological and Venereal Department, which resulted in his rapid professional development, as well as in the gaining of experience and skills necessary in the work of a dermatologist. On 12 January 1937, he officially took over the position of the Head of the Dermatological and Venereal Department of the 9th Regional Hospital, although in practice he held this position as early as in 1935; his superior was the Senior Head of the Department, Lieutenant Colonel R. Funk, MD. Płoński was highly appreciated by his superiors, which was reflected in his promotion to the rank of captain in 1935. An excellent illustration of the evaluation of his work is also the official opinion issued by his former superior, Lieutenant Colonel Faustyn Derecki, MD: "Very talented and hard-working, he achieved very good results in his speciality as well as in the care of the families of military personnel in general medicine. Very obliging. In addition to his knowledge, he has shown a great deal of knowledge and experience in the field of treatment and rescue of gassed persons".

The Brest period was probably one of the happiest stages of his life, as during that time he gained a very good professional position, which also enabled him to create the right conditions for starting a family. In August 1935, he married Irena Helena Miazga, with whom he had two children: Andrzej (1937) and Bożena (1942).

At the 9th Regional Hospital, the private relations between all the officers and their families were very good. Not only did this foster an excellent working atmosphere, but it also created interpersonal bonds, which later resulted many times in mutual help and support in the darkest years of war and occupation. A good example illustrating life in this garrison was the baptism of the first-born son of Captain Płoński in 1937, with the

chaplain of the hospital, Captain Józef Mendelowski, as his godfather, and the wife of the then unit commandant, Jadwiga Butrymowicz, as his godmother.

The crowning achievement of Captain Płoński's professional career during the Interwar period was the taking over of the position of Senior Head of the Dermatological and Venereal Department of the 9th Regional Hospital in Brest-on-the-Bug on 1 July 1939. This idyllic period came to an end two months later, when World War II broke out [1, 3, 8-15].

Figure 4. Capt. Kazimierz Jan Płoński, MD (stands first from the right) with colleagues from the 9th Regional Hospital and the spouses of the officers' staff, Brest-on-the-Bug, second half of the 1930s, (courtesy of Nikodem Butrymowicz)

Rycina 4. Kpt. dr Kazimierz Jan Płoński (stoi pierwszy z prawej) z kolegami z 9. Szpitala Okręgowego oraz małżonkami kadry oficerskiej, Brześć nad Bugiem, II połowa lat 30. XX wieku (dzięki uprzejmości Nikodema Butrymowicza)

The 1939 Defensive War and the German-Soviet occupation

At the time of mobilisation, a large part of the 9th Regional Hospital's professional staff was allocated to line units, and their place in the home institution was taken by reserve physicians mobilised by the KZ. Captain Płoński became the commander of the Field Hospital No. 902, which after 17 September 1939 was taken over by the Red Army. The officers of this unit were arrested by the NKVD, locked in railway cars and transported eastward. Luck favoured the dermatologist from Brest, who together with other officers managed to unscrew a few boards, which made it possible for the whole wagon (about 70 people) to escape. During this dangerous escapade, probably nobody thought that most of the officers captured by the Soviets, including the doctors of the 9th Regional Hospital, would be murdered a few months later by a shot to the back of the head by the NKVD, while they, by escaping, would save their lives.

Płoński returned to Brest-on-the-Bug, where Soviet order was already in force. The 9th Regional Hospital no longer existed, and the apartments of the personnel had been devastated and robbed or were occupied by new "owners". At the same time, the threat of arrest or deportation to the east was growing, as Płoński was well aware. He decided to leave the town and move to the territories occupied by the Third Reich, to the familiar town of Biała Podlaska. At the beginning of December 1939, taking advantage of the early-days poor supervision of the border zone between the occupation zones of the USSR and the Third Reich, he said goodbye to the capital of Polesia and found himself in Biała Podlaska. He lived with his family at 43rd Sitnicka Street

and started working as a Social Insurance doctor. He also earned extra money by running a private practice.

After stabilising his professional situation, he became a soldier of the Home Army of the Biała Podlaska District under the pseudonym "Bożena". His neighbour, and at the same time a collaborator in the conspiracy, was a graduate of the Jan Kazimierz University in Lviv, a surgeon from Buczacz, Franciszek Mroczkowski, MD. In Biała Podlaska, there were also other military doctors involved with the Home Army, including colleagues of Płoński's, such as Lieutenant Colonel Stanisław Cepryński-Ciekawy, the former Senior Head of the Internal Department of the 9th Regional Hospital, or a colleague from the 1st Promotion in the Medical Cadet School, Captain Franciszek Krajewski, MD.

A very important part of Płoński's activity was the cooperation with the partisan unit of Lieutenant Stefan Wyrzykowski "Zenon" (1916-1985), i.e. the 34th Infantry Regiment of the Home Army. This unit was set up in December 1943, and at the peak of its activity it numbered about 350 soldiers (besides Poles, it consisted of Russians, Hungarians, Jews and others). Its greatest successes include its participation in the Operation "Most III" [Bridge 3rd] in May 1944, i.e. the extraction and transfer to London of the V2 rocket taken over in Sarnaki.

This was the time when the former Eastern Borderlands of the Second Republic of Poland were being gradually taken over by the Soviets, and the Home Army soldiers participating in Operation "Burza" [Storm] were being disarmed, arrested or deported to the east (Vilnius, Lviv). At the same time, the area was threatened by the activities of criminal bands of Ukrainian nationalists, the so-called Ukrainian Insurgent Army (UPA, *Ukraińska Powstańcza Armia*), which carried out mass and extremely cruel murders of the Polish people. On 15 May 1944, a Ukrainian bandit kurin led by Taras Onyszkiewicz "Hałajda" attacked Honiatycze, the home town of Płoński. The population of the village organised by the local Home Army outpost daringly managed to repel the attack, but almost the entire village was burned down. In response to these dramatic events, Płoński immediately took his family to Mszczonów, while he returned to Biała Podlaska, where he supported the "Zenon" unit until the invasion of the Red Army. In the situation of a huge military advantage of the Soviets, and at the same time an almost open betrayal of Poland's "great allies" – USA and Great Britain, who behind the back of the legal Government of the Republic of Poland decided to deprive Poland of part of its territory and subjugate it to the USSR, the military actions did not make much sense, as they only meant a futile bloodshed of these most patriotic people. In August 1944, in fear of being arrested by the NKVD in connection with his activities in the Home Army, Płoński left Biała Podlaska and moved to Tomaszów Lubelski.

The Polish Committee for National Liberation (PKWN, *Polski Komitet Wyzwolenia Narodowego*), established by the Soviets on 15 August, issued a decree on the mobilisation of the birth cohort of 1921-1923, of reserve officers up to 50 years old, and of professional officers up to 60 years old, which meant that a large number of draft boards had to be created. This was not easy because there was a huge shortage of physicians. It should be remembered that only within the framework of the Katyn massacre, several hundred representatives of this profession were murdered, many were killed by Germans during the infamous Operation AB, directed against the Polish intelligentsia, as well as in death camps or Gestapo torture houses. The moment Płoński appeared in Tomaszów Lubelski, he was appointed to the position of a doctor on the local draft board. As he recalled years later: "The work of the board was characterised by primitiveness and haste (...) The work of the board from morning to evening, the decisions were based on subjective and physical examination without any additional tests (X-ray, blood, urine)." In October 1944, in accordance with the PKWN decree, he was called up to the Polish Army [1, 3, 8, 11, 16, 17].

In the 2nd Polish Army and in the post-war period

The Health Service Department of the Polish Army in Lublin directed him to the Field Evacuation Point No. 3 (abbreviated from Russian as PEP No. 3) in Czemierniki, whose commander, Major Leon Gecow, MD, was at that time organising thirteen field hospitals to serve as a base for the 2nd Polish Army. Captain Płoński was appointed to the position of the Head of the Dermatological and Venereal Department of the Hospital for the Slightly Injured No. 28 in Siedlce. The unit was stationed in the former officer's house of the 22nd Infantry Regiment, and the patients of the 200-bed ward were mainly venereal patients, who were considered to be poorly disciplined, imprudent and difficult to treat. The living conditions were very difficult, lacking the most basic equipment and drugs, which made the process of diagnostics and treatment much more difficult. Only the excellent training and experience of Płoński, combined with the knowledge of the soldiers' psyche, resulted in a significant improvement in discipline among patients and their rapid recovery. As a result of this success, in January 1945 his superiors appointed him to the position of Chief Venereologist of the 2nd Polish Army and referred him to an additional training course at the Venereal Hospital No. 3196 in Lublin. In April 1945, during preparations to force the Lusatian Neisse, he and the entire Health Service Headquarters of

the 2nd Polish Army arrived in Ruszów (German: Rauscha), which at that time was a large hospital base. When the offensive began at 6 a.m. on 16 April 1945, he was at the Divisional Medical Point (DPM, *Dywizyjny Punkt Medyczny*) of the 8th Infantry Division, where he took a direct part in rescuing Polish wounded soldiers and coordinating the evacuation. The following days brought very large losses, being the result of the flanking of some of the 2nd Polish Army units by the Army Group "Środek" [Middle] under the command of Field Marshal Ferdinand Schörner (1892-1973) in the area of Budziszyn and Dresden. Some of the Polish units were surrounded and almost completely destroyed, and numerous war crimes were committed against Poles, including in the area of the town of Horka. The inability to provide rapid assistance and the awareness of the enormous losses caused a feeling of immense depression in the entire management, which Płoński recalled years later. Fortunately, these were the last chords of the criminal activity of the Third Reich, which in May 1945 was finally defeated.

Summing up the activities of the military health service of the 2nd Polish Army during the fight with Germany, Płoński wrote a beautiful sentence, which is an expression of homage to all the soldiers of the sanitary facility: "Despite the darkness of the night, the roar and fire of the bullets, the glow of fires, the blood of the wounded, the horror and danger of war, the people in white were boldly moving forward in order to conscientiously fulfil their duty as a doctor, feldsher, nurse or medic."

The taste of this victory was particularly bitter for Poles, especially those from the Eastern Borderlands of the Second Republic of Poland. As a result of the disgraceful treaties in Yalta and Potsdam, millions of Płoński's fellow countrymen were deprived of their homes and private property and expatriated to the so-called Recovered Territories. Płoński, who was promoted to the rank of major on 3 May 1945, was a realist and perfectly aware of the conditions under which he would have had to function. His former 9th Regional Hospital no longer existed, many colleagues had been murdered by the NKVD, and Brest-on-the-Bug was outside Polish borders. Being convinced that World War III between the USA and the USSR is a complete pipe dream and that armed resistance had no chance at that time, he decided to stay in the army and do what he knew best, i.e. help the sick. In August 1945, the 2nd Polish Army was dismantled, and Płoński was temporarily appointed the Head of the Dermatological and Venereal Department of the Regional Hospital No. 5 in Poznań. In November of the same year, he was transferred to Warsaw, where he was appointed Chief Dermatologist of the Polish Army and Head of the Dermatological and Venereal Department of the Central Hospital of the Ministry of National Defence at Koszykowa Street. On 31 December 1945, he was promoted to the rank of lieutenant colonel. From April 1947 to March 1948, while still serving as the Chief Dermatologist of the Polish Army, he became the Head of the Dermatological and Venereal Surgeries of the Central Medical Clinic of the Ministry of National Defence. Then he took the position of the Head of the Public Health Service of the Organisation "Służba Polsce" [*Serving Poland*], which he held until July 1955. He was promoted to the rank of Colonel on 22 July 1949, which sugared the pill of putting the military mainstream aside. In the years 1955-1957, he was still the Head of the Health Service of the Military Coal Corps at the Ministry of Mining. As a result of the October 1956 changes, a large part of the Soviet officers serving in the Polish Army returned to the USSR, which in turn made it possible for many Polish officers to take up management positions again. In June 1957, Płoński again became the Chief Dermatologist of the Polish Army and Head of the Dermatological Clinical Institute of the 2nd Central Teaching Hospital of the Military Medical Academy, and he held this position until July 1964. Retired on 9 June 1965.

Colonel Kazimierz Jan Płoński, MD died of acute myeloid leukaemia on 1 May 1970. He was buried in the cemetery in Tomaszów Lubelski, where his parents are also buried. In recognition of his combat merits and fruitful medical work, he was awarded the Commander's Cross and Officer's Cross of the Order of Polonia Restituta, the Gold Cross of Merit, and the Silver Cross of Merit twice, Medal of the Decade of Independence, Medal of the 10th Anniversary of the People's Republic of Poland, Medal of the 1918-1921 War, Order of the Cross of Grunwald 3rd class, Grunwald Badge, Partisan Cross, "Za Odrę, Nysę i Bałtyk" Medal [*For the Oder, Neisse and Baltic Sea*]. His children took over the family tradition in the medical profession – his son Andrzej graduated from the Military Medical Academy and became a military dermatologist, his daughter Bożena also worked as a dermatologist [1, 3, 8, 12, 17].

Conclusions

The life of Kazimierz Płoński, extremely abundant in dramatic events, is a perfect reflection of the fate of a large group of doctors who lived during breakthrough moments in history. The greats of this world are all too often able to change borders or governments in different countries, either politically or militarily, with unreflective ease, which, in any case, usually means the suffering of millions of ordinary people. For the generation of young Poles who grew up during the partitions, the outbreak of World War I and the possibility of fighting with weapons in hand and under Polish banners for their homeland was the fulfilment of dreams that came true for the young

Płoński. His free homeland, although not devoid of numerous flaws (especially after May 1926), gave him the opportunity to gain a respected profession of a physician and officer epaulettes, as well as a salary enabling him to live a comfortable life. The outbreak of World War II and its consequences brought about a complete change in the social and political situation, as well as in his personal situation. In the new Poland, his merits to date, his participation in the Polish-Bolshevik war and his activity in the Home Army were a heavy burden, especially on the former "Sanation" officer. The authorities of the Office of Security or Military Information in a relatively short time broke up the independence underground and arrested thousands of people. They were surely aware that a large number of physicians during the occupation were either in the Home Army or in cooperation with it, and on the territory of the country there were many former officers of the military health service of the Second Republic of Poland. Fortunately, there were no mass arrests, although there were single persecutions (e.g. the known case of the death of the Westerplatte crew doctor, Major Mieczysław Słaby, MD). It may be argued that the huge shortage of medical staff in Poland after the end of World War II made the new authorities decide that it was necessary to "turn a blind eye" to the unfavourable (in the opinion of the rulers) biography and previous activity in the underground, because this is the only way to secure the health service organisation in the country. This situation was exploited by Płoński, who, as an experienced dermatologist, and previously a front soldier of the Second Polish Army, made a brilliant career in the military health service. Probably not without significance was the mutual support given to each other by former Medical Cadet School graduates holding high positions in the army. It is worth noting that Płoński also maintained contacts with former doctors of the 9th Regional Hospital in Brest-on-the-Bug, with whom he would recall that period of his life, as well as with his colleagues murdered in Katyn. From a broad perspective, one can say that he was certainly a realist, had an excellent sense of observation and the ability to quickly assess the situation, which saved his life several times. He was able to adapt to life in diametrically different social, political and economic conditions without unnecessary complaining. This, of course, required a compromise, which was not an easy and pleasant thing for him, but it ensured the possibility of decent functioning and education of his offspring as honest people. The system, governments and borders are transient things, as Płoński has learned many times, while the internal system of values received with parental education, faithfulness to the principles proclaimed by Hippocrates and patriotism understood as serving one's own nation even in the most unfavourable circumstances are the most durable foundations of true humanity and civic attitude. Colonel Płoński, MD never embezzled them, both as the uhlan of the 211th Volunteer Regiment of Niemen Uhlans, the Head of the 9th Regional Hospital in Brest-on-the-Bug, a soldier of the Home Army and the 2nd Polish Army, as well as the Chief Dermatologist of the Polish Army.

It is worth looking at the biography of this military physician in order to ask ourselves whether, in such dramatic circumstances, we would have behaved in the same way or whether we would have chosen a different path.

References

1. Centralne Archiwum Wojskowe [Central Military Archive]. AP-982, KZ-17-1026
2. II Sprawozdanie Dyrekcji Król.-Polskiego Gimnazjum i Prywatnego Gimnazjum Żeńskiego w Zamościu za rok szkolny 1917/18 [II Report of the Board of the Royal-Polish Gymnasium and Private Female Gymnasium in Zamość for the school year 1917/18]. Zamość, 1918: 38.
3. Account of Andrzej Płoński of 2019
4. Czechowski J. Międzynarodowe uwarunkowania Litwy Środkowej (9 X 1920-6 IV 1921) [International conditions of Central Lithuania (9 X 1920-6 IV 1921)]. Dzieje Najnowsze, 2017, 2: 189-204;
5. Łukomski G. Walka Rzeczypospolitej o kresy północno-wschodnie 1918-1920 [The fight of the Republic of Poland for the north-eastern borderlands 1918-1920]. Wyd. Naukowe UAM, Poznań 1994: 53-58, 143
6. Englert JL, Domar Domaradzki A. Szkoła Podchorążych Sanitarnych 1922-1939 [Medical Cadet School 1922-1939]. London, 1997: 16-23;
7. Woynarowska B, ed. Podchorążowie z Ujazdowa. Wspomnienia Szkoły Podchorążych Sanitarnych w 50-tą rocznicę założenia Szkoły. [Cadets from Ujazdów. Memories of Medical Cadet School on the 50th anniversary of the establishment of the School]. London, 1972: 37-38;
8. Materiały archiwalne udostępnione dzięki uprzejmości Nikodema Butrymowicza [Archival materials shared thanks to the kindness of Nikodem Butrymowicz].
9. Felchner A. Pod znakiem Eskulapa i Marsa. Służba zdrowia Wojska Polskiego (od jesieni 1918 r. do mobilizacji w 1939 r.) [Under the sign of Aesculapius and Mars. The health care of the Polish Army (from autumn 1918 until the mobilisation of 1939)]. Wyd. Napoleon V, Oświęcim 2016: 249; 253
10. Kopociński K. Pułkownik Nikodem Butrymowicz – lekarz i oficer dwóch wojen światowych [Colonel Nikodem Butrymowicz – physician and officer of two world wars]. Mil. Phys., 2004; 80 (4): 282-283;
11. Kopociński K. Waleczny doktor trzech wojen, czyli rzecz o płk. dr. Stanisławie Cepryńskim-Ciekawym [A brave doctor of three wars, i.e. a story of Colonel Stanisław Cepryński-Ciekawy]. Mil. Phys., 2008; 86 (2-4): 114-116;
12. Kopociński K., Kopociński Z. Zarys organizacji i działalności 9. Szpitala Okręgowego w Brześciu nad Bugiem w latach 1920-1939 [An outline of the structure and operation of the 9th Regional Hospital in Brest-on-the-Bug in 1920-1939]. Archiwum Historii i Filozofii Medycyny [Archive of History and Philosophy of Medicine], 73: 46-48;
13. Kopociński K. Podpułkownik Leonard Szmurło – oficer i lekarz z Kresów Wschodnich Polski [Lieutenant Colonel Leonard Szmurło – an officer and physician from the Eastern Borderlands of Poland]. Mil. Phys., 2004; 80 (4): 284-285;
14. Kopociński K. Mjr dr Wilhelm Piotr Kokiński – jeden z twórców laryngologii wojskowej w Brześciu [Major Wilhelm Piotr Kokiński, MD – one of the founders of military laryngology in Brest]. Mil. Phys., 2007; 83 (2): 48-49;
15. Kopociński Z, Kopociński K, Jeśman C. Płk dr Jan Józef Krusiewicz (1873-1930) – twórca i pierwszy komendant 9. Szpitala Okręgowego w Brześciu nad Bugiem [Colonel Jan Józef Krusiewicz, MD (1873-1930) – founder and first commander of the 9th Regional Hospital in Brest-on-the-Bug]. Mil. Phys., 2016; 94 (4): 456-460;
16. Account of Alina Zofia Chrzanowska „Martá. www.kpbc.umk.pl/Content/198450/Chrzanowska_2885_WSK.pdf (access: 17.01.2019)
17. Płoński K. W Szeregach Służby Zdrowia 2 AWP. Ze wspomnień lekarza 2 Armii WP [In the ranks of the Health Care of the 2nd Polish Army. From the memories of the doctor of the 2nd Polish Army]. Wyd. MON, Warsaw 1969 10-29, 85-104, 161-167