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Author's or Authors' (max. 10 people) first and last names, including academic degrees, full name of 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, telephone (fax) and email 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 first three, followed by "et al.". References should be numbered using the keyboard, please do not use automatic numbering. Examples of citations:

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Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002: 338-340

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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.

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SPIS TREŚCI

Intestinal parasitic infections in Sub-Saharan population illustrated with an example of inhabitants of the Central African Republic

Zarażenia pasożytami jelitowymi w populacji subsaharyjskiej na przykładzie mieszkańców Republiki Środkowej Afryki

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Abstract. Aim. The article presents the results of a research study into the prevalence of intestinal parasitic infections in residents of the Central African Republic. Material and methods. Parasitological examination was performed in December 2014 on stool samples obtained from 44 patients treated in a municipal hospital for internal diseases and 54 asymptomatic workers employed in the food processing and dining facilities at the multinational military base UCATEX in Bangui, the country's capital. The samples were examined with direct smear, decantation and flotation techniques in the Department of Epidemiology and Tropical Medicine of the Military Institute of Medicine in Gdynia, Poland. Results. The study found that 9 (20.5%) of 44 hospital patients and 6 (11.1%) of 54 asymptomatic workers employed on the military base were infected with pathogenic intestinal parasites. The most commonly detected pathogens included *Entamoeba histolytica sensu lato* and *Schistosoma mansoni.* None of the 54 employees working in the base were found to be infected with nematodes, which might be explained by the fact that they had regularly received antiparasitic treatment (a single dose of 400 mg albendazole once a year), in contrast to the hospital patients, who had not received antihelminthic therapy. Conclusions. A wide variety of intestinal parasites found in Sub-Saharan Africa requires regular screening of the local populations in order to implement a targeted antiparasitic therapy instead of deworming recommended by WHO, which is effective only in eliminating some nematode species.
Key words: Central African Republic, deworming, intestinal parasites

Streszczenie. Cel. W pracy przedstawiono wyniki badań w kierunku występowania zarażeń pasożytami jelitowymi wśród mieszkańców Republiki Środkowej Afryki. Materiał i metody. Badania parazytologiczne kału wykonano w grudniu 2014 r. u 44 pacjentów leczonych w szpitalu miejskim z powodu chorób wewnętrznych oraz u 54 bezobjawowych pracowników bloku żywnościowego międzynarodowej bazy wojskowej UCATEX w stolicy kraju, Bangui. Badania wykonano metodą rozmazu bezpośredniego, dekantacją i flotacją w Zakładzie Epidemiologii i Medycyny Tropikalnej WIM w Gdyni. Wyniki. Wśród 44 pacjentów szpitalnych zarażenia patogennymi pasożytami jelitowymi wykryto u 9 osób (20,5%), wśród 54 bezobjawowych pracowników bazy wojskowej u 6 osób (11,1%). Do najczęściej diagnozowanych patogenów należały *Entamoeba histolytica sensu lato* oraz *Schistosoma mansoni*. Zwracał uwagę brak zarażeń helmintami obłymi w grupie pracowników bloku żywnościowego, którzy w ramach działań prewencyjnych otrzymywali co roku dawkę 400 mg albendazolu, w przeciwieństwie do pacjentów szpitala miejskiego, którzy takiego leczenia nie otrzymywali. Wnioski. Występowanie różnorodnych typów pasożytów jelitowych w populacji subsaharyjskiej wymaga prowadzenia badań przesiewowych w celu ukierunkowanego leczenia zarażonych, w miejsce dewormingu zalecanego przez WHO, który jest skuteczny jedynie w eliminacji niektórych gatunków helmintów obłych.
Słowa kluczowe: Republika Środkowej Afryki, deworming, pasożyty jelitowe

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Introduction

The Central African Republic (CAR) is located in Sub-Saharan Africa in the tropical climate zone. Across the country, there is a significant risk of developing infectious and invasive diseases and this risk especially applies to food- and water-borne infections. It is mostly associated with widespread soil and water pollution, limited access to uncontaminated drinking water, lack of hygiene at all stages of food production and sale, a limited number of healthcare providers, severe shortages of basic medicines and medical equipment, low vaccination rates for infectious diseases, a large number of asymptomatic carriers and mass migration of the local population. Diarrheal diseases are also endemic across the whole country and occur all year round. Treatment difficulties frequently arise from the limited availability of laboratory diagnostics. One of the most common etiological factors for diarrhoeas in the CAR is *Escherichia coli* (a study carried out during the outbreak of diarrhoeal diseases in 1996 demonstrated that 108 of the patients examined were infected with ETEC, four of them died). A study into a group of outpatients treated for diarrheal diseases in Bangui, the country's capital, between 2004 and 2005, showed that 3% of the subjects were infected with salmonellosis.

A population-based study into children demonstrated a shigellosis prevalence of 9.7%. In 2005, an outbreak of hepatitis E was reported from Bangui (213 confirmed cases, the source of infection being contaminated water). In 2016, an outbreak of cholera was reported; the disease was confirmed in 265 patients, 21 of whom died [1]. Food- and water-borne diseases of parasitic etiology are also widespread in the Central African Republic. Screening tests conducted in 3,352 Bangui residents in the 1980s, revealed that as many as 46.8% of the subjects were found to be infected with intestinal parasites, of which 26.7% were infected with ancylostomiasis, 20.8% with schistosomiasis *(Schistosoma mansoni),* and 18.2% with amoebiasis. The authors of the study emphasized that polyparasitism was widespread among study participants [2]. Over the last 30 years, the CAR has been experiencing serious civil unrest which led to the outbreak of civil war. As a consequence, the level of medical care, including screening for infectious and invasive diseases, has deteriorated considerably. Owing to limited diagnostic and therapeutic capabilities of the local healthcare providers, treatment is often administered without laboratory confirmation of the etiological agent and the infections are managed with a limited range of pharmaceutical products. Between 2014 and 2015, a multinational UN-mandated military operation was conducted in Bangui, the capital of the Central African Republic. Soldiers from the Polish Military Contingent participated in the mission. The Head of the Department of Epidemiology and Tropical Medicine of the Military Institute of Medicine, responsible for the epidemiological surveillance in the area, decided to perform parasitological examination among residents of the area where Polish troops were deployed. The examination was possible thanks to the cooperation with the missionaries from the Society of African Missions who run the public hospital in Bangui, and the managers of the *Ecolog* company employing workers at the food processing and dining facilities in the UCATEX base in Bangui. Biological material was obtained from two study groups.

The aim of the study was to assess the prevalence of intestinal parasites in residents of the Central African Republic.

Material and methods

Study population

Parasitological stool examination was conducted in December 2014. Samples were collected from 44 patients treated for internal diseases in the municipal hospital in Bangui as well as from 54 asymptomatic workers from the food processing and dining facilities in the UCATEX base in Bangui (EUFOR RCA military operation).

The group of hospital patients involved 21 children aged 1–14 and 23 adults aged 18–65; 28 females and 16 males. The group of asymptomatic workers consisted of 10 females and 44 males aged 18–52. Single fresh stool samples obtained from the study participants (both groups) were fixed in 10% formalin and then transported by air from the Central African Republic to the Department of Epidemiology and Tropical Medicine of the Military Institute of Medicine in Gdynia, Poland where coprological examinations were performed.

Parasitological examination

The diagnostics of intestinal parasites was performed by means of three stool testing methods using a light microscopy [3, 4].

Direct smear in Lugol's solution

Approximately 2 mg of stool is collected with a glass rod and applied onto a slide, a drop of Lugol's solution is added and the material is smeared over a 4 cm^2 surface. Then, a cover slide is placed on top of the preparation and the material is examined microscopically under adequate magnification objective (first ×10, then ×40).

Preparation from decantation in distilled water

Approximately 2 g of stool specimen is mixed thoroughly with a small amount of water in a test tube. Next, water is added to the top of the tube. After 30 minutes the supernatant is decanted and another portion of water is added. This procedure is repeated until clear supernatant is obtained, generally three to four times. The sediment is then placed on a slide and stained with Lugol's solution for microscopic examination (×40 magnification).

Table 1. Intestinal parasitic infections in patients hospitalized in Bangui, CAR in December 2014 (n=44)
Tabela 1. Zarażenia pasożytami jelitowymi u pacjentów hospitalizowanych w Bangui, RŚA w grudniu 2014 r. (n=44)

parasite infections		number of infections	% of tested patients (n=44)
single parasite infections	**pathogenic parasites**		
	Entamoeba histolytica sensu lato	3	6.8
	Schistosoma mansoni	2	4.5
	Giardia intestinalis	2	4.5
	Ancylostoma diodenale / Necator americanus	2	4.5
	Strongyloides fuelleborni	1	2.3
	Enterobius vermicularis	1	2.3
	non-pathogenic parasites		
	Entamoeba coli	9	20.5
	Blastocystis sp.	4	9.1
	Iodamoeba bütschlii	2	4.5
	Endolimax nana	2	4.5
co-infections	Sm, AN, B	1	2.3
	Ib, Ec, B	1	2.3
	Sf, Ev	1	2.3
	Eh, B	1	2.3
	Eh, En	1	2.3
	Ec, En	1	2.3

AN – Ancylostoma duodenale/Necator americanus, B – Blastocystis sp.*, Eh – Entamoeba histolytica sensu lato, En – Endolimax nana, Ec – Entamoeba coli, Ev – Enterobius vermicularis, Ib – Iodamoeba bütschlii, Sf – Strongyloides fuelleborni*

Preparation from Fülleborn's flotation
Approximately 2 g of stool specimen is mixed with saturated NaCl solution in a test tube. Then, water is added to the top of the tube. A cover slide is placed gently on the top of the tube and in contact with the suspension. After 30 minutes, the cover slide is gently removed with tweezers and placed the wet side down on a slide. The preparation is ready for microscopic examination (× 10 magnification).

Results

The present study carried out to assess the prevalence of intestinal parasites among the resident s of Bangui found intestinal parasitic infections in 20.5% of the hospital patients (9/44; 5/21 children and 4/23 adults; 7/28 females and 2/16 males) and in 11.1% of the asymptomatic workers (6/54 adults; 2/10 females and 4/4 4 males). The most commonly detected pathogens included *Entamoeba histolytica sensu lato* and *Schistosoma mansoni*. Apart from pathogenic parasites, non-pathogenic protozoan infections were also found in both study groups (Table 1–2).

It is worth noting that none of the 54 employees working in the base were found to be infected with nematodes; this was associated with the implementation of appropriate preventive measures, i.e. the administration of a single dose of 400 mg albendazole once a year, a medication which proved to be effective in eliminating nematode infections. In contrast, nematode infections, including *Ancylostoma duodenale / Necator americanus* (Figure 1), *Strongyloides fuelleborni*, *Enterobius vermicularis*, were detected in the group of hospital patients, none of whom had received antiparasitic treatment. Infections caused by protozoa and trematodes were present in both groups, as these must be managed with different doses or different types of drugs (Table 3). Apart from infections caused by cosmopolitan pathogens, the study revealed infections with tropical parasites, including *Schistosoma mansoni* (Figure 2), an etiological factor for schistosomiasis, a neglected tropical disease which is endemic in the Central African Republic.

Table 2. Intestinal parasitic infections in workers of UCATEX base in Bangui, CAR in December 2014 (n=54)
Tabela 2. Zarażenia pasożytami jelitowymi u pracowników bazy UCATEX w Bangui, RŚA w grudniu 2014 r. (n=54)

parasite infections		number of infections	% of tested workers (n=54)
single parasite infections	**pathogenic parasites**		
	Entamoeba histolytica sensu lato	3	5.6
	Schistosoma mansoni	2	3.7
	Giardia intestinalis	1	1.8
	non-pathogenic parasites		
	Entamoeba coli	9	16.7
	Endolimax nana	7	13.0
	Blastocystis sp.	3	5.6
	Iodamoeba bütschlii	1	1.8
co-infections	*Eh, Ec*	1	1.8
	Sm, Ec	1	1.8
	Gi, Ec, En	1	1.8
	Ec, En, Ib	1	1.8

Eh – Entamoeba histolytica sensu lato, En – Endolimax nana, Ec – Entamoeba coli, Gi – Giardia intestinalis, Ib – Iodamoeba bütschlii, Sm – Schistosoma mansoni

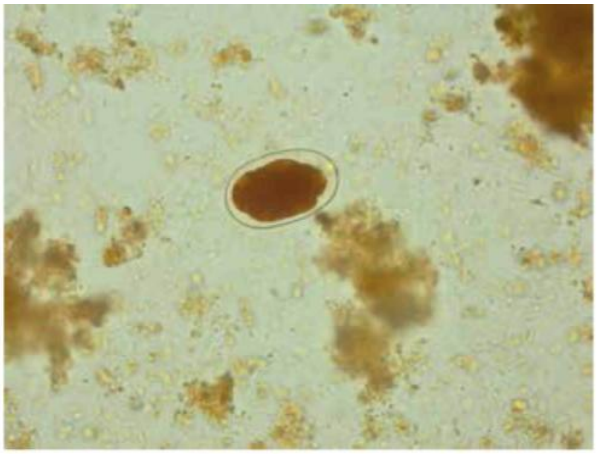

Figure 1. Ancylostoma duodenale/Necator americanus egg. Source: Epidemiology and Tropical Medicine Department of the Military Institute of Medicine
Rycina 1. Jajo *Ancylostoma duodenale*/*Necator americanus*. Źródło: Zakład Epidemiologii i Medycyny Tropikalnej WIM

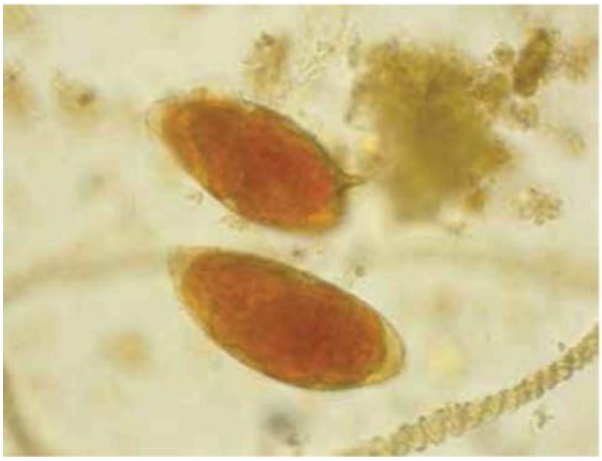

Figure 2. Schistosoma mansoni eggs. Source: Epidemiology and Tropical Medicine Department of the Military Institute of Medicine
Rycina 2. Jaja *Schistosoma mansoni*. Źródło: Zakład Epidemiologii i Medycyny Tropikalnej WIM

Discussion

In the developing countries, mass deworming is usually carried out by administering the WHO-recommended drugs [5]. As a rule, the World Health Organization recommends the administration of single doses of albendazole or mebendazole; this strategy is primarily aimed at the eradication of roundworm infections [6]. Unfortunately, sometimes it proves ineffective. For example, parasitological examination of more than 8,000 children from 30 districts of Rwanda, Sub-Saharan Africa, found that 66% of the subjects were infected with soil-transmitted helminths. A study conducted one year after the administration of the WHO-recommended antihelminthic drugs demonstrated that the prevalence rates of ascariasis and trichuriasis fell only by 14%, while the prevalence of *Ancylostoma duodenale*/*Necator americanus* infections increased by 72% [7]. A successful infection control strategy to prevent transmission of intestinal parasitic infections should be based on prevention and regular chemotherapy aiming at lowering the morbidity in local populations [8].

Table 3. Treatment of intestinal parasitic infections
Tabela 3. Leczenie zarażeń pasożytami jelitowymi

intestinal parasite	treatment
protozoa	
Entamoeba histolytica	
intestinal colonisation (asymptomatic carrier)	paromomycin – 8–12 mg/kg orally 3 times a day for 7 days
amoebic colitis	metronidazole – 750 mg orally 3 times a day for 10 days (adults and children >12 years) children <12 years 30–50 mg/kg in 3 doses for 10 days
amoebic liver abscess	metronidazole – 750 mg orally or *i.v.* metronidazole – 750 mg orally 3 times a day for 10 days (adults and children >12 years) children <12 years 30–50 mg/kg in 3 doses for 10 days
Giardia intestinalis	metronidazole 250 mg orally 3 times a day for 5–7 days or 500 mg orally twice a day for 5 days (adults and children >12 years) 250 mg orally twice a day for 5 days (10–12 years) 125 mg orally 3 times a day for 5 days (6–10 years) 125 mg orally twice a day for 5 days (2–5 years)] children <2 years 1 × 5 mg/kg for 5 days
non-pathogenic protozoa: *Iodamoeba bütschlii, Entamoeba coli, Endolimax nana* Blastocysts hominis	in case of intestinal symptoms (nausea, vomiting, stomach ache, diarrhoea) – metronidazole 250 mg orally 3 times a day for 5–7 days or 500 mg orally twice a day for 5 days (adults and children >12 years) dosage in younger children similarly to *Giardia intestinalis* infections
nematodes	
Necatoramericanus / Ancylostoma duodenale	albendazole 400 mg orally once (>2 years) 200 mg orally once (children 1–2 years)
Enterobius vermicularis	albendazole 400 mg orally once (>2 years) 200 mg orally once (children 1–2 years) treatment to be repeated after 2 weeks
Strongyloides fuelleborni	ivermectin 200 µg/kg orally once a day for 2 days or albendazole 400 mg orally twice a day for 10–14 days
trematodes	
Schistosoma mansoni	praziquantel 20 mg/kg orally twice a day for one day

Source: Kappagoda S, Singh U, Blackburn BG. Antiparasitic therapy. Mayo Clin Proc, 2011; 86 (6): 561–583

In South Korea, for example, a drastic decrease in the prevalence of parasitic infections was possible thanks to the introduction of the nationwide epidemiological surveillance and regular administration of targeted antihelminthic chemotherapy. The first study conducted in 1971 presented the overall helminth egg positive rate of 84% among Koreans. Regular preventive measures (diagnostics and antiparasitic treatment) led to a dramatic decrease in the overall helminth egg positive rate down to 2.4% in 1997 [9]. The deworming programs run by the World Health Organization are primarily aimed at selected population groups, especially pre-school and school children and women of the reproductive age [8]. Owing to a large diversity of pathogens found in Third World countries, it seems that the preventive deworming with single dose chemotherapy (albendazole 400 mg or 500 mg mebendazole) may not prove very effective in eradicating intestinal parasites. If mass deworming should become successful, a more comprehensive treatment is needed (albendazole 400 mg one dose, metronidazole 250 mg three times a day for five days, and praziquantel 5–25 mg/kg one dose), especially for the management of a large number of infections or infections caused by a variety of different pathogens (nematodes, cestodes, trematodes or protozoa).

Conclusions

A wide variety of intestinal parasites found in Sub-Saharan Africa requires regular screening of the local population in order to implement a targeted antiparasitic therapy instead of the WHO-recommended deworming strategy, which is only effective in eliminating some nematode species.

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Assessment of helmet and boonie hat effectiveness in sunstroke prevention, based on the example of German soldiers in North Africa (1941) and Polish and American soldiers in Iraq (2003)

Ocena skuteczności hełmów i kapeluszy tropikalnych w zapobieganiu udarowi słonecznemu na przykładzie żołnierzy niemieckich w Afryce Północnej (1941 r.) oraz żołnierzy polskich i amerykańskich w Iraku (2003 r.)

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Abstract. The article describes assessment of helmets and boonie hats among soldiers of the German Africa Corps in 1941 and soldiers of the Polish Military Contingent and United States Armed Forces in Iraq in 2003, in terms of their effectiveness in protection against solar radiation in the aspect of sunstroke prevention. Conclusions. The assessment of a helmet's safety should be conducted not only for ballistic protection but also for effectiveness of protection against solar radiation and hyperthermia. Boonie hats should be subjected to similar assessment for prevention of heat injuries.
Keywords: sunstroke, hyperthermia, helmet, boonie hat

Streszczenie. W artykule dokonano oceny hełmów i polowych kapeluszy tropikalnych żołnierzy Niemieckiego Korpusu Afrykańskiego w Afryce Północnej w 1941 roku oraz żołnierzy Polskiego Kontyngentu Wojskowego i Sił Zbrojnych Stanów Zjednoczonych w Iraku 2003 roku pod kątem skuteczności ochrony przed promieniowaniem słonecznym w aspekcie zapobiegania udarowi słonecznemu. Wnioski. Ocena bezpieczeństwa hełmów powinna być prowadzona nie tylko pod kątem ochrony balistycznej, ale również skuteczności ochrony przed promieniowaniem słonecznym oraz przegrzaniem. Podobnej ocenie pod kątem prewencji udarów cieplnych powinny podlegać kapelusze tropikalne.
Słowa kluczowe: udar słoneczny, przegrzanie, hełmy, kapelusze tropikalne

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German Africa Corps in North Africa

When the first contingent of the German Africa Corps (Deutsches Afrikakorps – DAK) led by Erwin Rommel disembarked in Tripoli on 14 February 1941, nobody suspected how unprepared the Wehrmacht was to conduct operations in tropical conditions. From the beginning, only the propaganda of the Third Reich was perfectly prepared to publicise the African campaign of DAK, intended merely to support Mussolini's army, fighting on the defensive. It should be emphasised that the spectacular success of General Rommel, nicknamed

"Desert Fox" by the media, took place against the political, military, logistic and climatic factors. The African theatre of operation was not the priority for the decision makers in Berlin. Therefore, DAK was primarily composed of formations improvised for operations in the desert.

However, the soldiers sent to North Africa had to face difficult environmental conditions, with temperatures reaching +57°C in summer, and falling below zero in winter. Such high daily temperature amplitudes affected not only the planning and nature of the combat operations, but even meal distribution (cold meals were given during the hottest time of day, whereas hot meals were consumed in the evenings). Omnipresent sand, dust and sand storms, induced by *hamsin* and *ghibili*, combined with challenging sanitary conditions, increased health risks.

Individual equipment of DAK soldiers

New models of desert uniforms, designed in 1940 in the Tropical Medicine Institute in Hamburg, were produced based on the experience of German soldiers in the colonies of South West Africa (Fig. 1.). Therefore, the first DAK units landing in Tripoli in North Africa, already had uniforms adapted to local environmental conditions, in contrast to the weapons and equipment.

The German desert outfit from 1941 comprised a light cotton jacket *(Feldbluse),* long-sleeved shirt, and three types of trousers:

- long trousers *(lange Hose),*
- short trousers *(kurze Hose),* and
- desert breeches *(Stiefelhose).*

A double-breasted greatcoat of dark brown wool, and sweaters and gloves protecting from the cold during the nights in the desert, completed the uniform. Only motorcycle riders had a different coat, made of thick cotton twill. Sunglasses, goggles, thin scarves and sashes for protection against the sand were also commonly used, as well as leather coats worn by generals and senior officers. The entire equipment was olive green.

The design of DAK uniforms soon revealed its faults, as the fabric used to make them quickly faded, losing its masking effect. Due to the logistic difficulties throughout the African campaign, seawater was used for washing, which caused shrinking of the fabric, and the uniforms became too tight. Therefore, many DAK soldiers wore Italian jackets *(Sahariana)* or British shorts, gained in large quantities in Tobruk in June 1942.

Figure 1. Tropical helmet (*tropenhelm)* of the German Army, around 1910 (source: commons.wikimedia.org/wiki/File:Tropenhelm_(1910).jpg)
Rycina 1. Hełm tropikalny (*tropenhelm)* armii niemieckiej z ok. 1910 r. (źródło: commons.wikimedia.org/wiki/File:Tropenhelm_(1910).jpg)

Footwear

DAK soldiers wore high desert boots with leather soles. They often cut off the canvas uppers, laced-up at the calf, turning the boots into shoes. They also wore low lace-up shoes *(Schnurschuhe)* of a similar design.

Accessories

Belts and straps were made from reinforced canvas, more practical in the desert climate than leather.

Helmets

The cork helmet, characteristic for the tropics, proved impractical in the limited space of combat vehicles, and it was quickly replaced by a cotton side cap *(Feldmutze),* and later with a field cap made of diagonal cotton. The cork helmet was often used by back units and drivers [1].

Figure 2. Soldiers of 1st rotation (PMC) at the parade in tropical uniforms (mark 124/MoD) before departing to Iraq, Szczecin, 31 July 2003 (source: L. Kolarz, own collection)
Rycina 2. Żołnierze I zmiany PKW w czasie defilady w mundurach tropikalnych (wz. 124/MON) przed wylotem do Iraku, Szczecin 31.07.2003 (źródło: L. Kolarz, zbiory własne)

Individual equipment of the soldiers of the 1st rotation of the Polish Military Contingent

Similarly to German soldiers, the Polish Military Contingent (PMC) in Iraq in 2003 needed to have their uniforms adapted to the hot climate environmental conditions. Before they were sent to the theatre of operation, the soldiers of the PMC 1st rotation received desert uniforms model 124/MON, made of a single layer cotton fabric, inadequate for the tropical climate. Therefore, a few months later, the Ministry of National Defence issued decision 371/MON, which introduced a tropical uniform model 124 PI/MON, in which the US-21 fabric was used, composed of 83% cotton and 17% polyester, with the *rip-stop* weave.

Polish Military Contingent in Iraq

In May 2003, by the order of the Chief of the General Staff, the Ministry of National Defence established the Multinational Division Central South (MND CS), comprising soldiers from 21 countries. The division was 9,000 men strong, with the Polish Military Contingent of 2,300 soldiers being the most sizeable (Fig. 2.). The area of MND CS covered 65 thousand square kilometres, with five provinces of central-southern Iraq (Fig. 3.).

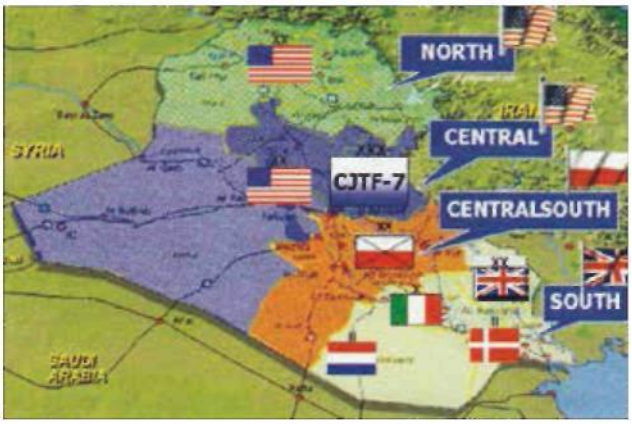

Figure 3. Zones of stability in Iraq (source: references, item 2)
Rycina 3. Strefy stabilizacyjne w Iraku (źródło: 2. pozycja piśmiennictwa)

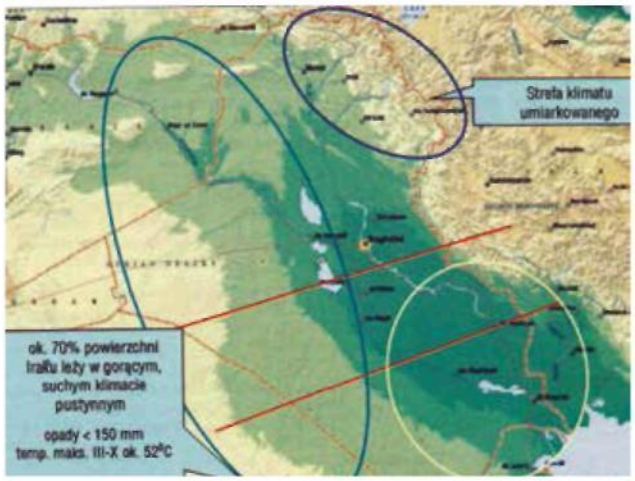

Figure 4. Climate zones of Iraq (source: references, item 2)
Rycina 4. Strefy klimatyczne Iraku (źródło: 2. pozycja piśmiennictwa)

Climate in Iraq

Iraq is in the dry tropical climate zone. Only the northern regions of the country are located in the more humid subtropical zone. The vicinity of the Persian Gulf has no effect on the climate, which is predominantly continental, due to the spatial relation of the country to the huge Asian continent (Fig. 4.). The warmest region of Iraq is its southern part.

Approximately 70% of the territory in the central-southern Iraq, where the MND CS troops were deployed to, is within the hot, dry, desert climate, with temperatures exceeding +32°C observed on 25–30 days per month in summer, on average (absolute maximums for the summer are 46–52°C).

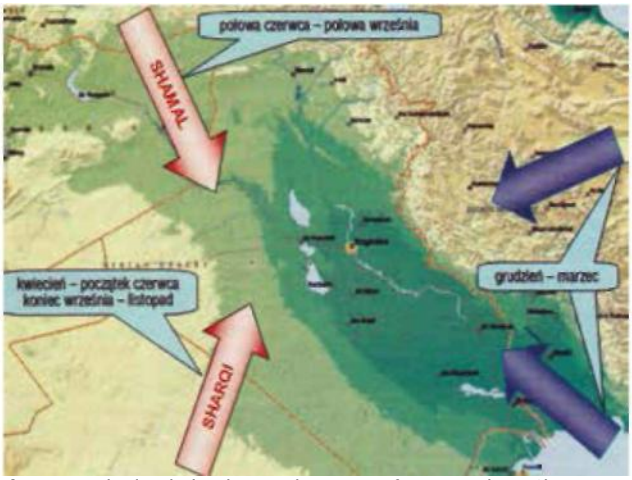

Figure 5. Air circulation in Iraq (source: references, item 2)
Rycina 5. Cyrkulacja powietrza w Iraku (źródło: 2. pozycja piśmiennictwa)

In the seasonal pattern, summer (VI - IX) and winter (XII-III) dominate, while spring (IV-V) and autumn (X-XI) are transitional seasons. Along with the change of seasons, the influx of air masses changes direction, altering their properties (Fig. 5.).
From April to early June (spring) and from late September to November (autumn), Iraq is in the zone affected by *sharqi* – a dry wind, carrying dust and sand, originating from the central Arabian Peninsula. It can reach 25–30 m/s (10–11ºB), giving rise to dangerous sand storms and dust storms, sometimes lasting up to a few weeks [2].

From mid-June to mid-September (summer), a dry wind, *shamal,* comes from the north. It reduces the temperature of the air, but strong sunlight still contributes to intensive heating up of surfaces (Fig. 6.–7.). If the wind in this period persists for over a month, it is called *barih* [3].

Rainfall

In summer, the mean monthly rainfall in Iraq in the region where the PMC was stationed, is no more than 13 mm. The maximum monthly rainfall observed in April is 76–127 mm (2–5 rainy days), and 51–127 mm in May (3–5 rainy days) for the area where the PMC was stationed. The maximum rainfall for this area is observed in December–February; then the unpaved roads, squares, courts and landing zones in military bases turn to muddy ponds (Fig. 8.).

Figure 6. Sand storm in Camp Coyote (Kuwait), 12 August 2003 (source: L. Kolarz, own collection)
Rycina 6. Burza piaskowa Camp Coyote (Kuwejt), 12.08.2003 (źródło: L. Kolarz, zbiory własne)

Figure 7. Dust stirred up by helicopters landing in Camp Lima (Iraq), 25 August 2003 (source: L. Kolarz, own collection)
Rycina 7. Wzniecony pył po wylądowaniu helikopterów w Camp Lima (Irak), 25.08.2003 (źródło: L. Kolarz, zbiory własne)

Figure 8. Mud in Camp Babylon (Iraq), 12 December 2003 (source: L. Kolarz, own collection)
Rycina 8. Błoto na terenie Camp Babilon (Irak), 12.12.2003 (źródło: L. Kolarz, zbiory własne)

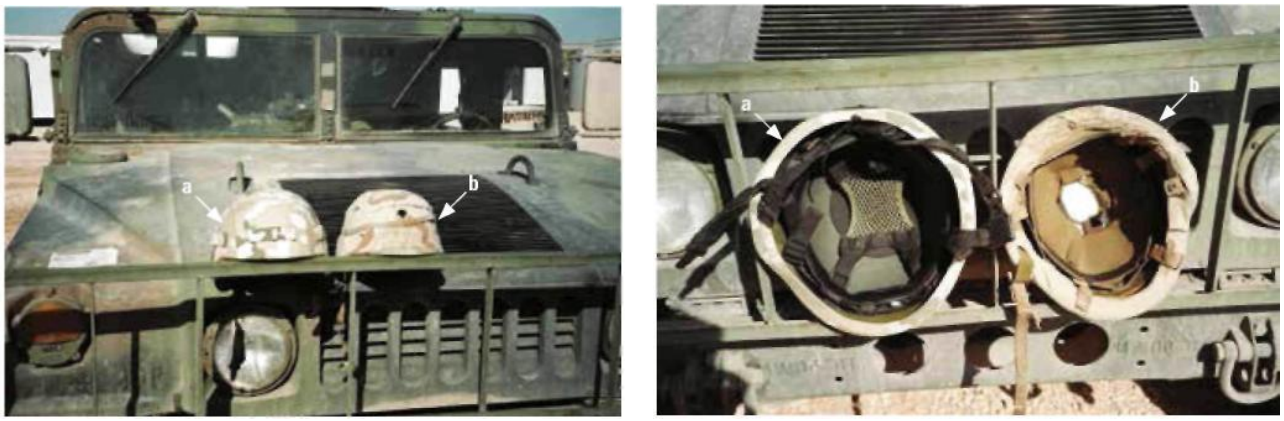

Figure 9. Composite helmet, mark 2000 (PM [a]) and composite helmet PASGT (U.S. Army [b]) (source: L. Kolarz, own collection)
Rycina 9. Hełm kompozytowy wz. 2000 (WP [a]) i hełm kompozytowy PASGT (U.S. Army [b]) (źródło: L. Kolarz, zbiory własne)

Risk of hyperthermia and sunstroke in dry hot climate

Direct exposure to the sun is the primary factor contributing to sunstroke, caused by excessive impact of the sun, the infrared radiation in particular, on the top of the skull. Because of elevated internal temperature in the brain, the permeability of blood vessels increases, cerebral oedema occurs and the pressure of the cerebrospinal fluid increases, which causes neurological symptoms. Sunstroke occurs suddenly; therefore, proper prophylactic measures preventing the development of disease symptoms are important. Probably the development of pathological symptoms is primarily due to impaired thermoregulation in the head, which is relatively autonomous compared to other body parts in humans. Therefore, in the regions with strong sunlight, it is crucial to equip soldiers with proper headgear that covers the areas important for thermoregulation, such as

- the thermoregulation centre in the brain stem, between the anterior commissure and the optic chiasm (the area sensitive to elevated internal temperature),
- the lateral areas of the thalamus (neurons active in low temperatures),
- the set point in the hypothalamus, responsible for maintaining proper body temperature [4].

Intensive sweating and dilation of blood vessels additionally increases heat transmission.
Properly designed headgear may significantly improve the effectiveness of heat transmission, or reduce it. The studies on head protection against solar radiation conducted in Senegal demonstrated significant differences between maximum head temperatures under various types of hats:

- tropical helmet with ventilation and a white cover – +35.6°C,
- straw hat – +37.5°C,
- officer kepi with ventilation, without a cover – +39°C,
- sailor hat with a white cover – +40°C,
- sailor hat without a white cover – +41°C [5].

Aim of the study

The aim of the study was to assess the effectiveness of helmets and field boonie hats used by the soldiers of the German African Corps in North Africa in 1941, and those used by the Polish Military Contingent and USA Forces in Iraq in 2003 in protecting against the solar radiation and preventing sunstroke.

Material and methods

The following types of headgear were used for the assessment of helmet and boonie hat effectiveness in sunstroke prevention:

- composite helmet model 2000 (PM) (Fig. 9.) with camouflage cover model 93 "Panther", desert version, for the uniform model 124/Mon (Fig.124 (PM) (Fig. 10.),
- composite helmet PASGT (US Army) with the Desert 3 Color Pattern cover (Fig. 9.),
- boonie hat model 93 (PM) in desert camouflage (Fig. 11), and boonie hat model 93 (PM) with additional ventilation, for the uniform model 124/Mon (Fig. 10.),
- boonie hat desert version (US Army) Desert 3 Color Pattern (Fig. 12.),
- linen boonie hat (Fig. 13.).

The methodology of the study was inspired by the scheme proposed in 1885 by Hiller [6], who placed a mercury thermometer in a special holder in the free space between the helmet shell and the internal padding.

Figure 10. Field outfit in desert camouflage mark 124/MoD, Camp Coyote (Kuwait), 9 August 2003 (source: L. Kolarz, own collection)
Rycina 10. Ubiór polowy w kamuflażu pustynnym w z. 124 / MON, Camp Coyote (Kuwejt), 9.08.2003 (źródło: L. Kolarz, zbiory własne)

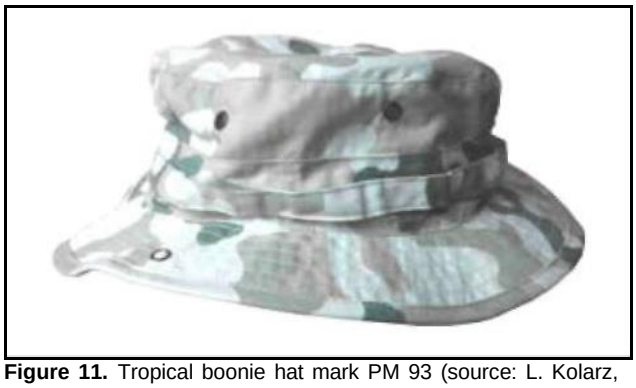

Figure 11. Tropical boonie hat mark PM 93 (source: L. Kolarz, own collection)
Rycina 11. Kapelusz tropikalny WP wz. 93 (źródło: L. Kolarz, zbiory własne)

Figure 12. Field outfit of U.S. Army soldiers in boonie hat (left) and fleece cap (right) in "Desert 3 Color Pattern" camouflage, Kuwait, August 2003 (source: L. Kolarz, own collection)
Rycina 12. Ubiór polowy żołnierzy amerykańskich w kapeluszu (po lewej) i czapce (po prawej) w kamuflażu pustynnym „Desert 3 Color Pattern", Kuwejt sierpień 2003 (źródło: L. Kolarz, zbiory własne)

Figure 13. Flaxen boonie hat (source: L. Kolarz, own collection)
Rycina 13. Kapelusz tropikalny lniany (źródło: L. Kolarz, zbiory własne)

Figure 14. Electronic car thermometer (source: L. Kolarz, own collection)
Rycina 14. Elektroniczny termometr samochodowy (źródło: L. Kolarz, zbiory własne)

Table 1. Measurement of temperature rise (şC) versus time (t)
Tabela 1. Pomiar narastania temperatury (şC) w funkcji czasu (t)

Camp Coyote (Kuwait) ambient temperature +40°C						**Camp Lima (Iraq)** ambient temperature +39.8°C				
t	09/08/2003		09/08/2003			**t**	29/08/2003		08/09/2003	
(min)	helmet		boonie hat			(min)	helmet		boonie hat	
	I	II	III	IV	V		I	II	III	IIIa
0	35.2	36.8	36.6	35.2	36.3	0	36.2	36.8	35.6	36.0
1	35.4	38.6	37.6	36.4	38.6	1	36.6	38.6	37.4	37.2
2	35.8	39.2	40.6	3 7.4	42.4	2	37.0	40.6	38.4	38.5
3	36.0	39.6	43.2	3 7.0	45.2	3	37.4	41.4	40.0	40.0
4	36.2	39.8	44.8	37.9	47.0	4	37.6	42.6	44.2	42.8
5	36.4	40.0	45.2	38.8	48.2	5	37.8	43.6	47.2	45.0
6	36.6	40.0	45.4	39.0	49.2	6	38.2	44.6	49.2	46.6
7	36.8	40.0	45.4	39.0	49.6	7	38.4	45.4	50.0	47.5
8	36.8	40.0	45.4	39.0	50.0	8	38.6	46.0	50.0	48.6
9						9	38.6	46.0	50.0	48.6

I – composite helmet model 2000 PM; II – composite helmet PASGT U.S. Army; III – boonie hat model 93 PM; IIIa – boonie hat model 93 PM boonie hat with accessory vent/holes; IV – boonie hat U.S. Army; III – linen boonie hat
Source: L. Kolarz, own study

The tests/measurements were conducted in the military bases:

- Camp Coyote (Kuwait) 9 August 2003, at 11:00–13:30 local time,
- Camp Lima near Karbala (Iraq), 29 August 2003, at 13:30–15:00,
- Camp Lima near Karbala (Iraq), 8 September 2003, at 13:30–15:00.

The temperature was measured using a digital car thermometer (Fig. 14.).

At the beginning of each test, a temperature sensor was placed under the helmet / hat before putting in on. Then, the temperature in an air-conditioned house / tent was calibrated (the starting point was set) to 36 °C (±1°C). After that, the headgear was exposed to the sun outside, and the temperature was registered at 1-minute intervals.

The measurements were conducted only when the wind speed was no more than 0 m/s, and until the temperature in two consecutive readings stabilised, but the tests lasted at least 8 minutes.

The test was stopped if the air temperature under the headgear reached 50°C.

The temperature measurements on 8 September 2003 involved only comparative tests of two boonie hats model 93 (PM), one of which was modified by adding ten vent holes, made with a paper punch, in the back and sides of the hat.

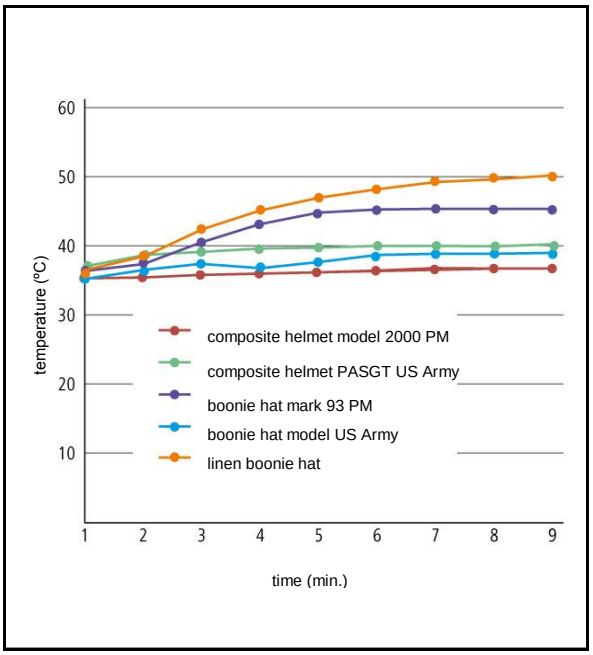

Figure 15. Measurement of temperature rise (ºC) versus time (t) for composite helmets and boonie hats, 9 August 2003, Camp Coyote base in Kuwait (source: L. Kolarz, own collection)
Rycina 15. Pomiary narastania temperatury (şC) w funkcji czasu (t) hełmów kompozytowych oraz kapeluszy tropikalnych 9.08.2003 na terenie bazy wojskowej Camp Coyote w Kuwejcie (źródło: L. Kolarz, opracowanie własne)

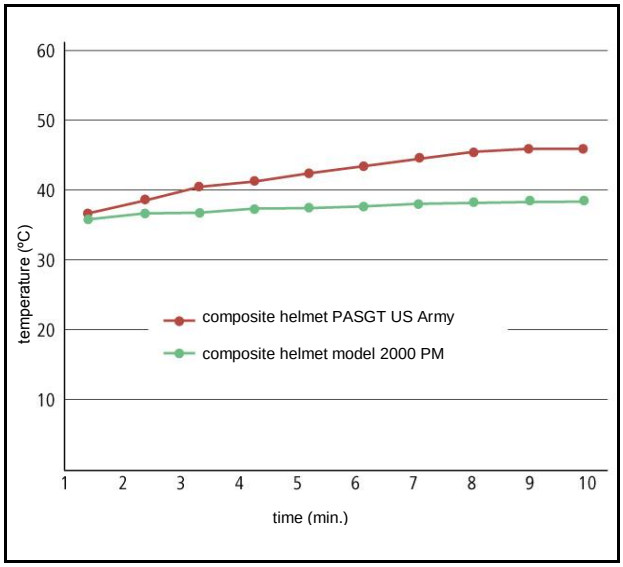

Figure 16. Measurement of temperature rise (ºC) versus time (t) for composite helmets, 29 August 2003, Camp Lima base in Iraq (source: L. Kolarz, own elaboration)
Rycina 16. Pomiary narastania temperatury (ºC) w funkcji czasu (t) hełmów kompozytowych 29.08.2003 roku na terenie bazy wojskowej Camp Lima w Iraku (źródło: L. Kolarz, opracowanie własne)

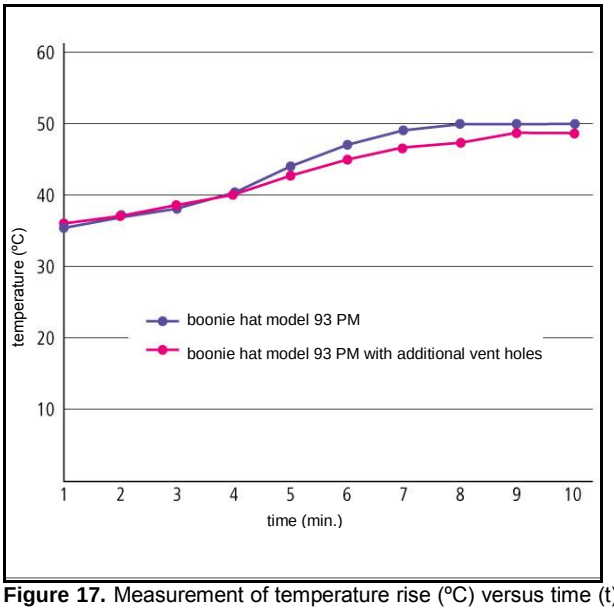

Figure 17. Measurement of temperature rise (ºC) versus time (t) for boonie hats with and without modification, 8 September 2003, Camp Lima base, Iraq (source: L. Kolarz, own elaboration)
Rycina 17. Pomiary narastania temperatury (ºC) w funkcji czasu (t) kapeluszy tropikalnych z modyfikacją i bez modyfikacji 8.09.2003 roku na terenie bazy wojskowej Camp Lima w Iraku (źródło: L. Kolarz, opracowanie własne)

Results

The results demonstrated differences in the temperatures achieved and the rates of temperature increase under various helmets and boonie hats (Table 1.).

A linen boonie hat offered the lowest protection against sunlight, despite the lightest colour of the fabric and similar sizes and number of vent holes than in the US Army boonie hat, characterised by the best thermal parameters (Fig. 15.).

Composite helmet model 2000 PM demonstrated a clear advantage over the composite helmet model PASGT US Army (Fig. 16.).

A visibly lower temperature was observed in the boonie helmet model 93 PM with additional vent holes, compared to the control group in which boonie hat model 93 PM without modifications was used (Fig. 17.).

Better protective parameters of the composite helmet model 2000 PM, compared to the composite helmet model PASGT US Army, were demonstrated in two tests, i.e. on 9 August 2003 in Kuwait (Camp Coyote), and on 29 August 2003 in Iraq (Camp Lima) (Fig. 18.).

The temperature readings obtained by the author under different types of headgear were varied. It appears that internal padding, which determined the effectiveness of ventilation, significantly affected the temperature under the helmets (Fig. 9.).

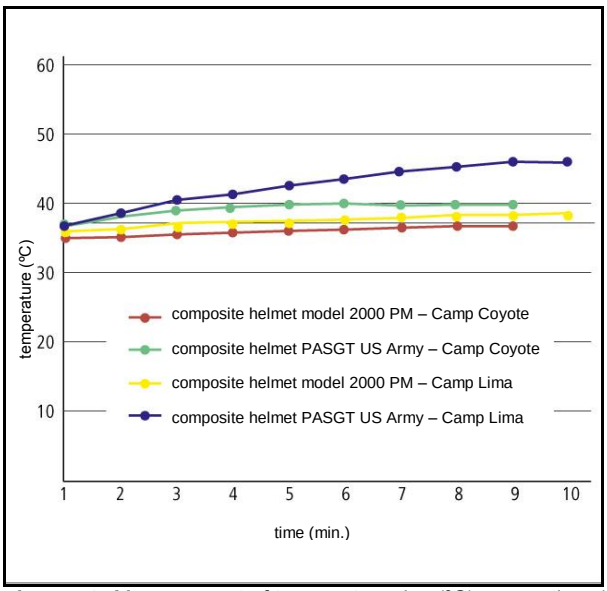

Figure 18. Measurement of temperature rise (ºC) versus time (t) for composite helmets in the military base, 8 September 2003 in Camp Coyote/Kuwait and 29 August 2003 in Camp Lima/Iraq (source: L. Kolarz, own elaboration)
Rycina 18. Pomiary narastania temperatury (ºC) w funkcji czasu (t) hełmów kompozytowych 08.09.2003 roku na terenie bazy wojskowej w Camp Coyote w Kuwejcie i 29.08.2003 roku w Camp Lima w Iraku (źródło: L. Kolarz, opracowanie własne)

Figure 19. Desert camouflage field outfit mark 124/MoD (left) 1st rotation PMC and modified version mark 124PI/MoD for 2nd rotation PMC (right), Camp Lima, 23 October 2003 (source: L. Kolarz, own collection)
Rycina 19. Ubiór polowy w kamuflażu pustynnym wz. 124/MON dla I zmiany PKW (po lewej) i zmodyfikowany wz. 124PI/MON dla II zmiany PKW (po prawej), Camp Lima 23.10.2003 roku (źródło: L. Kolarz, materiały własne)

Figure 20. Desert camouflage field outfit mark 123U T/MoD with boonie hat, 2013 [7] (source: L. Kolarz, own collection)
Rycina 20. Ubiór polowy wz. 123 UT/ MON w kamuflażu pustynnym z kapeluszem tropikalnym z 2013 roku [7] (źródło: L. Kolarz, materiały własne)

In soft headgear, the temperature depended not only on the fabric, but also on the total size of vent holes. This relationship was considered by the designers of the boonie hat model 93, who increased the size of holes in the model for the second PMC rotation in Iraq (Fig. 19.-20.). The results of tests with the Polish composite helmet model 2000 with a cover (Fig. 9.) demonstrate its superior protection against the sun, not only compared to the PASGT composite helmet used by the US Army (Fig. 9.), but also to all the tested boonie hats (Fig. 11.-13.).

Conclusions

The assessment of helmet safety should consider not only the ballistic protection, but also to the effectiveness of the protection they offer against solar radiation and overheating. Boonie hats should be similarly assessed for sunstroke prevention.

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7. Field outfit in desert camouflage with a hat. Modification of the resolution regarding the models and wearing of uniforms and military signs by professional soldiers and professional soldier candidates. Official Journal of Laws of 17th April 2013, item 466

Quality of life in chronically ill persons

Jakość życia u osób przewlekle chorych

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Abstract. The main task of the holistic approach in medicine and health psychology is to seek and explore the backgrounds and attitudes which are helpful in coping with a disease and its effects and, in consequence, deriving satisfaction from one's life. The quality of life evaluation shows statistically significant differences between healthy subjects and the group of chronically ill; at the same time, no significant differences were observed between individual groups of chronically ill, i.e. asthmatics and patients with hypertension. Life satisfaction assessment results of healthy and chronically ill people vary significantly in five key life areas. Not unexpectedly, the greatest discrepancies arose in the assessment of their own health. Second came the area of satisfaction from sexual activity, then the financial situation, which, again, seems obvious as it is a direct effect of work opportunities and expenses associated with treatment. Subsequent noticeable differences arose between the control group and the chronically ill in relation to the sense of satisfaction with themselves and with their marriage. The lowest quality of life rates relate to asthmatics and patients with cancer.
Key words: quality of life, chronic diseases, assessment of satisfaction in various areas of life, satisfaction with life

Streszczenie. Zasadniczym zadaniem holistycznego podejścia w medycynie oraz psychologii zdrowia jest poszukiwanie uwarunkowań i sposobów pomagających człowiekowi w radzeniu sobie z chorobą oraz jej skutkami, a w konsekwencji przeżywania satysfakcji z własnego życia. W ocenach ogólnej satysfakcji z własnego życia badanych grup przewlekle chorych występują istotne statystycznie różnice pomiędzy osobami zdrowymi a chorymi na astmę i na nadciśnienie tętnicze. Pomiędzy wyodrębnionymi grupami chorych nie stwierdzono natomiast istotnych różnic. Osoby zdrowe i przewlekle chore różnią się, w sposób znaczący, w ocenie zadowolenia w pięciu dziedzinach własnego życia. Ich oceny różnią się najsilniej, co wydaje się oczywiste, w ocenie własnego zdrowia. Na drugim miejscu pod względem różnic znajduje się ocena zadowolenia z aktywności seksualnej. Miejsce trzecie zajmuje ocena satysfakcji z sytuacji finansowej, co również wydaje się oczywiste, ponieważ może stanowić bezpośredni skutek możliwości podejmowania aktywności zawodowej i wydatków związanych z leczeniem. Kolejne zauważalne różnice w ocenie osób zdrowych i przewlekle chorych dotyczą poczucia zadowolenia z własnej osoby oraz z małżeństwa. Najsłabiej jakość własnego życia oceniają chorzy na astmę i chorzy na nowotwór.
Słowa kluczowe: jakość życia, choroby przewlekłe, poziom zadowolenia z poszczególnych dziedzin życia, zadowolenie z życia

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Background

In psychology of health, chronic diseases are currently a subject of particular interest. They are the most common causes of all deaths. Increasing costs of health care and growing awareness of the causal relationship between people's behaviour and their health are only two of many factors contributing to the development of psychology of health. Its primary task is to find conditions and methods of helping people to deal with the disease and its consequences, to experience satisfaction with oneself and one's life [1, 2].

Life satisfaction is a subjective, relatively stable assessment of the general life situation of a person. It does not depend on one's mood at a given moment, but on a balance of the general life situation [3, 4]. It results from a specific relationship between personality and environmental conditions (integration model). A subjective and global assessment of one's life situation, expressed in certain beliefs and emotional states, is the indicator of the quality of life [5].

Table 1. The Satisfaction with Life Scale: Average results and standard deviations in examined groups
Tabela 1. Skala Ogólnej Satysfakcji z Życia: wyniki średnie i odchylenia standardowe badanych grup

Study groups	N	M	SD
healthy subjects	80	21.13	4.92
ischaemic heart disease	41	19.95	6.07
arterial hypertension	35	17.33	6.28
neoplasm	36	17.97	6.55
diabetes	33	20.85	6.29
asthma	37	17.09	6.05

N – number of cases, M – mean, SD standard deviation

Aim of the study

The aim of the study was to assess and compare the quality of life in chronically ill and healthy people.

Research questions

- Does the level of general life satisfaction in chronically ill patients differ significantly from that declared by healthy individuals?
- To what degree does satisfaction with key areas of life decrease in the course of a chronic disease, and does this differ significantly from the satisfaction expressed by healthy individuals?

Material and methods

The study involved two groups: healthy individuals and chronically ill patients. The first group comprised 80 people who: feel healthy, do not take any medicines continuously, are not in therapy due to any conditions, are not invalids and do not require rehabilitation or care. The group of chronically ill subjects comprised 182 patients diagnosed as patients with ischaemic heart disease, following one myocardial infarction (N = 41), patients receiving continuous treatment due to primary arterial hypertension (N = 35), patients receiving treatment due to a malignant neoplasm (N = 36), diabetics (N = 33) and patients with bronchial asthma (N = 37). All the subjects were under constant medical care due to the consequences of their conditions.

The healthy subjects were slightly younger (M = 48.02, SD = 6.86) than the chronically ill patients (M = 53.03, SD = 7.97). The percentage of males and females in both groups was similar: 41 females and 39 males in the group of healthy subjects, and 95 females and 87 males in the group of chronically ill patients.

The duration of the disease varied between one year and several years (M = 10.37; SD = 8.08). Sixty-two patients were ill for 1 to 5 years, 52 patients were ill for 6-10 years, and 68 patients were ill for over 11 years.

The study was conducted in the years 2011-2015, individually at patients' homes, or in a hospital ward.

Many subjects declared a need of contact outside the study; therefore, meetings were often divided into two or three sessions. The time required to fill in the questionnaires usually was less than an hour.

The Satisfaction with Life Scale (SWLS) and Satisfaction Questionnaire were used in the study. The SWLS scale, comprising five questions, is used to test adult individuals, healthy or ill, and it is the most popular method of testing life satisfaction. So far, several million people on all continents were tested using this method. The authors of the scale are Diener, Emmons, Larson and Griffin [6], and it was adapted by Juczyński [7].

Using this tool, patients assess each statement in reference to their lives on a scale of one to seven. The ultimate result indicates the level of life satisfaction, and it ranges from 5 to 35 points. The higher the score, the greater life satisfaction it expresses.

The authors of Satisfaction Questionnaire (Fragebogen zur Lebenszufriedenheit – FLZ) are Fahrenberg, Myrtek, Schumacher and Brähler [8]. It is intended for testing adults, including seniors. The questionnaire can be used in psychological diagnostics regarding personality, in the life quality studies, as well as in the studies assessing the progress in rehabilitation and psychotherapy.

Satisfaction Questionnaire helps to assess ten important aspects of life satisfaction: health, work and profession, financial satisfaction, free time, contacts with one's children, oneself, contacts with other people (friends, relatives, and acquaintances), home, marriage/partnership and sexuality.

Each of the 10 subscales comprises seven statements. They are all evaluated on a seven-point scale, expressing the level of acceptance. A score of 7 to 49 points can be achieved on each subscale. The higher the score, the greater the acceptance of a given area of life it represents. In certain cases, three scales may not be applicable (work, marriage/partnership, and contacts with one's children).

The questionnaire's internal consistency measured by Cronbach's alpha is between 0.82 and 0.95. Its reliability

was determined with the use of factorial analysis and relationships between the results and personality variables tested with other tools. The results were normalised after testing 2,870 subjects in seven age groups [9].

Tests results

General life satisfaction

The scores obtained in the questionnaire measuring general life satisfaction are 5–35 points. The higher the score, the greater the life satisfaction it expresses.

The variance analysis indicates statistically significant differences between the results obtained in the study groups ($F = 4.05$; $p < 0.01$). According to further analysis, the differences are due to varying levels of life satisfaction in healthy and ill subjects ($t = 3.00$; $p = 0.003$). Life satisfaction in the group of healthy individuals ($M = 21.13$; $SD = 4.92$), as expected, is considerably higher than in the group of chronically ill patients ($M = 18.72$; $SD = 6.34$).

In the assessment of general life satisfaction in chronically ill patients, statistically significant differences were found between healthy subjects and individuals with asthma ($t = 3.66$; $p <0.001$) or arterial hypertension ($t = 3.43$; $p <0.001$). However, no significant differences were observed between different groups of subjects with chronic conditions.

The patients in the study were also divided into groups according to the duration of the disease: 1-5 years, 6-10 years and over 10 years. It appeared that duration of the disease does not affect the level of life satisfaction in chronically ill patients ($F = 0.72$; $p = 0.86$). The subject's age does not reduce general life satisfaction either ($F = 0.95$; $p = 0.56$); on the contrary, a slight increase in general life satisfaction may be observed with the passing of time.

Satisfaction with individual areas of life in chronically ill patients and in healthy subjects

The measurement of satisfaction includes the assessment of ten categories, considered the most important ones by the majority of people:

health, work and profession, financial status, leisure time, relationships with one's children, oneself, relationships with other people (especially with those who are close and important to us), housing situation, marriage (partnership) and sexual activity.

Table 2 presents the satisfaction scores regarding various areas of life, obtained in the study groups.

The scores in half of the areas studied demonstrate statistically significant differences between the groups. The largest differences are found in satisfaction with one's health ($F = 8.55$; $p <0.001$), then in satisfaction with marriage ($F = 2.69$; $p <0.05$), work ($F = 3.18$; $p <0.01$), assessment of the financial status ($F = 3.64$; $p <0.01$) and sexual activity ($F = 4.96$; $p <0.001$).

In the assessment of one's health condition, the scores in the group of healthy subjects are clearly superior to those in other groups. Patients diagnosed with neoplasms give the worst assessment of their health condition, and patients with asthma score only slightly better. Compared to these two groups, diabetics assess their health condition a little higher.

Satisfaction with one's work and profession is very similar in the group of healthy subjects, as well as in other groups. Only the scores in the group of asthma patients are different. The obtained mean result is also a negative result (the mean score for one item on the scale of seven statements in the group of patients with asthma is slightly above three points, 3.25). The results in this group differ statistically significantly not only from those obtained in healthy subjects, but also from the satisfaction from work in patients with hypertension and coronary disease.

Similarly to work, also the assessment of one's financial status is the lowest in the group of asthma patients. Statistically significant differences are found between the scores presented in this group and in the group of healthy subjects or diabetics. The results obtained in other groups are similar to those observed in healthy subjects.

Satisfaction with marriage (partnership) varies in different groups. The least satisfied are patients with arterial hypertension and those with asthma. The most satisfied are patients with diabetes, who presented more positive scores than healthy subjects. The greatest differences in scores were found between patients with arterial hypertension and those with diabetes; the scores of healthy subjects and patients with hypertension were similar, and slightly smaller differences are observed between diabetics and patients with asthma.

Regarding satisfaction with sexual activity, the scores of healthy subjects are clearly positive (4.92 on a 7-point scale). Among all the groups of chronically ill subjects, only patients with diabetes and those with asthma also obtained positive mean scores (4.62 and 4.21 respectively, on a 7-point scale).

Table 2. Average results for chronically ill and healthy subjects in the assessment of satisfaction in individual areas of life in the Life Satisfaction Questionnaire
Tabela 2. Wyniki średnie uzyskane przez badanych chorych i osoby zdrowe w poszczególnych dziedzinach życia w Kwestionariuszu Zadowolenia

areas of life	ischaemic heart disease		hypertension		neoplastic disease		diabetes		asthma		healthy	
	N = 41		N = 35		N = 36		N = 33		N = 37		N = 80	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
health	26.00	7.37	27.06	8.54	24.71	8.48	28.09	7.55	24.75	7.35	32.30	6.38
work	27.73	6.96	27.94	6.39	26.55	6.72	26.91	6.60	22.78	7.96	27.75	5.38
finances	25.68	8.67	27.30	7.73	26.26	9.01	28.70	8.38	22.56	8.48	28.74	6.95
free time	30.95	7.72	30.55	7.16	30.74	8.84	31.12	7.65	29.47	7.54	30.90	7.92
children	38.52	6.88	37.53	6.55	34.28	9.35	36.09	6.54	34.97	8.51	36.53	9.61
myself	33.71	6.52	33.42	5.28	32.26	7.64	34.24	6.55	32.28	6.38	34.76	7.01
others	33.88	7.16	35.18	7.15	34.16	7.07	35.97	5.73	32.28	6.43	35.39	5.57
housing situation	35.15	7.13	33.85	7.36	31.52	9.29	35.30	7.59	32.50	8.24	35.44	6.23
marriage	32.41	11.81	30.55	11.1	34.00	2.6	37.33	7.67	32.23	8.20	36.05	7.82
sex	28.78	9.47	28.94	8.83	26.45	11.6	32.36	7.98	29.44	10.29	34.42	7.78
general satisfaction	31.31	5.17	30.71	5.42	29.96	5.82	32.60	5.21	29.44	4.54	33.09	4.42

N – number of cases, M – mean, SD standard deviation

Table 3. Average results and their comparison for healthy (N = 74) and chronically ill subjects (N = 172) in the assessments of overall satisfaction with individual areas of life and general life satisfaction
Tabela 3. Wyniki średnie i ich porównanie u badanych zdrowych (N = 74) i przewlekle chorych (N = 172) w poszczególnych dziedzinach życia i zadowoleniu ogólnym

categories	healthy		diseased		df	t	p
	M	SD	M	SD			
health	32.30	6.38	26.14	7.86	248	6.12	0.000
work	27.75	5.38	26.46	7.11	248	1.43	0.153
finances	28.74	6.95	26.10	8.61	248	2.40	0.017
free time	30.90	7.92	30.59	7.71	248	0.30	0.768
children	36.53	9.61	36.43	7.65	241	0.08	0.934
myself	35.11	5.86	33.31	6.46	248	2.12	0.035
others	35.39	5.58	34.29	6.78	248	1.26	0.208
housing situation	35.44	6.23	33.76	7.95	248	1.66	0.099
marriage	36.05	7.82	33.27	10.67	243	2.06	0.041
sex	34.42	7.78	29.21	9.74	248	4.20	0.000
general satisfaction	33.09	4.42	30.85	5.44	248	3.22	0.001

M – mean, SD – standard deviation, df – degrees of freedom, t – Student's t-test, p – probability value

Other groups present scores bordering on approval and disapproval. All the mean scores in these groups are statistically significantly different from those found in healthy subjects and in diabetics. The lowest scores were observed in patients with neoplasms (3.78 on a 7-point scale), which clearly demonstrates dissatisfaction with sexual fulfilment. Mean results in the other three groups oscillate around a neutral score (4 points on a 7-point scale).

The scores regarding contacts with children are definitely the most positive ones, and most similar in all the groups. The highest level of satisfaction with contacts with their children is observed in patients after myocardial infarction (higher than in healthy subjects), and the lowest in patients with neoplasms.

Regarding self-assessment, the results in all the studied groups are very similar. The scores are not high, but positive (mean results on a 7-point scale are 4.61-4.97). The lowest self-assessment scores were found in the group of patients with neoplasms and with asthma, whereas the highest ones were observed in healthy subjects and by diabetics.

Subjects with asthma provided the lowest score regarding relations with friends and relatives. Their assessments are statistically different from those made by diabetics or by the healthy group. Mean results regarding satisfaction with interpersonal relations in the immediate environment are relatively positive in all the study groups, and similar to those observed in healthy subjects.

The most critical assessment of one's housing situation was found in patients with neoplasms. Their scores significantly differ from those in the healthy group ($p < 0.02$) and patients after myocardial infarction ($p < 0.05$). Patients with asthma perceive their housing situation only slightly better. The other groups, including healthy subjects, patients with hypertension, patients who had a myocardial infarction and diabetics, express a similar, moderately positive level of satisfaction with their housing conditions.

The differences in general satisfaction with all the areas of life are found primarily between the healthy subjects and two out of five groups of chronically ill subjects: patients with asthma and those with neoplasms. All the study groups express a very limited level of life satisfaction. On a 7-point scale, the mean scores are between 4.21 and 4.73. Patients with diabetes presented the mean life satisfaction scores closest to those of healthy subjects.

The assessment of general satisfaction with all areas of life does not change significantly in relation to the subject's age ($F = 1.13$; $p = 0.29$). Also, duration of the disease does not affect considerably the satisfaction with any of the tested life areas ($F = 0.96$; $p = 0.36$).

Healthy individuals and chronically ill patients differ significantly in their satisfaction with five aspects of life (Table 3.). The greatest difference is observed, understandably, in their assessment of health. Satisfaction with sexual activity comes second in terms of assessment discrepancy, followed by satisfaction with the financial situation, which also seems to be understandable, as it is directly related to reduced working opportunities and treatment expenses. Other visible differences between healthy and chronically ill subjects are found in satisfaction with oneself and one's marriage.

In the remaining five areas: satisfaction with relationships with children, leisure time, work and profession, relations with friends and family, and housing situation, the differences between the studied healthy subjects and chronically ill patients are not statistically significant. The smallest differences are observed in satisfaction scores regarding contacts with one's children and leisure time.

Conclusions

- The levels of general satisfaction with life, as well as satisfaction with its most important areas, are different in healthy individuals and chronically ill patients, with the latter demonstrating significantly lower scores.
- Although there are no significant differences in the assessment of one's life between various groups of chronically ill subjects, patients with asthma and those with neoplasms differ the most from healthy individuals in terms of life satisfaction.
- Duration of the disease does not cause any differences between the patient groups.

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Risk factors analysis of atelectasis in patients operated due to non-small cell lung cancer

Analiza czynników ryzyka niedodmy u chorych operowanych z powodu niedrobnokomórkowego raka płuca

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Abstract. Background. The aim of the study was to evaluate the incidence of atelectasis and predisposing risk factors in patients operated for non-small cell lung cancer. Material and methods. The authors retrospectively analysed 67 medical histories of patients who underwent lobectomy, segmentectomy and bilobectomy at the Military Medical Academy University Teaching Hospital - Central Veterans' Hospital in 2015. The postoperative atelectasis was determined by chest radiographic reports. It was examined if age, sex, BMI, size and histological type of tumour, type of surgery and preoperative FEV_1 have impact on the incidence of atelectasis. Results. Postoperative atelectasis was observed in 26 patients, 11 in females and 15 in males. Age, sex, histological type of tumour and tumour size, did not reach values defining the risk of postoperative atelectasis ($p < 0.05$). On the other hand, obesity, preoperative $FEV_1 \leq 80$ and the procedure performed on the left lung were reported to be statistically significant. Conclusions. BMI >30 patients with preoperative $FEV_1 \leq 80$, and those who underwent surgery on their left lung are more susceptible to the postoperative complication of atelectasis.
Keywords: atelectasis, lung cancer, thoracic surgery

Streszczenie. Cel badania. Celem badania była ocena częstości występowania niedodmy oraz czynników ryzyka predysponujących do tego stanu u operowanych z powodu niedrobnokomórkowego raka płuca. Materiały i metody. Przeanalizowano retrospektywnie historie chorób 67 chorych, którzy przebyli lobektomię, bilobektomę i segmentektomię w Szpitalu Klinicznym im. Wojskowej Akademii Medycznej-Centralnym Szpitalu Weteranów w 2015 roku. Pooperacyjną niedodmę określano na podstawie radiogramów klatki piersiowej. Zbadano, czy wiek, płeć, BMI, rozmiar i typ histologiczny nowotworu, rodzaj operacji i przedoperacyjny FEV_1 ma wpływ na częstość występowania niedodmy. Wyniki. U 26 chorych pojawiła się pooperacyjna niedodma (11 kobiet i 15 mężczyzn). Wiek, płeć, typ histologiczny nowotworu i wielkość guza nie osiągnęły wartości określającej pooperacyjne ryzyko niedodmy ($p < 0,05$), natomiast otyłość, przedoperacyjna wartość $FEV_1 < 80$ oraz zabieg wykonywany na płucu lewym były istotne statystycznie. Wnioski. Chorzy z BMI >30, z przedoperacyjna wartością $FEV_1 \leq 80$ oraz po lewostronnej torakotomii, u których wykonywano wycięcie miąższu płuca lewego, są bardziej narażeni na pooperacyjne powikłanie pod postacią niedodmy.
Słowa kluczowe: niedodma, rak płuca, operacja torakochirurgiczna

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Background

Lung cancer is the most common cause of death due to neoplasms in the world. Clinically, two types of lung cancer are distinguished: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is found in approximately 85% of cases. Excision is the basic, beneficial method of treatment in TNM stages I and II in TNM [1-4]. The following surgical techniques are used: lobectomy, segmentectomy, wedge resection and "sleeve" resection of pulmonary parenchyma, which according to Marios Kontantinou et al. has better long-term survival than classic pulmonectomy.

Risk factors analysis of atelectasis in patients operated due to non-small cell lung cancer [5]. The general rate of complications following pulmonary parenchymal resection is approximately 30% (between 7-49%). The most common complications are: prolonged air leak (1-15%), pneumonia (4.8-15%), ARDS (2.4-10%) and atelectasis (1-20%) [7]. Atelectasis is a condition in which gas exchange in certain parts of the lungs is reduced. Opening the chest and manipulating the lung may contribute to the condition [10]. Other important risk factors include reduced cough reflex, inadequate pain control and impaired pulmonary or diaphragm function. Atelectasis facilitates the collection of secretion in the bronchial tree, which may promote bacterial growth and pneumonia [11]. Therefore, we decided to study the potential risk factors for atelectasis, the most common pulmonary complication.

Aim of the study

The aim of this study was to assess the incidence of atelectasis and to analyse the risk factors in patients operated due to non-small cell lung cancer.

Material and methods

The retrospective analysis comprised the medical history of 67 patients who received a lobectomy, bilobectomy or segmentectomy at the Department of Thoracic, General and Oncological Surgery of the Military Medical University Clinical Hospital in 2015. Postoperative atelectasis was determined based on thoracic radiographic reports. The calculations were made using IBM SPSS 23.0 software. Contingency tables and chi-square tests of independence were used to analyse the relationships between the variables, and to assess the significance of differences in frequency distribution between the groups with nominal variables, and with nominal and ordinal variables. The assumed significance level was $p < 0.05$.

The effect of age, sex, BMI, size and histological type of the neoplasm, type of procedure and pre-operative FEV_1 on the incidence of atelectasis was analysed.

Conclusions

- No statistically significant relationship was found between atelectasis and age, sex, histological type and size of the tumour.
- Postoperative atelectasis is more frequently observed in obese patients with BMI >30 ($p < 0.05$).
- The patients whose preoperative FEV_1 was ≤80 are at a higher risk of postoperative atelectasis ($p < 0.05$).
- Procedures involving the left lung are associated with a greater risk of atelectasis ($p < 0.05$).

Discussion

Pulmonary complications are a very important factor contributing to increased mortality rates following thoracic surgeries. In Japan, based on over 7 thousand thoracic surgeries, a 30-day mortality rate of 1.3% was found due to acute respiratory distress [9]. Atelectasis, being the most common complication, is responsible for 1-20% of the total number [7].

In our study, atelectasis was found in 26 patients (38.8%) out of 67 study subjects. This number is higher than those reported by other authors, e.g. Stolz (n=412) 6.6% [7], Korst (n=218) 7.8% [13], Gray (n=106) 22% [10], Fernandes (n=189) 11.5% [13] or Agostini (n=234) 14.5% [8]. However, their studies were based on a larger number of patients, which could have affected the results.

In our study, age did not play an important role in terms of final objectives. No statistical significance was obtained in that respect. This problem was analysed by Stolz [7] and Agostini [8]. The former did not find a relationship between age and the incidence of postoperative atelectasis. Agostini demonstrated that patients over 75 years old are more susceptible to the complication. The most numerous group in our study included patients aged 60 to 74 years old. Only eight patients were over 75 years old, which could contribute to the results of the statistical analysis.

Stolz analysed the issue of sex, and, similarly to our outcomes, he demonstrated that it does not affect the frequency of postoperative atelectasis [7].

None of the authors of the publications we analysed focused on the relationship between the histological type and size of the neoplasms, and the studied complication. Only Agostini studied the effect of neoplasms originating in the lung and metastases [8]. However, he did not demonstrate an increased risk of postoperative atelectasis.

Neither of the examples above reached the $p < 0.05$ value.

The parameter presenting a statistical significance was the type of the procedure ($p < 0.047$). Our analysis did not include the removal of specific lobes, but we focused on right-sided and left-sided lobectomy. Segmentectomy was performed in 10 out of 67 cases, due to the appropriate tumour size and location. It allowed preserving a significant amount of pulmonary parenchyma in patients with cardiopulmonary diseases [6]. According to our data, procedures on the left lung are associated with a greater risk of postoperative atelectasis. Therefore, a left-sided tumour location can be considered as less favourable for the patient.

Gray presented a similar conclusion in his publication, although it applied to paediatric patients. He attributed it to worse patient compliance after the surgery, and smaller bronchi [10]. In our study group, the youngest patient was 41 years old. According to Stolz, procedures on the right lung are associated with a higher risk of atelectasis in the postoperative period [7]. Agostini analysed the effects of lobectomy, pulmonectomy and segmentectomy. In his study, the type of procedure did not affect the studied complication [8].

BMI > 30 was another variable that reached statistical significance (p <0.013). These patients more often present reduced total lung capacity (TLC) and vital capacity (VC) [14]. Our conclusions comply with those published by Agostini [8].

The last analysed parameter associated with the risk of atelectasis following thoracic surgeries is preoperative FEV_1. Fernandes demonstrated that FEV_1 value of <60 is an important risk factor [13]. Based on our study results, we demonstrated that patients with FEV_1 ≤80 (p <0.026) are already at a higher risk of the studied pulmonary complication. It suggests that a more restrictive approach should be adapted to spirometry in the patients undergoing surgery due to non-small cell lung cancer.

The basic measure that allows preventing postoperative atelectasis is respiratory rehabilitation, which is the first-line therapy. It consists in sufficiently deep breathing, the percussion of the chest and coughing. Early bronchoaspiration is a more invasive, but equally effective method. Another important element is using nebulised bronchodilators. They dilate the airways, which may increase the effectiveness of the mechanisms clearing them from secretion. Proper analgesia of the patient in the perioperative period is also very important [15, 16].

The aim of the presented study is to present pulmonary complications following thoracic surgeries, and emphasise their seriousness. Due to the analysis of the risk factors, we can to some extent predict complications and implement in the perioperative period the management which can reduce their occurrence.

Results

The study involved the medical history of 67 patients undergoing surgery due to non-small cell lung cancer.

Postoperative atelectasis occurred in 26 patients (38.8%), 11 females and 15 males (Fig. 1.). No statistical relationships between the variables were found. Therefore, sex does not affect the postoperative risk of atelectasis.

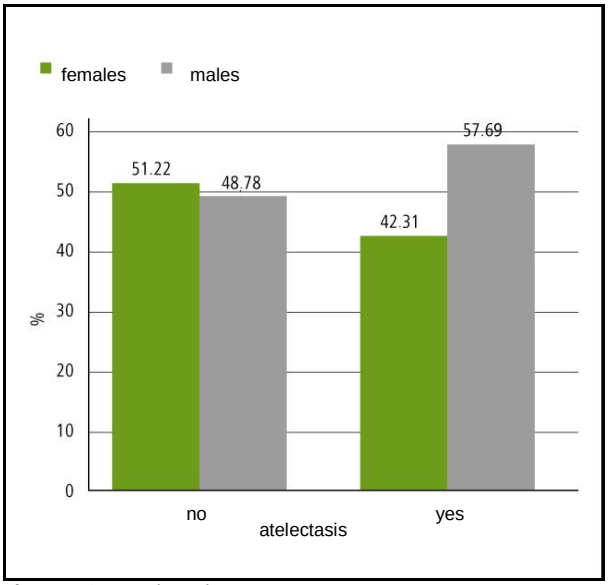

Figure 1. Sex. Atelectasis
Rycina 1. Płeć. Niedodma

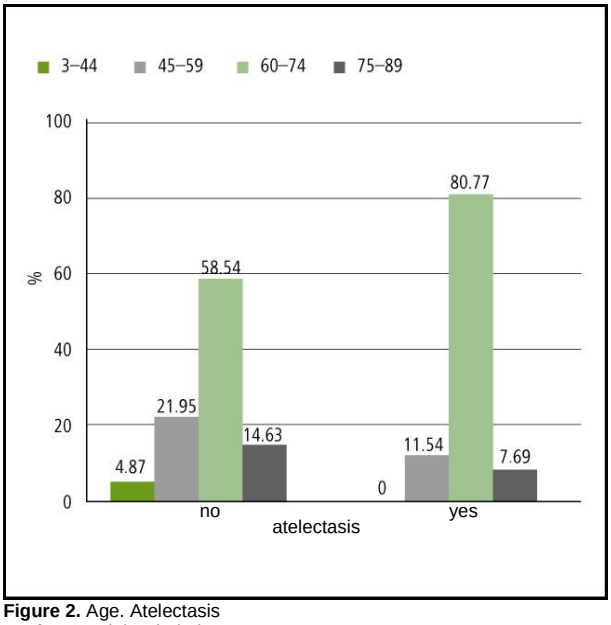

Figure 2. Age. Atelectasis
Rycina 2. Wiek. Niedodma

Another parameter analysed in the study was age. Four age groups were distinguished (Fig. 2.). Atelectasis developed most frequently in patients aged 60 to 74 years old (n = 45). However, no statistical relationships were observed.

BMI *(body mass index)* was analysed in three ranges: 18.5-24.9, 25-29.9, >30 (Fig. 3.).

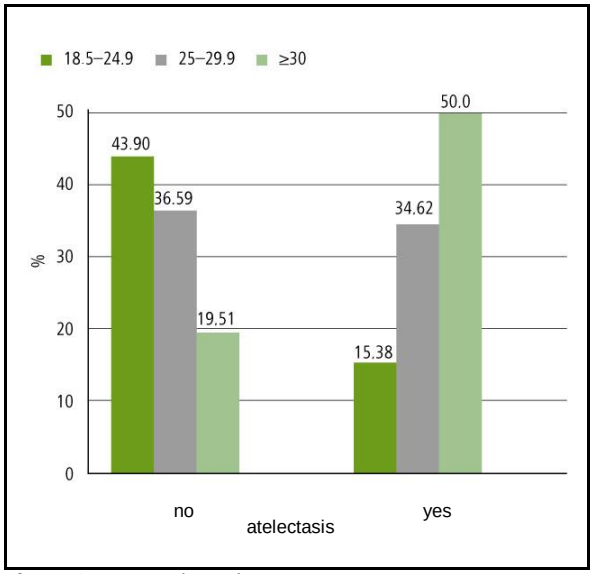

Figure 3. BMI. Atelectasis
Rycina 3. BMI. Niedodma

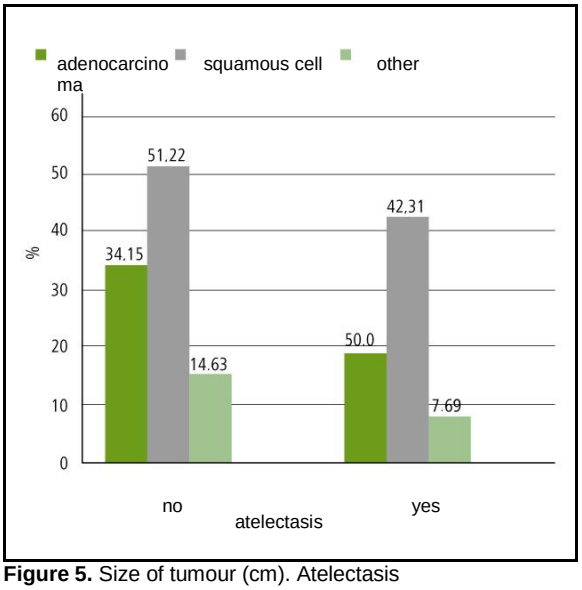

Figure 5. Size of tumour (cm). Atelectasis
Rycina 5. Rozmiar guza przedziały (cm). Niedodma

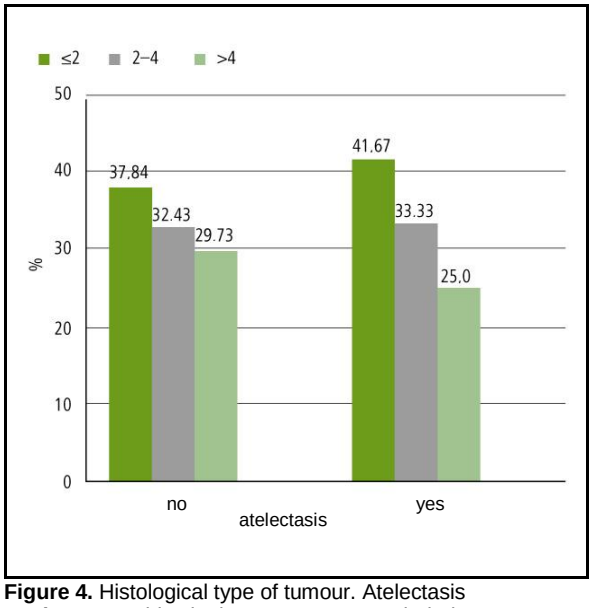

Figure 4. Histological type of tumour. Atelectasis
Rycina 4. Typ histologiczny nowotworu. Niedodma

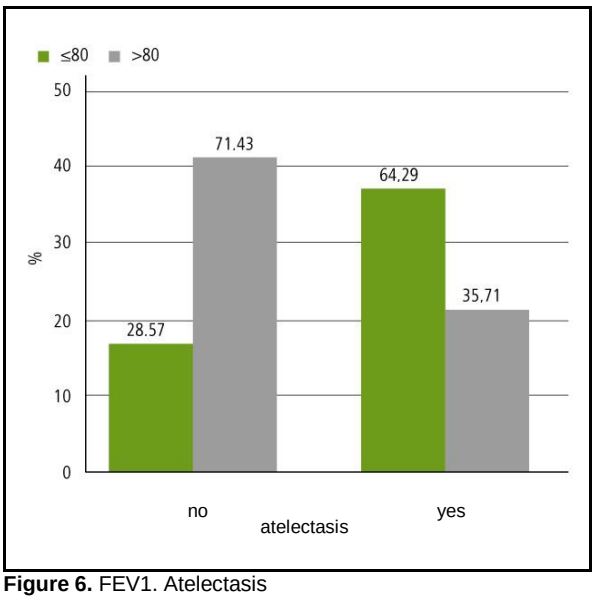

Figure 6. FEV1. Atelectasis
Rycina 6. FEV1. Niedodma

The most predisposed for postoperative atelectasis were the patients with BMI of >30 ($p < 0.05$).

Next, the effects of the histological type and size of the neoplasm on the studied complication were analysed. Most of the tumours were squamous cell neoplasms (27) and adenocarcinomas (32). Others included 4 neuroendocrine tumours, 3 large cell neoplasms and 1 anaplastic tumour (Fig. 4.). The size was analysed in three groups: <2 cm, 2-4 cm, >4 cm (Fig. 5.).

No statistically significant correlations were found in neither of the analysed problems.

Preoperative FEV_1 ≤80 was another parameter where $p < 0.05$ was reached.

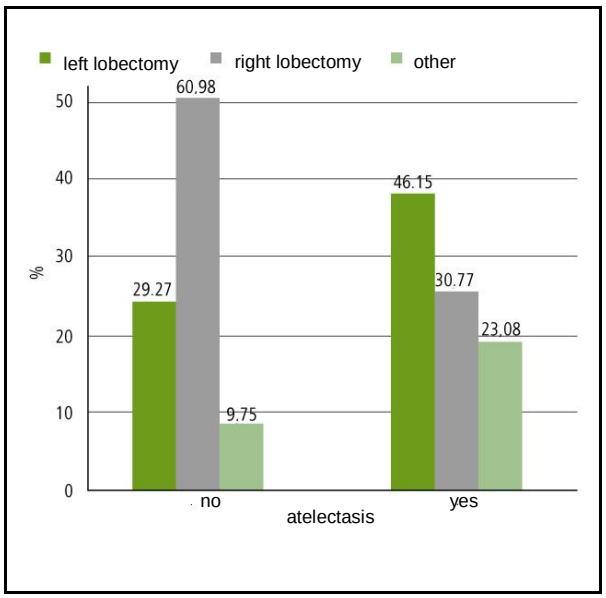

Figure 7. Type of surgery. Atelectasis
Rycina 7. Rodzaj zabiegu. Niedodma

(Fig. 6.). The obtained data indicate that atelectasis developed more often in patients with FEV_1 of <80 (n = 25).

The relationship between the scope of surgery and the development of atelectasis was also analysed. Most surgeries were right-sided (33) and left-sided (24) lobectomies. In other cases, segmentectomies were performed (Fig. 7.).

A statistically significant correlation was found for lobectomies of the left lung.

Conclusions

- No statistically significant relationship was found between atelectasis and age, sex, histological type or size of the tumour.
- Postoperative atelectasis is more frequently observed in obese patients with BMI >30 ($p < 0.05$).
- The patients whose preoperative FEV_1 was ≤80 are at a higher risk of postoperative atelectasis ($p < 0.05$).
- Procedures involving the left lung are associated with a greater risk of atelectasis ($p < 0.05$).

Final remarks

During the analysis of the risk of pulmonary complications in patients before thoracic surgery, the following parameters should be considered: BMI, preoperative FEV_1 and the type of procedure.
They can be predictors suggesting which patients will require particular attention in the perioperative period. It may facilitate making decisions that will improve the quality of life of patients after thoracic surgeries.

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Pharmacological pre-treatment with long acting somatostatin analogue in acromegaly

Przedoperacyjne zastosowanie analogów somatostatyny o przedłużonym działaniu u chorych z akromegalią

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Abstract. The aim of the study was to evaluate the impact of the long-acting somatostatin analogue (aSS, lanreotide) for the serum GH and IGF-I concentration, pituitary tumour volume and its invasiveness. The results of pharmacological aSS treatment in 17 patients (11 females and 6 males, mean age 43.-35 years, range: 32-64 years) were analysed. GH, IGF-1 levels, tumour volume and its invasiveness were measured. Mean initial serum GH and IGF-1 levels were 20.506 ng/ml and 864.824 ng/ml, respectively, while after the treatment they decreased to 7.259 ng/ml and 544.765 ng/ml, respectively. Mean initial pituitary tumour volume was 3332.765 mm^3 and decreased to 2345.206 mm^3, which was statistically significant. None of the patients showed invasive lesions caused by the pituitary tumour during the treatment. The results demonstrated that aSS significantly decreases serum level of GH and IGF-1 and shrinks the pituitary tumour. The authors did not observe any impact of the treatment on the pituitary tumour invasiveness.
Key words: pituitary adenoma, acromegaly, growth hormone, somatostatin analogue

Streszczenie. Celem pracy była ocena wpływu analogu somatostatyny (aSS) u chorych z akromegalią w przebiegu guza przysadki na stężenie hormonu wzrostu (GH) i insulinopodobnego czynnika wzrostu (IGF-1), wielkość guza przysadki oraz zakres naciekania zatok jamistych. Dokonano analizy wyników leczenia farmakologicznego aSS u 17 chorych (11 kobiet i 6 mężczyzn, średnia wieku 43,35 roku, w zakresie 32-64 lat). W trakcie badania oceniano stężenia GH, IGF-1 oraz objętość guza i zakres wzrostu okotosiodłowego. Średnie początkowe stężenia GH i IGF-1 wynosiły 20,506 ng/ml i 864,824 ng/ml. Po leczeniu stężenia analizowanych hormonów uległy zmniejszeniu do 7,259 ng/ml i 544,765 ng/ml. Średnia początkowa objętość guza wynosiła 3332,765 mm^3 i uległa zmniejszeniu do 2345,206 mm^3. Uzyskane wyniki były istotne statystycznie. U żadnego z badanych chorych nie stwierdzono zmian w zakresie inwazji zatoki jamistej przez gruczolaka przysadki w czasie leczenia. Na podstawie uzyskanych wyników stwierdzono, że aSS powoduje znamienne statystycznie zmniejszenie stężenia GH oraz IGF-1 i wpływa istotnie na objętość gruczolaka przysadki. Stosowane leczenie nie miało znaczenia dla wzrostu okotosiodłowego guza przysadki.
Słowa kluczowe: gruczolak przysadki, akromegalią, hormon wzrostu, analog somatostatyny

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Background

Acromegaly is a rare disease. Its symptoms involve enlargement of the face, hands and feet, as well as hyperplasia of soft tissues, bones and internal organs resulting from autonomous secretion of growth hormone (GH), and secondary secretion of insulin-like growth factor (IGF-1) [1]. Usually, the disease is caused by pituitary adenoma, originating in somatotropic cells. In very rare cases, acromegaly is caused by hypothalamic tumours or neuroendocrine neoplasms secreting growth-hormone releasing hormone (GH-RH) or GH. Excessive, uncontrollable secretion of GH and IGF-1 causes typical somatic symptoms and organ complications, e.g. of cardiovascular, osteoarticular, respiratory or metabolic nature (prediabetic condition and diabetes), which significantly deteriorate patient's quality of life and increase morbidity and the risk of death, compared to the general population [1-2].

Table 1 A. Detailed data of the analysed group of patients - pituitary tumour at diagnosis
Tabela 1 A. Szczegółowe dane grupy badanej - guz przysadki w chwili rozpoznania choroby

patient	age	sex	GH (ng/ml)	IGF-1 (ng/ml)	Knosp grade	dimensions of adenoma (mm)	tumour volume by DiChiro-Nelson formula
1	41	F	17.5	890	1	12 x 12 x 17	1281.1
2	46	F	35	1120	2	28 x 23 x 20	6740.5
3	32	F	17.2	610	1	30 x 18 x 17	4804.2
4	39	F	19.4	967	1	19 x 13 x 12	1551.2
5	64	F	16.2	670	1	14 x 22 x 13	2095.4
6	39	M	8.3	530	2	25 x 18 x 21	4945.5
7	39	F	23.1	970	2	14 x 13 x 14	2028.4
8	37	F	30.1	893	1	25 x 20 x 20	5233.3
9	49	M	32.4	923	2	24 x 22 x 20	5526.4
10	35	M	11.8	820	0	12 x 12 x 13	979.7
11	43	F	24.8	960	2	24 x 12 x 14	2110.1
12	41	M	23.7	1050	3	24 x 19 x 21	5011.4
13	62	F	9.7	745	1	13 x 12 x 10	816.4
14	38	M	16.7	810	2	14 x 15 x 10	1099.0
15	45	M	21.4	930	4	20 x 30 x 15	4710.0
16	43	F	8.9	924	2	21 x 15 x 24	3956.4
17	44	F	32.4	890	1	20 x 18 x 20	3768.0

In acromegaly, the management of choice involves selective, transsphenoidal removal of the pituitary tumour, which normalises GH and IGF-1 secretion. The effectiveness of this treatment depends on tumour size, invasion of adjacent structures, and experience of the neurosurgeon performing the procedure. According to the recommendations of the Polish Society of Endocrinology, patients diagnosed with acromegaly in the course of pituitary tumour should be prepared for surgical treatment by therapy with one of the available somatostatin analogues, in order to alleviate the symptoms of the disease, lower preoperative GH concentration, and reduce the size of the pituitary tumour [2].

Aim of the study

The aim of the study was to assess the effect of long-lasting somatostatin analogue (Lanreotide, Somatuline, Auto-gel 120 mg) in patients diagnosed with acromegaly in the course of pituitary adenoma on

- GH and IGF-1 concentrations,
- size/volume of the pituitary adenoma, and
- scope of invasion of the cavernous sinuses by the pituitary adenoma.

Material

Seventeen consecutive patients diagnosed with acromegaly were included in the study, 11 females and 6 males, aged 32-64 years old (mean age 43.35 years, SD ±8.49 years), subsequently treated at the Department of Neurosurgery of the Military Institute of Medicine in Warsaw, from January to December 2014. The detailed characteristics of the study group are presented in Table 1.

Methods

Acromegaly was determined based on the characteristic clinical picture and abnormal biochemical test results: IGF-1 concentrations above the normal range for sex and age, and absence of inhibition of GH secretion ≤1 µg/l after the 75 g oral glucose load.

Table 1B. Detailed data of the analysed group of patients - pituitary tumor after treatment with somatostatin analogue
Tabela 1B. Szczegółowe dane grupy badanej - guz przysadki po leczeniu analogiem somatostatyny

patient	age	sex	GH (ng/ml)	IGF-1 (ng/ml)	Knosp grade	dimensions of adenoma (mm)	tumour volume by DiChiro-Nelson formula
1	41	F	3.1	427	1	12 x 12 x 10	753.6
2	46	F	4.4	310	2	20 x 12 x 17	2135.2
3	32	F	7.9	530	1	29 x 16 x 14	3399.6
4	39	F	6.9	392	1	17 x 9 x 11	880.1
5	64	F	6.2	540	1	13 x 21 x 11	1571.6
6	39	M	1.8	317	2	23 x 14 x 20	3370.3
7	39	F	7.1	740	2	13 x 9 x 13	796.0
8	37	F	19.1	545	1	24 x 20 x 20	5024.0
9	49	M	13.4	480	2	23 x 20 x 19	4573.9
10	35	M	5.1	710	0	12 x 12 x 12	904.3
11	43	F	7.2	945	2	23 x 10 x 13	1564.8
12	41	M	9.4	610	3	24 x 19 x 19	4534.2
13	62	F	3.4	390	1	12 x 9 x 10	565.2
14	38	M	7.9	575	2	14 x 15 x 10	1099.0
15	45	M	6.1	590	4	20 x 28 x 14	4102.9
16	43	F	3.4	430	2	18 x 14 x 19	2505.7
17	44	F	11.0	730	1	19 x 14 x 15	2088.1

Plasma GH concentration was determined using electrochemiluminescence, with the use of a Hitachi analyser Cobas e601 (distributed by Roche Diagnostics Polska Sp. z o.o.) and the ELSA-ACTH assay from CIS bio International, France. The analytical sensitivity of the test was 0.05 ng/ml. Plasma GH concentrations of 0-5 ng/ml were adapted as reference values.

IGF-1 concentration was determined using the ELISA method, with a commercially available test from LDN (LABOR DIAGNOSTIKA NORD GmgH & Co.KG). The analytical sensitivity of the test was 9.75 ng/ml. Table 2. presents referential values for serum IGF-1 in different age groups.

All patients received an MR test of the optic chiasm area, performed with the use of the 1.5T device (GE Signa) in sagittal and frontal planes, T_1- and T_2-weighted, before and after administration of contrast medium, following the diagnosis of the disease, and after six injections of somatostatin analogue injections. Based on the test, three typical tumour dimensions were assessed: sagittal, frontal and axial, and the tumour volume was calculated using the formula for the volume of a spheroid:

$$V = \frac{a \times b \times c}{6} \times \pi$$

Table 2. Serum reference values of IGF-1 in age groups of patients
Tabela 2. Wartości referencyjne IGF-1 w surowicy w grupach wiekowych

age (range in years)	IGF-1 concentration (ng/ml)			
	mean	median	min.	max.
19-39	233	219.6	138.8	353.1
40-59	176.3	159.7	111.4	256.8
60-80	137.2	127.3	86	213.8

where: V – tumour volume, a – sagittal dimension, b – frontal dimension (bitemporal), c – axial dimension (craniocaudal), π – irrational number, defined as the ratio of a circle's circumference to its diameter; its approximate value is 3.14159.

Moreover, the growth of the parasellar tumour into the cavernous sinus was assessed, using the Knosp scale criteria [3].

All patients received six injections of somatostatin analogue Lanreotide (Somatuline P.R. by Ipsen) at a dose of 120 mg *i.m.* in 28-day intervals. After the treatment, concentrations of GH and IGF-1 were assessed, and MR test of the optic chiasm was conducted to evaluate the pituitary tumour size and its parasellar expansion.

Table 3. Detailed results in the study group
Tabela 3. Szczegółowe wyniki uzyskane w grupie badanej

		baseline value – diagnosis	value after the treatment	P
GH (ng/ml)	N	17	17	0.00001
	mean	20.506	7.259	
	SD	8.484	4.255	
	median	19.4	6.9	
	minimum	8.3	1.8	
	maximum	35	19.1	
IGF-1 (ng/ml)	N	17	17	0.000001
	mean	864.824	544.765	
	SD	153.609	168.243	
	median	893	540	
	minimum	530	310	
	maximum	1120	945	
volume of adenoma (mm^3)	N	17	17	0.001598
	mean	3332.765	2345.206	
	SD	1921.345	1529.045	
	median	3768	2088.1	
	minimum	816.4	565.2	
	maximum	6740.5	5024	

Statistical analysis

Descriptive statistical methods were used in the statistical analysis (mean, median and standard deviation). The T-Student test was used to study the significance of differences between the mean values of the constant variable in two groups (the variables demonstrated normal distribution). The assumed statistical significance level was $p < 0.05$.

The results were analysed using Statistica 7.1, StatSoft. Inc. 1984-2005.

Results

The obtained results are presented in Table 3.

In the studied group, mean baseline GH concentration was 20,506 ng/ml (median of 19.4 ng/ml, range of 8.3-35 ng/ml, SD ±8.484 ng/ml), and mean baseline IGF-1 concentration was 864.824 ng/ml (median of 893 ng/ml, range of 530-1120 ng/ml, SD ±153.609 ng/ml).

Therapy with somatostatin analogue reduced mean GH concentration to 7.259 ng/ml (median of 6.9 ng/ml, range of 1.8-19.1 ng/ml, SD ±4.255 ng/ml), and mean IGF-1 concentration to 544.765 ng/ml (median of 540 ng/ml, range of 310-945 ng/ml, SD ±168.243 ng/ml).

The analysis revealed that mean GH and IGF-1 concentrations and their medians decreased in the course of the treatment, and the obtained differences were statistically significant.

In the studied group, mean tumour volume at the diagnosis was 3332.765 mm^3 (median of 3768 mm^3, range of 816.4-6740.5 mm^3, SD ±1921.345 mm^3). Mean tumour volume evaluated after the pharmacological treatment according to the study protocol was 2345.206 mm^3 (median of 2088.1 mm^3, range of 565.2-5024 mm^3, SD ±1529.045 mm^3). The obtained values were statistically significantly different ($p = 0.001598$).

In the study group, eight adenomas were found (47%), growing in the parasellar region, without invasion to the cavernous sinus (Knosp grade 0 or 1), seven tumours (41%) pressing the medial wall of the cavernous sinus, and two tumours (11%) invading the cavernous sinus.

The applied pharmacological treatment did not affect in any of the cases the scope of invasion of the cavernous sinus by the pituitary adenoma.

Discussion

The treatment of choice in acromegaly is transsphenoidal selective resection of the pituitary tumour [1]. The Polish Society of Endocrinology recommends preoperative pharmacological preparation with the use of long-lasting somatostatin analogues [2]. It is estimated that this management is beneficial for the clinical course of the disease prior to surgery, due to the lowering of GH and IGF-1 concentrations, and the reduction of the pituitary tumour mass [4].

Somatostatin is a natural polypeptide secreted in the hypothalamus, other parts of the nervous system, and in the gastrointestinal tract [5]. It affects target cells through G protein-coupled specific somatostatin receptors (SSTR 1-5) [7]. The effect of somatostatin is proportional to the number of membrane receptors. The basic activity of somatostatin consists in inhibition of GH and thyroid-stimulating hormone (TSH) secretion in hypothalamus and pituitary gland. High expression of somatostatin receptors in somatotropic adenomas is responsible for the therapeutic effect in acromegaly. It reduces GH secretion and IGF-1 secretion, which is reflected in reduced arterial pressure, decreased insulin requirement, increased activity of the respiratory centre, and improved contractility of skeletal muscles and the cardiac muscle [1, 5, 6]. The analgesic effect is important, as in the case of associated degenerative osteoarticular lesions it improves the patient's quality of life [2].

Somatostatin was demonstrated to have an antiproliferative effect, both in the pituitary adenoma and in other neoplastic tissues, due to affinity to SSTR2 [7]. Somatostatin inhibits the activity of ERK mitogen-activated kinases, increases the expression of the inhibitors of cyclin-dependent kinases (p21 and p27), and inhibits the PI3K/Akt pathway [8, 9].

There are numerous reports assessing the beneficial effects of somatostatin analogues on preoperative GH and IGF-1 levels. Wass et al. were among the first to find reduced GH and IGF-1 secretion in all the treated patients [10]. Lamberts and Plockinger obtained identical results [4, 11], confirmed by a retrospective study by Colao et al. in 2007 [12]. The study demonstrated that preoperative treatment reduces GH and IGF-1 concentrations. Moreover, titrated doses of somatostatin analogue have a beneficial effect on the tumour size, particularly in young patients with large, invasive pituitary tumours, as average reduction in the tumour size by 25% is observed. However, this has an adverse effect on carbohydrate metabolism. A multicentre, prospective study by Mercado et al. demonstrated a reduction in tumour volume of at least 20% in over 60% of subjects after 24 weeks, and in over 75% of patients after 48 weeks of treatment with somatostatin analogue [13]. Attanasio et al. presented similar observations [14] The results of our study also reveal beneficial effects of somatostatin analogue on preoperative GH and IGF-1 levels, as well as on the volume of the pituitary adenoma.

There is limited data on the effect of this management on the growth of a parasellar pituitary adenoma, which directly determines the outcomes of neurosurgical treatment.

The analysis of own material demonstrated that preoperative treatment with somatostatin analogue does not affect the growth of the parasellar somatotropic pituitary tumour, measured with the Knosp scale. Based on the results of a Spanish multicentre study, Lucas et al. confirmed the beneficial effect of somatostatin analogues on the volume of pituitary adenoma in acromegaly [5]. However, they revealed that the therapy does not affect the growth of a parasellar tumour. Also, Chang et al., based on the analysis of their own material, found no effect of the preoperative treatment on the scope of invasion of the cavernous sinus [15]. Caolo et al. did not observe any effect of the treatment with somatostatin analogues on the invasion of the cavernous sinus by a somatotropic pituitary tumour [16]. Studies conducted by other authors confirmed this thesis [17, 18].

Conclusions

Using long-lasting somatostatin analogue in the period before a neurosurgical procedure in patients diagnosed with acromegaly in the course of pituitary adenoma results in a statistically significant reduction of GH and IGF-1 concentrations, associated with a considerable reduction of the volume of the pituitary adenoma.

Pharmacological treatment does not affect the parasellar expansion of the pituitary adenoma into the cavernous sinuses, which is considered a prognostic factor for radicality of the procedure.

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Infective endocarditis – a multifaceted disease. Case report

Infekcyjne zapalenie wsierdzia – choroba o wielu twarzach. Opis przypadku

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Abstract. Infective endocarditis is a well-known cardiovascular disease that is associated with poor prognosis. Its prevalence is estimated at 1.7-7.9 cases per 100,000 people [1]. Although recently significant progress in the diagnosis and treatment of infective endocarditis has been made, mortality from this disease remains high. Mortality ranges from 13 to 25%, and further 9-20% of patients die within the first year after being discharged from hospital [1]. The diversity of clinical manifestation makes diagnosis difficult. Moreover, treatment often requires the interdisciplinary cooperation of numerous specialists. The paper presents a case of a patient which perfectly illustrates how insidious this disease is, and how important it is to involve various specialists in its treatment.
Key words: infective endocarditis, ischemic stroke, hemorrhagic stroke, thromboembolic complications, bicuspid aortic Valve

Streszczenie. Infekcyjne zapalenie wsierdzia (IZW) jest chorobą układu sercowo-naczyniowego, która wiąże się z niekorzystnym rokowaniem. Częstość jej występowania szacuje się na 1,7-7,9 przypadków/100 000 mieszkańców. Mimo że w ciągu ostatnich lat dokonały się znaczne postępy w diagnostyce i leczeniu IZW, śmiertelność w tej jednostce chorobowej nadal jest duża. Śmiertelność wewnątrzszpitalna waha się w granicach 13-25%, a kolejne 9-20% pacjentów umiera w ciągu pierwszego roku po wypisie ze szpitala. Zróżnicowana manifestacja kliniczna sprawia wiele trudności diagnostycznych, a leczenie często wymaga interdyscyplinarnej współpracy wielu specjalistów. W pracy przedstawiono przypadek, który doskonale obrazuje, jak podstępna jest to choroba i jak ważne jest zaangażowanie w jej leczenie lekarzy wielu specjalności.
Słowa kluczowe: infekcyjne zapalenie wsierdzia, udar niedokrwienny, udar krwotoczny, powikłania zakrzepowo-zatorowe, dwupłatkowa zastawka aortalna

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Background

Infective endocarditis (IE) develops as a result of infection of cardiac structures, most often in heart valves, but it may also involve ventricular and atrial endocardium, or endocardium covering the prosthetic valves, stimulator leads or cardioverter-defibrillator leads [2]. Due to a varied clinical picture and changing epidemiological profile, IE often poses a diagnostic and therapeutic challenge [3, 4]. Frequently, the disease is suspected only after its complications, such as stroke, circulatory failure, myocardial infarction or embolic incidents occur [5]. The most serious IE complications, having the greatest effect on the prognosis, are congestive heart failure and neurological complications: ischaemic stroke, intracranial haemorrhage, mycotic intracranial aneurisms, brain abscess and meningitis. However, it is worth remembering that embolisms may be found is any organ [6]. The

potential consequences of right-sided IE include septic pulmonary embolism, pulmonary oedema, pulmonary abscess, pleural effusion/abscess and pneumothorax [7]. Complications of IE often affect kidneys or spleen; usually it is due to septic embolisms, leading to infarction. Clinically, they may manifest by pain in the lumbar area or haematuria. Moreover, both renal ischaemia and nephrotoxic therapy may result in renal failure [6].

The clinical course may vary, depending on the etiology, pre-existing heart disease, presence of an artificial valve or an implantable device. Therefore, the clinical manifestations are varied. IE may imitate rheumatological, autoimmune or neurological diseases, or even suggest the presence of a neoplastic process [3-4]. Despite progress in diagnostics and treatment, this disease is still associated with high mortality rates, resulting from comorbidities, virulence of pathogens, or insufficient diagnostic and therapeutic strategies [2-4].

Infective endocarditis is a relatively rare disease (1.7 - 7.9 cases/100,000 people), with unfavourable prognosis; the hospital mortality is 13-25%, and another 9-20% of patients die within the first year following hospital discharge [1].

Case report

A 42-year-old man after carditis, with a history of transient complete block and atrioventricular conduction delays, with two-leaf aortic valve, was initially hospitalised in the neurology department due to an ischaemic stroke with symptoms including speech and vision disorders. Then, the patient was transferred to the cardiology department. Prior to hospitalisation, the patient reported headache, vision disorders and temporary pain in the lower limbs, without signs of infection, although out-patient laboratory tests revealed elevated concentrations of inflammatory markers. Head computed tomography performed in the neurology department revealed a hypodense lesion in the parieto-occipital border zone, on the right, near the vasculature of the medial and posterior cerebral arteries. Due to suspected infective endocarditis, the patient was transferred to the cardiology department. On admission, diastolic murmur in the aortic valve auscultation area, and individual petechiae on the skin and nail plate were observed. Laboratory tests revealed: elevated acute-phase protein (CRP) concentrations – 29.1 mg/dl, leukocytosis – 20.38 thousand, and increased fibrinogen concentration – 787 mg/dl. An electrocardiographic test (ECG) revealed regular sinus rhythm, 1 degree atrioventricular block (PQ 280 ms), and negative T waves in lead III. Due to suspected IE, the patient's blood was collected for cultures: 3 samples at 30-minute intervals, 10 ml of blood each, for aerobic and anaerobic mediums, following the ESC recommendations [3]. Intravenous, empirical antibiotic therapy was introduced: ampicillin with sulbactam 4 g in 4 doses, and gentamycin 3 x 80 mg. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) revealed a two-leaf aortic valve, thickened front leaf with a clear echographic shadow of approximately 8 x 5 mm, with the attached pedunculated structure of approximately 6 x 3.5 mm, and significant regurgitation. A diagnostic abdominal ultrasound examination was performed, suggestive of splenic infarction. Due to the absence of clinical symptoms, conservative treatment was recommended after a surgical consultation. As the patient reported vision disorders, he was consulted with an ophthalmologist, who found lesions in the eye fundus caused by microembolisms. Continuation of the anticoagulation therapy (low molecular weight heparin at prophylactic doses, administered since the beginning of hospitalisation) was recommended. Due to the knee joint pain reported by the patient, orthopaedic consultation was deemed necessary. Knee joint ultrasound and x-ray examinations did not reveal signs of active inflammation. The patient was qualified for a cardiosurgical procedure. To exclude potential infection, the patient had consultations with a stomatologist and laryngologist, who did not find signs of active infection. Before the planned surgical treatment, the patient's condition deteriorated, including speech disturbance and numbness in the left lower limb. ECG revealed irregular sinus rhythm and atrioventricular rhythm. Head computed tomography (CT) was performed, demonstrating a haematoma in the left parietal area. Following a neurosurgical consultation, antioedema therapy was recommended, antibiotic therapy was modified – ampicillin was switched to vancomycin, and gentamycin was continued. In the following days, cerebral angioCT and angiography were performed, and after another neurosurgical consultation, no contraindications for the cardiosurgical procedure were found. However, the surgery was postponed due to diffused maculopapular rash that occurred on the torso and limbs. Allergy to the antibiotics or contrast medium used during the angiographic examination was suspected. After a consultation with a dermatologist, gentamycin was discontinued, vancomycin was still administered, and oral steroid and antihistamines were introduced, with good results.

Eventually, after the maxillary surgeon and laryngologist excluded the presence of active inflammatory foci, a biological prosthesis Perimount 23 mm was implanted in the aorta.

On the second day after the surgery, an increase in leukocytosis to 54 thousand was observed, with no bacterial growth on the valve, and sterile results of the blood cultures grown at the admission. After another consultation, the maxillofacial surgeon decided to remove five teeth that were potentially the source of infection. Antibiotic therapy with vancomycin was continued, and the patient's condition improved.

Discussion

In its current guidelines, ESC emphasises the necessity of multidisciplinary approach to patients with IE, engaging doctors of many specialisations: cardiologists, surgeons, microbiologists, specialists in infectious diseases, and often other specialists, referred to as "IE Team" [3, 4, 8, 9]. Clinical manifestation of IE is varied, and it depends on the

type of microorganism inducing IE, comorbidities, and complications, including embolisms, which in left-sided IE are usually located in the brain and spleen [3, 4]. As often not only cardiological, but also rheumatological, infective and neurological symptoms develop, the collaboration of many specialists is necessary [3, 4, 9]. Summing up, IE is a deceitful disease, and patients often visit different specialists due to complications which manifest first, without typical cardiac symptoms.

The situation is complicated by the fact that frequently blood cultures are sterile, which prevents targeted treatment. It is probably a result of previous antibiotic therapy. It should also be emphasised that blood cultures in IE can be sterile if the disease is caused by mycotic infection or by atypical bacteria. Additional serological tests should then be performed for *Coxiella burnetii, Bartonella spp., Aspergillus spp., Mycoplasma pneumoniae, Brucella spp.* and *Legionella pneumophila,* as well as the polymerase chain reaction (PCR) tests for *Tropheryma whipplei, Bartonella spp.* and fungi *(Candida spp., Aspergillus spp.)* [3, 4, 10].

It should also be emphasised that the current ESC guidelines suggest limiting antibiotic prophylaxis to patients at high risk of IE who undergo high-risk stomatological procedures. There are only three groups of patients who should receive such prophylactic treatment:

- patients with artificial valves or artificial material used to fix a valve,
- patients with a history of infective endocarditis, and
- patients with an uncorrected cyanotic heart defect and patients with congenital heart defects following palliative surgeries involving artificial connections, conduits or other artificial materials (after procedures without residual defects, six months of antibiotic therapy is recommended after the surgery, until the artificial material endothelialises).

Patients with a two-leaf aortic valve, as in the case in question, or individuals with mitral valve prolapse or aortic valve stenosis due to calcification do not require antibiotic prophylaxis [3, 4].

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Granulomatosis with polyangitis – a diagnostic challenge. Case report

Ziarniniakowatość z zapaleniem naczyń - wyzwanie diagnostyczne. Opis przypadku

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Abstract. Granulomatosis with polyangitis (GPA) is an autoimmune, systemic disease, characterized by necrotizing vasculitis predominantly affecting small vessels. As it imitates other diseases, a diagnosis of GPA is often difficult. The paper presents the case of a 42-year-old woman, suspected of having tuberculosis or lung cancer, which clearly illustrates the challenge. Only the subsequent development of multiorgan involvement enabled a proper diagnosis. These included skin lesions, affecting upper and lower airways, gastrointestinal tract, kidneys, general symptoms, elevated inflammatory markers (leukocytosis 24.6 G/l, C-reactive protein 11.8 mg/dl, procalcitonin 1.16 ng/ml, thrombocythemia 620 x 10^3/l, hyperfibrinogenemia 600 mg/dl), and deep anemia with hemoglobin 6.5 g/dl. The diagnosis of severe generalized GPA was made (BVAS -33 points, BVAS/WG- 17 points). The remission inducing treatment following the modified CYCLOPS trial regimen was introduced. The remission was quickly achieved (the only persistent symptoms: BVAS -3 points, BVAS/WG - 2 points, VDI - 3 points). As could be seen from this case, GPA can have multiple clinical manifestations. Therefore, clinical vigilance to consider GPA in the differential diagnosis should be maintained by doctors of all specialties.
Key words: granulomatosis with polyangitis, CYCLOPS, tuberculosis, lung cancer

Streszczenie. Ziarniniakowatość z zapaleniem naczyń (GPA) jest chorobą autoimmunologiczną, ogólnoustrojową, charakteryzującą się martwiczym zapaleniem dotyczącym głównie małych naczyń. GPA może imitować inne jednostki chorobowe, co nierzadko utrudnia prawidłowe rozpoznanie. Przedstawiony przypadek 42-letniej pacjentki, u której podejrzewano gruźlicę lub nowotwór płuca, jest tego przykładem. Dopiero rozwój typowych dla GPA objawów wielonarządowych umożliwił ustalenie rozpoznania. Były to zmiany skórne, zajęcie górnych i dolnych dróg oddechowych, przewodu pokarmowego, nerek, objawy ogólne, wysokie parametry zapalne (WBC 24,6 G/l, CRP 11,8 mg/dl, prokalcytonina 1,16 ng/ml, nadpłytkowość 620 tys./l), hiperfibrynogenemia 600 mg/dl, głęboka niedokrwistość z HGB 6,5 g/dl. Rozpoznano uogólnioną ciężką postać choroby (BVAS - 33 pkt, BVAS/WG - 17 pkt). Wdrożono leczenie indukujące według zmodyfikowanego schematu CYCLOPS, uzyskując szybką remisję (utrzymujące się zmiany utrwalone; BVAS - 3 pkt, BVAS/WG - 2 pkt, VDI - 3 pkt). Jak pokazuje przedstawiony przykład, GPA może przyjmować różne manifestacje kliniczne. Dlatego lekarze wszystkich specjalności są zobligowani do zachowania czujności klinicznej w zakresie uwzględniania GPA w diagnostyce różnicowej.
Słowa kluczowe: ziarniniakowatość z zapaleniem naczyń, CYCLOPS, gruźlica, rak płuca

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Background

Granulomatosis with polyangitis (GPA), formerly referred to as Wegener's granulomatosis, is an autoimmune disease, and primary systemic vasculitis. It is characterised by necrotising vasculitis predominantly affecting small vessels. In the microscopic image, the pathognomonic features include the presence of

epithelioid granulomas and fibrinoid necrosis in the perivascular space and in tissues [1, 2]. In GPA, anti-neutrophil cytoplasmatic antibodies (cANCA) against proteinase 3 (PR-3), an enzyme found in the cytoplasm of neutrophils, are found in blood serum. Therefore, GPA is classified as ANCA-associated vasculitis (AAV) [3].

Systemic vasculitis with the presence of cANCA antibodies is found predominantly in Caucasians (ca. 80% of all cases), and there are no differences in incidence between men and women. Granulomatosis with polyangitis is diagnosed most frequently in individuals between 45 and 65 years old, although the disease may develop at any age. This condition is rare. The incidence in Europe is estimated as 2-15 cases per 100,000 people [3].

The disease usually affects the airways and kidneys, although it may affect all the systems. Therefore, GPA in its clinical course can imitate a number of other diseases, which may prevent and delay accurate diagnosis [4-7].

Case report

A 42-year-old patient, previously not treated for chronic diseases, was admitted to the Department of Internal Diseases, Nephrology and Dialysis of the Military Institute of Medicine with a suspected severe generalised form of systemic vasculitis.

Approximately five months earlier, the patient started experiencing shifting articular pains. Due to a family history of rheumatoid arthritis (in patient's sister), a rheumatoid factor was determined (with a positive result). A review thoracic x-ray was also performed, revealing a large, round shadow (37 x 70 mm) in the left lung, close to the chest wall. As tuberculous or neoplastic lesions were suspected, the patient was referred for invasive diagnostics to the Department of Surgery. Bronchoscopy and transthoracic fine needle aspiration biopsy (BAC) of the tumour was performed. The cytological examination of bronchial lavage revealed the presence of inflammatory cells, and BAC of the tumour showed necrotic lesions and individual atypical cells.

During hospitalisation at the Department of Surgery, skin lesions resembling purpura occurred on the patient's feet and lower legs. The patient was consulted with a dermatologist, and hyperergic purpura was suspected. After a few days, haemoptysis, nasal congestion, purulent-bloody secretion from the nose and crusting occurred.

The laboratory tests revealed anaemia (HGB 6.5 g/dl), which required repeated transfusion of packed red blood cells (six units of PRBC in total).

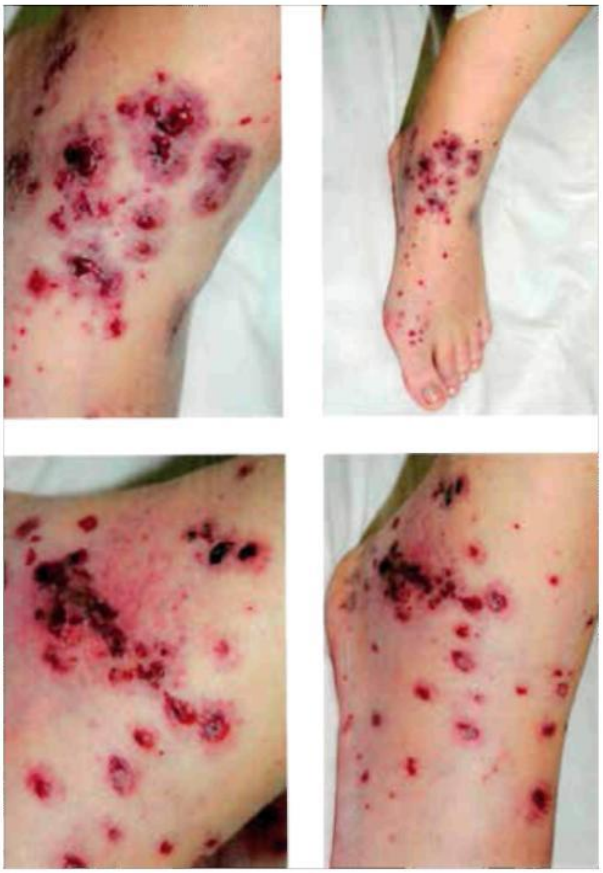

Figure 1. Skin lesions
Rycina 1. Zmiany skórne

Additional tests demonstrated elevated inflammatory marker values: leukocytosis 24.6 x 10^9/l with neutrophil smear, CRP 11.8 mg/dl, procalcitonin 1.16 ng/ml, ESR 93 mm/h, thrombocytosis 620 x 10^3/l, hyperfibrinogenemia 600 mg/dl, as well as increasing parameters of nitrogen retention: creatinine 1.9 mg/dl, urea 67 mg/dl, eGFR 31 ml/min/1.73 m^2 (one month earlier creatinine was 0.46 mg/dl). In urinalysis – active urinary sediment was present: dysmorphic erythrocytes loosely covering the high power field, protein, small-grain casts. Daily urine collection revealed nephrotic proteinuria 4.1 g/d with hypoproteinemia: albumins 2.8 g/dl, total protein 6.1 g/dl.

After consultation with a nephrologist, due to suspected systemic vasculitis with the pulmonary-renal syndrome, the patient was transferred to the Department of Nephrology.

On admission to the hospital, the patient was in a moderate general condition, with strong articular pain preventing independent movement, weak, and pale. The physical examination revealed oedema of elbow joints, knee joints, ankles and small joints of the feet, purpuric lesions, bloody blisters, ulcerations and necrotic foci on the skin of the feet and lower legs (Fig. 1.), in auscultation – exacerbation of vesicular murmur in the central field of the left lung (in the location corresponding to the site of the

tumour in the lung).

The immunological test confirmed the presence of cANCA antibodies in high titres (cANCA 121 IU/ml, positive result: >3 IU/ml), no pANCA antibodies, antinuclear antibodies (ANA), anti-glomerular basement membrane antibodies (anti-GBM) were found.

Thoracic high-resolution computed tomography (HRCT) confirmed the presence of the tumour of 70 x 37 x 73 mm described in the x-ray report, and revealed satellite nodules of up to 10 mm, as well as ground glass opacities (Fig. 2.). Due to persistent haemoptysis, another bronchoscopy was performed to exclude intraalveolar bleeding. It demonstrated inflammatory lesions in the subglottic area of the larynx, inflammatory changes in the bronchial mucosa; the histopathological examination revealed signs of small vessel vasculitis, chronic mucositis with ulceration of the covering epithelium. No active bleeding was shown, and cytological examination did not reveal hemosiderin-laden macrophages, typical for alveolar bleeding. The laryngological examination presented pronounced inflammatory lesions and ulceration of the nasal mucosa, as well as ulcerations covered with fibrin in the glottis. Computed tomography of the paranasal sinuses revealed inflammatory lesions in the maxillary sinuses and in the left frontal sinus. Gastroscopic examination demonstrated haemorrhaging erosions covering the entire circumference of the gastric cardia, without signs of active bleeding. In the skin sample, a perivascular lymphocyte was found. The diagnostic kidney biopsy (performed 2 months after the diagnosis) revealed necrotic *pauci immune* glomerular nephritis with complete sclerosis in 5 out of 11 assessed glomeruli, and fibrotic crescents in 4 out of 11 glomeruli.

Based on the complete clinical picture, the patient was diagnosed with severe generalised granulomatosis with polyangitis, with general symptoms (articular pain, weakness, reduced body weight), signs of chronic inflammation (elevated inflammatory parameters, anaemia, thrombocytopenia), with the involvement of the skin (purpura, ulceration, blisters with secondary haemorrhaging), kidneys (glomerular nephritis with acute renal damage), upper respiratory tract (nose, paranasal sinuses, glottis, subglottic area of the larynx), lower respiratory tract (inflammation of the bronchial mucosa, inflammatory pulmonary tumours, interstitial pulmonary lesions), and gastrointestinal tract (erosive gastritis).

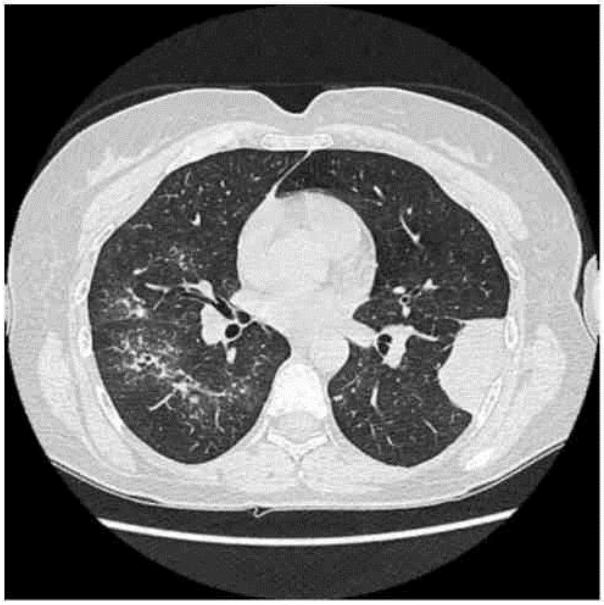

Figure 2. HRCT of the chest before treatment: tumours, ground-glass opacity, suspicion of alveolar hemorrhage
Rycina 2. HRCT klatki piersiowej przed leczeniem: zmiany guzowate, obszary mlecznej szyby, podejrzenie krwawienia pęcherzykowego

According to the scales in use, the disease activity was scored 33 points BVAS (Birmingham Vasculitis Activity Score version 3), and 17 points on a shortened BVAS/WG scale (Birmingham Vasculitis Activity Score for Wegener's Granulomatosis).

Immunosuppressive treatment following the CYCLOPS regimen, i.e. gluccocorticosteroids and cyclophosphamide, was introduced in the remission induction phase. Initially, intravenous methylprednisolone was administered (3 x 1,000 mg), then the treatment was continued with oral preparation, prednisone, at the initial dose of 1 mg/kg b6/d. A total of 10 pulses of cyclophosphamide was administered intravenously, 750 mg each, with mesna, at intervals following the CYCLOPS regimen.

During the treatment, the patient's general condition improved, the skin and articular lesions disappeared, ulceration in the nasal cavities healed (but the feeling of congestion and chronic sinusitis persisted), haemoptysis disappeared, pulmonary lesions decreased (the ground-glass lesions disappeared, the size of the inflammatory tumour decreased to 30 x 40 mm, the satellite nodules disappeared [Fig. 3.]), cANCA levels were reduced to 13 IU/ml, the inflammatory markers normalised, haematuria disappeared and proteinuria decreased to 1.1. g/d, and the renal parameters were reduced to the level of G3aA3 stage of chronic renal disease: creatinine concentration 1.1 mg/dl, urea concentration 50 mg/dl, eGFR according to MDRD 58 ml/min/1.73 m^2.

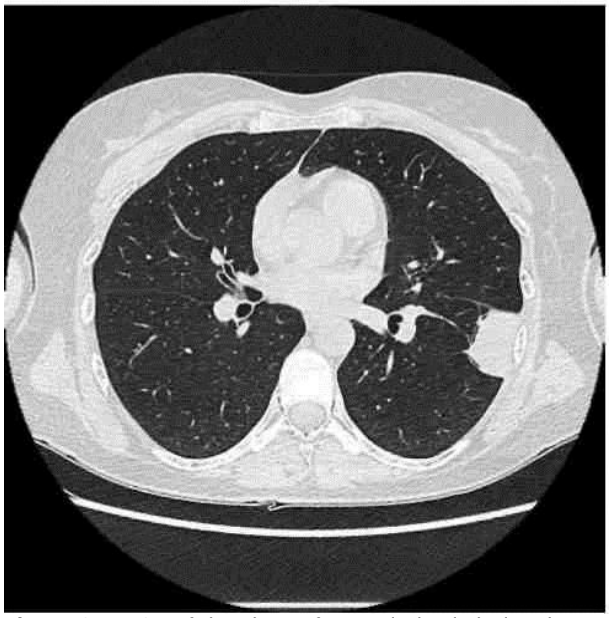

Figure 3. HRCT of the chest after remission-inducing therapy: reduction of tumour size, resolution of interstitial lesions
Rycina 3. HRCT klatki piersiowej po leczeniu indukcyjnym: redukcja zmian guzowatych, zanik zmian śródmiąższowych

The diagnosis of chronic renal disease was confirmed by increased cistatin C concentration 1.51 mg/l (normal range: 0.53-0.95 mg/l) and with the glomerular filtration index calculated based on cistatin C clearance, using simplified Hoek's formula: $eGFR_{Cysc}$ 49 ml/min/1.73 m^2.

After the treatment inducing and consolidating remission, i.e. after six months, the disease activity was assessed using the scales: BVAS - 3 point (fixed changes: invasion of the paranasal sinuses, proteinuria >0.2 g/d), shortened BVAS/WG scale - 2 points (fixed changes: invasion of the paranasal sinuses, inflammatory lung tumour), VDI (Vasculitis Damage Index) - 3 points (nasal congestion, chronic sinusitis, proteinuria >0.5 g/d).

For the past three months, the patient has been receiving supportive treatment with 2 x 75 mg of azathioprine and15 mg/d of prednisone.

Discussion

Systemic vasculitis may be manifested in various forms. Therefore, before patients with GPA are properly diagnosed, they often visit different specialists with non-specific symptoms. The presented case illustrates that patients may look for the help of a dermatologist, internist, pulmonologist, surgeon, haematologist, rheumatologist or nephrologist.

Since organs are affected by the disease at different times, the clinical picture is non-specific, which often makes diagnosis very difficult [4-7]. Accurate diagnosis is the starting point of treatment lasting several months or even years. Choosing the right management strategy is of key importance. Initially, in the remission induction and consolidation phase, the standard treatment involves gluccocorticosteroids (GCS) and cyclophosphamide (CYC), in the most severe cases accompanied by plasmapheresis, i.e. therapeutic plasma exchange (TPE).

In the described case, patient qualification for plasmapheresis raised doubts. TPE is indicated in rapidly progressing glomerulonephritis (RPGN), and diffuse alveolar haemorrhage (DAH).

In the described case, due to rapidly progressing renal impairment, suggestive of RPGN, and haemoptysis, which could be indicative of alveolar haemorrhage, the patient was a potential candidate for plasmapheresis. As DAH was not confirmed in imaging tests or bronchoscopic examination, and renal parameters did not increase after steroid therapy (maximum creatinine concentration was 1.9 mg/dl), therapeutic plasma exchange was dismissed. A diagnostic renal biopsy performed later revealed the presence of advanced, non-active lesions, which confirmed that the adapted treatment strategy was correct.

The inducive GCS+CYC therapy may be conducted according to three regimens [9, 10]:

- standard – six intravenous pulses of cyclophosphamide at a dose of 0.75 g/m^2 bsa, administered at 4-week intervals,
- CYCLOPS – ten intravenous pulses of cyclophosphamide at a dose of 15 mg/kg bw, initially administered at 2-week intervals, then every 3 weeks;
- optionally – cyclophosphamide administered orally at a dose of 2 mg/kg bw.

In the described case, the CYCLOPS immunosuppressive treatment, dedicated for moderately severe generalised granulomatosis with polyangitis (i.e. without life-threatening symptoms), was associated with better control over the patient's condition.

Frequent hospitalisations due to the cyclophosphamide administration regimen allowed for comprehensive monitoring of the patient with the very active disease, affecting many organs, particularly with respect to the renal function, haemoptysis and anaemia. In the course of treatment, it appeared that after the first two pulses of cyclophosphamide following the CYCLOPS regimen the renal function started improving gradually, and anaemia subsided.

Modification of the steroid therapy was a deviation from the CYCLOPS regimen in the described case. The rate of GCS dose reduction was lower than according to the regimen, due to severe disease activity, which raised doubts about the excessively rapid reduction of prednisone.

Summary

CYCLOPS demonstrated effectiveness in inductive treatment in the patient with highly active generalised granulomatosis with polyangitis manifested by general symptoms, affecting numerous organ systems, with high levels of inflammatory markers and high immunological activity.

ANCA-associated vasculitis has different clinical manifestations and varied courses. The clinical picture is

different in each patient. AAV often "disguise" as other diseases, which makes it possible for any specialist to see a patient with developing systemic vasculitis. Therefore, all specialists should maintain clinical vigilance, in particular with patients presenting non-specific symptoms affecting many organ systems, so as not to overlook granulomatosis with polyangitis in the differential diagnosis.

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Serious renal biopsy complication overlapping systemic lupus erythematosus flare – case report

Ciężkie powikłanie diagnostycznej biopsji nerki nakładające się na ostrą fazę tocznia rumieniowatego układowego – opis przypadku

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Abstract. Percutaneous renal biopsy is a relatively safe diagnostic procedure. It is believed that severe hemorrhagic complications occur in approximately 7% of cases, and only about 0.3% require radiological or surgical intervention, including nephrectomy. The article presents the case of a 22-year-old female with a severe complication of renal biopsy as retroperitoneal hemorrhage, performed during initially unrecognized systemic lupus erythematosus flare. After the biopsy, the patient required urgent life-saving endovascular intervention.
Key words: systemic lupus erythematosus, renal biopsy, superselective embolization

Streszczenie. Diagnostyczna biopsja nerki jest zabiegiem względnie bezpiecznym. Uważa się, iż do poważnych powikłań krwotocznych dochodzi w około 7% przypadków i tylko w około 0,3% wymagają one interwencji radiologicznej lub chirurgicznej, z nefrektomią włącznie. W artykule przedstawiono przypadek 22-letniej pacjentki z ciężkim powikłaniem biopsji nerki w postaci krwotoku do przestrzeni zaotrzewnowej, nałożonym na wstępnie nierozpoznany ciężki rzut tocznia rumieniowatego układowego. Po biopsji chora wymagała pilnej, ratującej życie interwencji wewnątrznaczyniowej.
Słowa kluczowe: toczeń rumieniowaty układowy, biopsja nerki, superselektywna embolizacja

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Background

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease. The kidneys in the course of SLE are affected in 60% of patients (in 25-50% at the moment of diagnosis), which increases the risk of renal failure, cardiovascular diseases and death. The renal symptoms vary from limited, asymptomatic proteinuria to rapidly progressive glomerulonephritis. Nephrotic proteinuria is found in 45-65% of cases [1].

Neither clinical symptoms, nor laboratory or serological test results allow to predict the abnormalities revealed in the histopathological examination of renal bioptate. Therefore, the symptoms of renal involvement in the form of proteinuria > 500 mg/d, especially in the presence of active urinary sediment, are indications for diagnostic kidney biopsy in SLE patients. The procedure should be performed within a month since the disease onset, preferably before the immunosuppressive treatment [2].

Percutaneous renal biopsy has been the key diagnostic tool for over 60 years. In this period, a lot has been improved in the renal biopsy procedure, which allows to collect proper material for histopathological examination in over 98% of cases [3-5]. However, a diagnostic renal biopsy (DRB) is sometimes associated with complications. The most common ones, observed in over 30% of cases,

include haemorrhaging due to blood vessel injury caused by the biopsy needle [3-7]. Nevertheless, the intervention of a radiologist or surgeon is required very rarely, only in 0.3% of cases [3, 9].

Case study

The study presents the case of a patient with an initially undiagnosed SLE flare, who experienced a serious haemorrhaging complication after a diagnostic renal biopsy, which required radiological intervention and embolization.

A 22-year-old patient with suspected SLE was admitted to the Department of Nephrology at the Military Institute of Medicine for diagnostics and treatment. On admission, the patient's overall general condition was good. She reported pain in the ankle joints and small joints of the hands and feet, persisting for approximately 2 months, with a rash that disappeared spontaneously a few months before admission. Antinuclear antibodies (ANA) determined in ambulatory conditions by indirect immunofluorescence at a titre of 1:640. The physical examination revealed regular cardiac activity of approximately 70/min., with a tendency for bradycardia in the course of a day, arterial pressure RR 140/90 mmHg, normal vesicular murmur over the lungs, soft abdomen, without pain or pathological resistance, limited oedema around the ankle joints. In the laboratory tests the following abnormalities were found: pancytopenia, ESR of 50 mm/h, potassium concentration of 5.5 mmol/l, creatinine concentration of 1.0 mg/dl, eGFR >90 ml/min/1.73 m^2; total protein concentration of 5.8 g/dl, albumin concentration of 2.5 g/dl. In urinalysis: proteinuria 500 mg/dl with active urinary sediment, in daily urine sample proteinuria 9.0 g/d was observed. Additionally, reduced concentrations of complement compounds C_3 - 22 mg/dl and C_4 <2 mg/dl were found. The results of ELISA immunoenzymatic assay revealed positive antinuclear antibodies (ANA) with a ratio of 3.5; anti-dsDNA (double-stranded DNA) antibodies were also demonstrated at 451 IU/ml. No ANCA (antineutrophil cytoplasmic antibodies) or APLA (antiphospholipid antibodies) were found. The images of lungs and heart in the thoracic X-ray examination were normal. Abdominal ultrasound revealed two hyperechogenic lesions in the liver, corresponding kidneys of normal size, with increased cortical echogenicity, without focal lesions or signs of urinary stasis. Based on the tests performed, the patient was diagnosed with systemic lupus erythematosus with renal involvement. Due to high immunological activity, intravenous pulses of methylprednisolone were administered, 500 mg each, for 3 consecutive days.

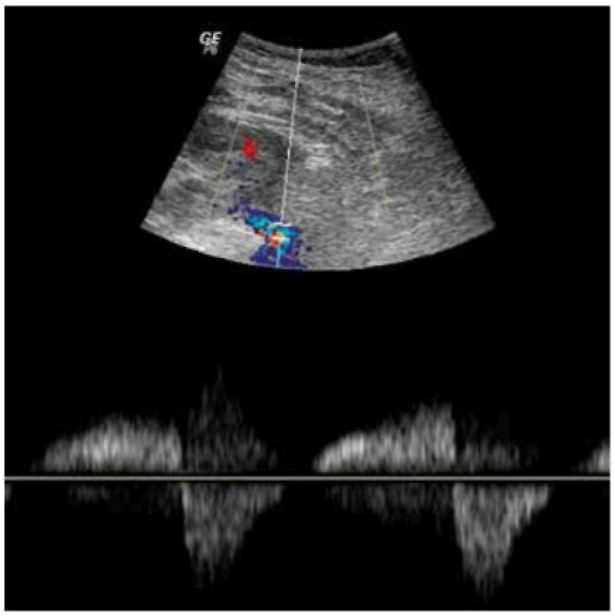

Figure 1. Renal hemorrhage – ultrasound image of turbulent bidirectional flow in retroperitoneum
Rycina 1. Krwotok nerkowy – ultrasonograficzny obraz zaburzonego dwukierunkowego przepływu w przestrzeni zaotrzewnowej

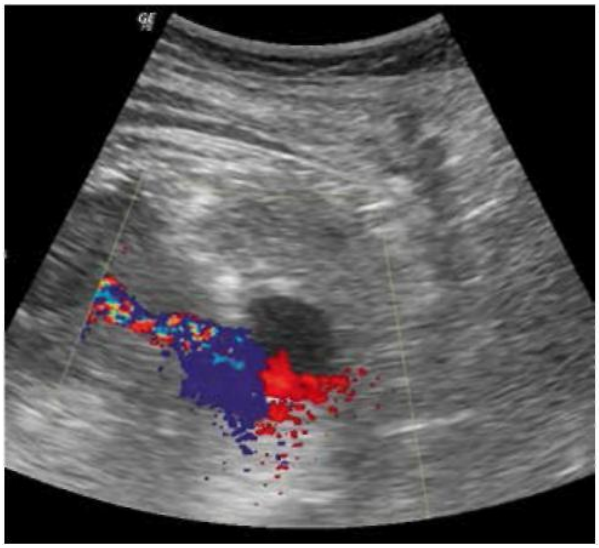

Figure 2. Renal hemorrhage – ultrasound image of pseudoaneurysm in retroperitoneum to aneurysms
Rycina 2. Krwotok nerkowy – ultrasonograficzny obraz pseudotętniaka w przestrzeni zaotrzewnowej

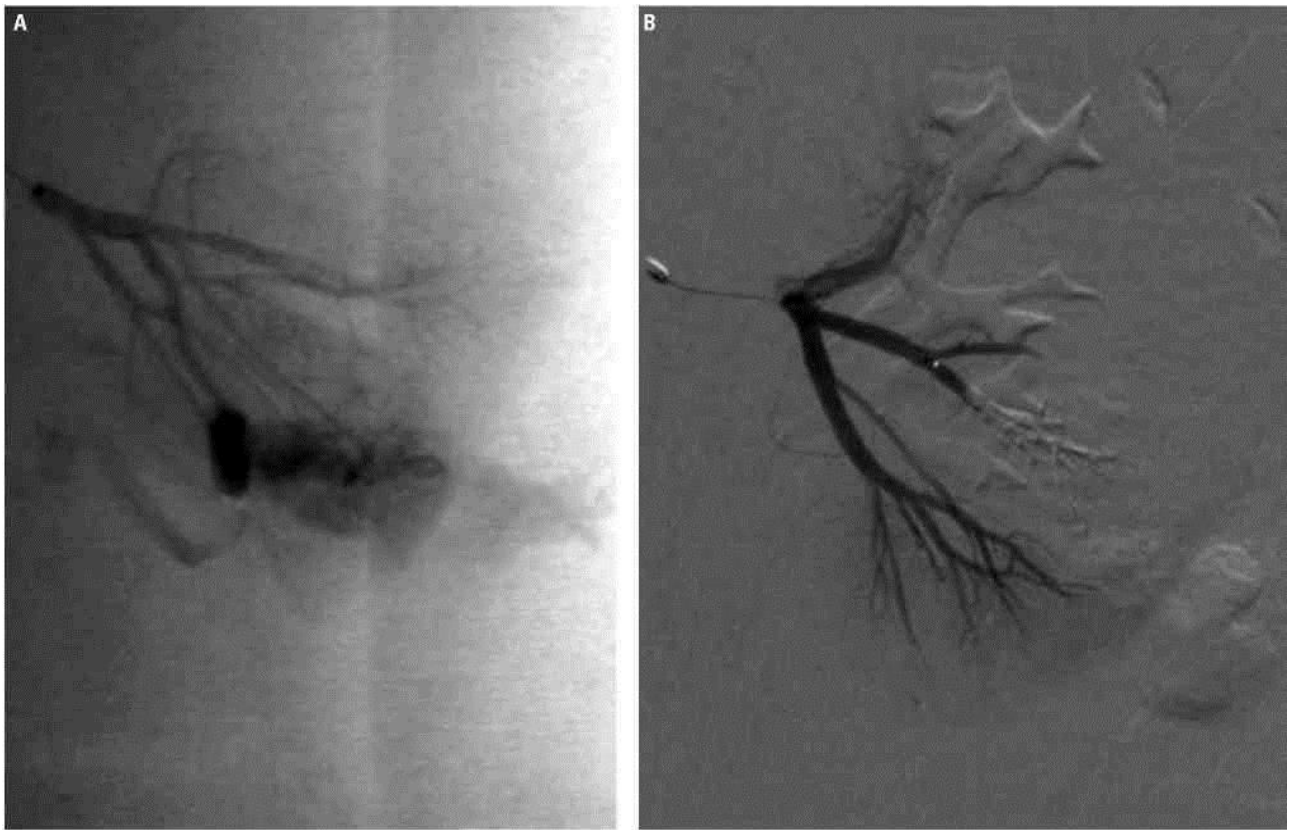

Figure 3. Selective angiography of the lower pole of left kidney. A. Hemorrhage from a subsegmental artery. B. Hemostasis after subsegmental artery embolization
Rycina 3. Selektywna angiografia dolnego bieguna nerki lewej. A. Krwotok z tętnicy subsegmentalnej. B. Hemostaza po embolizacji tętnicy sub-segmentalnej

The patient was qualified for diagnostic renal biopsy, to which the patient gave an informed consent. The ultrasound-controlled biopsy was performed using a device with an automatic needle release mechanisms (BARD MAGNUM Reusable Core Biopsy System, CR BARD Inc.), and the material was collected form the lower pole of the left kidney. After DRB, haematuria was observed, and the patient reported increasing distension pain in the left middle abdomen. An urgent abdominal ultrasound examination revealed active haemorrhage from the lower pole of the left kidney into the peritoneal area (Fig. 1.), probably along the biopsy channel, ending with a pseudoaneurysm of 23 x 23 mm (Fig. 2.).

The patient was urgently qualified for an endovascular procedure. Superselective angiography of the renal artery with embolization of the subsegmental artery to the lower pole of the left kidney was performed, without any significant complications, and haemostasis was obtained (Fig. 3.).

Diuresis was maintained at approximately 3,000 ml/d, and haematuria gradually subsided. Due to post-haemorrhagic anaemia with HGB of 6 g/dl, three units of packed red blood cells (PRBC) were transfused. On the first day following the renal biopsy, deterioration of the kidney function was observed (creatinine concentration of 1.4 mg/dl). A control ultrasound examination of the abdominal cavity revealed ascites and fluid in both pleural cavities, as well as pararenal haematomas in the left retroperitoneum. Despite intensive conservative therapy of the renal failure and antibiotic therapy (ceftriaxone, ciprofloxacin and metronidazole), in the following days the acute renal damage progressed and the creatinine concentration increased to a maximum of 3.2 mg/dl, eGFR increased to 19 ml/min/1.73 m^2, oliguria and massive peripheral oedema occurred (body weight increased by 10 kg). The clinical picture indicated a rapidly progressive glomerulonephritis in the course of SLE. Unfortunately, the result of the histopathological test of the renal biopsy material had no diagnostic value (the cells were collected from the renal medulla). Due to a severe disease course and loss of kidney function, three other pulses of methylprednisolone were administered, 1,000 mg *i.v.* each, and the treatment was continued orally. The patient was qualified for therapeutic plasma exchange (TPE). Five TPE procedures were performed in total, resulting in improved renal function (creatinine concentration of 1.4 mg/dl, urea concentration of 120 mg/dl), and diuresis of approximately 2-2.5 l/d. During TPE, the patient required a transfusion of additional three units of PRBC. Due to elevated inflammatory markers (CRP 9.2 mg/dl,

procalcitonin 0.33 ng/ml), a thoracic HRCT examination was performed, revealing fluid in both pleural cavities, and parenchymal densities in the left lung. Levofloxacin and aciclovir were introduced, resulting in an improvement. After elimination of the sources of infection, immunosuppressive treatment with cyclophosphamide was implemented, to induce a disease remission. Intravenous infusions of 500 mg of Endonax were administered (six infusions at 2-week intervals). During the hospitalisation, the patient's general condition and renal function improved. Renal replacement therapy was not necessary.

Discussion

Systemic lupus erythematosus with renal involvement is a systemic disease with a potentially aggressive course; therefore, it requires fast and possibly accurate therapeutic decisions. The type of immunosuppressive therapy should be based on the renal biopsy results, and lead to a complete remission (proteinuria of <0.5 g/d with normal or close to normal renal function), and minimise the adverse effects of the treatment [8].

With time, technical advancement increased the safety of the procedure, thus reducing the risk of death due to DRB from 0.12 to 0.02% [3, 5]. In the 1980s, real-time ultrasonographic imaging was introduced. The biopsy needle was also improved. However, DRB is still associated with a risk of complications.

The most common ones are haemorrhagic complications, observed in up to 30-96% of cases [3-7]. Most of them are pararenal and subcapsular haematomas and haematuria. Pseudoaneurysms or arteriovenous fistulas are found much less often. Most haemorrhagic complications are clinically mute, and disappear spontaneously [4-7], but in over 7% of cases serious, life-threatening haemorrhagic complications occur. Among the most frequent ones is anaemia associated with blood transfusion, whereas approximately 0.3% of cases are complications which require radiological (angiography, embolization) or surgical intervention, including nephrectomy [3, 9].

Numerous authors attempted to determine what increases the risk of post-biopsy complications. Well-established risk factors for haemorrhagic complications following renal biopsy include increased creatinine concentration, uncontrolled arterial pressure and prolonged bleeding, none of which were found in the described case [5, 6, 9]. Other authors also mention age and sex, prolonged aPTT (activated partial thromboplastin time), acute tubular necrosis, autoimmune diseases such as vasculitis of SLE, the number of renal biopsies and amyloidosis [4, 6, 9]. Despite the attempts to identify the patients at high risk of complications following a renal biopsy, it is impossible to determine whether complications will occur, and if they are going to be life-threatening. Therefore, a careful patient observation for at least 24 hours after the kidney biopsy is necessary [5].

In the discussed case, a very rare DRB in the form of active haemorrhage was observed. The SLE diagnosis was definitely an important risk factor. The severe course of the disease was due to the complications following the renal biopsy, as well as the unrecognised flare of the disease. Administration of the first series of methylprednisolone pulses probably falsified the clinical picture of the developing flare, and the biopsy was performed when the disease was starting to exacerbate, which increased the risk of complications. On the other hand, in the described case it is possible that the flare was induced by the stress caused by the biopsy and its complications. Such an order of events is supported by normal renal function prior to the biopsy, and its gradual deterioration after the procedure. In the described case, the endovascular embolization of the interlobar renal artery was necessary as a life-saving procedure.

Embolization of damaged renal vessels has been performed for 50 years; however, great advancement in intervention radiology enabled using superselective catheters for angiography, which makes the method safe, effective and competitive with the surgical procedure. Complications of embolization are rare. A specific complication of this procedure consists in infarction of the parenchyma supplied by the closed artery, associated with subsequent deterioration of the renal function. The literature reports that using less selective embolization methods was associated with large infarctions, covering 30-50% of the total renal parenchyma, whereas superselective techniques led to smaller infarctions, covering 0-15% of the renal parenchyma [10, 11].

Due to high effectiveness of the procedure, few complications and fast restoration of haemostasis, superselective embolization should be considered as the method of choice in acute renal haemorrhage.

In the described case, superselective embolization of an intrarenal artery was performed, but the renal parameters increased already on the day of the procedure. Kidney ischaemia is the main risk factor in impaired renal function following embolization, but the harmful effect of the contrast agent administered during angiography should be considered. In some reports, an increased creatinine concentration during embolization was mentioned, which was attributed primarily to massive haematuria and possible obstruction of the urine flow by blood clots. The nitrogen retention parameters normalised within a week to a month after an effective embolization procedure [10, 20].

In the presented case a rapid deterioration of renal function and oliguria were observed, despite the conservative treatment. The natural course of the underlying disease, overlapping with the period of DRB complications and potential complications of the treatment, complicated the patient's clinical situation. However, the entire clinical picture indicated a rapidly progressive glomerulonephritis in the course of systemic lupus erythematosus as the primary cause of the organ dysfunction. A non-diagnostic result of the histopathological examination of the renal biopsy material further complicated the situation. Although in several studies TPE did not demonstrate significant benefits regarding improved renal function and survival in induction

treatment, in particularly severe SLE forms with renal involvement, especially accompanied by the symptoms of central nervous system involvement, some authors recommend using this procedure [13, 14]. In the described case, glucocorticoid therapy, supported with therapeutic plasma exchange procedures, allowed to improve the patient's renal function and clinical status.

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Pulmonary-renal syndrome in the course of systemic anti-neutrophil cytoplasmic antibodies associated vasculitis

Zespół płucno-nerkowy w przebiegu układowego zapalenia naczyń związanego z ziarniniakowatością i obecnością przeciwciał antyneutrofilowych

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Abstract. Pulmonary-renal syndrome (PRS) is a combination of diffuse alveolar hemorrhage and glomerulonephritis. Its etiology is diverse but the majority of cases are related to ANCA-associated vasculitis. The most characteristic symptoms are hemoptysis and rapidly progressing glomerulonephritis. Treatment consists in induction of remission by application of cyclophosphamide, corticosteroids and, in particular cases, carrying out plasmapheresis. The paper presents a case of a 55-year-old female with massive alveolar hemorrhage and acute renal failure. The patient underwent initial treatment with-cyclophosphamide, according to the CYCLOPS trial, corticosteroids and plasmapheresis. This case proves that the PRS may be a life-threatening systemic disease. Its treatment must be individualized and require considerable experience from the attending physician.
Key words: pulmonary-renal syndrome, ANCA, rapid progressive glomerulonephritis

Streszczenie. Zespół płucno-nerkowy (PRS) to współistnienie rozlanego krwawienia do pęcherzyków płucnych i kłębuszkowego zapalenia nerek. Etiologia jest różnorodna, jednak do rozwoju PRS dochodzi najczęściej w wyniku ANCA-zależnych samoistnych zapaleń naczyń. Najbardziej charakterystyczne objawy to krwioplucie i gwałtownie postępujące kłębuszkowe zapalenie nerek. Leczenie polega na indukcji remisji poprzez podanie cyklofosfamidu, glikokortykosteroidów oraz, w szczególnych przypadkach, zastosowania plazmaferez. W pracy przedstawiono przypadek 55-letniej pacjentki z masywnym krwawieniem do pęcherzyków płucnych i gwałtownie pogarszającymi się parametrami funkcji nerek. Wdrożono terapię cyklofosfamidem według schematu CYCLOPS, glikokortykosteroidami oraz zastosowano plazmaferezy. Przypadek pacjentki dowodzi, iż zespół płucno-nerkowy może być stanem zagrożenia życia, a jego leczenie powinno być zindywidualizowane i wymaga dużego doświadczenia ze strony lekarza prowadzącego.
Słowa kluczowe: zespół płucno-nerkowy, ANCA, gwałtownie postępujące kłębuszkowe zapalenie nerek

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Background

Pulmonary renal syndrome (PRS) is a combination of diffuse alveolar haemorrhage and glomerulonephritis.
The first case was described in 1919 by Goodpasture. The symptoms of pulmonary-renal syndrome are directly caused by injuries of small blood vessels in the lungs and kidneys, in different mechanisms [1]. Although the first case report discussed a patient with antiglomerular basement membrane antibodies (anti-GBM), in majority of

cases PRS is associated with spontaneous ANCA-associated vasculitis, e.g. granulomatosis with polyangiitis [2]. The incidence is 8.5/million (5.2 - 12.9/million), with similar frequency in both sexes [3]. The symptoms of the syndrome vary, and they include both respiratory and renal symptoms. Sudden dyspnea, oliguria, anaemia and shadows in the thoracic x-ray image are the most common clinical indications of PRS, but they lack specificity [4]. The treatment principles presented in the KDIGO (Kidney Disease Improving Global Outcomes) guidelines divide the management into remission induction, maintenance treatment, and treatment of relapses [5]. As a life-threatening condition, PRS requires detailed diagnostics and prompt implementation of therapy, which improves prognosis and reduces mortality rates [6]. This study presents the case of a patient with severe pulmonary-renal syndrome.

Case study

A 55-year-old patient was urgently admitted to the Department of Internal Diseases, Nephrology and Dialysis of the Military Institute of Medicine due to massive haemoptysis with respiratory failure which occurred three days before reporting to the hospital. The subfebrile condition, night sweating and articulomuscular pain had persisted for three months. Therefore, the patient was diagnosed at the rheumatological department, and the diagnosis was rheumatic polymyalgia. Differential diagnosis included determination of anti-neutrophil cytoplasmic antibodies (ANCA). The patient did not receive the results. She had a history of hyperthyroidism in the course of nodular goitre, arterial hypertension, degenerative disease of the knee joints, condition after the hysterectomy and oophorectomy due to a malignant neoplasm of the uterus. Then, dysmorphic haematuria, subnephrotic proteinuria (0.722 g/d), normal parameters of nitrogen retention (creatinine concentration of 0.8 mg/dl [N <0.8 mg/dl], urea concentration of 43 mg/dl [N 15 – 36 mg/dl], hypoalbuminemia 3.3 g/dl [N 3.9 – 4.9 g/dl]), presence of anti-neutrophil cytoplasmic antibodies – anti-PR3 *(cytoplasmic ANCA* – c-ANCA). The physical examination revealed a moderate general condition, RR of 150/70 mmHg, regular cardiac function – 100/min., *tachypnoe,* SpO_2 without additional oxygen – 83%, bilateral multiple wheezing sounds over the lung fields on auscultation. Laboratory tests disclosed severe anaemia – haemoglobin concentration (Hgb) of 5.5 g/dl (N 11.0 – 18.0), mean corpuscular volume (MCV) – 79 fl (N 80-100 fl), haematocrit (HCT) – 19% (N 35-55%), elevated values of inflammatory markers: CRP *(C-reactive protein)* – 19.5 mg/dl (N 0-0.8 mg/dl), erythrocyte sediment rate (ESR) after 1h – 120 mm (N 0-12 mm), renal parameters elevated compared to the month before: creatinine concentration – 6.2 mg/dl, urea concentration – 142 mg/dl.

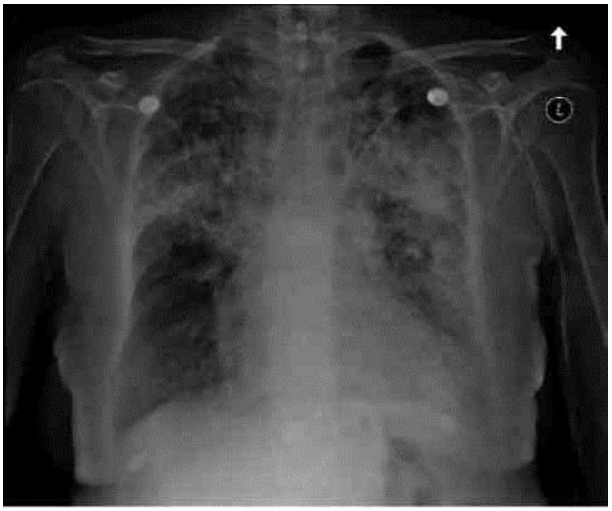

Figure 1. Chest X-ray PA-massive interstitial changes
Rycina 1. RTG klatki piersiowej PA-masywne zmiany śródmiąższowe

General urinalysis revealed active urinary sediment. As the abnormalities were suspected to have immunological basis, immunological tests were performed. No ANA (anti-nuclear antibodies), anti-dsDNA (antibodies against double-stranded DNA), anti-MPO (myeloperoxidase) antibodies (perinuclear ANCA – pANCA) were found, but the result of anti-PR3 determination was positive (63 IU/ml). In a review, thoracic x-ray small nodular densities were described, covering bilaterally the entire lung fields, with irregular shadowing of the left hilar upper pole, with small nodular densities in the apex of the right lung, the heart minimally enlarged, signs of stasis in the pulmonary circulation (Fig. 1.). High-resolution computed tomography (HRCT) examination demonstrated massive parenchymal densities in both lungs, merging shadows including the acini, less pronounced in the lower lobes – the image corresponded to alveolar haemorrhage (Fig. 2.). Due to a positive titre of anti-PR3 antibodies determined four weeks before (the results were obtained from the rheumatological department), the patient was diagnosed with pulmonary-renal syndrome induced by granulomatosis with polyangiitis.

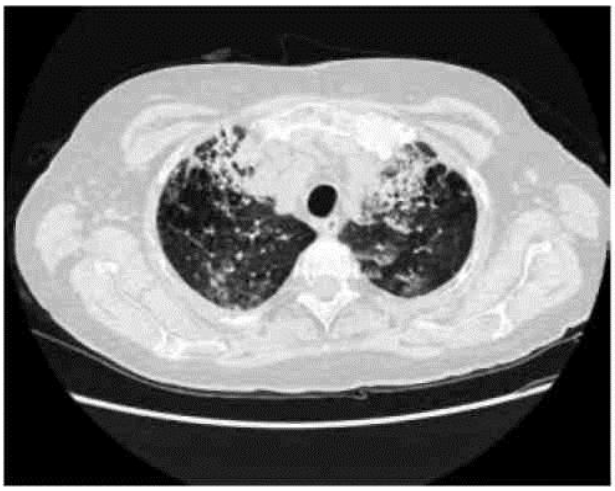

Figure 2. HRCT-massive interstitial densities in both lungs, pulmonary hemorrhage picture
Rycina 2. HRCT klatki piersiowej - masywne zagęszczenia miąższowe w obu płucach - obraz odpowiada krwawieniu do pęcherzyków płucnych

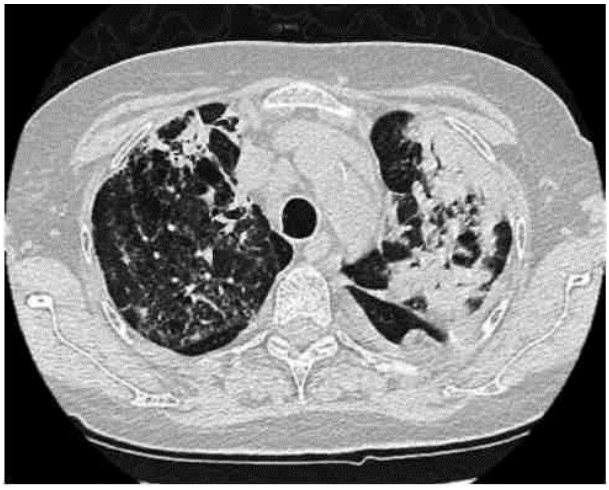

Figure 3. Chest HRCT-intensified lesions consistent with ground-glass opacity and diffuse alveolar hemorrhage
Rycina 3. HRCT klatki piersiowej - nasilenie zmian o charakterze mlecznej szyby i rozlanego krwawienia dopęcherzykowego

The patient's clinical condition deteriorated. The respiratory failure increased. Intensive treatment was applied. Therapy was started without current results of anti-neutrophil antibodies assay. Infusions of methylprednisolone were administered (5 g in total). Then, the treatment was converted to oral prednisone at 1 mg/kg b.w. Simultaneously, symptomatic therapy of alveolar haemorrhage was implemented. Eight units of fresh frozen plasma (FFP) were administered, together with ethamsylate, tranexamic acid, and due to increasing respiratory disorders, a non-invasive supportive treatment with continuous positive airway pressure (CPAP) was introduced. Due to anuria, exacerbating peripheral oedema and increasing parameters of renal failure (maximum creatinine concentration – 6.5 mg/dl, maximum urea concentration – 162 mg/dl), a sharp left femoral catheter was implanted, and renal replacement therapy by haemodialysis (HD) was initiated.

To intensify the causal treatment, as the patient's condition was critical and required respiratory therapy, she was qualified for therapeutic plasma exchange (TPE) – plasmapheresis. Five sessions of TPE were performed, difficult from the technical point of view due to pronounced haemorrhagic diathesis. The necessity to use heparin increased anaemia and alveolar haemorrhage (Fig. 3). Simultaneously, cyclophosphamide (CYC) therapy was introduced, following the CYCLOPS regimen (3, 7]. Severe anaemia in the course of alveolar and nasopharyngeal haemorrhage required a transfusion of 12 units of packed red blood cells (PRBC) and 8 units of FFP.

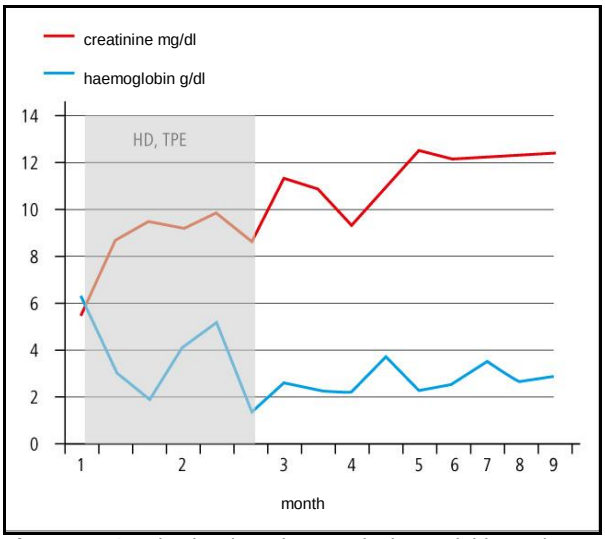

Figure 4. Graph showing changes in hemoglobin and serum creatinine overtime
Rycina 4. Wykres przedstawiający zmiany stężenia kreatyniny oraz hemoglobiny w czasie

As a result of the treatment, the patient's general condition improved, dyspnea and haemoptysis disappeared, diuresis systematically recovered, the renal parameters decreased and the haemoglobin concentration stabilised. The patient needed only 9 HD procedures. Figure 4 presents changes in creatinine and haemoglobin concentrations over 9 months of follow-up.

The patient was discharged in a relatively good general condition after 26 days of hospitalisation, without the need for HD procedures.

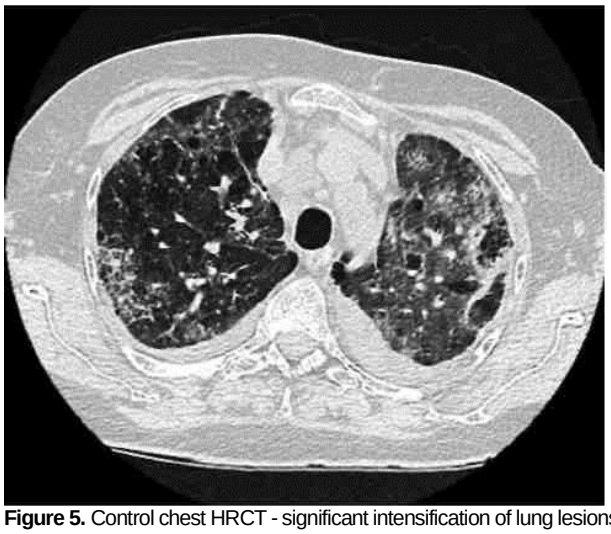

Figure 5. Control chest HRCT - significant intensification of lung lesions - areas of ground-glass opacity parenchymal densities, fibrotic and fibrous-atelectatic lesions, emphysemic, bronchiectatic peribronchial thickening. Swollen lymph nodes
Rycina 5. Kontrolne HRCT klatki piersiowej - znaczne nasilenie zmian płucnych - obszary zagęszczeń miąższowych typu matowej szyby, zmiany włókniste i włóknisto-niedodmowe, rozedmowe, rozstrzeniowe, zgrubienia okołooskrzelowe. Powiększone węzły chłonne

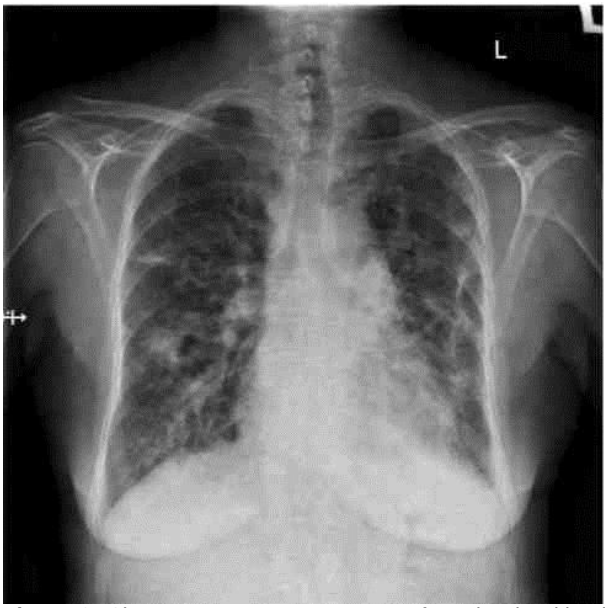

Figure 6. Chest X-ray. Numerous areas of patchy densities in both lung fields
Rycina 6. RTG klatki piersiowej. Liczne plamiste obszary zagęszczeń w obu polach płucnych

After almost two weeks, the patient returned to the hospital due to increasing paroxysmal dyspnea, light-headedness, palpitations, increased thirst and asymmetrical oedema of the lower limbs. The patient denied thoracic pain, loss of consciousness, disuric symptoms, fever and haemoptysis.

The physical examination revealed individual wheezes over the lung fields. The diuresis was 2.6 – 2.7 l/d. The differential diagnosis of dyspnea included a number of additional tests. The laboratory tests did not disclose pronounced anaemia: Hgb 13 g/dl. The inflammatory markers: WBC (white blood cells) – 16.56 thousand/ml (N 4.0 – 11.0 thousand/ml), neutrophil smear (NEUT absolute value): 15.16 thousand/ml (N 1.9 – 8.0 thousand/ml), CRP 4.3 mg/dl, and procalcitonin concentration – 0.7 ng/ml (N <0.3) were elevated. Extended coagulogram revealed: D-D concentration – 6.74 µg/ml (N 0.00-0.50 µg/ml), fibrinogen concentration – 554 mg/dl (N 200-400 mg/dl), without other abnormalities. The renal failure did not exacerbate; creatinine concentration was 2.6 mg/dl (the value was stable compared to previous hospitalisation). General urinalysis did not show signs of urinary tract infection. Urine culture demonstrated growth of *Escherichia coli* and *Klebsiella pneumoniae* ESBL+ *(extended-spectrum beta-lactamases).* Anti-PR3 antibodies concentration was lower than at the end of the previous hospitalisation – 5.7 IU/ml. The tests revealed significantly increased value of N-terminal pro b-type natriuretic peptide (NT-proBNP) – 27,261.0 pg/ml (N <222.0 pg/ml).

Thoracic x-ray demonstrated multiple patchy areas in both lung fields (Fig. 5.). HRCT revealed significantly increased pulmonary lesions, compared to the previous tests. Ground-glass opacity parenchymal densities, fibrotic, emphysemic and bronchiectatic lesions, peribronchial thickening and small quantities of fluid in the pleural cavities were found (Fig. 6.). Transthoracic echocardiogram (TTE) revealed small quantities of pericardial fluid, mitral and tricuspid valve insufficiency, and signs of pulmonary hypertension: pulmonary trunk enlarged to 3 cm, with moderate insufficiency of the tricuspid valve, and tricuspid insufficiency pressure gradient of 55 mm Hg.

An extensive differential diagnosis did not provide a clear information about the main cause of dyspnea in the analysed case. Therefore, antibiotic therapy with imipenem 2 x 1 g was initiated (the dose adjusted to the current eGFR) for 14 days. Intravenous diuretics were also introduced, and prednisone administration was continued. As it was impossible to exclude pulmonary embolism (high risk of contrast-induced nephropathy and poor general condition of the patient prevented pulmonary perfusion scintigraphy), low molecular weight heparin was administered at a therapeutic dose: enoxaparin 2 x 40 mg.

Table 1. Causes of pulmonary-renal syndrome
Tabela 1. Przyczyny zespołu płucno-nerkowego

frequent	
ANCA-associated spontaneous vasculitis microvasculitis granulomatosis with polyangiitis eosinophilic granulomatosis with polyangiitis	60-70%
disease induced by anti-GBM	15-25%
rare	
other vasculitis or connective tissue diseases drug-induced vasculitis with ANCA: penicillamine, hydralazine, propylthiouracil Henoch-Schonlein purpura vasculitis in the course of cryoglobulinemia systemic lupus erythematosus systemic sclerosis rheumatoid arthritis mixed connective tissue disease antiphospholipid syndrome	10%
other, non-immunological causes of PRS: thrombotic thrombocytopenic purpura and haemolytic uremic syndrome cholesterol embolism	5%
the most common diseases imitating PRS infections: atypical bacteria, Hantavirus, leptospirosis virus, HIV, neoplasms: mostly of the lungs and the lymphatic system pulmonary embolism circulatory failure drug hypersensitivity syndromes	

The treatment improved the clinical condition and reduced the inflammatory markers. After 14 days of antibiotic therapy with imipenem, another pulse of CYC was administered (750 mg). The CYCLOPS remission inducing treatment was continued. In total, 7.75 g of CYC was administered. The dose of prednisone was gradually reduced. Next, maintenance treatment with mycophenolate mofetil (MMF) was introduced, and well tolerated.

Discussion

The study presents a case of a 55-year-old patient with severe PRS due to granulomatosis with c-ANCA-associated polyangiitis. The patient presented typical symptoms of pulmonary-renal syndrome, such as alveolar haemorrhage, manifested by massive haemoptysis, and associated respiratory failure. Moreover, the signs of rapidly progressive glomerulonephritis were observed. Initially, only mild symptoms were present (fever, articular pain, and haematuria). The described severe flare of the disease required an intensive immunosuppressive therapy. Immediate introduction of steroids, plasmapheresis and CYC resulted in remission. Each TPE procedure was associated with a high risk of haemorrhagic complications, thus requiring lower heparin doses and administration of fresh frozen plasma. The discussed case illustrates how varied and rapid the image of the pulmonary-renal syndrome can be.

Summary

Pulmonary-renal syndrome is usually caused by systemic vasculitis. It is a life-threatening condition. Prompt diagnostics is crucial to exclude other conditions. The aim of the initial treatment is to obtain possibly fast remission. Both preliminary diagnostics and the assessment of the response to treatment require extensive experience and individual approach to each patient. The patients should be referred to centres where a team of experienced specialists can be found.

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Evolution of organizational structures of tactical unit health service in Polish Armed Forces at the turn of 20th and 21st centuries

Ewolucja struktur organizacyjnych służby zdrowia Związku Taktycznego (ZT) Sił Zbrojnych RP (SZ RP) na przełomie XX i XXI wieku

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Abstract. Since the beginning of the 1950s, the Polish Army has been through different changes regarding manpower and organizational structures. These changes also took place in the Military Health Service. New organizational structures of medical units were realising tasks focusing on maintaining an appropriate level of health in the army, enabling a suitable level of combat readiness. The reform of organizational structures of the Military Health Service at the beginning of 21st century, separating brigade health services from military units and change in the medical service funding, had a negative impact on the performance of tasks to be fulfilled by these units.
Key words: military health service, level of medical support

Streszczenie. Wojsko Polskie od początku lat 50. XX wieku przechodziło różnego rodzaju zmiany dotyczące liczebności stanów osobowych oraz struktur organizacyjnych. Zmiany te zachodziły również w wojskowej służbie zdrowia (WSZ). Nowo powstałe struktury organizacyjne pododdziałów i oddziałów medycznych realizowały zadania, szczególny nacisk kładąc na utrzymanie odpowiedniego stanu zdrowia wojsk, który pozwalał na utrzymanie gotowości bojowej na odpowiednim poziomie. Przeprowadzone na początku XXI wieku reformy struktur organizacyjnych WSZ, wydzielające służbę zdrowia brygad poza jednostki wojskowe, oraz zmiana zasad finansowania usług medycznych negatywnie wpłynęły na realizację zadań stojących przed tą służbą.
Słowa kluczowe: wojskowa służba zdrowia, poziom zabezpieczenia medycznego

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Introduction

The condition for implementation of the motto included in the introduction is the possession of certain capabilities by the Polish Armed Forces (PAF) within the scope of performing tasks, as well as the level of completion and the possibility of smooth development of their potential. Considering the above, the Polish Armed Forces should at a time of peace maintain the necessary level of operational capability, ensuring border integrity, and at a time of a small-scale armed conflict – the defence of the state with the defence capability focused on a single operational direction [1].

Combat readiness of the Polish Armed Forces is affected by the degree of completeness of general military and logistic detachments and units, including the military health service.

The military health service has been and continues to be responsible for the medical support of the PAF, taking care of physical and mental condition of the soldiers, and therefore it is responsible for maintenance of combat strength. Proper fulfilment of these tasks depends on the performance of particular activities within the scope of:

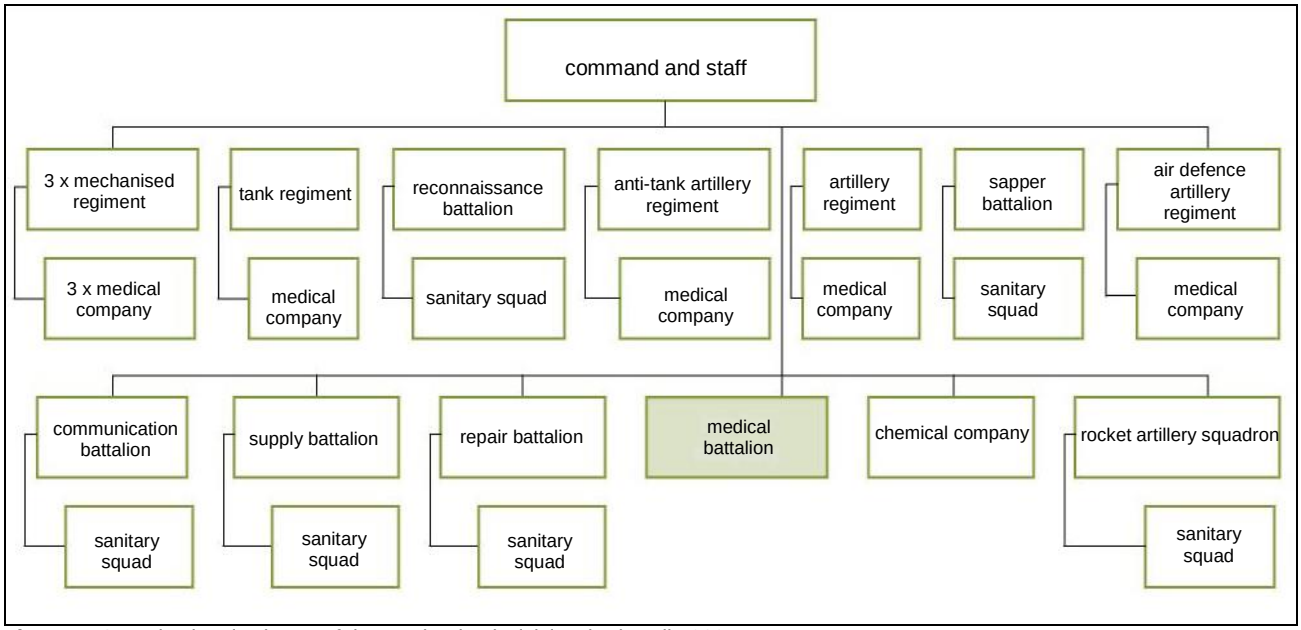

Figure 1. Organizational scheme of the Mechanized Division (DZ) until 1989
Rycina 1. Schemat organizacyjny dywizji zmechanizowanej (DZ) do roku 1989

- medical evacuation support,
- hygiene, sanitary and anti-epidemic support,
- sanitary support against weapons of mass destruction (WMD)
- supply of equipment and medical materials,
- health service management,
- sanitary training,
- keeping medical documentation [2].

In the analysed time period, the Polish Armed Forces and military health service functioned in different political, military and economic conditions, which to a certain degree influenced the performed tasks and organizational structures of the Polish Armed Forces. Experience gained in that time should shape and improve the system of medical support, but not all of this influence has been and is favourable in the opinion of the authors.

It should be taken into account that medical support is governed by principles, which assume:

- the compatibility of assistance with the International Humanitarian Law of Armed Conflict (IHLAC),
- the observance of ethical rules,
- the observance of the highest standards stemming from available medical knowledge and experience acquired during the provision of medical assistance,
- the well-being and needs of patients,
- the observance of the time requirements for medical support,
- the continuity, stages and consequentiality of medical assistance based on the four levels of medical support,
- the proportionality of forces and resources of the health service to the needs,
- multinationality – the possibility of using the personnel, medical materials and procedures of different members of a coalition [3].

History

After the end of World War II until the early 1950s, the number of personnel in the Polish Army was maintained at a high level and starting in 1953 it was gradually reduced, which is why the organizational structures of military units and detachments have changed. Until 1989, the Polish Armed Forces were dominated at the tactical level by the divisional structure (Fig. 1.) [4]. Divisions consisted of tank and mechanised regiments; depending on the ratio of tank regiments to mechanised regiments they were respectively called armoured or mechanised divisions. Health service at the level of a division was represented by a medical battalion (Fig. 2.) [5].

The personnel in the medical battalion numbered 188 people, including 24 physicians of the following specialties:

- 1 Organisation of the Military Health System (OMHS),
- 13 surgeons.

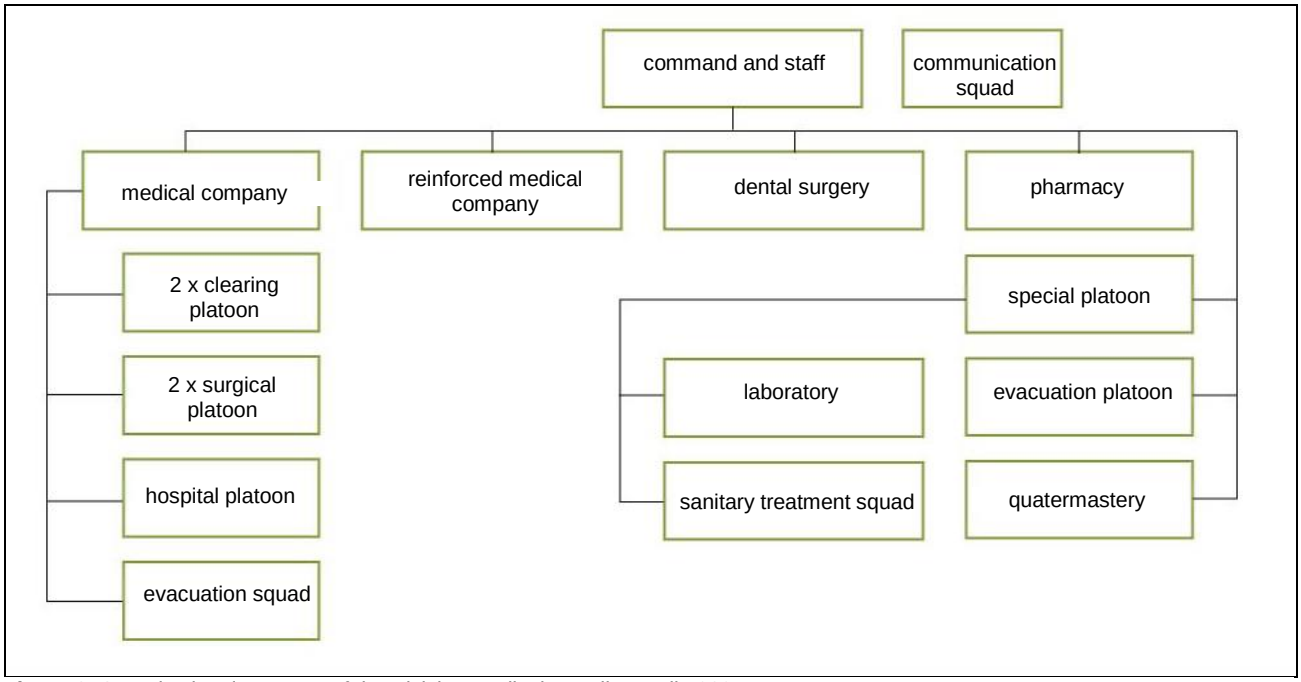

Figure 2. Organizational structure of the Division Medical Battalion until 1989
Rycina 2. Struktura organizacyjna batalionu medycznego dywizji do roku 1989

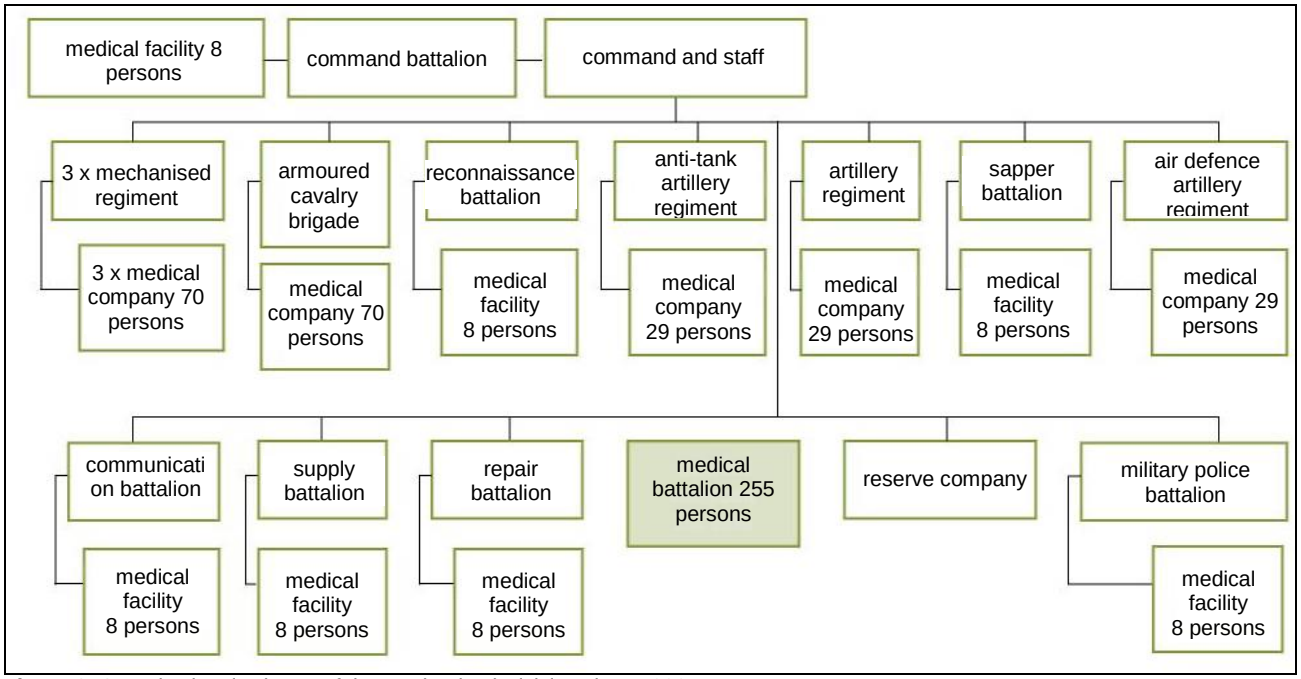

Figure 3. Organizational scheme of the Mechanized Division since 1996
Rycina 3. Schemat organizacyjny dywizji zmechanizowanej od roku 1996

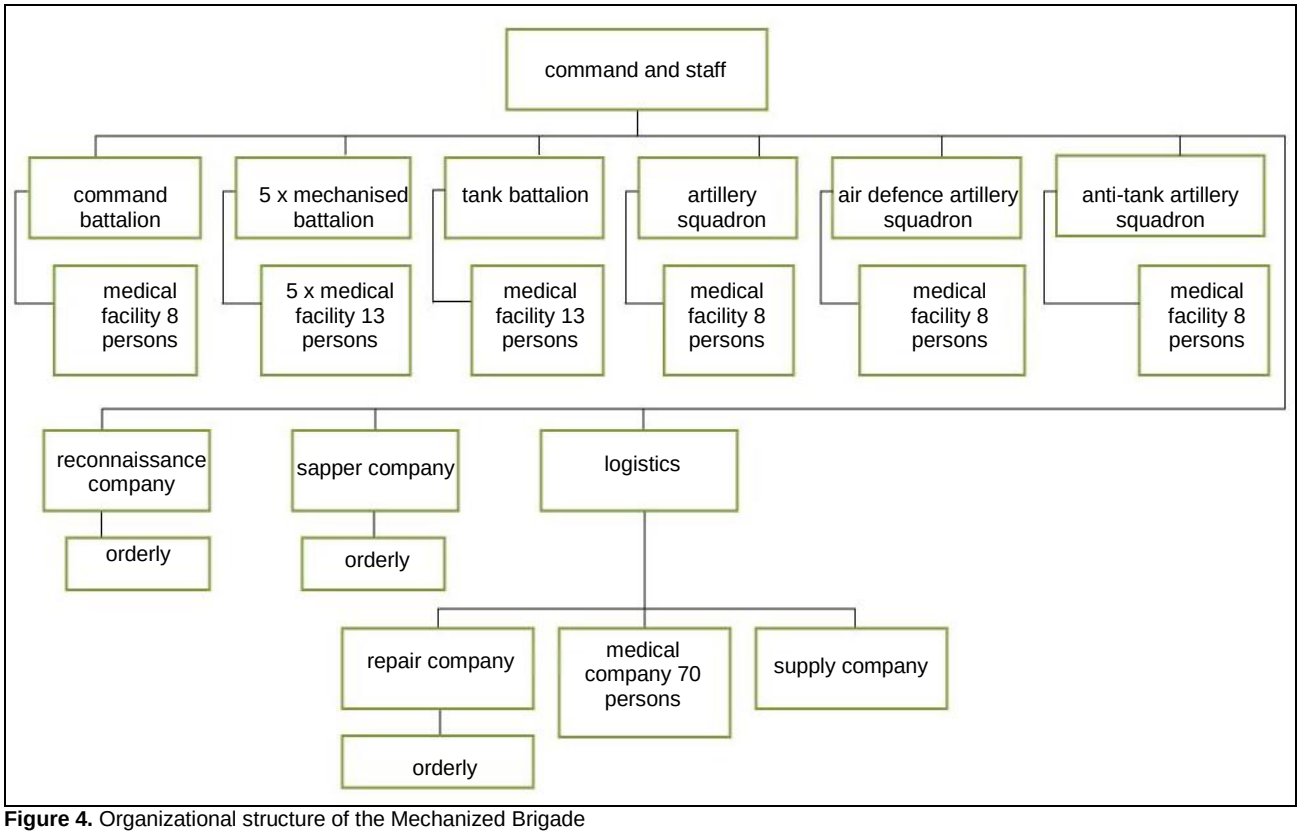

Figure 4. Organizational structure of the Mechanized Brigade
Rycina 4. Struktura organizacyjna brygady zmechanizowanej

- 2 anaesthesiologists,
- 3 internists,
- 1 general practitioner,
- 1 epidemiologist,
- 1 microbiologist,
- 1 toxicologist,
- 1 dentist.

In times of peace, the battalion, partly developed, functioned as a small military hospital, and during combat operations it developed a Divisional Medical Facility (DMF), provided qualified medical assistance to the injured and ill within a system of medical evacuation support for combat operations, and within the framework of health service support for regiments it could also isolate an additional reinforcement medical company from its ranks.

In mechanised and tank regiments there was an 11-person medical company which during combat operations developed the Regiment Medical Facility (RMF), providing medical assistance in a medical evacuation system, and in battalions – sanitary squads providing premedical aid. On the battlefield, first aid was provided according to the principles of self-aid, mutual aid or aid provided by an orderly.

After 1989, the number of division personnel decreased from 15 to 9, armoured divisions were liquidated and replaced with mechanised divisions. Units and detachments of military health service remained in unchanged structures.

In the mid-1990s, another change in the organizational structure of a division was implemented – mechanised regiments were replaced with mechanised brigades and tank regiments were replaced with an armoured cavalry brigade (Fig. 3. and Fig. 4.) [6].

This change also affected the military health service – organizational structures of all units and detachments changed. The 188-person medical battalion was replaced with a 255-person medical battalion (Fig. 5.). [2]

It consisted of 35 physicians of different specialties,

- 4 Organisations of the Military Health System,
- 18 surgeons,
- 6 anesthesiologists,
- 2 internists,
- 1 epidemiologist,
- 1 toxicologist,
- 1 microbiologist.

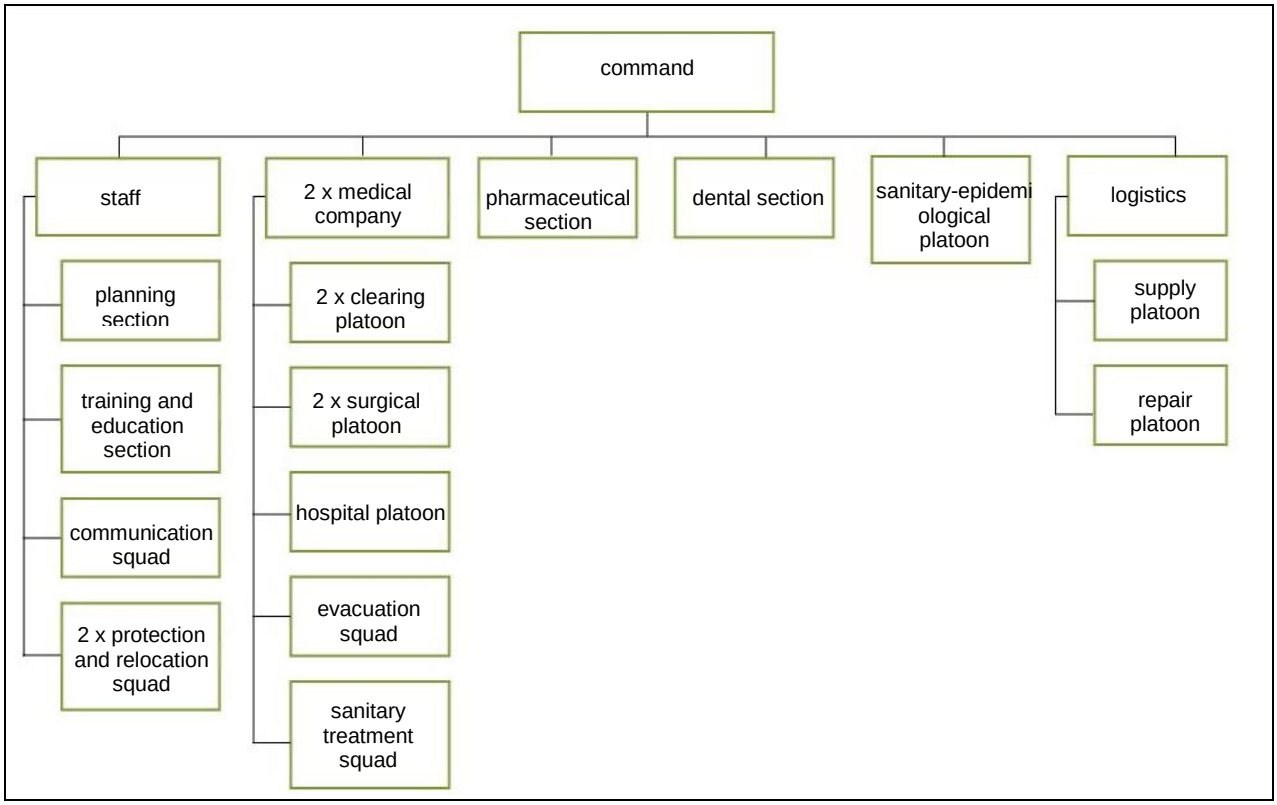

Figure. 5. Organizational structure of the Mechanized Division Medical Battalion
Rycina 5. Struktura organizacyjna batalionu medycznego dywizji zmechanizowanej

- 1 radiation protection,
- 1 dentist,

as well as nursing personnel consisting of 29 nurses and auxiliary personnel.

During combat operations the battalion could develop two independent Divisional Dressing Stations (DDS) in the directions of operation of first-line brigades, providing qualified medical assistance profiled as surgery and internal medicine, depending on the tactical and medical situation within the following scopes: full, narrow and limited to life-saving indications.

Due to an increase in the number of personnel of the brigades in comparison with the number of personnel of regiments, the number of personnel of a medical company of a brigade increased, which in the new structures consisted of 70 people (Fig. 6), including:

- 13 physicians of different specialties (7 surgeons, 3 anesthesiologists, 1 epidemiologist, 1 toxicologist, 1 dentist),
- a pharmacist,
- a laboratory assistant,
- 9 nurses (2 dressing nurses, 4 operating theatre nurses, 3 general nurses).

The task of a medical company was to develop a Brigade Dressing Station (BDS) and provide qualified medical assistance of the same type and within the same scope as in the case of a DDS.

Medical platoons consisting of 13 persons were created in mechanised and tank battalions with 2 physicians, whereas in other battalions and divisions there were medical platoons consisting of 8 persons with a single physician. These detachments formed parts of battalions and divisions, with the task of providing first medical aid in the course of combat operations.

Present day

In 1999, Poland became a member of the North Atlantic Treaty Organisation (NATO). Membership in the North Atlantic Alliance has not resulted in serious organizational changes in the military health service at the tactical level. Changes that occurred mainly concerned names, elements of medical doctrine and some of the standards of medical support; however, they have not changed the generally adopted principles of functioning of the military health service.

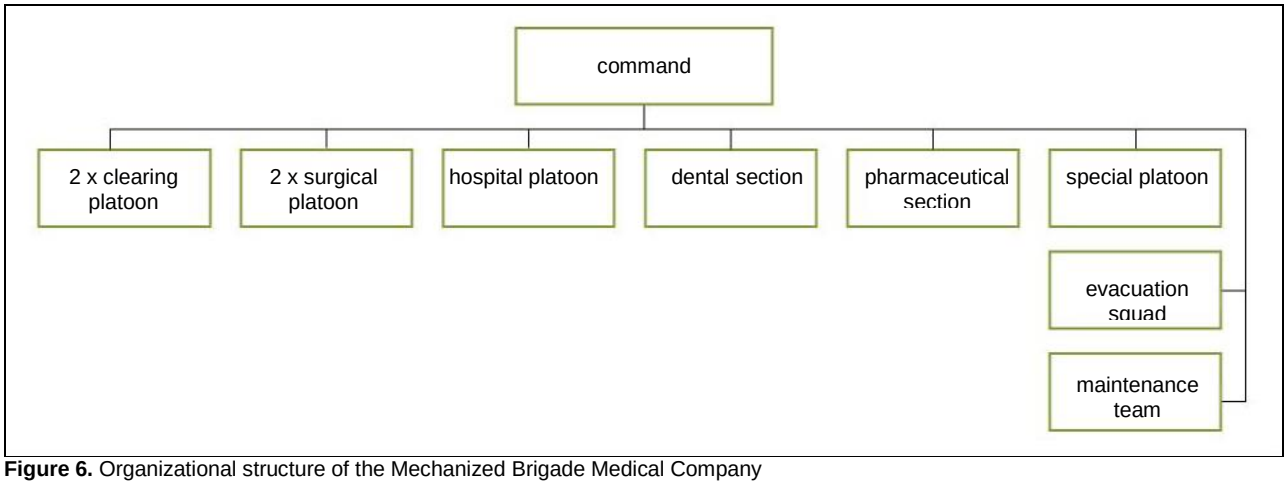

Figure 6. Organizational structure of the Mechanized Brigade Medical Company
Rycina 6. Struktura organizacyjna kompanii medycznej Brygady Zmechanizowanej (BZ)

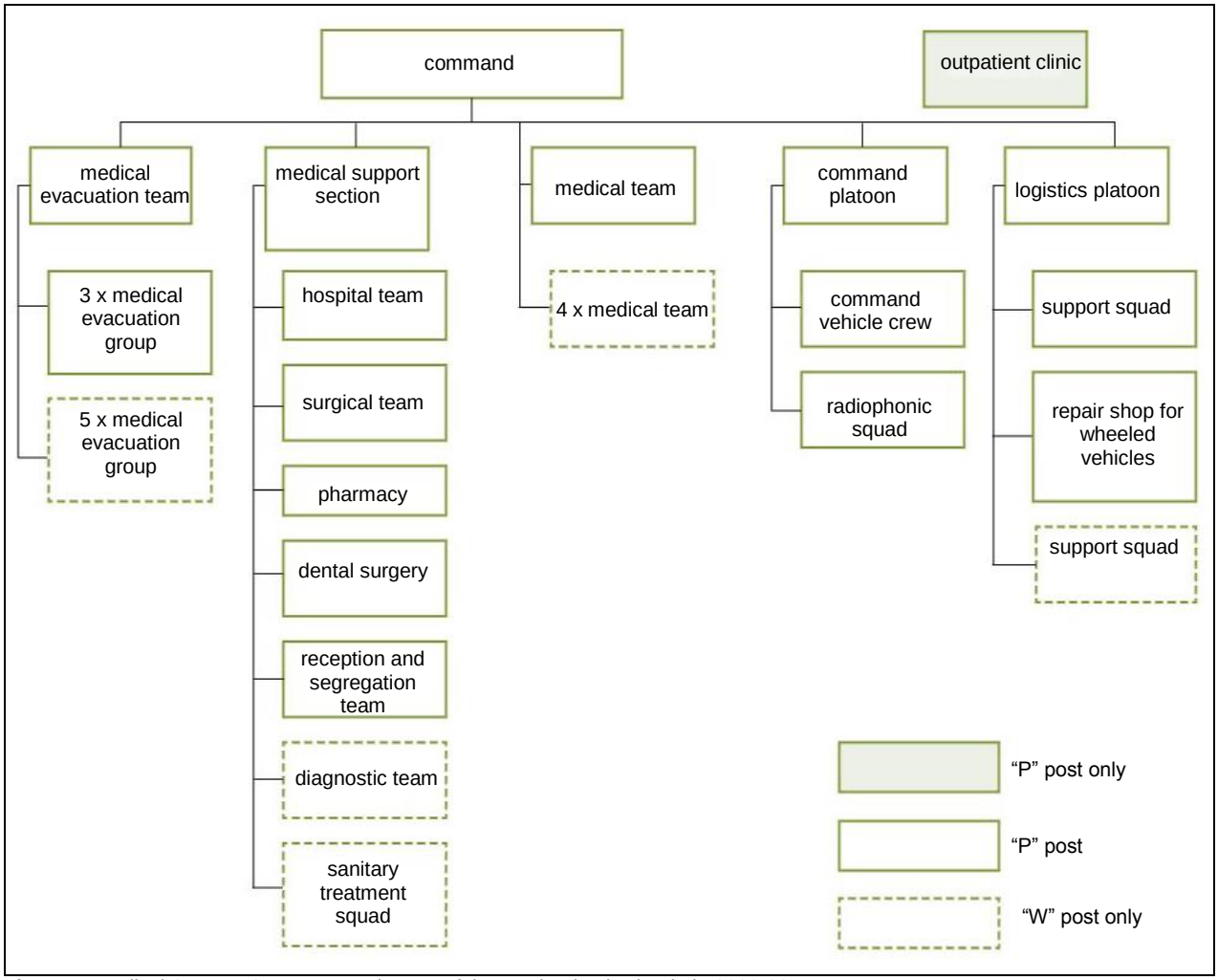

Figure 7. Medical Support Group as an element of the Mechanized Brigade in 2006-2011
Rycina 7. Schemat organizacyjny Grupy Zabezpieczenia Medycznego BZ w latach 2006-2011

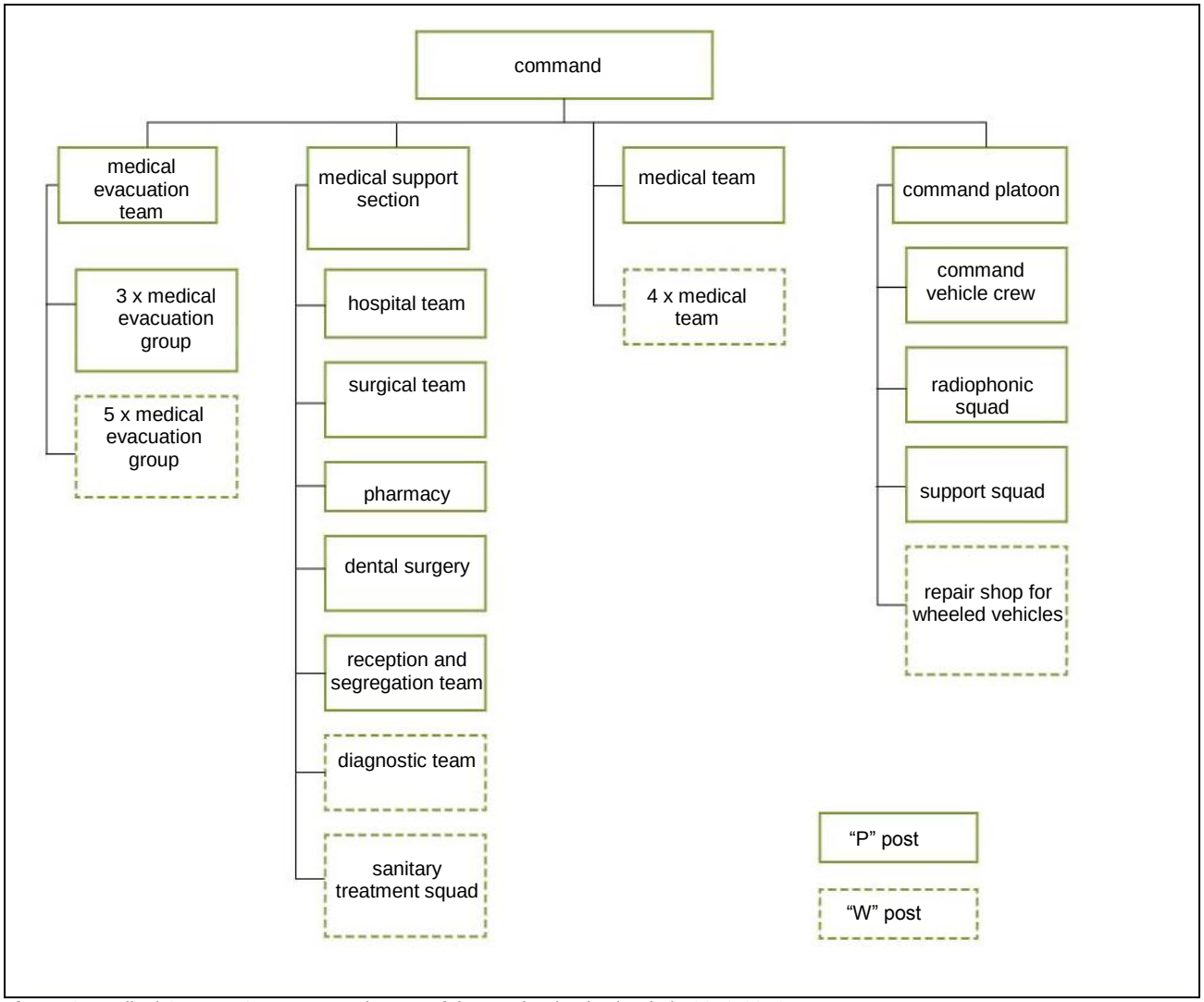

Figure 8. Medical Support Group as an element of the Mechanized Brigade in 2013-2016
Rycina 8. Schemat organizacyjny Grupy Zabezpieczenia Medycznego BZ w latach 2013-2016

For the military health service, the early 21st century symbolises the fall of military-medical education. In 2002, the Bolesław Szarecki Military Medical Academy in Łódź, which was the only one in Poland to educate medical personnel for the needs of the Polish Armed Forces, was dissolved. The previous system of obtaining medical personnel ceased to function. Medical education for the needs of the military was initiated by the Military Medical Faculty at the freshly established Medical University of Łódź. Liquidation of the university coincided with the liquidation of healthcare funds, including the funds of uniformed services. These changes fundamentally affected the inflow of new medical personnel to the military health service, as well as the functioning of the military health service in a military unit.

The years of 2006-2007 mark a period of further significant structural changes in tactical unit military health service.

Due to the dwindling number of medical personnel in the Mechanised Division, the medical battalions were dissolved. It was assumed that a Mechanised Division would be supported by a military field hospital, acting on the 3rd level of medical support.

In the Mechanised Brigade, the detachments of the military health service were grouped in Medical Support Groups (MSG [Fig. 7]).

The main task of the newly established units was 1st and 2nd level medical support to the Mechanised Brigade detachments and units. Medical detachments forming MSG, referred to as medical teams of the 1st and 2nd level, were meant to be assigned to general military detachments for the time of performance of a combat mission. In the years 2006-2011, MSG was positioned with a brigade, including an outpatient clinic and healthcare

institution authorisation, comprehensively supporting a military unit. The wide availability of the provided services had a positive influence on functioning and performance of all the planned tasks. Functioning within the structures of a brigade ensured proper harmonisation and development of medical personnel for the time of mobilisation and war. However, the scope of medical services and duties was transferred to the Military Support Unit, which crippled the process of medical support for brigades.

In 2011-2013, the Outpatient Clinic of the Medical Support Group with an Infirmary was isolated from the establishment of MSG to a brigade's establishment and subordinated to a brigade commander, and in 2013 entirely removed from the structures of a brigade [7]. From 2013, MSGs were placed under the command of military field hospitals in Bydgoszcz and Wrocław without the introduction of changes, which only extended the line of command, support and cooperation with the command of the brigades (Fig. 8.).

The reformation of MSG into an independent military unit, without isolating establishments of the chief of staff, personnel section, operational and logistic section, shows that this decision was unconsidered, lacked imagination and care for the maintenance of operational capability of the established structures of the MD and MSG. It seems that only the return of MSG to brigade structures would allow for comprehensive fulfilment of health service tasks in the process of planning, training and functioning within the framework of a single component and eliminate the problems related to the organisation of mobilisation and achievement of readiness of MSG to take action in war structures.

Detachments and units of the military health service have formed an integral part of general military detachments and units, only the subordination of the head of the health service changed, directly to the commander or the logistician. Irrespective of the functional relations between the medical and logistic areas, the subordination and direct access of the head of the health service to the commander is the most favourable solution, in accordance with the provisions of the document of the NATO Military Committee - MC 326/3: NATO Principles and Policies of Medical Support. Such placement of health service would definitely facilitate the fulfilment of tasks assigned to the military health service and security of the process of training and harmonising detachments of a military unit. Any organizational changes are only reasonable if they lead to improvement of the already functioning system. Another motivation for the implementation of changes seems nonsensical and harmful from the point of view of the organisation it pertains to.

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Polish Armed Forces paramedic qualifications under State Medical Rescue Act regulations and requirements of contemporary battlefield medicine

Uprawnienia ratownika medycznego Sił Zbrojnych RP w kontekście zapisów ustawy o Państwowym Ratownictwie Medycznym i wymogów współczesnej medycyny pola walki

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Abstract. The Act of 25 September 2015 on amending the State Medical Rescue Act, the Act on Medical Activity and the Act amending the Act on Medical Activity and some other acts, has introduced a number of significant amendments extending the qualifications of paramedics. Pursuant to the amendment, paramedics received the right to practice their profession within the structures of the Polish Armed Forces, and not, as to date, only on the basis of the State Medical Rescue. The new legal regulations have had a major impact on the range of the medical support for soldiers during their service in peacetime and on a battlefield. To answer the question if the received rights are sufficient for pre-hospital care of the wounded soldiers, they were compared to medical standards described in guidelines of Tactical Combat Casualty Care (TCCC), considered worldwide as the gold standard in the battlefield care for wounded. At the same time, the paper is an attempt to implement the TCCC guidelines in Polish conditions, where the scope of medical support is limited by the State Medical Rescue Act.
Key words: State Medical Rescue, Tactical Combat Casualty Care, health services other than medical rescue activities

Streszczenie. Ustawa z dnia 25 września 2015 r. o zmianie ustawy o Państwowym Ratownictwie Medycznym, ustawy o działalności leczniczej oraz ustawy o zmianie ustawy o działalności leczniczej oraz niektórych innych ustaw wprowadziła szereg istotnych zmian umożliwiających rozszerzenie uprawnień ratowników medycznych. Na mocy nowelizacji ratownicy medyczni otrzymali uprawnienia do wykonywania swojego zawodu w strukturach Sił Zbrojnych RP, a nie jak do tej pory tylko w warunkach systemu Państwowego Ratownictwa Medycznego (PRM). Nowe uregulowania prawne mają duży wpływ na zakres zabezpieczenia medycznego żołnierzy w czasie służby zarówno w warunkach pokoju, jak i pola walki. Aby odpowiedzieć na pytanie, czy nadane uprawnienia są wystarczające do opieki przedszpitalnej nad rannym żołnierzem, odniesiono je do standardów postępowania zawartych w wytycznych Tactical Combat Casualty Care (TCCC), uznanych na świecie za „złoty standard" w pomocy rannym na polu walki. Jednocześnie praca jest próbą implementacji wytycznych TCCC do polskich warunków, w których uprawnienia ratowników medycznych są ograniczone zapisami ustawy o Państwowym Ratownictwie Medycznym.
Słowa kluczowe: Państwowe Ratownictwo Medyczne, Tactical Combat Casualty Care, świadczenia zdrowotne inne niż medyczne czynności ratunkowe

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Introduction

In order to fulfil the tasks of the State consisting in providing aid to every person faced with a sudden health risk pursuant to the State Emergency Medical Services Act of 8 September 2006, the system of State Emergency Medical Services (SEMS) was created. The act, as subsequently amended, defined the principles of organising, functioning and financing of this system. In its assumptions, the system of emergency medical services was based on units of a system composed of: emergency medical services teams (EMST), including air emergency medical teams (AEMT) and hospital emergency departments (HED). At the same time, to support the system, the act imposed the tasks of aiding people at sudden health risk within the scope of emergency medical services, in particular on: organisational units of State Fire Service, fire protection units included in the national fire and rescue system (KSRG), other units that are subordinated or supervised by the minister in charge of internal affairs and the minister of national defence. Fire-fighters and soldiers, to be able to perform these tasks, have been trained in providing qualified first aid, received the title of a paramedic, and the entities they serve in gained the status of units cooperating with the system. According to these regulations, the paramedics serving in the Polish Armed Forces could provide qualified first aid, that is if they had previously completed an appropriate course and received the title of a paramedic. The performance of medical rescue activities assigned to the paramedic profession was limited to civilian conditions within the SEMS system.

State Emergency Medical Services Act

The State Emergency Medical Services Act was the first document to sanction the paramedic profession [1]. It specified who can engage in this profession and what requirements have to be fulfilled within the scope of education. In the first version of the act, which entered into force on 1 January 2007, the paramedic profession – pursuant to Art. 11.1 – consisted in:

- ensuring the safety of persons at the place of event and undertaking actions to prevent an increase in the number of casualties or environmental degradation,
- evaluating the health condition of individuals faced with a sudden health risk, and performing medical rescue activities,
- transportation of individuals faced with a sudden health risk,
- communicating with the person faced with a sudden health risk and providing mental support in a situation of sudden health risk,
- organizing and teaching classes in first aid, qualified first aid and medical rescue activities.

The listed medical rescue activities were defined as health care services within the meaning of regulations on publicly funded health care services, provided by an emergency medical services team outside of hospital in order to rescue a person faced with a sudden health risk. In practice, this provision closed the door to paramedics, regardless of their qualifications, to engagement in this profession and the possibility of providing medical care within this scope outside the system of State Emergency Medical Services. The increasing popularity of the paramedic profession, increase in public trust and the increasing recognition of other professional groups dealing in widely understood emergency services led to paramedics being employed in the structures of State Fire Service, Police and the military, where it was recognised that their skills are useful in fulfilment of their own tasks. It is worth mentioning that the wording of Art. 11.1 fits perfectly the tasks that should be performed by a paramedic, both in the battlefield environment and during service in the Polish Armed Forces. According to the analysis of the Tactical Combat Casualty Care (TCCC) guidelines [2, 3], a paramedic soldier:

- can participate in combat and, if needed, respond with fire, attempt to protect the casualty from taking more damage, evacuate the casualty to a place providing cover and concealment, extract from burning vehicles,
- if the casualty cannot be reached at a given time, communicates with the injured, instructing the injured person what the person should do to provide first aid independently,
- in the course of care for the patient, assesses the patient's injuries and vital parameters, and therefore the patient's health condition, and implements appropriate medical interventions, e.g. external haemorrhage control, restoration of airway,
- after providing preliminary support to the injured soldier transports the casualty to an appropriate hospital.

Nevertheless, military paramedics were disregarded by the legislator and deprived of the capability of performing medical rescue activities. The side effect of this decision was a significant weakening of the potential of military health service, restriction on the practice of the profession and the statutory requirements of professional training, as well as a lower level of support for war operations and exercises. For example, in many cases, the support for exercises was provided with forces and means of private entities providing services within the scope of emergency medical services.

Professional tasks of a paramedic

The Act of 25 September 2015 on amending the State Medical Rescue Act, the Act on Medical Activity and the Act amending the Act on Medical Activity and some other acts [4] introduced a number of significant amendments extending the qualifications of paramedics, which currently also extend beyond the SEMS system. At the moment, engaging in the paramedic profession consists in fulfilment of professional tasks, particularly in:

- providing health care services, including medical rescue activities, independently or under the supervision of a physician,

- ensuring the safety of persons at the place of event and undertaking actions to prevent an increase in the number of persons faced with a sudden health risk,
- transportation of individuals faced with a sudden health risk,
- providing mental support in a situation causing a sudden health risk,
- health education and promotion of health.

In addition, pursuant to Art. 11.3, paramedics perform professional tasks:

- in healthcare institutions,
- within the framework of mountain and ski rescue (TOPR, GOPR),
- within the framework of water rescue (WOPR),
- within the framework of mine rescue,
- within the framework of maritime search and rescue service (SAR),
- in units subordinate to the minister of national defence that are not healthcare institutions,
- in units subordinate to the minister in charge of internal affairs that are not healthcare institutions, carrying out counter-terrorism operations,
- in fire protection units included in the national fire and rescue system (KSRG) within the scope of exercises, training and operations in hazard zones,
- at airports,
- within the framework of healthcare institutions, performing tasks within the scope of medical support for mass events,
- within the framework of ambulance transport,
- in sobering-up centres,
- in the position of a medical dispatcher.

Introduction of the amendment to the State Medical Rescue Act on the possibility of engaging in the paramedic profession in units subordinate to the minister of national defence that are not healthcare institutions is a landmark step, allowing fulfilment of tasks within the scope of emergency medical services in the Polish Armed Forces by this professional group. As the term “medical rescue activities”, in accordance with the wording of the act, was reserved to health care services provided by emergency medical services teams, the amendment contained an added new term – “health services other than medical rescue activities” – which refers to health care services provided by paramedics outside the SEMS system.

Health services other than medical rescue activities

Both the scope of medical rescue activities and health services other than medical rescue activities was described in detail in the Regulation of the Polish Minister of Health of 20 April 2016 on medical rescue activities and health services other than medical rescue activities that can be provided by paramedics [5]. The Regulation includes four appendixes:

- medical rescue activities that can be provided by a paramedic independently – specified in Appendix 1 to the Regulation,
- medical rescue activities that can be provided by a paramedic under the supervision of a physician in the system – specified in Appendix 2 to the Regulation,
- medical rescue activities other than medical rescue activities that can be provided by a paramedic independently – specified in Appendix 3 to the Regulation,
- medical rescue activities other than medical rescue activities that can be provided by a paramedic to order – specified in Appendix 4 to the Regulation.

Appendixes 3 and 4 pertain to paramedics performing tasks in units subordinate to the minister of national defence that are not healthcare institutions, therefore belonging to the personnel group of emergency medical services in the medical services specialty. Appendix 3 lists 29 health services that can be provided by military paramedics independently without the supervision of a physician. These are:

- assessment of patient condition,
- placing a patient in a proper position according to the patient's condition or injuries suffered,
- initiation and maintenance of basic and advanced cardiopulmonary resuscitation in accordance with current medical knowledge,
- restoration of airway without the use of devices,
- restoration and securing airway with the use of devices, in particular: oropharyngeal tube, nasopharyngeal tube, supraglottic devices, needle cricothyroidotomy,
- respiratory suction,
- initiation of active oxygen therapy or respiratory assistance or artificial lung ventilation by means of non-device and device methods, with the use of oxygen or air, including the use of a respirator,
- performing endotracheal intubation and maintenance of non-invasive ventilation in the event of sudden cardiac arrest,
- performing automated defibrillation,
- performing manual defibrillation based on an electrocardiogram or a cardiac monitor,
- monitoring of the respiratory function,
- monitoring of the circulatory function with non-invasive methods,
- recording and assessing an electrocardiogram,
- cannulation of peripheral veins and of external jugular vein,
- intraosseous access using a ready-to-use kit,
- administering drugs by intravenous, intramuscular, subcutaneous, oral, sublingual, inhalatory, intratracheal, rectal and intraosseous routes,
- reducing tension pneumothorax by puncture of the pleural cavity,
- collecting vein blood and capillary blood for diagnostic tests,
- wound care,
- external haemorrhage control,
- immobilization of fractures, sprains and twists,
- immobilization of the spine, especially the cervical segment,
- childbirth management,

- performing primary triage and secondary triage,
- catheterisation of the urinary bladder,
- measurement of core temperature,
- determination of critical parameters with the use of available equipment,
- preparing a patient for transportation and medical care during transportation,
- administering drugs listed in the table attached as an appendix to the regulation.

In comparison with Appendix 1, specifying medical rescue activities performed independently within the framework of the SEMS system, military paramedics have been deprived of the possibility of transcutaneous pacing in cases of bradycardias and cardioversion in cases of tachyarrhythmias. At the same time, the legislator allowed for independent collection of vein blood and capillary blood for diagnostic tests, as well as catheterisation of the urinary bladder.

Table 1. Medicines and life-saving activities
Tabela 1. Leki i czynności ratujące życie

TCCC guidelines	Ordinance to the SMR Act
analgesics	
meloxicam	ibuprofen
paracetamol	paracetamol
fentanyl lollipop	not specified
not specified	fentanyl
morphine	morphine
ketamine	not specified
other drugs	
naloxone	naloxone
ondansetron	metoclopramide
tranexamic acid	not specified
antibiotic therapy	
moxifloxacin	not specified
cefotetan	not specified
ertapenem	not specified
restoration of airway	
cricothyroidotomy	needle cricothyroidotomy
fluid resuscitation	
blood and its products	not specified

Within the scope of independent administration of drugs, the regulation allows all paramedics to administer 47 drugs in appropriate form independently. They are: acetylsalicylic acid (tablets), adenosine (solution for injection), amiodarone (solution for injection), atropine (solution for injection), sosorbide (tablets), budesonide (suspension for inhalation), captopril (tablets), clemastine (solution for injection), clonazepam (solution for injection), dexamethasone (solution for injection), diazepam (tablets, solution for injection, rectal infusion), drotaverine (solution for injection), adrenaline (solution for injection), fentanyl (solution for injection), flumazenil (solution for injection), furosemide (solution for injection), nitroglycerin (tablets, sublingual aerosol), glucagon (solution for injection), glucose 5% (intravenous infusion solution), glucose 20% (solution for injection), heparin (solution for injection), hydrocortisone (solution for injection), hydroxyzine (tablets, solution for injection), ibuprofen (tablets), ketoprofen (tablets, solution for injection), lidocaine (solution for injection, gel), magnesium (solution for injection), mannitol 15% (intravenous infusion solution), metamizole (solution for injection), metoclopramide (solution for injection), metoprolol (solution for injection), midazolam (solution for injection), morphine (solution for injection), naloxone (solution for injection), NaCl 0.9% (intravenous infusion solution), bicarbonate of soda 8.4% (solution for injection), papaverine (solution for injection), paracetamol (suppositories, tablets, solution for injection),

isotonic multi-electrolyte saline solution (intravenous infusion solution), colloid solutions which do not require blood collection for blood typing or cross-matching (hydroxyethyl starch, modified starch – intravenous infusion solution), salbutamolum (solution for injection, solution for inhalation), Ringer's solution / balanced electrolyte solution (intravenous infusion solution), thiethylperazine (suppositories, solution for injection), medical oxygen (gas), and urapidil (solution for injection). In addition, the legislator allowed for the administration of the following drugs: ticagrelor (tablets) and clopidogrel (tablets), following consultation with a physician assessing the patient's electrocardiogram. Outside of hospital, the assessment is conducted by means of teletransmission of an electrocardiographic record to the assessing physician.

Tactical Combat Casualty Care

Entitlements of a paramedic to independently provide health care services have a direct influence on the health safety of soldiers performing their tasks both within the country and abroad. Currently, the military paramedics have been entitled to provide care also in the battlefield environment. To answer the question if the entitlements are sufficient for the care for an injured soldier, one should refer to the TCCC guidelines. These recommendations appeared for the first time as a supplement to the *Military Medicine* journal in 1996. In accordance with the assumptions of military medicine, in order to achieve the objective of a mission, guarantee safety to the soldiers who participate in it and provide proper care to the casualties, medical care has to be provided in proper time and place. Therefore, the scope of medical care was deemed dependent on the current tactical situation on the battlefield and divided into three subsequent phases: the first phase of care is Care Under Fire (CUF); the second phase is Tactical Field Care (TFC); the third is Tactical Evacuation Care (TEC) – evacuation of the casualty from the battlefield. The key to the effectiveness of medical activities was to focus on treatment of the injuries that occur on the battlefield most frequently. Procedures were implemented that increased the survival rate of injured soldiers by means of using: tourniquet, nasopharyngeal tube, prehospital antibiotic therapy, fluid therapy, pain-alleviating drugs, surgical cricothyroidotomy and thoracocentesis. It should be emphasised that the TCCC committee was appointed to ensure a continued update of recommendations with the appearance of new scientific data. In practice, the TCCC guidelines were changed even up to three times per year, whereas the Regulation of the Polish Minister of Health of 20 April 2016 on medical rescue activities and health services changed twice in the last ten years, in 2009 and 2016.

Life-saving activities

When analysing the influence of the provisions of the State Emergency Medical Services Act on medical support of the soldiers of the Polish Armed Forces, one should take into account the possibility of military paramedics providing health care services other than medical rescue activities, which can be provided independently, as well as the possibility of administering appropriate drugs. In the case of performing rescue activities, their scope is close to those specified in the TCCC guidelines. In the case of haemorrhage control and injury care, military paramedics can use different methods, including the use of tourniquet, hæmostatic dressings, pressure dressing and dressings for open chest injuries. They can also reduce tension pneumothorax by puncturing the pleural cavity and gaining peripheral vein and intraosseous access [5]. Within the scope of restoration of airway, they can apply methods without the use of devices (jaw thrust, head tilt, chin lift), appropriate body positioning and methods with the use of devices, such as nasopharyngeal tube, supraglottic devices (laryngeal tube, laryngeal mask airway), endotracheal intubation and needle cricothyroidotomy. It should be noted that Polish law limits the possibility of performing endotracheal intubation only to the situation of securing airway in the case of a sudden cardiac arrest (SCA) [5]. This means that other methods should be used in a patient with maintained vital signs, e.g. based on supraglottic devices, which in most cases are as effective as endotracheal intubation, simpler to apply and without the risk of the most dangerous complication, being placement of the tube in the oesophagus instead of the trachea [6]. The TCCC guidelines are also not indiscriminate in regard to the endotracheal intubation method. They allow its application, but only if all the other methods of restoration of airway based on manual procedures and use of the nasopharyngeal tube have failed. In addition, the tactical and clinical situation, availability of equipment, as well as the skills and experience of the operator have to allow its effective implementation. Finally, the paramedic can abandon it and use the supraglottic devices or use the surgical method of restoration of airway, i.e. cricothyroidotomy. Endotracheal intubation, due to the complexity of this activity during operation, should only be used in the TEC phase.

One of the more important procedures that a military paramedic should be able to implement is cricothyroidotomy. It is most often used in the case of airway obstruction above the larynx, e.g. caused by facial skeleton injury. Polish law allows a paramedic to conduct needle cricothyroidotomy. It consists in a transcutaneous puncture of the median cricothyroid ligament with a large diameter catheter and introduction of the catheter into the airway, directly into the trachea. The TCCC guidelines

recommend a different technique, called surgical cricothyroidotomy, in which the cricothyroid ligament should first be cut with a blade, and then the intubation tube should be inserted through the opening. Ready-to-use kits are used for both methods. The first technique is simpler, but due to a smaller diameter of the catheter independent breathing or mechanical ventilation are less effective. The most modern needle cricothyroidotomy kits are also fitted with a cuff sealing up in the tracheal lumen. Surgical cricothyroidotomy is a more advanced procedure, requiring greater knowledge and experience, but due to a larger diameter of the tube ventilation is more effective. The TCCC guidelines currently recommend using simplified surgical cricothyroidotomy techniques, in which a one-time cricothyroid ligament and skin incision is made with a special blade, and a tube is inserted into its lumen through the opening with a guide protruding at the end [7]. The latter method should also be allowed to be used by military paramedics.

Analgesics

Pain is a subjectively unpleasant sensory and emotional experience caused by stimuli damaging tissue. One of the factors releasing acute pain are injuries sustained in combat. Decreasing pain is an important element of treating casualties with body injuries. For treatment of mild and moderate pain in soldiers able to continue combat, the TCCC guidelines recommend the use of meloxicam (Mobic, Opokam), in a single oral *(p.o.)* dose of 15 mg. Paracetamol (Tylenol) is used as a supplement in oral (p.o.) doses of 650 mg (2 x 325 mg) every 8 hours. These drugs do not cause altered states of consciousness nor impairment of coagulation. In accordance with Polish law, paracetamol preparations can be used by paramedics in the form of solutions for injections, suppositories or tablets. Meloxicam is not included in the list of drugs that can be administered by a paramedic, but it is available as an OTC drug under the name Opokan. This preparation is recognised as the safest drug in the group of Nonsteroidal anti-inflammatory drugs (NSAIDs). Their activity consists in inhibition of prostagladin synthesis participating in inflammatory processes, causing the appearance of pain, swelling and fever. NSAIDs that can be used by paramedics include: ibuprofen (tablets), acetylsalicylic acid (tablets) and ketoprofen (tablets, solution for injection). Depending on the influence on COX-1 and COX-2, drugs in this group differ in terms of intensity of adverse effects. These most often are: impairment of coagulation and the risk of bleeding in the gastrointestinal tract.

A drug of similar properties that could be used in Polish conditions instead of meloxicam is ibuprofen. However, it should be emphasised that administering ibuprofen, as well as any other NSAIDs which mainly affect COX-1 should be more restrained in the case of soldiers at the risk of battlefield injuries due to their influence on the impairment of coagulation. In Poland, both ibuprofen and meloxicam are drugs available over-the-counter and in practice they can be taken independently by a soldier, for example to alleviate back pain or reduce fever. In this situation, it seems justified to allow the possibility of paramedics administering all OTC drugs in accordance with the information contained in the leaflet.

In the treatment of moderate and strong pain, if the casualty is not in shock and is respiratorily stable, the TCCC guidelines recommend the use of an OTFC lollipop with fentanyl in a dose of 800 μg. Fentanyl belongs to the group of strong analgesics called opioids. Its use in the form of a lollipop (as the route of administration) allowed independent dosing of the drug by the casualty, at the same time limiting the possibility of overdosing it. The fentanyl lollipop is fastened to a finger of the casualty and placed in the mouth. The casualty decides individually when to stop taking the drug as the pain recedes. In the case of an overdose, with loss of consciousness and drop of the hand the lollipop is removed from the mouth and the administration of the drug is stopped.

Alternatively to fentanyl lollipops, it is possible to use morphine in an initial dose of 5 mg. However, intravenous *(i.v.)* or intraosseous *(i.o.)* access has to be obtained earlier, as these are the recommended routes of administration for this drug.

Soldiers of the Polish Armed Forces are equipped with an Individual Medical Package (IPMed), which includes an auto-syringe with morphine in a dose of 20 mg. Although the intramuscular route of administration for morphine is not covered in the TCCC guidelines, it can be an alternative in the event of lack of availability of fentanyl lollipops. Morphine, similar to fentanyl, is a strong analgesic from the group of opioids. Its advantage is that it also has a calming and sleep-inducing effect. Adverse effects are related to respiratory depression – overdose can lead to respiratory arrest and lowering of blood pressure, which is disadvantageous for a patient in shock. Therefore, in the case of casualties in shock or with respiratory disorders or when there is a risk of their appearance, the TCCC guidelines recommend the use of ketamin intramuscularly *(i.m.)* in a dose of 50 mg every 30 minutes or in a dose of 20 mg every 20 minutes intravenously *(i.v.)* or intraoessusly *(i.o.).*

Ketamin is a drug used for general anaesthesia. Depending on the dose it has a sleep-inducing or analgesic effect. Its advantage is the possibility of administering the drug intramuscularly and using it simultaneously with morphine or fentanyl, without the risk of intensifying adverse effects of these drugs. Contrary to opioids, it does not cause respiratory depression nor lowering of blood pressure. However, it is a substance causing dissociative anaesthesia, consisting in selective inhibition of CNS structures and simultaneous stimulation of other ones, therefore apart from the loss of consciousness, it can cause hallucinations, nystagmus and involuntary movements resembling convulsions. The recommended doses are meant to reduce pain, but individual reactions to them can differ depending on the route of administration and the body weight of the patient. It does not inhibit visceral pain from internal organs and does not neutralise protective reflexes in the throat area. In

Poland, ketamin is a drug used for general anaesthesia, which is why it can only be used under the supervision of an experienced physician. On the other hand, paramedics can still successfully use opioid (fentanyl, morphine) and non-opioid (paracetamol, metamizole, ketoprofen) analgesics administered intramuscularly and intravenously. Administration of opioid analgesics, such as fentanyl and morphine, can result in respiratory depression in a patient, as well as decrease the frequency of respiration, and even lead to respiratory arrest. This is why in such cases naloxone (Narcan) should be available and administered intravenously *(i.v.)* or intramuscularly *(i.m.)* at an initial dose of 0.4 mg. Naloxone is a so-called opioid antagonist, reversing the effect of opioids and neutralising the reactions they caused: respiratory depression, miosis, hypotension and sedation (sleepiness). This drug is approved for use by paramedics in Poland.

Antiemetics

The possibility of administering antiemetics is an important element of the strategy of preventing airway obstruction and aspiration pneumonia caused by inhaling vomit. The appearance of nausea and vomiting can be a side effect of opioid analgesics or a result of craniocerebral traumas. They are a particular threat in unconscious patients. In the case of appearance of vomiting or in order to prevent them, the TCCC guidelines recommend the administration of ondansetron preparation (Zofran) intravenously *(i.v.),* intraosseously *(i.o.)* or intramuscularly *(i.m.)* in a dose of 4 mg every 8 hours with an option of repeated dose if no therapeutic effect is identified after 15 minutes. Compared to the previous edition of the TCCC guidelines, ondansetron replaced the previously used promethazine (Diphergan), first-generation antihistamine, also inhibiting vomiting reflexes. Promethazine administered with morphine could intensify its depressive effect on the CNS leading to a decrease in blood pressure, excessive sedation, coma and apnoea. In Poland, the antiemetics which can be administered by a paramedic include metoclopramide 0.5% intravenously *(i.v.)* or intramuscularly *(i.m.)* in a dose of 10 mg or Thiethylperazine (Torecan) intravenously *(i.v.)* or intramuscularly *(i.m.)* in a dose of 6.5 mg. Torecan is a neuroleptic drug and it can intensify the side effects of opioid analgesics. Therefore, in the case of lack of ondansetron, it seems justified to replace it with metoclopramide, which partly indicates a similar effect on 5-HT3 serotonin receptors.

Antibiotics and chemotherapeutic agents

Antibiotics are a group of drugs used in the prevention of infections. Early administration of antibiotics can prevent further complications, such as severe sepsis. The TCCC guidelines have taken into account this group of drugs already in the phase of prehospital care, recommending the use of three preparations. For casualties able to swallow a tablet, the recommended preparation is Avelox, in which the active substance is moxifloxacin. It is a synthetic chemotherapeutic agent with a broad-spectrum antibiotic effect. Due to its chemical structure, it is recognised as a fluoroquinolone drug. The drug is administered orally *(p.o.)* in a dose of 400 mg/d. In the case of casualties unable to take drugs orally, e.g. with altered states of consciousness or in shock, it is recommended to administer Cefotetan (cephamycin), a beta-lactam antibiotic from the cephalosporin group with a broad-spectrum antibacterial effect.
It is administered in a dose of 2 g intravenously *(i.v.)* within 3-5 minutes or deeply intramuscularly *(i.m.).* If this drug is unavailable or its administration is contraindicated, ertapenem can be used as an alternative, an antibacterial beta-lactam antibiotic of the carbapenem group. It is administered intravenously *(i.v.)* in a dose of 1 g or deeply intramuscularly *(i.m.).*

Rights of paramedics related to the provision of health services do not include the option of administering antibiotics. This decision can only be made by a physician.

The analysis of the grounds for use of this group of drugs in the prehospital phase should take into account that they are not drugs directly saving lives in the initial phase of paramedic activities, however, they definitely increase the survival rate and reduce disabilities in injured soldiers going through further stages of treatment.

One such example is eye injuries. In battlefield and training conditions, the organ of vision is one of the organs most at the risk of damage. Even a small injury to the cornea accompanied by a bacterial infection can lead to loss of visual acuity and require a cornea transplant. Early administration of chemotherapeutic agents can prevent unpleasant consequences of infection and help keep the sight of the casualty. Taking into account the possibility of a significant delay in access to a physician and specialised treatment of the injured soldier, it seems justified to allow administration of broad-spectrum antibiotics in a situation where these drugs would have been administered in a hospital anyway due to the risk of development of infection as well as its distant consequences. If this is not possible, the wound should be initially cleansed physically with a 0.9% NaCl solution in order to flush soil, microbes and tissue remains from the wound.

Antihemorrhagics

The main cause of death induced by bodily injuries sustained on the battlefield are haemorrhages. Although effective stemming of external haemorrhages, especially those concerning upper and lower limbs is possible with the use of a tourniquet, in the case of internal haemorrhages it is not possible in prehospital conditions. A drug that can limit such bleeding is tranexamic acid (Exacyl) [8, 9]. It is a drug with an antihemorrhagic effect, which due to its effect on the plasminogen reduces the activity of plasmin and stabilises the process of coagulation. It should be administered within the first hour from the injury, but its distant influence on survivability is

still noticeable upon administration within up to 3 hours of sustaining the injury. In accordance with the TCCC recommendations, tranexamic acid should be administered within 3 hours of sustaining the injury intravenously *(i.v.)* in a dose of 1 g in the case of patients whose condition will require a blood transfusion, that is the ones in haemorrhagic shock. If fluids have been transfused to the patient, due to dilution of the plasma coagulation factors, a second dose (1 g) of tranexamic acid should be administered. Currently, this preparation is not allowed for administration by paramedics and it cannot be substituted by a different one with similar properties.

Transfusion and fluid therapy

Significant loss of circulating blood volume leads to life-threatening hypovolemic shock. In the case of loss of up to 30% of circulating blood volume, in order to maintain homeostasis, the organism initiates compensation mechanisms, aimed at maintenance of blood pressure ensuring vascular perfusion. In the case of massive haemorrhage, in order to maintain blood pressure in areas of vital organs, such as brain and heart, the phenomenon of centralisation of circulation occurs. In its course, there occurs a strong narrowing of peripheral blood vessels of upper and lower limbs, which manifests clinically in pulse fading in distal arteries, for example in the radial artery. In the case of a loss of greater volumes of blood, the compensation mechanisms become ineffective and to prevent further drops in pressure their intravascular volume should be supplemented. The TCCC guidelines recommend conducting fluid resuscitation with small volumes until the appearance of pulse in the radial artery or quantitative improvement in the state of consciousness or achievement of blood pressure of 80-90 mm Hg. The guidelines recommend that fluid resuscitation should be conducted in the first place, if available, with whole blood (WB) preparations or blood components: packed red blood cells (RBC), plasma (FFP), platelet concentrate (PC) in the following ratio: 1:1:1. In accordance with Polish legislation, the person ordering transfusion of blood or its component is a physician. The physician takes into consideration the balance of advantages and the risk of occurrence of adverse effects of transfusion [10, 11]. In the case of lack of access to blood products, in accordance with the TCCC guidelines, in prehospital conditions fluid therapy can be conducted with hydroxyethyl starch preparations (Hextend) or if they are unavailable – with crystalloids, such as Lactated Ringer's, a fluid containing electrolytes and an addition of lactates, or Plasma-Lyte A, a fluid similar in terms of osmotic pressure and electrolyte to blood plasma. Paramedics can currently conduct fluid therapy in accordance with the TCCC guidelines, except for transfusion of blood and its components. In the Regulation of the Polish Minister of Health of 20 April 2016 on medical rescue activities and health services other than medical rescue activities that can be provided by paramedics, colloidal fluids based on hydroxyethyl starch have been added in the table of drugs that can be administered independently by paramedics, for example Voluven 6% HES 130/04, or those based on modified gelatin, for example Gelafundin 4%. In addition, in order to cause a short-duration increase in the volume of the circulating blood, or balance the water-electrolyte disturbances in the course of dehydration, it is possible to use infusion fluids: isotonic sodium chloride solution – Natrium Chloratum 0.9%, Solutio Ringeri and balanced electrolyte solutions.

Conclusion

The specificity of activities of military paramedics on the battlefield is different from that of the civilian environment. It is influenced by the threats and tactical limitations of the battlefield, nature of injuries of the soldiers, potentially increased evacuation time, limited access to medical equipment, as well as work in extreme climate conditions, darkness and noise. In such environment, the essential factors for the effectiveness of activities are not limited to access to appropriate drugs and medical resources, but also includes the possibility of performing life-saving actions. Considering the currently binding rights of paramedics, it should be stated that they grant good opportunities of providing medical care to injured soldiers within the scope of both the drug administration and performance of life-saving actions (Table 1.). In order to provide the best care possible to injured soldiers and at the same time take into account the knowledge and skills acquired in the course of education and professional improvement of paramedics, they should be statutorily entitled to administer tranexamic acid preparations and perform cricothyroidotomy. The decision about the introduction of transfusion of blood and its products, even limited to a specific situation, such as haemorrhagic shock, requires broader legal regulations. The procedure of transfusion itself requires special supervision of persons responsible for management of blood issued from the hospital.

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Chronic coronary artery disease in the elderly

Przewlekła choroba wieńcowa w wieku podeszłym

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Abstract. The incidence of coronary artery disease increases with age. As a result, it is the most common cause of death among the elderly. In this group of patients, numerous comorbidities and the atypical nature of symptoms cause frequent underestimation of the severity of the reported complaints. Therefore, older patients are often diagnosed and treated for coronary artery disease with a delay. The choice of the best method of treatment for this group of patients is also difficult. This is due in part to the fact that the number of randomised trials with elderly patients is limited.
Key words: chronic coronary artery disease, the elderly, coronary angiography, coronary artery bypass grafting

Streszczenie. Częstość występowania choroby wieńcowej zwiększa się wraz z wiekiem. W efekcie jest ona najczęstszą przyczyną zgonów osób starszych. W tej grupie chorych liczne choroby współistniejące i nietypowy charakter objawów są przyczyną częstego niedoszacowania istotności zgłaszanych dolegliwości. W efekcie niejednokrotnie pacjenci starsi są diagnozowani i leczeni z powodu choroby wieńcowej z opóźnieniem. Wybór najlepszej metody leczenia w tej grupie chorych jest również trudny. Wynika to między innymi z faktu, że liczba badań z randomizacją z udziałem pacjentów w podeszłym wieku jest ograniczona.
Słowa kluczowe: przewlekła choroba wieńcowa, osoby starsze, koronarografia, pomostowanie aortalno-wieńcowe

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Introduction

The development of civilization is associated with a progressive ageing of the population. This is due to advances in medicine, improved economic conditions and growing public awareness of healthy lifestyle and prevention. According to forecasts, in 2050, the population over 65 years old will exceed 22% [1]. So far, a unique definition of old age has not yet been established. Among the different divisions, it seems most practical to distinguish 3 groups: *older* people aged 65-75, *elderly* people aged 76-85, and *very elderly* people aged >85 [2].

As defined by the European Society of Cardiology (ESC), stable coronary artery disease (CAD) is a clinical symptom complex resulting from imbalances between coronary blood flow rate and the demand of the cardiac muscle for oxygen and energy compounds. This disproportion is most often triggered by physical effort and emotion [3]. CAD is the most common cause of death among the elderly – in a population over the age of 70, 60% of all deaths are caused by a myocardial infarction [4]. Post-mortem examinations have shown that, in 70% of the deceased over the age of 90, there is at least one obstructed coronary artery [4]. Age has also a significant impact on the sex ratio of patients with CAD. In a population of patients over the age of 65, as opposed to younger people, the incidence of CAD is the same among men and women (10-20% *vs* 10-15%) [5].

Physiology of the ageing process of the cardiovascular system

With age, the human body undergoes physiological changes related to the ageing process. They are the backdrop of pathological processes, which makes diagnosis much more difficult. The consequences of the ageing process include changes in the structure of the arterial wall. Replacing elastic elements with collagen leads to the stiffening of arteries, resulting in increased total peripheral resistance, increased afterload and mean blood pressure. With age, the process of endothelial cell degeneration also progresses, nitric oxide release is reduced, which predisposes to vasoconstriction. Particularly increased endothelial dysfunction is associated with the occurrence of diabetes and arterial hypertension, which significantly accelerates the development of atherosclerosis [2].

Changes also occur in the electrical conduction system of the heart, which may result in a decreased conduction rate in the atrioventricular node, and thus in chronotropic insufficiency and/or advanced atrioventricular conduction disturbances.

The ageing process also affects the heart valves. These changes are most often due to the formation of massive calcifications within the aortic valve, the narrowing of which is the most common valvular heart disease in the elderly population. The second most common valvular heart disease is mitral insufficiency, which often results from left ventricular remodelling caused by ischemia [6].

The processes described above cause frequent co-occurrence of CAD in the elderly people with major valvular heart diseases, cardiac dysrhythmias or heart failure symptoms. The complexity of symptoms may cause diagnostic difficulties. An additional problem is comorbidities (peripheral atherosclerosis, lung diseases, motor system diseases), which often mask the symptoms of even advanced CAD. Atypical symptoms and a prevailing stereotype of "old age" contribute to the underestimation of the reported complaints.

Diagnosis of coronary artery disease in the elderly

Despite the increasing availability of non-invasive and invasive examination, the basis for the diagnosis of CAD is still to take a detailed history of a patient. In the elderly, a complex symptomatology of CAD is observed, although the incidence of typical stenocardia is lower [2, 4, 7]. The most commonly reported complaints related to CAD in the elderly are weakness, increased perspiration, dyspnoea, nausea, abdominal pain and fainting. It is also important to remember that silent ischemia may occur, which is due to an increased pain threshold caused by the ischemia of sensory nerve fibres and autonomic dysfunction [2, 8, 9]. In addition, low physical activity or concomitant atherosclerosis of the lower extremity arteries may reduce the indications of ailments resulting from CAD.

Electrocardiographic examination, which is a basic diagnostic test for CAD, has some limitations in the case of elderly patients. In a resting electrocardiogram, there are often visible changes that make it difficult or impossible to detect ischemia. For example, in NMRI tests, a left bundle branch block (LBBB) was observed in 34% of patients over the age of 85 [10]. Other changes impeding the assessment of ischemia include ventricular conduction abnormalities, left ventricular hypertrophy or previous myocardial infarction.

The advanced age of patients should also be included in the echocardiographic assessment. Undoubtedly, ultrasound examination of the heart is crucial in CAD. It is used to exclude other causes of reported complaints, to assess contractility disorders, including the measurement of left ventricular ejection fraction, which is an important prognostic parameter [3, 11, 12]. However, it should be remembered that mild diastolic dysfunction is a physiological phenomenon in the elderly that may also be the first manifestation of active ischemia [13, 14].

When choosing diagnostic tests, the ESC guidelines should be followed (Table 1). According to these guidelines, in men over the age of 70 with typical anginal complaints that persist despite optimal pharmacological treatment, coronary angiography should be performed first. With such a high probability of coronary artery disease (89 and 93%), the aim of the test is not a diagnosis of coronary artery disease, but risk stratification based on the anatomy of arterial lesions. In other patients, the diagnosis should begin with non-invasive examination. [3].

The possibility of performing cardiac stress tests in the discussed group of patients is limited. Very often, elderly patients are unable to perform a stress test due to degenerative arthritis, atherosclerosis of the lower extremity arteries, muscle weakness and reduced exercise tolerance. Lack of cooperation and difficulty in using the treadmill may also pose a problem. In addition, as mentioned above, changes in the resting electrocardiogram make it impossible to assess ischaemia and are thus a contraindication to the stress test. It should also be borne in mind that, in this group of patients, the stress test is more likely to produce false negative results [15]. Nevertheless, it is still believed that this test should continue to be an initial test in the assessment of elderly patients with suspected coronary artery disease [3].

Among other non-invasive tests, imaging tests may prove to be useful, for instance, myocardial scintigraphy (optionally including pharmacological stress), dobutamine stress echocardiogram and coronary computed tomography angiography. The advantage of functional imaging tests is the possibility to identify an area at risk of myocardial ischemia

Table 1. Clinical probability of coronary artery disease before testing in patients with stable chest pain [3,33]
Tabela 1. Kliniczne prawdopodobieństwo choroby wieńcowej przed testem u pacjentów ze stabilnymi zespołami bólu w klatce piersiowej

	typical angina pectoris		atypical angina pectoris		atypical pain	
age	men	women	men	women	men	women
30-39	59	28	29	10	18	5
40-49	69	37	38	14	25	8
50-59	77	47	49	20	34	12
60-69	84	58	59	28	44	17
70-79	89	68	69	37	54	24
>80	93	76	78	47	65	32

probability of the disease before testing is <15%
probability of the disease before testing is <15-65% – the first test may be an exercise stress test
probability of the disease before testing is <66-85%, therefore, non-invasive functional imaging test should be performed to diagnose the disease
probability of the disease before testing is >85%, it can be assumed that stable coronary artery disease occurs

– if this area exceeds 10% of cardiac muscle mass, coronary angiography is required.

The final examination confirming the diagnosis of CAD is angiography of coronary arteries. The changes observed in the coronary angiography in the elderly population have particular characteristics. This is due to more advanced atherosclerosis – left coronary artery stenosis is more frequent, lesions are often multilevel, located peripherally and affect more vessels (multi-vessel coronary artery disease) [3, 5]. In addition, the course of the arteries is tortuous and calcifications are often present, which increases the difficulty of angioplasty and the risk of complications [16, 17]. It is also important to remember that elderly patients are more likely to experience local complications. In the Niebauer et al. study [18], involving patients over the age of 80, local complications were reported in 2.1% of patients after coronary angiography and in 11.6% of patients after angioplasty.

How to treat the elderly?

In the analysis of retrospective studies assessing the influence of age on the direct and long-term effects of coronary angioplasty, it has been shown that age is one of the most important risk factors for percutaneous treatment [19]. In a study of more than 21,000 patients, the risk associated with angioplasty was observed to increase with age. Other significant risk factors for mortality during hospitalisation include heart failure and urgent procedure [20]. In the McCallister et al. study [21], being aged above 70 and impaired left ventricular ejection fraction (<40%) were the most important risk factors after percutaneous treatment in long-term follow-up. These data are confirmed in the paper by Wenneberg et al. [22], which identified that the risk of death during hospitalisation after angioplasty in patients over the age of 80 was 5.5 times higher than in the population over the age of 60, whereas perioperative myocardial infarction occurred 1.5 times more often. In a subsequent analysis, it was found that the risk of death is 5 times higher in patients over the age of 70, and over 9 times higher in patients over the age of 80 [23].

The authors of the existing guidelines emphasize that elderly patients should have the same access to invasive diagnostics and treatment of CAD as younger people. The negative phenomenon of more frequent disqualification of elderly patients from these procedures should be eliminated. An argument in favour of this recommendation is the result of the APPROACH study, in which patients treated with invasive methods had a significantly longer survival than patients treated pharmacologically. Most importantly, the older the age group, the greater the benefit from intervention therapy [24].

Another study involving patients over the age of 75, in which pharmacological and invasive treatment was compared, was the TIME study [25]. It involved 305 patients with at least class II anginal complaints, according to the CCS (Canadian Cardiovascular Society) grading system, who were treated with antianginal medications. The patients were randomised to 2 groups – invasively treated patients (coronary angiography and later angioplasty or coronary artery bypass grafting were performed) and conservatively treated patients (pharmacological treatment was optimised). In the 30-day follow-up period, a significantly higher proportion of deaths was observed among patients subjected to invasive treatment (invasive treatment group *vs* pharmacological treatment group: 10% *vs* 3%). It should be noted, however, that half of the deaths in the invasively treated group occurred in patients who did not undergo

revascularisation, most often due to end-stage CAD. After 6 months of follow-up, there was no significant difference observed in the number of deaths and myocardial infarctions between the groups; however, there was a significant increase observed in the number of hospital admissions, the frequency of the aggravation of the symptoms of CAD and the need for coronary angiography or urgent angioplasty in the conservatively treated group. It was the cause of more adverse events in this group (19% in the invasive treatment group *vs* 49% in the pharmacological treatment group). After 6 months of follow-up, improvement in the quality of life and reduced severity of anginal complaints were also observed, although this change was significant only in the group undergoing revascularisation. After extending the follow-up to one year, the quality of life continued to improve in both groups, but the difference between the groups was smaller than before. In the one year follow-up, there were no significant differences in mortality (invasive treatment group *vs* pharmacological treatment group: 11.1% *vs* 8.1%); however, there was an even greater difference in the incidence of adverse events in the conservatively treated group (25.5% *vs* 64.2%), which was due to a greater number of hospital admissions and the need for urgent revascularisation [26, 27]. These results highlight the importance of the individual approach to each patient, taking into account the risk of acute intervention, but also the benefits of its implementation in long-term prognosis.

Surgical revascularisation offers a greater possibility of full revascularisation than percutaneous treatment, which reduces the risk of recurrence [17]. Partial revascularisation, resulting also from the lack of technical capacity to perform angioplasty of all stenosis, is associated with a worse prognosis [4]. A comparison of percutaneous treatment and surgical revascularisation was undertaken by Dacey et al. [28]. The study involved patients aged 80-89 years who underwent coronary artery bypass grafting and angioplasty due to two- or three-vessel disease without left main disease. In-hospital mortality was 3% in the group undergoing angioplasty and 5.9% in the group undergoing coronary artery bypass grafting. There was a significantly higher number of strokes reported in patients after surgical treatment than in patients after percutaneous treatment (2.84% *vs* 0.57%). In the first 6 months of follow-up, the survival of patients undergoing surgical myocardial revascularisation was worse than in patients undergoing angioplasty, whereas later in the follow-up (after 6 months), survival was significantly better in surgical patients [28]. In a meta-analysis of 10 randomised trials (mean age of 61 years), comparing coronary artery bypass grafting and coronary angioplasty, no differences were found in the survival of patients treated with either method, although surgical revascularisation was associated with significantly better survival compared to percutaneous treatment in the group of patients over the age of 65. A significant percentage of re-revascularisation was reported in the group of patients undergoing angioplasty (36.4% *vs* 10.1%) [29]. Therefore, cardiac surgery should not be avoided in elderly patients, as most of them will benefit from it in a similar way as younger patients.

The remaining problem in the treatment is a limited number of scientific evidence. In many large randomised clinical trials of acute coronary syndromes and stable CAD, the number of elderly people was small and, in some cases, advanced age was an exclusion criterion.

In the COURAGE study, which compared optimal pharmacological treatment with percutaneous coronary intervention in patients with stable coronary artery disease, the mean age was 61.6 years [30]. Similarly, in the BARI 2D study, which involved 2368 patients with type 2 diabetes and chronic coronary artery disease, the mean age of the population was 62.4 years [31]. In another study (RITA-2) evaluating the effectiveness of conservative treatment and angioplasty in a 7-year follow-up, the median age was 58 years [32].

Therefore, we have limited data assessing the safety and efficacy of various treatments in this group of patients.

Conclusions

Diagnosis and treatment of CAD in the elderly pose a considerable challenge. The existing guidelines [3] oblige us, however, to use all available diagnostic and therapeutic means, regardless of age. Undeniably, the decision as to the method of treatment of elderly patients should be taken on an individual basis and must take into account factors such as the severity of CAD, the coronary angiogram, comorbidities, biological age, current lifestyle and social status. Nonetheless, chronological age alone should not be a criterion disqualifying from diagnosis and/or treatment. One should be aware that invasive treatment is becoming more effective and safer. Nowadays, percutaneous treatment involves modern stents coated with antimitotic drugs, which mitigates the risk of thrombosis and restenosis and reduces the duration of dual antiplatelet therapy. Surgical revascularisation is performed more often without full sternotomy or from a small-scale transthoracic approach, which reduces the risk of perioperative complications. Therefore, the elderly can be offered full treatment, even in the case of advanced CAD.

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Medical diagnostic laboratory – management by quality

Medyczne laboratorium diagnostyczne – zarządzanie przez jakość

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Abstract. The usefulness of the diagnostic and clinical result of a single laboratory test is determined by the proper quality of its performance in the interest of patients. A laboratory diagnostician is obliged to perform an assessment of the analytical quality of the test result according to current knowledge based on the available scientific evidence. A helpful element of laboratory work, both analytical and microbiological, is participation in external and internal laboratory quality control of tests and correct interpretation of control results obtained in the laboratory. Creating quality management systems in medical diagnostic laboratories and, in the near future, developing principles for a national system of work quality assessment in such facilities are very important factors that will determine the quality of the provided diagnostic services.
Key words: quality, quality control, quality assurance, evaluation system

Streszczenie. W trosce o dobro pacjenta o użyteczności diagnostyczno-klinicznej pojedynczego wyniku badania laboratoryjnego decyduje należyta jakość jego wykonania. Do diagnosty laboratoryjnego należy obowiązek wykonania oceny jakości analitycznej wyniku badania zgodnie z aktualną wiedzą opartą na dostępnych dowodach naukowych. Pomocnym elementem w pracy laboratoryjnej - zarówno analitycznej, jak i mikrobiologicznej - jest uczestnictwo w prowadzonej zewnętrznej i wewnątrzlaboratoryjnej kontroli jakości badań i właściwej interpretacji uzyskanych w laboratorium wyników kontrolnych. Tworzenie systemów zarządzania jakością w medycznych laboratoriach diagnostycznych, a także w niedalekiej przyszłości wypracowanie zasad dla krajowego systemu oceny jakości pracy w takich placówkach, jest bardzo ważnym czynnikiem, który będzie warunkował jakość świadczonych usług diagnostycznych.
Słowa kluczowe: jakość, kontrola jakości, zapewnienie jakości, system oceny

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Introduction

The history of total quality management in Europe is inextricably linked to the establishment of the European Community in 1956 [1]. The creation of a common market for goods and services has given rise to the need to establish common requirements and test and control methods also in the field of laboratory medical diagnostics. In 1977, the German Institute for Standardization submitted an application to the International Organization for Standardization (ISO) for the unification of national standards, becoming a pioneer in this field. The first results of the work of the ISO Technical Committee for Quality Management and Quality Assurance established in 1980 was the ISO 8402 standard, followed by the ISO 9000 series, and, subsequently, the PN-EN ISO/IEC 17025 standard which describes the requirements for testing laboratories [2]. The specifics of the requirements for conducting tests in diagnostic laboratories were comprised much later in the PN-EN ISO 15189:2008 standard, updated in 2013 [3].

All stages and steps of the work performed by laboratory employees contribute to the quality in each laboratory. The correct assessment of the uncertainty of laboratory results can be controlled only through a comprehensive approach to laboratory analyses. Accreditation, the process of which is shown in the diagram in Figure 1, constitutes objective evidence that a laboratory operates in accordance with the best laboratory practice [4, 5].

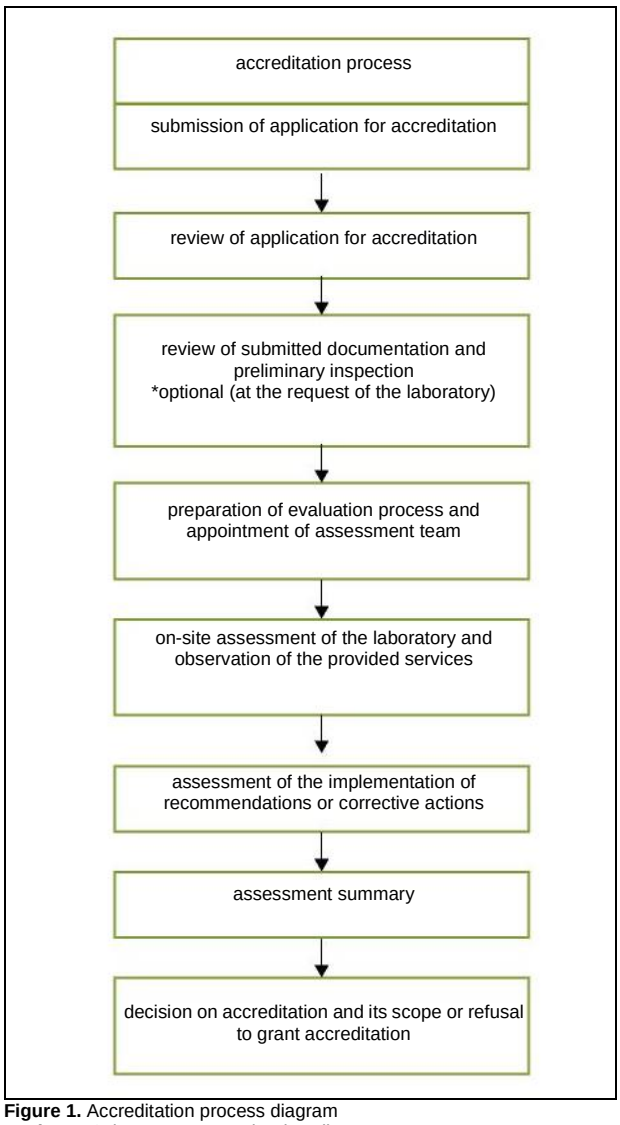

Figure 1. Accreditation process diagram
Rycina 1. Schemat procesu akredytacji

The process of preparing a laboratory for PCA accreditation

The two standards mentioned above, i.e. ISO PN-EN 17025 and ISO PN-EN 15189:2013-05, apply to medical laboratories, together with the document of the Polish Centre for Accreditation (PCA) with the symbol DAB-07 "Accreditation of medical laboratories – detailed requirements" [5], developed in cooperation with the Technical Committee for Medical Diagnostic Laboratories. The list of accredited medical entities – Polish medical laboratories (data available on the PCA website) – is presented in Table 1.

The whole process of preparing a laboratory for application for accreditation can be divided into two stages.

Stage one

Appropriate documentation of the management system should be prepared, which includes the Quality Manual (QM), General Procedures (GP), Testing Procedures (TP), and Instructions (I), as well as other documentation related to the equipment of a medical diagnostic laboratory. Most often in medical facilities, such as the hospital, there are several different laboratories with different profiles. In this case, since it is the main entity that applies for accreditation, general documentation should be prepared separately from testing documentation in the individual organisational units, e.g. bacteriological, analytical, immunological, biochemical, etc. The team of experts preparing general documentation should be trained with respect to the applicable standards and agreements and the method of preparing the documents [6]. The task of the team mentioned above is to create documentation of the QM and the GP in order to describe the already existing work practices and to adapt those that are not described or, alternatively, to modify them so that they conform to the system described in the selected standards.

Testing documentation should be prepared by people employed in the laboratory who participate in the diagnostic process. If laboratory employees do not perform the tests described in the standards, they are required to describe the activities performed in the appropriate procedures. The prepared procedure must be verified and approved by the head of the laboratory and submitted for approval to the management of the medical facility.

Stage two

It begins after the approval of the aforementioned documents [7]. The documentation is best implemented through the training of employees. The best method to verify the effects of these activities is by carrying out internal audits. The PN-EN ISO 17 025: 2005 standard does not specify the number of internal audits that should be conducted per year. It is assumed that such verification should be carried out at least once a year. In order to prepare for the audit, a schedule should be drawn up with separate sections for each organisational unit of the medical facility. The managers of individual laboratories should be notified about the scope of the audit and its date. If non-compliance is found, the person responsible for a given testing area should identify its cause and propose corrective measures to remedy the non-compliance and prevent its re-occurrence.

Table 1. List of accredited medical laboratories in Poland
Tabela 1. Lista akredytowanych laboratoriów medycznych w Polsce

medical laboratory	accreditation	brief scope of activity
Laboratorium Medyczne BRUSS Grupa ALAB Sp. z o.o. 9b Powstania Styczniowego St. 81-519 Gdynia	**AM001** **certificate expiry date:** 16.11.2018 **accreditation since:** 17.11.2010	clinical chemistry and medical analytics – whole blood, serum, urine, body fluids, plasma; hematology, coagulation profile – whole blood, plasma bacteriology, parasitology, virology, infectious serology – serum, urine, faeces, swabs, body fluids transfusion serology – whole blood, blood morphology, plasma sampling – whole blood
Synevo Sp. z o.o. 3 B Gdecka St. 04-137 Warszawa	**AM002** **certificate expiry date:** 13.12.2018 **accreditation since:** 14.12.2010	clinical chemistry and medical analytics – whole blood, serum, plasma urine hematology, coagulation profile – whole blood, plasma immunology – serum bacteriology, infectious serology – urine, faeces, swabs, serum transfusion serology – whole blood, blood morphology, serum, plasma sampling – whole blood
Diagnostyka Sp z o.o. 16 Prof. Michała Życzkowskiego St. 31-864 Kraków	**AM 003** **certificate expiry date:** 03.05.2019 **accreditation since:** 04.05.2011	clinical chemistry – serum, plasma hematology, coagulation profile – whole blood, plasma virology – plasma, serum transfusion serology – whole blood toxicology – whole blood, serum, urine sampling – whole blood
Diagnostyka Sp. z o.o. Laboratorium Oddziału Śląsk 53 Mikotowska St. 40-065 Katowice	**AM004** **certificate expiry date:** 24.01.2020 **accreditation since:** 25.01.2012	clinical chemistry and medical analytics – whole blood, serum, plasma semen hematology, coagulation profile – whole blood, plasma immunology – serum bacteriology – urine, faeces, swabs, whole blood sampling – whole blood
ALAB laboratoria Sp. z o.o. 22/30 Stępińska St. 00-739 Warszawa	**AM 005** **certificate expiry date:** 01.07.2020 **accreditation since:** 02.07.2012	clinical chemistry – whole blood, serum, plasma, urine hematology and coagulation profile – whole blood, blood morphology, plasma immunology – serum bacteriology, mycology, infectious serology – faeces, swabs, serum, other tissues and cells transfusion serology – blood morphology/plasma medical genetics – swabs sampling – whole blood
Diagnostyka Sp. z o.o. Laboratorium Oddziału Warszawa 26 Poniatowskiego St. 08-110 Siedlce	**AM 006** **certificate expiry date:** 2.09.2020 **accreditation since:** 3.09.2012	clinical chemistry – serum, plasma hematology – whole blood, blood morphology sampling – whole blood
INVICTA Sp. z o.o. 3 Trzy Lipy St. 80-172 Gdańsk	**AM007** **certificate expiry date:** 25.03.2021 **accreditation since:** 26.03.2013	clinical chemistry – serum, plasma hematology, coagulation profile – whole blood, plasma immunology – serum sampling – whole blood
ALAB Laboratoria Sp. z o.o. 22/30 Stępińska St. 00-739 Warszawa	**AM008** **certificate expiry date:** 28.09.2018 **accreditation since:** 29.09.2014	clinical chemistry and clinical analytics – whole blood, serum, plasma, urine hematology and coagulation profile – whole blood, plasma immunology – serum, plasma sampling – whole blood

Source: Polish Centre for Accreditation

Table 1. List of accredited medical laboratories in Poland
Tabela 1. Lista akredytowanych laboratoriów medycznych w Polsce

DIAKLIN Sp zo.o. 4 Bielska St. 43-400 Cieszyn	**AM009** **certificate expiry date:** 15.02.2019 **accreditation since:** 16.02.2015	clinical chemistry – serum, plasma sampling – whole blood
Franciszek Łukaszczyk Oncology Centre in Bydgoszcz 2 I. Romanowskiej St. 85-796 Bydgoszcz	**AM0010** **certificate expiry date:** 10.02.2019 **accreditation since:** 11.02.2015	bacteriology, mycology, infectious serology – whole blood, serum, urine, faeces, swabs clinical chemistry – serum
Norbert Barlicki Memorial Teaching Hospital No. 1 in Łódź 22 Kopcińskiego St. 90-153 Łódź Centrum Diagnostyki Laboratoryjnej Maryla Drynkowska-Panasiuk 19 J.U. Niemcewicza St. 93-024 Łódź	**AM0011** **certificate expiry date:** 31.01.2020 **accreditation since:** 1.02.2016	clinical chemistry and medical analytics – whole blood, serum, plasma urine, body fluids, faeces hematology, coagulation profile – whole blood, plasma immunology – serum, urine, body fluids transfusion serology – whole blood, blood morphology, serum, plasma sampling – whole blood

Source: Polish Centre for Accreditation

Example of the flow of information and biological material in a medical diagnostic laboratory

In medical facility X, a laboratory delivery system for test orders can take one of two forms: uniform order forms (hard copy) and electronic orders [8]. Completed order forms for laboratory tests (with a barcode with the same number as the code sticker tag on the test tube(s) with the specimen) are sent from hospital wards or other specimen collection facilities, e.g. clinics, to the registration station at a medical diagnostic laboratory. At this point, they are scanned with a code reader and entered into the electronic laboratory system. Once the order form is scanned, the employee verifies the correctness of the registered tests against the order. In addition to the automatic registration of tests, in emergency situations, the system allows for manual registration, where the laboratory technician registers tests using a list and selecting the tests by code or name. The patient's biological material delivered to the laboratory should be handled separately, each sample being scanned with a barcode reader. At this stage, it is possible to detect the first mistakes related to the registration of samples or to correct any deficiencies in the specimen or orders. The sample is then sent to the appropriate laboratory testing station where it is analysed. The apparatus on which the sample is tested retrieves information about the type of analysis to be performed from the electronic database. This is possible because the data from the order scanned at the registration station is then sent electronically via the internal network of facility X to the diagnostic apparatus.

The second type of orders are electronic orders which are sent to the laboratory distribution station from hospital wards through the installed terminals or via the Internet in the case of external facilities. Electronic orders are verified similarly to those delivered with an already completed form, i.e. by scanning the specimen at the laboratory distribution station. The program used in the laboratory should communicate with the parent hospital system through protocols that are recognized as international standards in the exchange of medical information. Full synchronisation of the laboratory system of the flow of orders and samples with the parent system of the whole hospital is carried out by competent IT specialists working at the hospital. By connecting the two IT systems, it is possible to electronically order tests at the laboratory from the hospital system, and after the tests are completed and approved by a laboratory diagnostician, they can be sent from the laboratory network to the hospital system. Only personnel authorised by the management of a given facility have access to the module for ordering tests and receiving results by electronic means, as well as hard copies of the results. Monitoring the functioning of a laboratory is possible

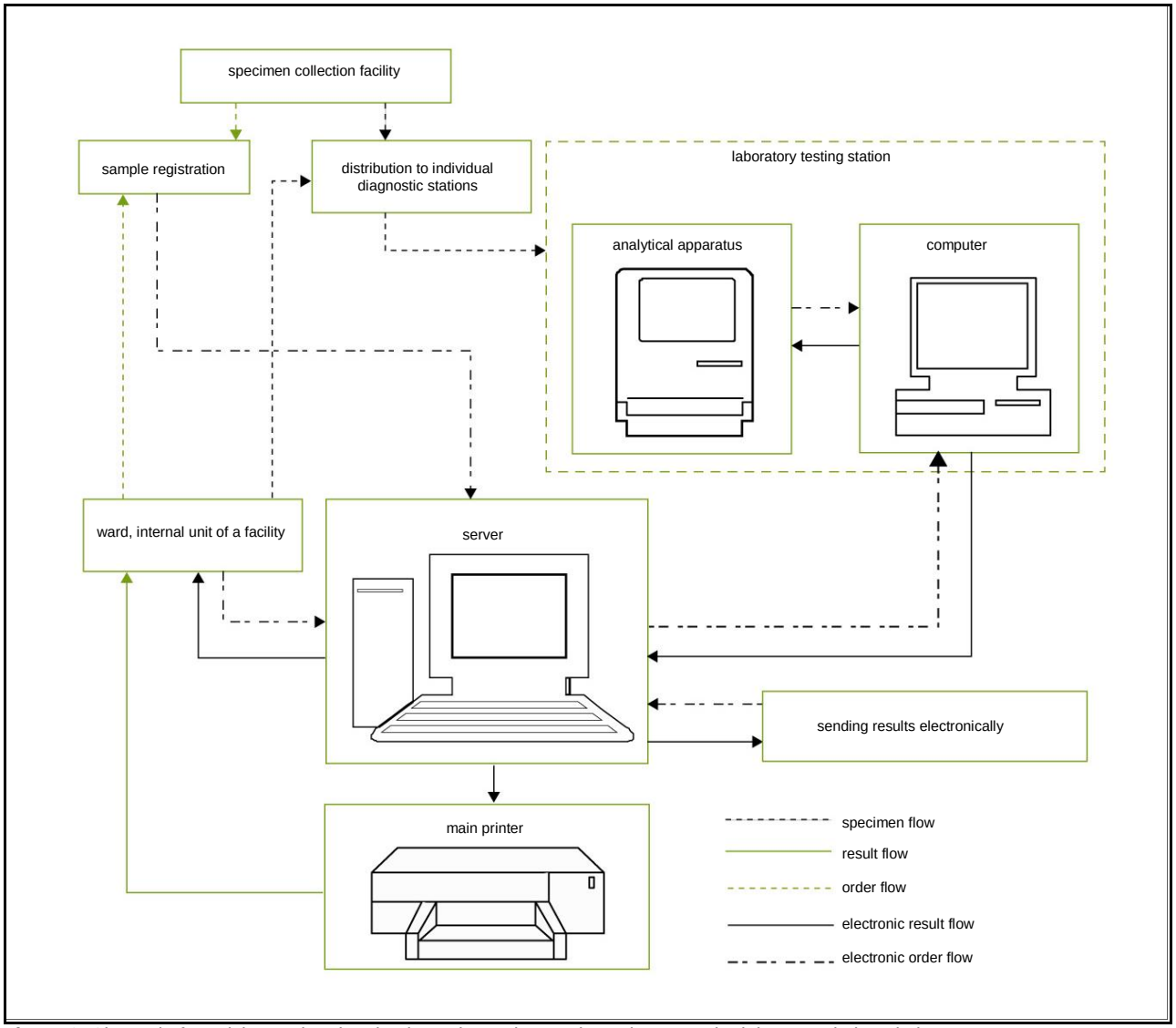

Figure 2. Channel of receiving and registering incoming orders and specimens at the laboratory in hospital X
Rycina 2. Droga przyjęcia i rejestracji zleceń i materiału przychodzących do laboratorium w przykładowym szpitalu X

by means of tracking a given order in the laboratory. This system shows, among other things, where a given sample is (at which stage of the test) and where it should be sent (to which laboratory station). The program should also provide information on the obtained results and the history of a particular order. It also records all entries and changes in the system – their date, time and user are recorded. Data should be archived on the basis of a database server. It stores all the information necessary for the functioning of the laboratory. Backup copies should be created at the end of each working day and stored on the server. Figure 2 shows a diagram of the flow of specimens and information in a medical laboratory.

Quality policy

The development and implementation of a Quality Management System in a laboratory are aimed at supporting and improving the quality of laboratory diagnostics and, in the case of a particular specialised laboratory, improving the quality of the conducted tests. The aim of all laboratory employees is to perform tests

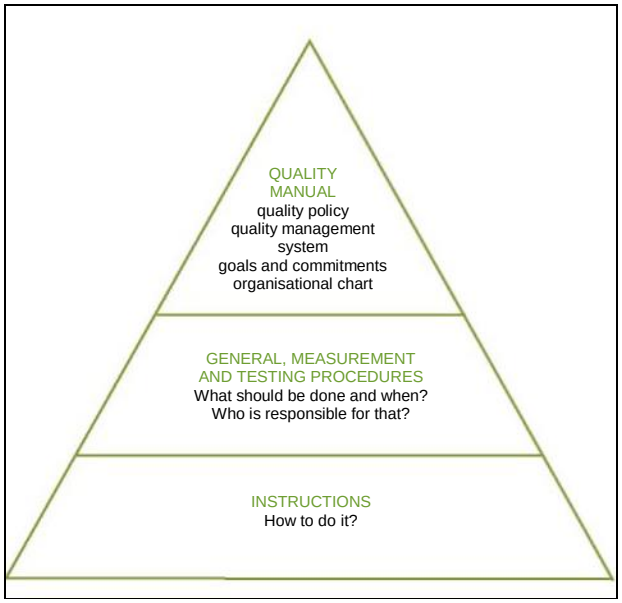

Figure 3. Structure of the management system documentation
Rycina 3. Struktura dokumentacji systemu zarządzania

on the patients' specimens in the most effective way possible. The basic conditions and principles governing the fulfilment of the quality objectives set by the management of the laboratory are described in the Quality Management Manual. This document contains information for the patient and analysts about the activities undertaken by the laboratory and individual laboratory stations to ensure the proper quality of all diagnostic services provided. The head of the laboratory and its personnel undertake to follow the processes described in the Quality Management Manual [9-11]. The adopted quality policy should aim to establish and maintain an effective quality management system that complies with the requirements of standards PN-EN ISO 9001, PN-EN ISO 17025 and PN-EN ISO 15184, as well as with the principles of good laboratory practice (GLP) [2, 3].

Quality control

The results of intra- and inter-laboratory control programs are the guarantee of the reliability of the tests performed by a medical diagnostic laboratory. It is important that all laboratory parameters are included in the quality control program [12, 13]. Intra-laboratory control should be based on quality control materials from reputable companies whose quality has been confirmed by certificates. The basic element in the development of an intra-laboratory control system is establishing the total allowable error. An additional tool for the quality control of tests is inter-laboratory control based on the participation in national and international inter-laboratory control programs (in a microbiological laboratory that can conduct diagnostics for detecting influenza viruses, e.g. the WHO External Quality Assessment Program for Detection of Influenza Virus Type A by PCR) [8]. The obtained results should be analysed in detail by the laboratory management and the personnel conducting the tests.

Personnel

The personnel of a medical diagnostic laboratory should be comprised mostly of diagnosticians and laboratory technicians, medical analysts and microbiologists. Each employee should be trained in quality system procedures, and laboratory personnel should also have the opportunity to undergo external training to enhance their knowledge with respect to laboratory work [8, 9].

Accreditation in a medical diagnostic laboratory – benefits or problems

On the basis of the regulation of 11 October 2016, uniform quality standards have been published for medical diagnostic laboratories and microbiological laboratories [14].

At every stage of carrying out an order for laboratory analyses of entrusted specimens, so-called evidence of the conducted work must be retained. These documents are necessary to reproduce the entire testing process for each analysed sample, in particular in the case of a complaint by the ordering party or non-compliance. Such activities necessitate the need to produce various records, which in the case of a large number of tests may make the work difficult. The practice shows that, if a laboratory decides to maintain paper management system documentation, it must be well prepared to manage these data. Too many documents may discourage laboratory employees from following the implemented system. It is worth considering introducing an electronic document storage system which can automatically generate the requested report. However, before introducing a computer system, the personnel should be first trained and familiarised with all the principles of the electronic management system.

Quality Manual, General Procedures, Testing Procedures, detailed Instructions for laboratory diagnosticians related to a medical diagnostic laboratory

The management of a laboratory that intends to apply for accreditation is responsible for preparing documentation related to the management system. This documentation specifies requirements and declares the intention to meet them. The most important document in the management system is written quality policy. It describes the laboratory strategy for the functioning, development and improvement of the management system. It should include

declarations of the management on the application of the required standards, continuous improvement, the allocation of the necessary financial resources for this purpose, the identification and fulfilment of the expectations and needs of the potential recipients of medical services. The purpose of the Quality Policy is to ensure that tests in the laboratories of a given entity are conducted to the highest possible standard and in accordance with good laboratory practice. As part of the implementation of the quality policy, the objectivity and independence of the conducted tests should be ensured by:

- developing rules that will guarantee the full responsibility of the personnel in the conduct of analytical tests, hence the need to employ highly qualified personnel with the right to practice the profession of laboratory diagnostics,
- continuous personnel training and immediate response to the needs of physicians regarding patient diagnosis,
- the introduction of the principle that the remuneration of the personnel does not depend on the number of conducted tests and is not in any way related to the results of the analytical tests performed.

The second important document in the management system is the Quality Manual (QM). It is a source of information about the management system in the laboratory, in particular about the introduction and maintenance of this system. A diagram representing a standard structure of management system documentation in a laboratory is shown in Figure 3. The top of the pyramid presents the key documents for the functioning of a laboratory management system. The documents at the top of the pyramid refer to the documents from lower levels.

The QM developed for a laboratory should include:

- quality policy,
- measurable quality objectives,
- process descriptions and their interrelationships,
- organisational structure, including the scope of responsibilities and powers,
- descriptions of the quality management system,
- structure and rules of distribution of management system documentation.

When preparing the Quality Manual, it is important to remember to use clear wording in order to ensure unambiguous interpretation [8, 11]. The structure of the QM, including division into chapters, layout, page numbering, should make it easy to introduce changes or to replace obsolete sheets.

What is essential for the proper functioning of a laboratory management system is also General Procedures (GP) and procedures for the measurement processes (MP) and/or Testing Procedures (TP). The purpose of the procedures is to specify the relationships between units or individuals involved in a given element of the system, as well as the method of performing these activities. The GP should include answers to the questions of what should be done, when it should be done and how, and indicate who is responsible for a given activity.

This document should include the following sections:

- purpose of the procedure,
- subject matter of the procedure,
- scope of application,
- responsibility,
- definitions,
- description of the steps of the procedure,
- documents and records,
- attachments,
- release status.

The Measurement and Testing Procedures have a similar structure, but they also include additional information on:

- the monitoring of environmental conditions,
- the equipment used for laboratory analytical tests,
- the test methods,
- the method of determining measurement uncertainty, documenting the results of analytical tests.

All laboratory procedures should have a uniform layout and labelling that allows for easy identification, updating and monitoring of the document.

Instructions are another document that functions in a diagnostic laboratory. They have the form of internal documents which are used to regulate recommendations related to a specific activity, e.g. weighing, pipetting, etc. Based on the instructions, a particular laboratory activity can be performed step by step. They should contain information on the method of performing the described activity and list the materials and equipment necessary to carry out the described analysis. Moreover, they should allow for the identification of the persons performing individual stages of laboratory work at each workstation. Also important are the conditions that must be met for the repeatability of a given method, as well as the rules for documenting analytical activities, registration, assessment, etc.

A diagnostic medical laboratory should also make use of forms developed and maintained to record data in order to be able to demonstrate compliance of the quality management system in the laboratory with the requirements of superior documents, such as standards. It is recommended that the forms be approved, legible, up-to-date, available and easy to find. They should also be protected from destruction, loss and damage throughout the storage period.

Changes in the scope of accreditation

Accreditation should be understood as recognition by the accreditation body of the competence of the laboratory to carry out specific analytical and testing activities [4]. Changes in the scope of accreditation for a diagnostic medical laboratory are possible in the case of:

- new testing facilities with already accredited methods,
- new test techniques or methods,
- new technical areas of diagnostic services provided throughout the medical facility.

Conclusions

Implementing a certified quality management system in a diagnostic medical laboratory not only allows to organise the laboratory work, but it also facilitates the activities of the whole facility. The overriding goal of accreditation for the entire hospital is to introduce an organised system of work. It provides a clearly defined scope of responsibilities and competencies for each employee, establishes clear procedures which are easy to communicate and which apply not only to diagnostic situations, as they can also systematically improve the qualifications of the personnel, based on the adopted schedule.

Accreditation is a mechanism employed to ensure public confidence in the quality and credibility of activities that are very important from the perspective of public health. In order to confirm the high quality of the conducted laboratory tests, medical diagnostic laboratories should participate in proficiency testing. Participation in such testing provides an opportunity to obtain confirmation of the competence of the laboratory by an independent external facility authorised to make assessments in a given analytical area. They may be national institutions, but also international ones, not only from the European Union.

Accreditation can be a tool that will greatly facilitate access to the global market for laboratory services in accordance with the principle "once tested or certified – accepted everywhere". Nevertheless, in Poland, it is still a matter of the future, because there are only 11 diagnostic laboratories accredited in compliance with the EN ISO 15189 standard, in comparison to 126 laboratories in France, 27 in Romania, 32 in Spain, and 13 in Norway [10].

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Contemporary treatment methods in neovascular type of age related macular degeneration

Współczesne metody leczenia wysiękowej postaci zwyrodnienia plamki związanego z wiekiem

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Abstract. Age-related macular degeneration (AMD) is a degenerative disease of the central retina, which leads to a serious reduction in visual acuity. The pathogenesis of the disease is not fully understood and assumed to be multifactorial. AMD occurs in two clinical types: non-exudative, dry form (geographic atrophy and/or drusen) and exudative, wet form (subretinal neovascular membrane). Currently, numerous studies are conducted on the development of effective treatment of neovascular AMD. The gold standard for the treatment of the wet AMD is the intravitreal administration of anti-angiogenic drugs. Drugs are being developed that could be given in the form of an implant and enable sustained release of the active substance, therefore reducing the need for frequent interventions. Ongoing studies on the analysis of disturbed metabolic pathways and genes that modulate progression of the disease would enable implementation of the targeted therapy. Attempts to treat the exudative form of AMD are not limited to injectable medications applied to the vitreous body. A search for a new, effective form of treatment is also focused on the surgical and laser intervention possibilities.
Keywords: AMD, macula, new methods of treatment, intravitreal injections

Streszczenie. Zwyrodnienie plamki związane z wiekiem (AMD) to choroba degeneracyjna siatkówki centralnej, która doprowadza do poważnego pogorszenia ostrości wzroku. Patogeneza choroby nie jest do końca poznana - przyjmuje się, że jest wieloczynnikowa. AMD występuje w dwóch postaciach klinicznych: suchej (postać zaniku geograficznego i/lub druzów) oraz wysiękowej (postać podsiatkówkowej btony neowaskularnej). Obecnie prowadzone są liczne badania nad rozwojem skutecznego leczenia wysiękowej postaci AMD. Złotym standardem leczenia wysiękowej postaci AMD jest podawanie doszklistkowe leków antyangiogennych. Opracowywane są leki, które byłyby podawane w postaci implantu i umożliwiały długotrwałe uwalnianie substancji czynnej, co ograniczyłoby potrzebę częstych interwencji zabiegowych. Trwają prace nad analizą zaburzonych szlaków metabolicznych i genów modulujących progres choroby w AMD oraz dostosowywaniem terapii do zaburzonych procesów. Próby leczenia wysiękowej postaci AMD nie ograniczają się do iniekcji preparatów do ciała szklistego. Poszukiwania nowej, skutecznej metody leczenia koncentrują się również wokół terapii zabiegowych, laserowych i operacyjnych.
Słowa kluczowe: AMD, plamka żółta, nowe metody leczenia, iniekcje doszklistkowe

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Age-related macular degeneration (AMD) is a degenerative disease of the central retina, leading to a serious reduction in visual acuity. The pathogenesis of the disease is not fully understood and assumed to be multifactorial. AMD occurs in two clinical types: dry form (geographic atrophy and/or drusen) and exudative form (subretinal neovascular membrane [Fig.]) [1].

The picture of the disease includes changes in photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane and in the choriocapillaris [2]. The development and course of the disease is determined by genetic, environmental, functional and metabolic factors, as well as their interactions. Four processes in the retina contribute to the development of AMD: lipofuscin genesis, drusen genesis, inflammatory process and neovascularization [3]. The risk factors for AMD include:

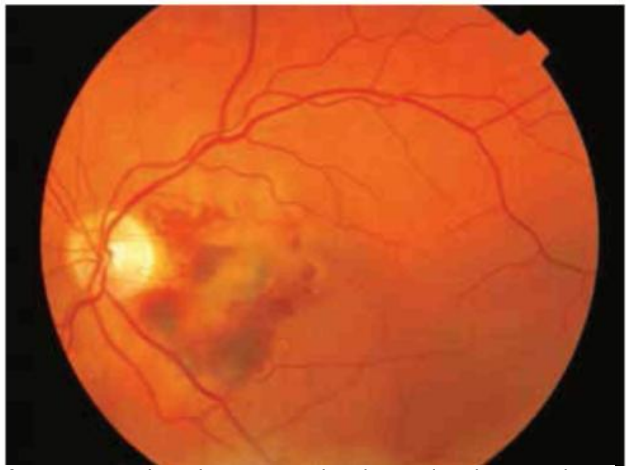

Figure 1. Fundus photo. Age-related macular degeneration - exudative form
Rycina 1. Fotografia dna oka. Zwyrodnienie plamki związane z wiekiem, postać wysiękowa

- age – in the group of 55-64 years old patients, the risk of the disease is 0.1%; in patients over 75 years old, it increases to 7%;
- sex – in patients over 75 years old, AMD is more frequently found in women;
- race – the disease more often affects white people (incidence of 0.5-1.9%) than black people (0.4-0.6%), and the incidence among Asians is 0.87%;
- genetic factors – increased frequency of age-related macular degeneration in the family of the patient affected by the disease; the genes responsible for the genetic predisposition for the disease have been identified, and the role of the complement in the pathogenesis of AMD has been confirmed;
- colour of the iris (people with light, blue irises develop the disease more often);
- refractive disorder (AMD is more often observed in patients with hyperopia);
- smoking tobacco – most studies confirm an increased incidence of AMD in smokers;
- arterial hypertension, coronary disease, atherosclerosis affect the development of AMD, especially of its advanced forms;
- ultraviolet radiation, visible light – excessive exposure to light contributes to the development of AMD.

Presence of AMD in one eye is associated with the risk of lesion in the other eye (the risk is estimated as 26-42% for the exudative form, and 25% for the dry form, within 5 years) [4].

Currently, numerous studies are conducted on the development of effective treatment of exudative AMD. Intravitreal administration of anti-angiogenic drugs is the gold standard for the treatment of this form of AMD. Drugs are being developed that could be given in the form of an implant, to enable sustained release of the active substance, therefore reducing the need for frequent interventions. Ongoing studies on the analysis of disturbed metabolic pathways and genes that modulate progression of the disease may enable the development of targeted therapy. Current clinical studies suggest that gene therapies are very likely to become the preferred treatment of neovascular AMD [5].

Presently, intravitreal injections of anti-angiogenic medicines are used in the therapy of neovascular AMD. They are VEGF-inhibitors (anti-VEGF). VEGF (vascular endothelial growth factor) is a family of 7 proteins, comprising 6 types (A to E), and placental growth factors (PIGF-1, PIGF-2). VEGF-A is considered the most important mediator of angiogenesis. VEGF is a protein responsible for the creation of new vessels, increasing their permeability and intensifying the inflammatory response [6]. Retinal pigment epithelial (RPE) cells appear to play the key role in the regulation of its concentration in the eyeball [7, 8].

Anti-VEGF-A therapy is a remarkable success in ophthalmology. Although it helps to improve visual acuity only in few patients, it allows to prevent progression of neovascular AMD in many cases [7].

The first medicine introduced to the market, authorised by the FDA in 2004, was pegaptanib sodium (Macugen), administered in intravitreal injections into the affected eye, in a dose of 0.3 mg, at 6-week intervals. Pegaptanib is a modified pegylated oligonucleotide which forms selective and strong binds with an extracellular form of the endothelial growth factor (VEGF165), and inhibits its activity [8]. Another medicine, one of the most commonly used worldwide, is bevacizumab (Avastin). The safety of bevacizumab is very controversial. It is a recombined, humanised monoclonal antibody produced in the ovaries of Chinese hamsters with the use of DNA technology. The administration regimen is 1.25 mg of bevacizumab in intravitreal injections into the affected eye. The treatment usually starts with a series of three injections at 4-6-week intervals (the loading dose). Next, the intravitreal therapy is continued according to the condition of the treated eye [9, 10].

The following year, ranibizumab (Lucentis) was launched in the American market. It is a fragment of monoclonal antibody produced in *Escherichia coli* cells using a DNA recombination technology. The medicine is used at 0.5 mg, in intravitreal injections into the affected eye. The treatment usually starts with a series of three injections at 4-6-week intervals (the loading dose). Next, the intravitreal therapy is continued according to the condition of the treated eye [11, 12].

In 2011, FDA authorised aflibercept (Eylea), a recombined chimeric molecule containing extracellular binding elements of VEGF 1 and 2 receptors, combined with the Fe portion of human immunoglobulin G, for the treatment of neovascular AMD. The product's anti-VEGF effect is based on the uptake of the circulating VEGF molecules. As a result, the neovascular lesions are inhibited, the intraretinal and subretinal fluid is resorbed, the retinal thickness is reduced and central vision is improved. The medicine is administered in intravitreal injections, at a dose of 2 mg, into the affected eye, in a

series of 3 injections at one-month intervals (the loading dose), then at 2-month intervals in the first year of therapy [13].

The treatment regimen recommended as a standard by the Polish Ophthalmological Society involved administration of the first three injections at one-month intervals, then the subsequent injections are administered at 2-month intervals [14].

There is a group of patients in whom retinal oedema persists, despite following the above treatment regimen. In this group of patients, periorbital steroid injections are planned, in order to reduce the inflammatory component of the disease [15, 16].

Triamcinolone demonstrates an anti-inflammatory and angiostatic effect. Studies demonstrated that it inhibits the inflow of leukotrienes ad prostaglandins, inflammatory mediators that participate in the pathogenesis of macular oedema. Steroids also block the production of VEGF and enhance the blood-retina barrier. As a result, central retinal oedema is reduced. The medicine is administered in intravitreal injections or under the Tenon's capsule at a dose of 4-25 mg [17].

Dexamethasone (Ozurdex) is a corticosteroid with a strong anti-inflammatory and antioedemal effect. It reduces fibrin deposition, capillary permeability, and migration of phagocytic cells in response to the inflammatory stimulus. The medicine is administered in the form of an implant slowly releasing dexamethasone (0.7 mg), after its placement in the vitreous chamber [18].

Implants in the vitreous humour, associated with fewer systemic complications and offering better disease control, may be a promising therapy for neovascular AMD.

New medicines for the treatment of the disease are being researched, demonstrating various mechanisms of action, whose aim is to increase the effectiveness and safety of treatment [5]. The following substances are currently studied: pazopanib (a strong inhibitor of tyrosine kinase in the vascular endothelial growth factor receptors [VEGFR]-1, -2 and -3, platelet-derived growth factor receptor [PDGFR] – and -β, and stem cell factor receptor [c-KIT], demonstrating multidimensional effects), bevasiranib, E10030, anti-tyrosine kinase, anti-receptor kinase, vatalanib, sirolimus, volociximab and anti-nicotine agents. However, clinical studies have not yet confirmed their effectiveness in preventing disease progression [19].

The attempts to treat neovascular AMD are not limited to injections of medicines into the vitreous humour. The search for a new, effective form of treatment is also focused on the surgical and laser intervention possibilities.

Targeted photodynamic therapy with PDT laser and verteporfin as the photosensitiser is in common use. The procedure consists in the intravenous administration of the medicine, followed by a laser application of light impulses into the affected area of the retina. Laser activates the medicine in the affected vessels of the neovascular membrane, leading to their selective occlusion. Contrary to thermal laser photocoagulation, the remaining retinal tissue remains undamaged in this procedure. There is evidence that the therapy reduces progression of the disease and stabilises visual acuity for many years; however, it is not recommended as first-line treatment in AMD [20].

Laser photocoagulation in the therapy of exudative AMD has a number of limitations. It is used to destroy new vessels of the neovascular membrane, but only in extrafoveal regions. Presently, this treatment option is rarely used [21].

Therapeutic effects of radiotherapy and brachytherapy were studied. Radiotherapy in monotherapy was not associated with any significant functional benefits for the treatment of neovascular AMD; however, epimacular brachytherapy may be a useful option [22]. This method would enable using limited vitrectomy and a source of beta radiation emitted on the area of the macula. Study on TheraSightTM Ocular Brachytherapy System is being conducted [23]. The Polish Ophthalmological Society guidelines do not recommend using radiotherapy or surgical procedures; therefore, these methods are not applied in everyday clinical practice.

Surgical treatment of AMD involves attempts to remove the neovascular membrane or subretinal haemorrhage, move the macula and transplant retinal pigment epithelial cells and stem cells.

Surgical removal of subretinal neovascular membranes as a method of AMD treatment was used as an alternative to laser therapy [24]. Submacular surgery requires pars plana vitrectomy and retinotomy to provide access into the subretinal space. Next, the neovascular membrane is removed instrumentally, together with the scar tissue and possible subretinal haemorrhage [25].

Macular translocation is another surgical procedure performed in AMD. It can be conducted after a partial or total displacement of the retina following circular retinotomy – 360 degrees. After these procedures, numerous complications are observed, including retinal detachment and tear, macular holes or wrinkling, and intraocular haemorrhage. Moreover, macular translocation following 360-degree retinotomy requires placing the head in an oblique position, which is corrected in subsequent stages by moving the attachments of the extraocular muscles [26].

In age-related macular degeneration, where not only neovascular membrane is formed, but also pigment epithelium is damaged, the epithelial cells are transplanted [27].

The retinal pigment epithelial cells may be obtained from exogenous foetal RPE or autologous RPE from the iris [28] or from peripheral regions of the retina [29]. Last year, at the Moorfields Eye Hospital in London, an innovative surgery using stem cells was performed. The procedure consisted in replacing the damaged retinal pigment epithelial cells with new ones, grown in a laboratory from stem cells [30].

Management standards have been set for the treatment of the exudative form of age-related macular degeneration. However, new therapeutic options are being studied, which gives hope for the future for many patients.

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Diagnosis, classification and clinical course of amyloidosis – a review of the literature

Diagnostyka, klasyfikacja i przebieg kliniczny amyloidozy – aktualny stan literatury

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Abstract. The article contains current data on the pathogenesis, classification and diagnosis of amyloidosis. Amyloidosis is a group of diseases associated with extracellular deposition of protein with abnormal conformational structure. Beta structure provides resistance to proteolytic enzymes. We know of many different proteins which have amyloidogenic properties. The most frequently observed type of amyloidosis is AL amyloidosis, the second being amyloidosis AA. Renal amyloidosis is common and depends on the type of amyloidogenic protein. Diagnosis is difficult and multidirectional. Amyloidosis is a chronic disease associated with poor prognosis, requiring a precise diagnosis concerning its type, thus allowing to determine the prognosis.
Key words: amyloidosis, amyloidosis AA amyloidosis AL, fibrillar protein

Streszczenie. W artykule podano aktualne dane dotyczące patogenezy, klasyfikacji i diagnostyki amyloidozy. Amyloidoza to grupa chorób związanych z pozakomórkowym odkładaniem białka o nieprawidłowej strukturze konformacyjnej. Struktura beta zapewnia odporność na działanie enzymów proteolitycznych. Dotychczas poznano kilkadziesiąt różnych białek, które mają właściwości amyloidogenne. Najczęściej stwierdzanym typem amyloidozy jest amyloidoza typu AL, następnie amyloidoza AA. Zajęcie nerek jest częste w amyloidozie i zależy od rodzaju białka amyloidogennego. Diagnostyka jest trudna i wielokierunkowa. Amyloidoza jest chorobą przewlekłą, związaną ze złym rokowaniem - wymusza to precyzyjne ustalenie rozpoznania jej rodzaju, co pozwala na ustalenie rokowania.
Słowa kluczowe: amyloidoza, amyloidoza AA, amyloidoza AL, białko fibrylarne

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Background

Amyloidosis is a heterogenic group of diseases associated with extracellular deposition of proteins with abnormal conformational structure. Changes in the spatial structure impair the function of the deposited protein, and result in resistance to proteolytic enzymes [1]. Excessive deposition may lead to multiorgan failure. The disease was described for the first time in 1842 by Rokitansky [2], while the term "amyloidosis" was introduced by Virchow, who observed in 1854 that after staining the affected tissues with iodine, the protein fibres turn blue [3].

Epidemiology

The most common type of amyloidosis in countries with high socioeconomic status is associated with the deposition of light chains of immunoglobulins; it is amyloid light-chain (AL) amyloidosis [4-6]. AL amyloidosis usually

develops spontaneously, although it may coexist with other plasma cell dyscrasias, such as multiple myeloma or, more rarely, Waldenstrom's macroglobulinemia. AL amyloidosis should always be suspected when proteinuria with concurrent cardiomyopathy, neuropathy or hepatomegaly is found, as well as in patients with multiple myeloma. In the last twenty years, a significant reduction was observed in the incidence of amyloidosis AA (amyloid A amyloidosis), associated with the deposition of plasma amyloid A protein, the precursor of acute phase protein. This effect may be attributed to a considerable improvement in the anti-inflammatory treatment of rheumatoid arthritis. In the 1980s, 33% of all the cases of amyloidosis were AA amyloidosis, and since 2008, the rate is 6-8% [7]. Moreover, an increase in the detection of transthyretin (TTR) amyloidosis from 0-2% to 4-6% was observed. Cardiac involvement is specific for transthyretin amyloidosis. The discussed increase was partially due to the widespread use of magnetic resonance (MR) in the differential diagnosis of cardiomyopathy. The third most common type of amyloidosis with renal involvement is associated with deposition of chemotactic factor type 2 for leukocytes – Lect2 (Lect2 amyloidosis, ALect2) [8]. Lect2 is a protein found in serum, produced by the liver, and playing the role of growth stimulator and the factor inducing the recovery of damaged cells. It demonstrates a stimulating effect on chondrocytes and osteoblasts. ALect2 occurs in young people, especially in Mexico, South Asia, in the Middle East and North Africa. Characteristic for this form of amyloidosis is a progressive renal disease with non-nephrotic proteinuria, which accounts for limited diagnosis of the disease. In renal biopsy, abnormalities are found primarily in the cortical parenchyma, with minimal medullary lesions. The disease may recur in a transplanted kidney. No amyloid deposition in the heart is observed. This form of the disease is often associated with hepatic lesions, and a characteristic circular arrangement of the deposits in the hepatic hilum. Due to the amyloid deposition in the lungs and kidneys, the disease may take a clinical form of pulmonary-renal syndrome. No effective treatment has been developed so far [9-11].

Approximately 30 different proteins with amyloidogenic properties have been discovered to date. The dynamic development of molecular medicine and the use of mass spectrometry to identify amyloid fibrils will likely contribute to a higher number of identified proteins [12]. The development of genetics, and searching for new mutations responsible for the coding of abnormal proteins will have a similar effect. The data on the prevalence of amyloidosis is limited and underestimated. It is estimated that 3-5 patients in 1 million people are diagnosed with amyloidosis [13]. In autopsy examination, amyloid deposits are found in up to 25% of people over 80 years old [14]. Table 1 presents short characteristics of the most common types of amyloidosis [12].

Risk Factors

Age is an established risk factor for amyloidosis. It is suspected that the risk of developing the disease increases with age [15]. The mean age of AL onset is 63 years [5]. More cases are reported in men than in women [16]. Men more often suffer from amyloidosis associated with the presence of light-chain immunoglobulins [5], whereas women more frequently develop AA, which is closely related to the higher incidence of rheumatoid and systemic diseases in females. AA amyloidosis with renal involvement may occur also in a patient with a long history of diabetes; it is then associated with more severe cardiovascular and renal complications [17]. There are reports of amyloidosis induced by insulin injections. Subsequent injections in the site of amyloid deposition may potentially reduce the control of glycaemia, and increase the need for insulin, due to impaired absorption [18].

Symptoms and clinical course

As amyloid fibrils may be deposited in different tissues and organs, the clinical symptoms of the disease vary. The commonly described set of symptoms typical for amyloidosis, including bruising around the eyes and enlarged tongue (macroglossia), is observed in less than one in three patients. Various clinical symptoms and initially minor abnormalities in laboratory tests delay accurate diagnosis. There are no precise sets of symptoms for individual types of amyloidosis; only a specific predisposition for the involvement of a particular organ or system by amyloid can be determined.

In AL amyloidosis, the first sign is often hepatic involvement, observed in 33-92% of patients. The symptoms may then include moderate jaundice and cholestasis. However, hepatic involvement does not lead to end-stage liver failure, or to the development of portal hypertension [19-21]. Histopathological examination reveals characteristic protein deposits, stained by Congo Red, in the sinusoids and Disses's spaces, in the vascular wall and in the connective tissue of portal spaces [22].

Kidneys are the second most frequently affected by amyloid deposits organ. Renal involvement is usually observed

Table 1. Short characteristics of selected types of amyloidosis, with type of amyloidogenic protein and its precursor [12]
Tabela 1. Skrócona charakterystyka wybranych typów amyloidozy z uwzględnieniem rodzaju białka amyloidogennego i jego prekursora [12]

fibrous protein	precursor protein	characteristics
AL	light-chain immunoglobulin	the most common type of amyloidosis amyloidogenic protein affects virtually all organs, with the exception of CNS both inherited and acquired forms are found In the diagnostics, it is important to determine the presence of light chains and their abnormal rates in blood serum
AA	amyloid A	second most common type of amyloidosis affects all organs, with the exception of CNS characterised by increased concentration of serum SAA protein – serum amyloid A protein, and β2-microglobulin the source of inflammation always needs to be detected, and the inflammation has to be reduced to prevent the disease's progress
ATTR	transthyretin	affects primarily the heart (especially in men), ligaments and tendon sheaths, peripheral and autonomous nervous system, heart, eyes cardiovascular involvement significantly aggravates the prognosis the diagnosis is based on immunohistochemical staining of tissues in order to detect transthyretin deposits increased serum transthyretic concentration has no diagnostic significance
AApoAI AApoAII AApoAIV	apolipoprotein A 1 apolipoprotein A II apolipoprotein A IV	much less common characterised by isolated renal involvement; however, amyloid deposits can be found also in the heart, liver, kidneys, CNS, testicles, larynx, skin no specific serum marker to identify this type of amyloidosis no other diagnostic tools than advanced immunohistochemical staining are available for identification of this type of amyloidosis
ALECT2	chemotactic factor for leukocytes	characterised by isolated renal involvement the only diagnostic option involves immunohistochemical staining of bioptates for the presence of chemotactic factor for leukocytes
AFib	fibrinogen alpha	characterised by isolated renal involvement and hereditary form of amyloidosis

in the course of: AL, AA, fibrinogen ayloidosis (AFib), ALect2 and amyloidosis associated with apolipoprotein type A1 deposition (AApol). Renal involvement may be asymptomatic for a long period, until advanced lesions in glomerulus develop. Then, the most common clinical symptom is nephrotic syndrome. Renal impairment is frequently observed at the diagnosis of amyloidosis. Low arterial pressure and renal insufficiency are indications for testing for amyloidosis [23, 24]. Haematuria is another symptom of amyloidosis, although the data about its incidence is ambiguous. In a study by Da Fonesca et al., haematuria was found in 75% of patients [15], whereas Petterson and Konttinen rarely observed haematuria [25]. Renal enlargement is rare in the course of the disease [26].

Deposition of the amyloid fibrils in the cardiovascular system significantly aggravates the prognosis [27]. The process usually affects patients with AL or trasthyretin amyloidosis, less often those suffering from AA [29]. In approximately 50-80% of patients with AL, abnormalities in the electrocardiographic test are found [28, 30, 31]. Characteristic features include low voltage of the QRS complex, and QS complexes that may indicate a history of myocardial infarction. Disorders in the cardiac conduction system are also observed, including first-degree atrioventricular block [30, 32, 33]. Typical changes found in echocardiographic examination include valvular insufficiency, impaired diastolic function, atrial enlargement, myocardial fibrosis, reduced cardiac compliance, thickening of the cardiac wall, and signs of restrictive cardiomyopathy with reduced left ventricular ejection fraction [31, 34]. Clinically, biventricular cardiac failure can be found, with reduced arterial pressure values, orthostatic blood pressure decreases, and fainting [30, 32, 34]. Laboratory tests reveal elevated concentrations of high-sensitivity troponin I and atrial natriuretic peptide, which aggravates the prognosis and is one of the factors qualifying for treatment [23, 35-37]. In x-ray examination,

the heart is of normal size, or slightly enlarged [38]. The presence of amyloid in coronary vessels (in media and adventitia), and in microcirculatory vessels may contribute to cardiac ischaemia [30, 31, 39].

Other symptoms in the course of amyloidosis include reduced body weight, weakness, paresthesias and carpal tunnel syndrome [40]. Amyloid deposits are rarely found in the pulmonary tissue. Also, head and neck organs are rarely the sites of amyloid deposition [41], and there are no specific symptoms for such situation. The following may occur: pain and palatal asymmetry, macroglossia, and with laryngeal involvement also coarseness, increasing dyspnea and haemoptysis [41-46]. Amyloid deposition in the Waldeyer's ring causes the sensation of an obstacle or discomfort in the throat, as well as difficulty with swallowing [41, 47]. Gastrointestinal symptoms of amyloidosis include disturbed stool frequency, loss of appetite, occult haemorrhage and malabsorption syndrome [48].

Diagnostics

As amyloid fibrils may be deposited in different tissues and organs, the gradual, often long-lasting progression of the symptoms makes the diagnostics difficult. Multidirectional and prompt diagnostics management is recommended, in order to establish an accurate diagnosis of amyloidosis, its advancement and the type of amyloidogenic fibres, which has important clinical consequences. The treatment based on the diagnosis is often burdensome and associated with many adverse effects. If the patient displays weakness, macroglossia, and renal and cardiac failure, diagnostics for amyloidosis should be conducted. The clinical symptoms, laboratory test, imaging studies and assessment of histopathological specimens stained with Congo red should be considered. The diagnostic procedures involve biopsy (of the gums, rectal mucosa, abdominal fat tissue, the organ involved or bone marrow). If there is no reaction to Congo staining in one of two sites in the biopsy, systemic amyloidosis may be excluded. Amyloidosis in any location, except for the larynx, is associated with plasma cell dyscrasia or haematological abnormalities [42, 45].

Mercan et al. demonstrated the usefulness of minor salivary gland biopsy (MSGB) in the diagnostics of amyloidosis. The method is safer for the patient than biopsies of other organs, associated with serious complications, especially of a haemorrhagic nature. Thirty-five patients with symptoms suggestive of amyloidosis were qualified for the study; 18 patients were diagnosed with the disease, and in 11 cases the diagnosis was confirmed as MSGB. The method's sensitivity was estimated at 61.1% [49].

To diagnose AL, plasmocyte dyscrasia needs to be detected (e.g. through bone marrow biopsy), and amyloidogenic protein must be found in tissues. Plasmocyte dyscrasia may be observed by detection of monoclonal light-chain immunoglobulins in blood serum or in urine. The normal kappa to lambda chains ratio is 0.26-1.65. In patients with AL, increased lambda chain concentrations are more frequently observed. Then, the kappa to lambda chains ratio is below 0.26. If the kappa chains concentration is elevated, the ratio will be >1.65. It is worth noting that in renal failure, the concentrations of kappa and lambda light-chain immunoglobulins increase, but their ratio remains unchanged. Light-chain immunoglobulins may be determined with two methods: immunofixation or nephelometry. The nephelometric test is characterised by higher sensitivity than immunofixation [35, 50, 51]. Amyloid deposits may be presented with radioisotope method using technet-99m (^{99m}Tc), especially in the diagnostics of cardiac amyloidosis [52]. Recently, establishing the source of the amyloid protein has been emphasised. The combination of laser microdissection method with mass spectrometry is the promoted method. It is the only one to identify the type of deposited protein in 100% of cases [53]. Determination of the type of amyloid with the above method is particularly important in Afro-Americans with monoclonal gammapathy, in men over 70 years old with cardiomyopathy, and in Hispanics with concurrent renal insufficiency. The test is to differentiate between genetic forms of amyloidosis: Afro-American amyloidosis with transthyretin amyloidosis in elderly patients and Lect2 amyloidosis in the Hispanic population. It should be emphasised that in the absence of plasma cell dyscrasia, AL should be diagnosed with caution, as patients with a genetic form of amyloidosis will not benefit from standard chemotherapy. Therefore, it is crucial to recognise the type of amyloid prior to treatment implementation.

The effect of amyloidogenic protein on the renal function is particularly important. In many studies, no differences were found between the toxicity of kappa or lambda light chains. It should be emphasised that renal failure is found in approximately 50% of newly diagnosed cases of plasma cell dyscrasia. In a study conducted in our department (in the years 1994-2000), involving 72 patients diagnosed with plasma cell dyscrasia, elevated serum creatinine concentrations of >1.5 mg/dl were observed in 31% of subjects, and eGFR values of <90 ml/min, derived from Baracskay formula, in as many as 89% of patients. The elevated calcium and uric acid concentrations were determined to be significantly correlated with reduced glomerular filtration. Moreover, the presence of Bence-Jones protein considerably reduces eGFR values. The study did not demonstrate a statistically significant difference in nephrotoxicity between various types of free light chains (kappa or lambda) depending on creatinine concentrations and eGFR values [54]. It is important to monitor kidney function both before and during the treatment. There is an ongoing discussion regarding the indicators which best reflect current renal function. Endogenous creatinine clearance calculated on the basis of a daily urine sample is still the best indicator of kidney function. However, due to difficulties in performing this test, especially in elderly patients, it is not used very often.

In the Department of Nephrology, Military Institute of Medicine, in 2001 a study comparing different methods of glomerular filtration assessment was conducted [55]. The study involved 32 patients (10 females and 22 males) with

newly recognised plasma cell dyscrasia. The patients were divided into two groups, based on the presence or absence of monoclonal protein in a daily urine sample. The study demonstrated that in patients without the monoclonal protein in urine there are no statistically significant differences in the assessment of eGFR with different methods, i.e. endogenous creatinine clearance, eGFR estimated on the basis of Crockcroft-Gault formula or Baracskay formula. Other results were obtained in the group of patients whose urine contained Bence-Jones protein. It appeared that in such cases only eGFR estimated using Crockcroft-Gault formula was not statistically significantly different from the endogenous creatinine clearance determined on the basis of a daily urine sample. This study demonstrated that eGFR estimated with the above formula should be commonly used in ambulatory practice to assess renal function in patients with plasma cell dyscrasia [55].

Academic accomplishments of the Department of Nephrology of the Military Institute of Medicine include also three studies on the diagnostics and treatment of plasma cell dyscrasia [56-58].

Summary

Amyloidosis is a heterogenic group of diseases which share one characteristic: extracellular deposition of protein. The disease has varied aetiology. It can be caused by genetic or environmental factors, or by concurrent inflammatory diseases. The type of amyloidogenic protein is sometimes difficult to identify, although the dynamic progress in medicine may soon provide faster and more precise diagnostic methods. In diagnostics, laboratory and histological assessment of haematological parameters plays an important role. It should also be noted that amyloidosis is a chronic disease that requires treatment, and due to its various forms and therapeutic methods, accurate diagnosis is necessary.

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Zika virus – a new risk for blood safety and tissue and organ transplantation?

Wirus Zika – nowe zagrożenie dla bezpieczeństwa krwi oraz przeszczepów tkanek i narządów?

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Abstract. Zika virus, which belongs to the *Flavivirydae* family, is transmitted by female mosquitoes of the genus *Aedes.* After spreading beyond Africa and Asia, it is responsible for new vector-borne infectious diseases. Most of Zika infections are subclinical or characterised by poorly expressed influenza-like symptoms. The complications resulting from Zika infection include neurological changes in the form of Guillain–Barré syndrome and microcephaly in infants born to infected mothers. The risk of transmission of Zika virus infection by blood components or tissue/organ transplants has not been defined, although a large number of asymptomatic infections, particularly among potential donors, makes it possible. Therefore, many countries in Europe and the Americas have introduced procedures recommended to donors returning from countries affected by the epidemic. This article analyses the current state of knowledge about the risks associated with transmission of Zika virus and the possible effects of infection on the safety of transfusions and transplants.
Key words: Zika virus, epidemiology, diagnostics, blood safety, transplant safety

Streszczenie. Wirus Zika, zaliczany do rodziny *Flaviviridae*, przenoszony jest przez samice komara z rodzaju *Aedes*. Po tym, jak rozprzestrzenił się poza Afrykę i Azję, jest odpowiedzialny za nowe transmisyjne choroby zakaźne. Większość zakażeń wirusem przebiega subklinicznie lub charakteryzuje się słabo wyrażonymi objawami grypopodobnymi. Do powikłań powstałych w wyniku zakażenia wirusem Zika należą zmiany neurologiczne w postaci zespołu Guillaina i Barrego oraz mikrocefalii u noworodków urodzonych przez zakażone matki. Nie zdefiniowano ryzyka przeniesienia zakażenia wirusem przez składniki krwi lub przeszczepy tkankowo-narządowe, chociaż duża liczba zakażeń przebiegających bezobjawowo, w tym u potencjalnych dawców, stwarza taką możliwość. Dlatego też w wielu krajach Europy oraz obu Ameryk wprowadzono procedury, które zarekomendowano dawcom powracającym z podróży do krajów objętych epidemią. W artykule dokonano analizy obecnego stanu wiedzy dotyczącego zagrożeń związanych z transmisją wirusa Zika oraz możliwego wpływu zakażenia na bezpieczeństwo przetoczeń i przeszczepów.
Słowa kluczowe: wirus Zika, epidemiologia, diagnostyka, bezpieczeństwo krwi, bezpieczeństwo przeszczepów

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Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus that has caught the attention of the medical community after it spread beyond Africa and Asia and caused the onset of complications and mortality of infants born to infected mothers. By July 2016, cases of virus transmission were reported in 56 countries in only 9 months. The World Health Organization (WHO) estimates that approx. 3-4 million people will be infected with Zika virus by the end of 2016 [1].

ZIKV was first identified in 1947 in Rhesus monkeys in the

Zika forest in Uganda (East Africa). Zika virus infection in humans was first described in 1952 in Uganda and Tanzania, and in 1953 a case of symptomatic infection in Nigeria was confirmed. In humans, ZIKV causes an acute infectious disease, known as Zika fever, whose symptoms resemble influenza. ZIKV is an enveloped RNA virus that belongs to the *Flaviviridae* family, the *Flavivirus* genus. It is related to viruses that cause dengue fever, West Nile fever, Japanese encephalitis, tick-borne encephalitis and yellow fever, among others [1, 2].

Epidemiology of Zika virus infections

Between the 1950s and the 1980s, the virus was circulating in Africa and Asia, rarely causing disease in humans. The situation changed in 2007, when the first epidemic outbreak was recorded outside the natural habitat of the virus, on the island of Yap in the Pacific. At the turn of 2013 and 2014, a Zika epidemic was reported in French Polynesia, where about 11% of the population showed symptoms of the disease. The geographic range of Zika virus has steadily increased [3]. Since February 2015, there have been domestic cases of Zika virus infection reported in Brazil, where ZIKV is now the biggest health problem. The Brazilian Ministry of Health estimates that, in 2015, 0.5-1.5 million people were infected [4]. The second country in the Americas with the highest number of infections is Colombia. Between October 2015 and 25 June 2016, 87,414 probable and 8,850 confirmed cases of Zika infections were reported worldwide [5]. Figure 1 shows areas with ZIKV infections.

According to WHO data, by 28 October 2016, Zika virus transmission was documented in 73 countries and regions worldwide, and in 12 countries: Argentina, Canada, Chile, France, Italy, Germany, the Netherlands, New Zealand, Peru, Portugal (Madeira), Spain, and the United States, non-vector, human-to-human transmission of Zika virus was reported [6, 7]. To date, no so-called airport infections have been reported (transcontinental flights with mosquitoes, the infection vectors, on board and cases of the disease in people who have not been in the endemic/epidemic areas of the disease), such as in the case of, e.g. malaria. Although the risk of importing mosquitoes with Zika virus in aircraft cabins is small, the WHO has issued detailed recommendations for the disinfection of aircraft, airport halls and areas around airports [8].

In the continental United States of America, in July 2016, the Department of Health in Florida confirmed 4 cases of domestic transmission of Zika infection as a result of a mosquito bite (in Miami-Dade and Broward counties). Then, in the next seven days, another 25 cases of domestic Zika infections were recorded at the turn of July and August 2016 [9]. By July 2016, a total of 1,403 cases of Zika infections were reported in the United States, including 400 in pregnant women and 15 infections through sexual contact [10]. In the course of the above infections, Guillain–Barré syndrome (5 cases) and microcephaly (3 cases) were observed [10].

Transmission routes of Zika virus

The main route of transmission of the virus to humans is through being bitten by infected female mosquitoes of the genus *Aedes*, mainly the species *Aedes aegypti* and *Aedes albopictus.*

The possibility of Zika virus transmission exists in the geographic areas where the *Aedes* mosquito occurs. The area of Zika infections largely coincides with the area where other arboviruses occur [2, 11]. The *Aedes aegypti* mosquito inhabits tropical and subtropical regions, in Europe on the Russian Black Sea coast. It is a vector of the Zika virus responsible for the current epidemic in the Americas [2]. The species *Aedes albopictus*, also called Asian or tiger mosquito, carries the virus primarily in Africa. It is resistant to low temperatures (in Japan, its presence was found in areas where the isotherm was +12°C). From the beginning of the 20th century, the expansion of *Ae. albopictus* has been observed around the world. In the 1970s, this mosquito appeared in Europe on the Mediterranean coast [2, 12]. The biological capacity of the two mosquito species to transmit the Zika virus is similar. However, within the *Aedes* species itself, there are differences in susceptibility to infection with the virus. It is unclear how the European *Aedes* population adapts to the Zika virus. It is believed that *Ae. albopictus* is less effective in the transmission of arboviruses, including ZIKV, than *Ae. aegypti.* On the other hand, *Ae. albopictus* occurs in many European regions and is involved in recent arbovirus infections in Europe [2, 12].

Apart from a mosquito bite, sexual contact is a confirmed human-to-human route of transmission of the infection [2]. The first case of sexually transmitted Zika virus infection was described in 2008 in the USA (a woman infected by her husband returning from Senegal) [13]. Cases of sexually transmitted infections were documented among the partners of men in the USA, Argentina, Chile, New Zealand, Peru, Canada, who travelled to the regions affected by the virus epidemic. In Europe, five countries have reported cases of transmission of ZIKV infection by this route: France (11 cases), Italy (2 cases), one case in the Netherlands, one in Portugal and one in Spain [14]. A characteristic feature of the published descriptions of sexually transmitted infections was the transmission of the virus from an infected male to his female or male sexual partner. In July 2016, the first case of Zika infection in a man who had intercourse with an infected woman was confirmed in the United States.

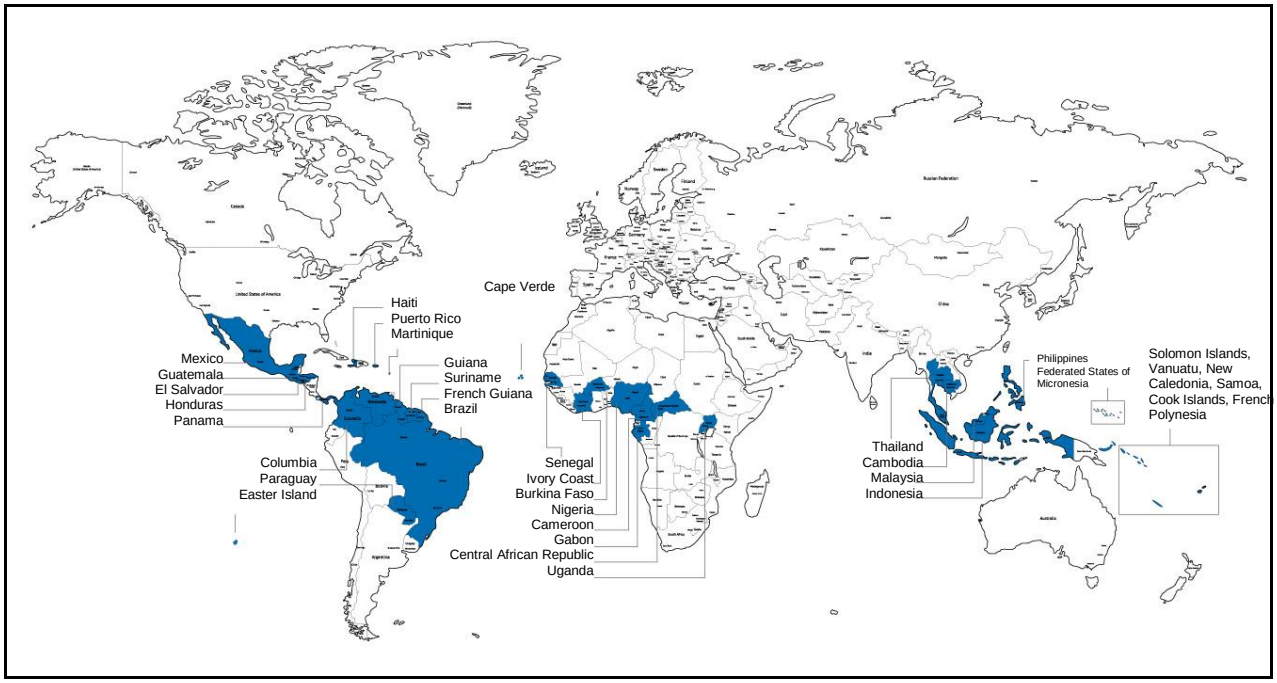

Figure 1. Areas with Zika virus infections (own work after: Centers for Disease Control and Prevention)
Rycina 1. Obszary występowania zakażeń wirusem Zika (oprac. własne za: Centers for Disease Control and Prevention)

[15]. The Zika virus presence in the semen lasts up to 24 days after the onset of the disease symptoms. Longer periods of viremia were also observed, even up to 6 months after infection [15, 16]. Most documented cases of sexually transmitted ZIKV infection occurred after transmission of the infection from a person with the symptoms, but there were also two cases of transmission from an asymptomatic carrier [15, 16]. The virus was also found in vaginal secretions. The data on the persistence of ZIKV RNA in the reproductive tract are divergent. The study by Prisant et al. indicates that the virus persists for up to 3 weeks after the onset of symptoms [17], whereas Murray et al. estimate this period to be 11, 13 or 14 days after the onset of symptoms [18]. Statistical data show that, although the sexual route of transmission may increase the risk of infection and the spread of the epidemic, it does not initiate or support it [17, 18].

Another confirmed route of transmission of the Zika virus is the intrauterine and perinatal route from an infected mother to her child [19]. The virus RNA was detected in amniotic fluid, blood and tissue samples, including nerve tissue. Medical personnel may also become infected during the diagnosis of virus-contaminated material, and the virus may also be transmitted from a donor to the recipient during blood transfusion [5, 20, 21]. An analysis of four cases of Zika infection brought from Venezuela to China showed that the viremia of the Zika virus in one asymptomatic patient was at a level (10,000 copies/ml) comparable with fully symptomatic cases between the 7th and 9th day after possible exposure to mosquito bites. These observations indicate that asymptomatic cases may have a viral load comparable with symptomatic cases [5].

Symptoms of Zika virus infection

About 80% of Zika cases occur asymptomatically or with mild clinical symptoms. The disease incubation period is 3-12 days. The symptoms of Zika virus infection, like other arbovirus infections, are similar to influenza-like infections. There is moderate fever (usually <38°C), maculopapular rash on the lower and upper limbs (on the 1st-2nd day of the disease in 90% of cases), headache and muscle aches, retrobulbar pain, conjunctivitis, swollen and painful joints, mostly small joints of hands and feet. The symptoms disappear after 2-7 days. The disease is self-limited in nature. Due to the lack of characteristic symptoms, the infection may be undiagnosed or mistakenly diagnosed as another disease, such as, e.g. dengue or chikungunya, which have a similar clinical picture and geographic range [22]. The occurrence of specific symptoms may help in the differentiation, i.e. hepatomegaly in dengue, not present in ZIKV infections, or conjunctivitis, which is rarely seen in dengue and chikungunya but often in ZIKV infections (50-90% of cases) [22].

Complications of Zika virus infection

The emergence of the Zika virus in Brazil in 2015 was temporally and geographically correlated with a sudden

increase in the incidence of microcephaly in infants, as well as Guillain–Barré syndrome (GBS). In March 2016, the WHO announced that there was unquestionable evidence of the relationship between Zika and Guillain–Barré syndrome and microcephaly or other neurological diseases in infants born to infected mothers [23, 24]. The incidence of GBS was estimated to be 0.24 per 1,000 infections, and the risk of microcephaly occurred in 95 out of 10,000 diagnosed infections [2]. Research results published in the literature indicate that the Zika virus has the capacity to multiply in human neural progenitor cells, causing cytopathic effect [23, 24]. Viral replication in these cells can last several weeks, and animal studies confirm the damaging effects of the virus, which inhibit cell proliferation and differentiation, leading to apoptosis. The research results are in line with the results of histopathological studies conducted on neural tissue samples taken from deceased infants and placenta tissues collected in the cases of spontaneous abortion. This leads to the conclusion that Zika virus has a destructive effect on the developing fetal brain.

In all cases, pregnant women reported rash and fever during the first trimester of pregnancy. ZIKV RNA was found in blood samples from pregnant patients. In addition, viral antigens were present in the cytoplasm of degenerated and necrotic neurons and glial cells in the brains of deceased infants with microcephaly [23, 24]. It appears that the greatest risk of development of central nervous system malformation arises when the infection occurs in the first and second trimesters of pregnancy. The impact of Zika virus infection on the risk of neurological complications in the third trimester is still poorly understood.

According to the WHO data of 20 October 2016, cases of congenital central nervous system malformation in infants associated with Zika infection in mothers have been reported in 23 countries in Central America, South America and Oceania. Most cases of microcephaly have been reported in Brazil and Colombia. In Europe, 15 cases of microcephaly have been confirmed in children whose mothers travelled to Brazil, Colombia, Venezuela, Mexico, Belize and Guatemala during pregnancy. Cases of Zika virus infection with concomitant Guillain–Barré syndrome have been documented in 19 countries of Central and South America [25].

Laboratory diagnosis of ZIKV

Diagnosis of Zika virus infection with clinical symptoms should take into account the patient's travel history, which may be hampered by the overlapping areas of endemic occurrence of other arboviruses. A laboratory diagnosis of ZIKV includes the serological method, the genetic method, neutralisation test and virus cultivation. The RT-PCR-based genetic method allows for the detection of ZIKV RNA in the blood serum of patients in the active phase of the disease until the 7th day after the onset of clinical symptoms. It is possible to diagnose ZIKV RNA by the PCR method in urine and saliva specimens. The virus lasts longer in urine and can be detected 10-20 days after the onset of the disease [26].

Bingham et al. compared the results of RT-PCR tests performed on 53 subjects and their urine, saliva and serum specimens taken on the same day and from the same patients [27]. Positive results were obtained in 49 urine samples (92%), 43 saliva samples (81%) and 27 serum samples (51%). The authors suggest that urine specimens may be the preferred test material, while the Center for Disease Control and Prevention in Atlanta recommends parallel serum and urine tests in patients suspected of being infected with Zika on the 7th day after the onset of symptoms or later [2, 27]. In people with a suspected active viral disease, a positive RT-PCR result confirms viral infection, but a negative result does not exclude it [27].

The serological method allows for the detection of distinctive IgM and IgG antibodies in the patient's blood by the ELISA method. IgM-class antibodies appear more than 4 days after the onset of disease symptoms. Data on the persistence time of IgM-class antibodies in the course of ZIKV infection are limited. IgG-class antibodies that neutralise the virus appear shortly after IgM antibodies, and it is possible that, like in the case of other flaviviruses, they persist long after infection, possibly for the rest of the patient's life. The ELISA method is fraught with the risk of cross-reactions with antibodies dedicated to other flaviviruses, primarily to the dengue virus. The neutralisation test *(plaque-reduction neutralisation test* – PRNT), which detects ZIKV-specific neutralising antibodies, seems to be a more distinctive method of detecting antibodies dedicated to ZIKV than the ELISA technique. It can be used to exclude false positive ELISA results and to identify the virus species in a person infected with a flavivirus for the first time. Serum or cerebrospinal fluid may be the test material. People who have suffered from yellow fever or Japanese encephalitis, or those who have been vaccinated against these diseases after exposure to another flavivirus, may experience a sudden significant increase in neutralising antibody titer directed to the flavivirus from the previous exposure. It may lead to the inability to determine unambiguously which flavivirus is responsible for the current infection in the patient [27].

In serum samples taken later than 7 days after the onset of symptoms, a negative RT-PCR result and negative results of the tests for IgM antibodies exclude recent infection. A negative result of the IgM antibody test, in the absence of RT-PCR testing, may also be due to taking the sample before the development of detectable antibodies and does not exclude ZIKV infection. For serum samples collected from 7 days to 12 weeks after the onset of symptoms, a negative result for the presence of ZIKV IgM antibodies excludes recent infection [27].

Pregnant women who have travelled to areas affected by a Zika epidemic should be tested for infection and foetal ultrasonography should be performed to exclude microcephaly.

In infants born to mothers infected with ZIKV, a diagnosis should be performed for infection with the virus. A differential diagnosis of the causes of neurological

abnormalities in fetuses and newborns should take into account other congenital infections such as toxoplasmosis, rubella, cytomegalovirus infection and infection with *Herpes simplex* virus (TORCH syndrome) [28].

A differential diagnosis of arbovirus infections should take account of the fact that the number of leukocytes and platelets in the basic laboratory tests remains normal in the case of Zika virus infection, whereas leucopenia and thrombocytopenia are present in dengue and chikungunya infections [28].

Assessment of the risk of ZIKV infection in Europe

In Europe, the WHO has not reported any domestic infections with Zika virus. Between 2015 and 22 July 2016, a total of 1,048 cases of infections brought from endemic regions were reported in 18 countries of the European Union. Two countries recorded the highest number of infections – France (534) and Spain (154); 46 cases concerned pregnant women. By travelling from epidemic countries, people infected with the virus can initiate local transmission of the virus in countries not affected by the epidemic where there is a competent vector capable of carrying the ZIKV. Circulation of the virus in epidemic areas coincides with summer holidays in Europe and it is possible that people returning from holidays may pose a risk of secondary virus transmission in areas with a favourable climate [29].

The risk associated with the spreading of the virus to ZIKV-free areas in the European Union is significant because the population in these areas remains immunologically naive, competent vectors are present, arbovirus epidemics transmitted by *Aedes* mosquitoes have been observed in the past, there is a favourable climate and intense migration of people between countries and regions [2].

The risk of a Zika virus epidemic in Europe varies between countries and regions and depends on many factors, the most important of which are the probability of local transmission of the virus and the capacity of the country to reduce transmission at an early stage [6, 11].

According to the announcement of the Chief Sanitary Inspectorate, Poland is a country where there are no environmental and climatic conditions conducive to the occurrence of *Aedes* mosquitoes. Low temperatures limit their reproduction. Therefore, the risk of Zika virus infections in people living in Poland is associated mainly with tourist trips to regions where ZIKV infection vectors are present [30].

ZIKV infection and the safety of blood and its components

Zika can be transmitted by transfusions of blood and its components. The Food and Drug Administration (FDA) has identified the Zika virus as a threat to the safety of haemotherapy. In French Polynesia, 2.8% of donations received from asymptomatic donors during the epidemic in 2013-2014 included ZIKV RNA. It indicates a potential risk of transmission of the virus by blood [2]. In a study conducted in Puerto Rico in 2016, about 1% of donations from asymptomatic donors tested positive in screening tests for the Zika virus [2]. Despite the scale of the epidemic in Brazil, only four probable cases of transmission of ZIKV infection by transfusion of blood components from three symptomatic donors have been reported. They did not manifest symptoms of infection on the day of donation, but the results of ZIKV RNA tests in the blood were positive [21, 31]. Similarly, recipients who have been diagnosed for post-transfusion infection with the virus, did not manifest any symptoms. Therefore, the Zika virus infection in recipients may be undiagnosed. The risk of Zika virus transmission through blood transfusion is high for many reasons.

- The large scale of the epidemic causes donors and recipients to be similarly exposed to mosquito-borne infections (recipients may already have produced antibodies).
- Epidemics are located mainly in underdeveloped countries where there are no systems monitoring the safety of blood and its components *(haemovigilance)*, even if the transmission factor has been identified and the symptoms are well described. In addition, there are no differentiation tests performed for arbovirus infections.
- Approximately 80% of infections are asymptomatic and may be transmitted sexually, probably even up to 6 months after infection [14].
- The incubation period of the disease lasts an average of 3-12 days during which the virus is present in the blood.
- Viremia is generally very high, even up to 8 million copies of the virus per millilitre of serum on symptomatic days. However, before the onset of symptoms and after their disappearance, viremia is low, which affects the number of asymptomatic infections and causes diagnostic difficulties [14, 24].
- Transmission of other flaviviruses such as West Nile virus, dengue virus or yellow fever virus through blood transfusion has been documented [2].

Most countries with systems monitoring the safety of blood and its components in place, including Poland, have introduced procedures for dealing with donors and blood components, mainly for the prevention of imported infections. They include: donor selection, waiting period for blood components, laboratory testing and pathogen inactivation. Donors returning from regions where Zika virus transmission has been reported should be temporarily deferred from blood donation.

The following criteria disqualify donors for a period of 28 days:

- diagnosed Zika virus infection,
- return from a region where the virus is wide spread,
- sexual contact with a person who has been diagnosed with ZIKV infection or with a person who has returned from a region where the virus is wide spread; areas of

new epidemics should be continuously monitored.

Implementation of the waiting period for all blood components is difficult to carry out due to different storage periods. The waiting period is determined by the length of the viremia period and the expiry date of a given blood component. For the Zika virus, it is 7-14 days. This procedure is limited by the high number of asymptomatic infections and short storage period of platelet concentrates. The Zika virus is likely to be neutralised in plasma and plasma-derived products by using existing virus inactivation and removal methods during the preparation of plasma-derived products, such as high temperature inactivation, solvent/detergent method (S/D) and low pH incubation [2]. These methods are highly effective in the removal of enveloped viruses in plasma-derived products but they are not used in the inactivation of cellular components. However, the solvent/detergent inactivation method is an FDA-approved method commonly used for inactivation in plasma pools.

The FDA has recently approved a method for reducing pathogens in plasma and platelets using amotosalen in combination with UV light (INTERCEPT). It demonstrates high efficacy in the reduction of a range of viruses, including flaviviruses such as dengue virus or West Nile virus, as well as the Zika virus. Similar efficacy is demonstrated by the pathogen inactivation method using vitamin B_2 (Mirasol), which is commonly adopted in Poland [2].

ZIKV infection and the safety of tissue and organ transplantation

The risk of ZIKV transmission through tissue and organ transplantation remains unclear. In Brazil, four cases of ZIKV infection have been reported in patients with immunosuppression. Two of them concerned kidney transplant recipients, another two – liver transplant recipients. These patients had symptoms of bacterial infection and required hospitalisation. In addition, they developed thrombocytopenia and experienced general health deterioration. However, no symptoms characteristic of Zika virus infection were observed, such as rash, conjunctivitis or neurological symptoms [32]. The small number of reported cases of Zika virus transmission through transplantation is still insufficient to assess the effects of ZIKV infection on the clinical status of immunosuppressed patients.

Conclusions

The Zika virus causes infections in tropical areas, mainly in Brazil and Colombia and in the Caribbean. Due to increased tourist traffic and population migration, infection with the virus has been classified as a new disease that can be transmitted by transfusion of blood and its components. In addition, this risk has been made more serious by the number of non-vector infections and the increasing geographical range of the virus. The areas affected by ZIKV and cases of diseases or virus transmission are closely monitored. However, there are many uncertainties in the collected data. Musso et al. pointed out the discrepancies between global organisations (WHO, CDC, ECDC, FDA) in the classification of individual regions as affected or not affected by the epidemic [33]. The European Centre for Disease Prevention and Control (ECDC) has identified New Caledonia and Papua New Guinea as areas affected by the epidemic in the last 9 months. According to the WHO, these countries are not included in the list of countries reporting new cases of infections in 2016. The CDC, in turn, has identified these countries as areas with active virus transmission. According to the CDC, Thailand is a country with a high virus prevalence, while neighbouring Vietnam is not. The WHO placed Vietnam on the list of countries with a high risk of epidemics (in December 2015, an imported case of Zika was reported in this country) [1, 10]. The published results of a small number of studies indicate a low risk of clinical effects after transmission of the virus by transfusion of blood components, most infections are asymptomatic or mild. The strongest evidence of the risk associated with ZIKV is severe complications in infants born to mothers infected with Zika virus and the proven teratogenic effects of the virus. The diagnosis of ZIKV also generates much discussion. Therefore, until the development of diagnostic tests of appropriate sensitivity and specificity that will allow for an accurate evaluation of the epidemiological situation in endemic and epidemic areas, donor selection, preventive restrictions on donations and diagnosing each donor returning from South East Asia and the Pacific Islands appear justified [1, 10].

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The role of gene polymorphisms in polycystic ovary syndrome

Rola polimorfizmów genów w zespole policystycznych jajników

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Abstract. Thanks to the sequencing of the human genome and to the dynamic advances in molecular biology techniques, genome-wide level studies became feasible. Identification of genomic risk factors that determine the variability in susceptibility to common diseases consists in searching the genome for genetic variants/polymorphisms associated with the disease *[genome-wide association study]* - GWAS. Numerous studies were conducted to elucidate the pathogenesis of polycystic ovary syndrome, albeit to no effect as of yet. It is believed that more than 70% of cases of polycystic ovary syndrome are of genetic origin. The conducted studies focus mainly on the variabilities in genes involved in regulation of sex hormones, genes responsible for insulin sensitivity, genes responsible for increased risk of cardiovascular diseases, and genes involved in steroid biosynthesis and detoxification. The main goal of the study is to identify a single gene/polymorphism to be used as a PCOS marker.
Key words: polycystic ovary syndrome, single nucleotide polymorphism, GWAS - genome wide association study

Streszczenie. Zsekwencjonowanie genomu ludzkiego oraz dynamiczny rozwój technik biologii molekularnej umożliwiają prowadzenie badań na poziomie całego genomu. Identyfikacja genetycznych czynników ryzyka, które kształtują zmienność w zakresie podatności na powszechnie występujące choroby, skupia się na badaniu genomu pod kątem obecności wariantów genetycznych/polimorfizmów pozostających w asocjacji z chorobą - GWAS [genome-wide assosiation study). Wiele badań przeprowadzono nad poznaniem patogenezy zespołu policystycznych jajników, która nadal pozostaje niewyjaśniona. Uważa się, że w ponad 70% przypadków zespół policystycznych jajników ma podłoże genetyczne. Prowadzone badania obejmują głównie zmienności genów biorących udział w regulacji hormonów płciowych, genów wrażliwości na insulinę, genów zwiększających ryzyko chorób sercowo-naczyniowych oraz genów zaangażowanych w biosyntezę i detoksykację steroidów. Głównym celem prowadzonych badań jest znalezienie pojedynczego genu/ polimorfizmu będącego markerem PCOS.
Słowa kluczowe: zespół policystycznych jajników, polimorfizm pojedynczego nukleotydu, GWAS - polimorfizm pozostający w asocjacji z chorobą

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Introduction

Research on gene polymorphisms contributes to a better understanding of the pathogenesis of a number of diseases, while the identification of polymorphisms can improve the prognosis in specific diseases, including the *polycystic ovary syndrome* – PCOS [1]. The aim of the research is to assess the relationship between specific genetic polymorphisms and particular disease phenotypes. The studies involve the identification and characterization of individual variability of natural variants or polymorphisms in a DNA sequence. They may relate to single nucleotide polymorphisms – SNPs. Numerous studies have been published which assess the role of

gene polymorphisms in the PCOS pathogenesis.

PCOS affects approximately 1 in 10 women of reproductive age and it is the most common metabolic disease in this age group. Hyperandrogenemia and anovulation are typical symptoms of PCOS [2, 3]. Approximately 80% of women with PCOS notice abnormal menstrual cycles [4], while the risk of maternal and neonatal complications in pregnancy and following childbirth is increased [5]. PCOS pathogenesis remains an open question. Twin research suggests that more than 70% of PCOS cases have a genetic background [6]. There is a significant impact of environmental factors such as diet and physical effort [7]. Family studies conducted in the USA have shown a strong correlation between the sensitivity to PCOS and the D19S884 dinucleotide in the area of chromosome 19p13.2 [8-10]. The particular gene responsible for this effect remains unknown. The studies conducted on PCOS pathogenesis focus mainly on the genes involved in regulation of sex hormones, genes responsible for insulin sensitivity, genes responsible for increased risk of cardiovascular diseases, and genes involved in steroid biosynthesis and detoxification [11, 12, 13].

The main goal of the study is to identify a single gene/polymorphism to be used as a PCOS marker. Studies conducted in the Chinese population and partially in the European population suggest a strong correlation between genes *(LHCGR, THADA, DENND1A, FSHR, C9orf3, INSR, HMGA2, YAP1, RAB5B/SUOX, T0X3, SUM01P1)* and PCOS [14].

Sex hormones and their regulators

It has been demonstrated that the adrenergic receptor polymorphism is associated with insulin resistance. The study included two variants of the gene encoding the alpha-2 (α2) adrenergic receptor (ADRB2): the p.Q27E variant was associated with greater propensity to PCOS, while in the cases of the P.R16G variant, no such relationship was noted. There is also no evidence that the polymorphism of p.IN64R in ADRB3 should increase the risk of PCOS. It was found, however, that its presence induces a greater concentration of triglycerides [15, 16].

Increased androgenic activity in patients with PCOS may result from the presence of shorter alleles in the androgen receptor (AR) gene, which is related to the length of the CAG microsatellite repeats [17, 18]. It has been demonstrated that the polymorphism of Accl in the gene which encodes the follitropin subunit beta (FSHB) may be lead to a greater propensity to PCOS, with obese patients being especially prone to it. The said polymorphism occurred more frequently in women with PCOS (12.6%) than in the control group (3.8%). The increased occurrence of the said polymorphism was found in obese patients with PCOS (respectively: 0.5% *vs* 31%) [19]. Furthermore, polymorphism rs11 031 006 in the gene encoding FSHB also induces a greater risk of PCOS and greater concentration of LH. Similarly, the increased risk of PCOS resulting from larger concentrations of LH may be observed in the case of the presence of AA haplotype and AC SNP rs11 031 010 in the gene for FSH [20].

Most published research, however, does not cover the gene for FSH, but the gene for the FSH receptor (FSHR). The FSHR gene contains two important SNPs in exon 10 which change the amino acids in position 307 and 680. Although the genotype p.N680S regulates the ovarian response to gonadotropins, it does not play a part in the pathogenesis of PCOS [21]. Moreover, the SNPs studies for GnRH (Trp16Ser [rs6185]), FSH receptor (FSHR, Ala307Thr [rs6165] and Asn680Ser [rs6166]), as well as LH receptor (18in-sLQ, Asn291Ser [rs12470652] and Ser312Asn [rs2293275]) have shown that only FSHR Ser^{680} is connected with larger concentrations of FSH, LH, and testosterone, as well as higher incidence of symptoms of androgenisation, yet it does not increase the risk of PCOS [22]. A clear relationship between the polymorphism in the FSHR gene and an increased risk of PCOS was also observed by Mutharasan and al. Their studies suggest that the presence of polymorphism rs1 922476 affects the concentration of FSH and triglycerides in women with PCOS [23].

The results of recent studies show a high correlation between polymorphism rs2479106 and rs10818854 in the DENN-D1A (9q33.3) gene and the risk of PCOS. The product of the gene, and namely the DENND1a protein, controls the activity of Rab GTPazy, which is necessary for the process of Calcium-dependent exocytosis of pituitary gonadotropins. Experimental studies, however, did not show any differences in concentrations of LH or FSH. It appears that the pathogenesis of PCOS in this case runs on another, unknown pathomechanism, in spite of the impact on the emission of gonadotropins. The expression of DENN-D1A was also observed in theca cells of ovaries. The presence of DEND1A determines hyperandrogenism and irregular menstruations in women with PCOS [24].

LHCGR (luteinising hormone/choriogonadotropin receptor) has a crucial role in the proper functioning of the ovary (ovulation), and in maintaining an early pregnancy. In the Chinese population, there is a clear link between the SNP (rs13405728G) LHCGR (2p16.3) and GTF21L (general transcription factor HA, 1-like) and PCOS. The presence of these polymorphisms determines the phenotype of PCOS with oligoovulation or anovulation, whereas in the European population, the SNP variant in LHCGR is rather rare, it is, therefore, difficult to assess its importance [25].

YAP1 protein is responsible for the development and proliferation of the cells. It also maintains correct homeostasis of growing follicles. Polymorphism in YAP1 is connected with the risk of PCOS, as has been observed in both the Chinese and European population [26].

SHBG

Women with PCOS exhibit reduced SHBG concentration (sex hormone binding globulins). Microsatellite repeats within the gene promoter for SHBG (TA-AAA)n, especially those with more than eight repeats, are linked to the risk of PCOS in the Greek population [27]. However, no link between the polymorphism of the gene p.D327N and the risk of PCOS was observed in the research conducted in

Slovenia and the Czech Republic [28-29]. Abu-Hijeleh points to a clear relationship between SNP rs727428 in the gene SHBG and the risk of developing PCOS. The presence of rs727428 polymorphism is related with a lower concentration of SHBG and a greater concentration of free testosterone [30].

Regulators of sex hormone activity

No connection with PCOS was observed in the studies on the following genes: follistatin (*FST)* [31, 32], G-protein alpha subunit of guanine nucleotide binding protein (*GNAS)* [33], leptin receptor *(LEPR)* [34] and luteinizing hormone *(LHB)* [35]. Gene polymorphisms (TaqI, ApaI, BsmI, FokI) of the vitamin D receptor *(VDR)* or vitamin D concentration have no effect on the PCOS pathogenesis [36]. Statistically significant relationships were found, however, between *VDR* polymorphisms and clinical and biochemical markers of PCOS. The *FokI* polymorphism is associated with infertility, whereas *Cdx2* proved to be linked with testosterone concentration. The presence of the CDx2 polymorphism exhibits protective features against PCOS [37]. The disease phenotype was also related to two SNP tested in the gene for FST [32], while the gene for G-protein signal transduction (GNAS) showed a relationship with the body weight indicator (BMI) and insulin resistance in women with PCOS [32,33].

Anti-Müllerian hormone (AMH), through its paracrine activity, hampers the growth and development of the primary follicles stimulated by FSH, while ensuring the selection of the dominant follicle.

A greater concentration of AMH in the group of women with PCOS may reflect abnormalities in signal transduction pathways. The studies on the connection between SNP AMHR2 - 482 A>G show, however, that the presence of homozygote GG is associated with smaller concentrations of LH and a lower LH to FSH ratio. A lower concentration of prolactin was also observed in the study group [38]. The exact pathomechanism of these disorders remains unknown.

Zheng et al. claim that the presence of polymorphisms in genes AMH and AMHR gives rise to the abnormal concentrations of LH and testosterone in the group of PCOS patients with insulin resistance exclusively. Such dependencies were not observed in women without insulin resistance [39]. Research conducted by XU et al., where SNP rs 8112542 was analysed on the basis of the HapMap database, showed that the presence of haplotype TA increases the risk of PCOS, whereas the presence of haplotype GA exhibits protective activity [40].

Metabolism and biosynthesis of steroids

There is ample research on polymorphisms of genes for enzymes involved in biosynthesis and metabolism of sex hormones in PCOS pathogenesis. 17β-hydroxysteroid dehydrogenase type 5 is an essential enzyme in the process of testosterone biosynthesis. The variant where adenine is substituted with guanine in position 71bp in the region of SNP-71G promoter was observed significantly more frequently in patients with PCOS than in the control group (53.7% vs 38.3%). It has been noted that the concentration of testosterone in serum is about 20% higher in homozygotes SNP-71G. This polymorphism occurs in approximately 10% patients with PCOS. In the abovementioned study, Qin et al. maintain the hypothesis that on testosterone biosynthesis pathway, SNP may cause genetic diversity, which in turn affects the phenotypic variation known as individual susceptibility to PCOS [41]. Polymorphism of CYP1A1 encoding cytochrome P450 1A1 exhibits a strong relation with PCOS ($p = 0.0139$) [42]. Pentanucleotide repeats in the gene for cytochrome P450 11A (CYP11A1) also foster PCOS [32, 43, 44]. A similar impact is exerted by the polymorphism of the gene for aldosterone synthase (CYP11B2) located in the promoter region [45]. No link, however, has been noticed between PCOS and the polymorphism in the gene for 17-hydroxylase (CYP17A1), an enzyme involved in estrogen biosynthesis [46, 47]. The gene CYP19A1 encodes major elements of aromatase. Certain studies indicate a relationship between the polymorphism of this gene (polymorphism SNP50) and the advancement of PCOS [48].

Metabolism of sex hormones

Low activity of haplotype H113-R139 of the gene encoding microsomal epoxide hydrolase (EPHX1) entails the risk of PCOS [49]. A variant of the gene H6PD accompanying cortisone reductase deficiency is also linked to increased incidence of PCOS [50], but this phenomenon has been confirmed by only selected studies on the issue [51]. Jones et al. concluded that the frequency of polymorphism rs898611 of the gene encoding 17β-hydroxysteroid dehydrogenase type 6 (HSD17B6) was significantly higher in patients with PCOS than in the control group. Its presence was linked to an increase in the HOMA and BMI indicators [52]. Research on 5 alpha-reductase isoforms has shown that SRD5A1 and SRD5A2 may be associated with the susceptibility to PCOS, yet only certain variants of haplotype SRD5A1 were responsible for increased hirsutism [53].

Genes related to type 2 diabetes and cardiovascular diseases

An increased risk of type 2 diabetes and cardiovascular diseases in women with PCOS has led to numerous studies being performed in this respect.

Adiponectin

It is common for patients with obesity, type 2 diabetes, insulin resistance, or PCOS to have a small concentration of adiponectin.

The studies pertained to the influence of SNPs in the gene for adiponectin (ADI-POQ) on the development of PCOS. A link with PCOS was not demonstrated in polymorphisms 45G/T and 276G/T [27, 54, 55]. However, it has been found that they affect the insulin concentration. Zhang et

al. suggest a significant relationship between the polymorphisms rs17 300539 and RS1 501 299 in ADIPOQ and the risk of PCOS [56].

Calpain-10

The gene for calpain-10 (CAPN10), which encodes cysteine protease, may induce the susceptibility to type 2 diabetes. No link with PCOS has been found for the 5 polymorphisms of this gene covered by the study: *UCSNP44* [56], *UCSNP45* [57], *UCSNP43, UCSNP19* and *UCSNP63* [58, 59]. Anastasie et al. suggest an influence of UCSNP-43 on the risk of developing cardiovascular disease in young women with PCOS [60]. The polymorphism UCSNP-43, moreover, affects the concentration of androstenedione and 17-OH-progesterone. Research in the Turkish population also showed a significant relationship between UCSNP-44 and PCOS. Polymorphism UCSNP-44 was observed in 69.15% of PCOS patients and in 50% of healthy patients. Women with this variant of the gene exhibited higher concentrations of testosterone in serum, androstenedione, DHEA-S, and fasting insulin. They also had a higher score on the Ferriman Galway scale, and more frequently acne, menstruation disorders, higher waist-hip ratio, higher HOMA IR and lower QUICKI [61].

Gene for the insulin receptor

The influence of polymorphism His1058 C/T of the gene INSR on PCOS was rather ambiguous, until the meta-analysis carried out in 2010 by loannidis et al. did not confirm the relation between His 1058 (rs1 799817) and the risk of PCOS [62]. No relationship has been found between the presence of SNP rs1 799817 and rs 2059806//VS/? and PCOS either. Chun Feng et al. suggest in turn that the presence of rs2059807 in the gene INSR may be connected with the development of PCOS. The importance of this polymorphism requires further studies [63].

Insulin-like growth factors

In respect of ApaI 'G' allele in the gene for IGF-2, homozygotes are observed more frequently in patients with PCOS than in healthy women (62.9% vs 38.1%; p=0.018). Polymorphisms in genes encoding IGF-1, receptor IGF-1, and receptor IGF-2 do not exhibit such a relationship. PCOS is accompanied by the variant-108C/T of the gene PON1 [54]. Polymorphism p.L55M does not exhibit such relationship, but it indicates a higher BMI and insulin resistance with homozygous 55m, compared with women with allele 55L.

THADA – *thyroid associated protein*

It appears that type 2 diabetes has the strongest relationship with the presence of polymorphism in the gene TCF7L2 (T-cell-specific transcription factor). The protein produced by the gene is involved in the signal transduction pathways which regulate the concentration of glucose in the blood. The disorder mechanism is associated with reduced insulin production [64]. Polymorphism in the gene TCF7L2 does not, however, show any connection whatsoever with the risk of PCOS [65].

A strong correlation with PCOS and a clear propensity for type 2 diabetes have been observed in the case of polymorphisms in the gene THADA (2p,21) [66]. Paradoxically, although carrying the risk of PCOS, the variant of THADA gene is associated with smaller testosterone concentrations [67].

Recent studies indicate a substantial relationship between mutations in the mitochondrial genome and the risk of PCOS and insulin resistance. Ding describes the combinations of ND5 T12338C and tRNASer (UNC) C7492T mutations that lead to mitochondrial dysfunction, which in turn is considered to be one of the hypotheses of PCOS pathogenesis [68].

Zulian et al. demonstrated a strong link to the risk of PCOS in the gene RAB5B. *RAB5B* is one of the oncogenes from the Ras subfamily. It participates in the signal transduction pathways as well as in the process of endocytosis. Polymorphism in the gene 12q13.2 is related to the risk of developing type 1 diabetes [69].

Genes related to cardiovascular disease risk

Polymorphism p.M235T of the gene for angiotensin (AGT) has been found to induce the susceptibility to PCOS [70]. Arefi claims that renin-angiotensin plays an important role in the PCOS pathogenesis. C90RF3 is an aminopeptidase involved in the synthesis of angiotensin IV. Polymorphism rs3802457 in the gene C90RF3 (9q22.32) shows a strong correlation with the risk of PCOS both in Chinese and European population. The results of studies suggest, however, that the presence of haplotype GG is a risk factor for PCOS, whereas haplotype GA is considered to be a protective factor in respect of PCOS development. The function of C9orf3 remains an open question [71].

Methylenetetrahydrofolate reductase (MTHFR) is a homocysteine metabolism enzyme. It has been found that the polymorphism p.A222V of the gene for MTHFR increases homocysteine concentration in the plasma, which is associated with an increased risk of cardiovascular diseases, yet it does not increase the risk of PCOS [72]. Glueck et al. claim there is a rather clear link between polymorphism C677T in the gene for MTHFR and the propensity to PCOS [73]. Plasminogen activator inhibitor-1 (SERPINE1) also participates in the blood clotting cascade. Polymorphism 4G/5G in the gene SERPINE1 appears to affect the risk of PCOS [74, 75], but it has not been confirmed in other reports [50, 76]. Women with PCOS carrying this polymorphism have an increased risk of miscarriage [73].

Dyslipidemia

Tian et al. presented a clear link between the presence of SNP in the fatty acid desaturase genes FADS1-FADS2 and the risk of PCOS. Polymorphism rs174570 CC

reduces the FADS2 expression and involves a greater concentration of testosterone in PCOS. It does not affect the concentration of lipids or glucose [77].

It appears that the increasing occurrence of SNP rs2 197976 and rs2 241 883 in the fatty acid binding protein gene FABP1 is of significant importance in respect of the PCOS pathogenesis ($p < 0.001$) [78].

Melatonin receptor (MTNR) is connected with insulin sensitivity, diabetes, and metabolic syndrome. It has been observed that polymorphism rs CC2119882 implies a greater risk of PCOS in the Chinese population [79].

Interleukins

In 2015, Guo et al. published a meta-analysis of three polymorphisms of genes for the tumour necrosis factor (TNF-a) – 308G/A, interleukin 6 (IL-6) – 174g/ C and interleukin 1 beta (IL-ip) – 511 C/T. TNF-a, IL-6 and IL-1 are crucial for human reproduction, as they regulate the production of sex steroids, the growth of ovarian follicles, ovulation, fertilisation, and implantation. These processes frequently fail to function properly in patients with PCOS [80]. From the 14 articles available, it has been concluded with high probability that the polymorphisms described above do not constitute genetic risk factors of PCOS. Further research is needed on a large scale, covering other loci in the genes TNF-alpha, IL-6 and IL-1.

Polymorphism rs1801282C>G in the gene for peroxisome pro/iferator-activated receptor gamma (PPARG) results in an increased PPARG activity. It appears that the presence of polymorphism is a protective factor in respect of PCOS development [81].

Genes related to risks of cancer

PCOS is known to engender a three times greater risk of endometrial cancer, most probably due to insulin resistance involved. Shafiee et al. observed an increased gene expression (IGF1, IGFBP1, PTEN) which participate in the transduction pathways of signals associated with insulin in the endometrial area in women with PCOS [82].

Summary

Thanks to the sequencing of the human genome and to the advances in molecular biology techniques (including microarrays), genome-wide level studies became feasible. Identification of genomic risk factors that determine the variability in susceptibility to common diseases consists in searching the genome for genetic variants/polymorphisms associated with the disease (*genome-wide association study* - GWAS). The GWAS analysis, based on the microarray plate technology, allows for simultaneous identification of hundreds of thousands SNP polymorphisms. Unfortunately, the majority of genetic variations of common diseases are still unknown. The HapMap catalogue of common patterns of human genetic variation does not include rare variants, which are much more difficult to identify. The data collated in the directory prove extremely useful in the cases of *linkage disequilibrium* (LD). It facilitates the possibility of evaluating another polymorphism correlated with the identified one, without the need for additional genotyping. Rarer variants are only identifiable thanks to genome sequencing projects, such as the 1000 Genomes Project. The dynamic advances in the field of genetics will surely contribute to new, currently unknown genes for disease risks, including PCOS, being discovered. By assuming such course of action towards the disease, it will be possible to approach every patient individually and incorporate targeted therapy options in the treatment.

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Lt. Col. Stanisław Andrzej Bonikowski MD (1913–1977) – Gestapo prisoner and the first president of the Garrison Military Medical Board in Żary

Ppłk lek. Stanisław Andrzej Bonikowski (1913–1977) – więzień gestapo i pierwszy przewodniczący Garnizonowej Wojskowej Komisji Lekarskiej w Żarach

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Abstract. In 2017, we celebrated the 40th anniversary of the death of Lt. Col. Stanisław Andrzej Bonikowski, military physician, Gestapo prisoner and the first president of the Garrison Military Medical Board in Żary. He was born in Stoczek Łukowski, on 20 April 1913. In 1939, he graduated from the Józef Piłsudski University in Warsaw. In 1938-1939, he served in the Polish Army at the famous Medical Cadet School and underwent training as part of the 1st Flying Squadron in Warsaw. During the occupation, he was active in the underground movement, and was arrested by the Germans in 1941. For almost three years, he was imprisoned in the infamous Gestapo torture chamber at Lublin Castle, where he worked as a physician eliminating the typhus epidemic among prisoners. After the liberation, he was called up to the Polish First Army. In 1950, he became the first full-time chairman of the Garrison Military Medical Board in Żary. In 1957, he was transferred to the reserve, and almost to the end of his life he was a professionally active physician. He died in Olsztyn, on 29 June 1977, aged 64.
Key words: Bonikowski, physician, officer, Lublin Castle, Żary, the Gestapo

Streszczenie. Na 2017 rok przypada 40. rocznica śmierci ppłk. lek. Stanisława Andrzeja Bonikowskiego, lekarza wojskowego, więźnia gestapo i pierwszego przewodniczącego Garnizonowej Wojskowej Komisji Lekarskiej w Żarach. Urodził się 20 kwietnia 1913 roku w miejscowości Stoczek Łukowski. W 1939 roku ukończył Uniwersytet Józefa Piłsudskiego w Warszawie. W latach 1938-1939 służył w Wojsku Polskim w słynnej Szkole Podchorążych Sanitarnych, zaś praktykę odbywał w 1. Pułku Lotniczym w Warszawie. W okresie okupacji aktywnie działał w podziemiu niepodległościowym, za co został przez Niemców aresztowany w 1941 roku. Prawie trzy lata był więziony w osławionej gestapowskiej katowni na Zamku Lubelskim, gdzie pełnił funkcję lekarza i zwalczał epidemię tyfusu wśród więźniów. Po wyzwoleniu zmobilizowany do I Armii Wojska Polskiego. W 1950 roku został pierwszym etatowym przewodniczącym Garnizonowej Wojskowej Komisji Lekarskiej w Żarach. W 1957 roku odszedł do rezerwy, niemal do końca życia był czynnym zawodowo lekarzem. Zmarł 29 czerwca 1977 roku w Olsztynie w wieku lat 64.
Słowa kluczowe: Bonikowski, lekarz, oficer, Zamek Lubelski, Żary, gestapo

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The certifying physicians of the Military Medical Board (WKL) constitute a very specific group of medical practitioners. It is their responsibility to select appropriate candidates to serve in the army by assessing their general state of health. It is easier to understand the challenges this involves by considering the following situation: an incorrect outcome of the health selection process leads to the selection of a candidate with significant mental disorders, who should never be given access to arms or explosives. Any tragic consequences of such an incorrectly performed health selection process would burden the conscience of the certifying physician, while it is not unlikely that legal charges related to such negligence would follow as well. On the other hand, the same assessment process has to deal with candidates who attempt to evade military service by simulating health issues. One of the roles of certifying physicians is to detect anyone attempting such an evasion, especially in the time of war since any passivity or ineptitude exhibited by a medical military board member could pose the risk of some level of failure by the armed forces. It is precisely the latter which contributes most to the negative image of the boards in communities maintaining a critical stance against drafting. The work of certifying physicians was described in a highly suggestive, witty and slightly malicious manner by Jaroslav Hašek, a Czech writer, in his immortal novel: "The Good Soldier Svejk and His Fortunes in the World War". The reader encounters the chief military doctor of Prague, Dr. Bautze, who "...only saw attempts to dodge the draft, the front, the bullets and shrapnel...", while his favourite saying was "Das ganze Volk tchechische ist eine Simulantenbande (...) Out of eleven thousand civilians, he managed to expel ten thousand nine hundred and ninety-nine draft dodgers in only ten weeks' work, and he would surely have taken on the eleven-thousandth, if only had that happy human being had not popped off at that moment when he shouted *Kehrt euch*..." This is, of course, an extremely exaggerated picture of certifying physicians during World War I, yet still fairly accurate for the Austro-Hungarian Army. It must be noted that the soldiers in that army were of different nationalities, including Poles, Czechs, Slovaks, and Hungarians, and who often came from countries conquered by the Austro-Hungarian monarchy. None of them, especially Poles, were interested in risking their lives for a partitioning state, hence the high propensity to simulate ill health in order to evade service under the yellow and black Austro-Hungarian flag, while certifying physicians often used unorthodox methods to detect those "evil" practices (enema, gastric lavage, starving, wrapping in wet linen, etc.) [1].

Figure 1. Lt. Col. Stanisław Andrzej Bonikowski (1913-1977) (with permission of Marta Grzywacz)
Rycina 1. Ppłk lek. Stanisław Andrzej Bonikowski (1913-1977) (za zgodą Marty Grzywacz)

Attempts to deceive the medical boards are not restricted to occupied territories, since similar situations occurred in independent Poland during the war of 1920 and World War II. Such extreme conditions call for wisdom, life experience, and medical knowledge from the certifying physicians, so that they can reliably fulfil their duty towards the state without lacking empathy, forcing people who are ill and incapable of bearing arms to be drafted into the army.

Lt. Col. Stanislaw Andrzej Bonikowski, the first ever full-time president of the Garrison Military Medical Board (GWKL) in Żary, undoubtedly represented all the characteristics of the ideal certifying physician. His attitudes to life and professional decisions were certainly influenced by the environment in which he was born and bred, and where he later fought for human dignity in the inhumane conditions of the infamous Gestapo torture prison. The dramatic story of his life allows us to fully understand his approach to other people and to his duties.

Youth, war and occupation

Stanislaw Bonikowski was born on 20 April 1913 in the town of Stoczek Łukowski, to Mieczysław and Michalina Bonikowski. He attended the prestigious Hetman Jan Zamoyski State Secondary School for Boys in Zamość, graduating in 1931. It was probably his interest in humanities that led him to enrolling in the Medical Faculty of the University of Warsaw. In 1937, after several years of hard work, he completed his studies; although due to financial problems following the death of his father he was unable to take the final exams. It was only in 1939 that he completed all the necessary formalities and obtained a doctor's diploma from his alma mater (by this time now known as the Józef Piłsudski University of Warsaw). He was drafted in 1938 to serve in the Centre for Sanitary Education in Warsaw. During his six years of compulsory military service, he received training under the Reserve Battalion of the famous School of Sanitary Cadets, which he completed as a corporal officer cadet. Then he completed his compulsory internship as a doctor of the 1st Air Regiment. With the coming of World War II, he took part in the September Campaign of 1939 together with this unit. During the German occupation, he settled in Ludwików, near Bielsk Podlaski, and immediately engaged in conspiracy activities and attempts to regain independence. In the second half of 1940, he began work at the Municipal Hospital in Siedlce but, warned of the Gestapo's plans to arrest him, he moved to Warsaw, where he worked as a volunteer in the Duchess Anna Mazowiecka Obstetric Unit in Karowa Street [2, 3]. Following his arrest on 28 October 1941, was detained in Pawiak for a week, and subsequently moved to the infamous place of Gestapo torture in Lublin Castle. The most probable reason for his survival was that a deadly typhus epidemic broke out among the prisoners at that time, instilling fear in the Germans. The German doctor working at the prison did not want to run the risk of tending to the sick, so when he discovered there was a Polish doctor among the detainees, he ordered him to be put to work in the hospital prison.

Stanislaw Bonikowski practically managed the entire infirmary, with two military surgeons, also Gestapo prisoners, to aid him. The conditions were extremely harsh, given the lack of basic medicines, with only simple surgical tools and dressings, rivanol, iodine and potassium permanganate, and a limited number of painkillers being available.

Figure 2. Commemorative plaque with inscription in honour of all chairmen of the Military Medical Commission in Żary, including Lt. Stanisław A. Bonikowski (23 October 2015, 105th Borderlands Military Hospital in Żary)
Rycina 2. Tablica pamiątkowa z inskrypcją ku czci wszystkich przewodniczących Wojskowej Komisji Lekarskiej w Żarach, w tym pptk. lek. Stanisława A. Bonikowskiego (105 Kresowy Szpital Wojskowy w Żarach, 23 października 2015 r.)

As a rule, no aid was provided during the night hours in prison, and even in an emergency requiring urgent medical response, those ill remained in their cells without any contact with a doctor until the morning. Several people died due to appendicitis or perforated stomach ulcer.

The prison hospital had 65 beds, but during outbreaks of typhus it had to accommodate 100-200 people. This left patients crammed on the ground or on mouldy straw beds, all surrounded by a terribly foul smell. The extremely poor hygiene fostered the spread of all kinds of diseases, including infectious ones. Most prisoners were covered with lice and fleas, poorly nourished, continually stressed, as well as beaten and tortured during lengthy interrogations.

The largest typhus epidemic occurred in the first half of 1942, with an average of 5-6 prisoners dying daily. On one day in particular, the hospital lost 16 patients. Stanislaw Bonikowski also came down with the sickness, but thanks

to the help he received from his surgeons he was able to recover. In total, as many as 1160 people died in the prison infirmary: 42.5% of typhus, 17.6% of tuberculosis, while almost 10% were murdered by the Gestapo or as a result of being heavily beaten during interrogations. The mortality rate in the unit was 18.78%, which means that one in every ten or eleven patients admitted would die there (in the case of typhus it was 1 in every 5-6 patients). It was only thanks to the great dedication and hard work of the medical staff that these statistics were not even more terrifying.

Despite the extremely limited possibilities, Stanislaw Bonikowski fought for every fellow inmate treated in the prison hospital. He made his name by his brave attitude, ready for sacrifice, rendering assistance and relief to the Polish patriots tortured by the Germans [4]. There are numerous testimonies of former prisoners from Lublin Castle, who remained very grateful to their doctor for helping them and often saving their lives. One of his greatest achievements was to secure and hide six admissions books, listing patients of the penitentiary hospital at Lublin Castle, which made it possible to list its residents after the war, as well as to document their deaths, to explain the mystery of missing people, and to describe the way the hospital operated. These books also served well as a source of secondary evidence for the Main Commission for the Investigation of Nazi Crimes in Poland.

Stanislaw Bonikowski was freed on 22 July 1944. On the previous day, the Germans killed 44 more prisoners before they left. These were the last victims of the Gestapo torture house [5, 6].

Back to the army

Upon his release, he resumed working at the Municipal Hospital in Siedlce. The day he was drafted was 3 January 1945, when the Regional Draft Office in Siedlce directed him to assume the position of junior doctor (as a corporal officer cadet) of the 1st battalion of the 2nd Independent Guards Brigade. As a member of this First Polish Army unit, he followed the entire trail of battles. By the end of the war he was serving as a military doctor in Ruda Pabianicka, Łowicz and Lubliniec. With time, he was promoted to the rank of major [2], and then at the end of 1950, Stanislaw Bonikowski was appointed president of the Garrison Military Medical Committee (GWKL) in Żary.

The latter was established in October 1944 as the 8th Mobile Field Surgical Hospital. Together with the Second Polish Army, this unit also followed the full trail of battles, making its name by securing the Nysa Łużycka crossing. In May 1946, the unit was permanently located in the town of Żóraw (currently Żary, Sorau in German), in the buildings of the former Brandenburg Mental Institution, where German psychiatrists had euthanized mentally ill patients during the time of Hitler under Operation T4. Each military hospital had a certifying office, involved in assessing the health status of wounded soldiers as part of the treatment, in order to determine their ability to continue military service, valid sick leave, etc. During the war, these tasks were performed by the Medical Board of the 8th Mobile Field Surgical Hospital. The board was formed in January 1945 and constituted an integral part of the facility. Certification tasks were additional duties for doctors who already had other full-time positions. After the end of the war, the field hospital was transformed into the Garrison Hospital, while the certification functions were assumed by the Garrison Military Medical Board, formed on 1 November 1945. Unfortunately, these tasks were still performed by doctors also employed full time at the hospital, which made their work for the board an additional and cumbersome obligation [7]. It was only at the end of 1950 and beginning of 1951 that a positive change took place, when Stanislaw Bonikowski assumed the newly created post of Board President. He was the first physician in the history of the facility who did not perform any functions apart from certification.

At that point when he assumed his duties, the board was located in Building No. 7, with two part-time members being appointed by the commander-in-chief of the hospital, selected from among those doctors with a smaller workload at the time. This manner of organising the work led to frequent friction and problems for the president due to the relatively large (often rotating) group of doctors who took part in the certification activities. They, due to their normal duties in the hospital, were often late or absent from the board meetings. Fortunately, Stanislaw Bonikowski was an experienced physician, always seeking dialogue and agreement with other doctors. Potential disputes were suppressed or settled quickly. He was always kind, polite, and respectful towards his patients, even ordinary privates and draft dodgers, which is not a universal standard, as the language norms from the barracks unfortunately permeate military hospitals. He assumed that it was better to grant a sick leave or even to release someone from service if any doubt arose as to their capabilities rather than to harm a really sick patient with an incorrect judgement (it should be noted that diagnostic possibilities were much more limited than today, with an increased chance of error).

In 1953, also thanks to Stanislaw Bonikowski's efforts, the board's headquarters was transferred to the freshly renovated Building No. 23, where it occupied the western part of the attic. In his opinion, the new premises, encompassing a medical room, waiting room, and changing room, fully met their needs. The main problem in terms of organisation was undoubtedly the lack of a single full-time member of the board who could assist the president with certification duties. He himself claimed that he had a level 1 specialisation in the field of internal diseases when he arrived in Żary, and despite his deepest wish to obtain level 2, he was unable to do so due to work overload. This was probably one of the reasons why he decided to quit professional military service. On 21 August 1957, as a lieutenant colonel, Stanislaw Bonikowski was transferred to the reserve at his own request and moved to Olsztyn with his entire family. His work surely laid the foundations for the development of the fully modern medical military certification unit in Żary [8].

Civilian life

In Olsztyn, the capital of Warmia and Mazury, Stanislaw Bonikowski became the head of the Health Department of the Board of the People's Council. At the same time, he began work as an assistant at the Internal Medicine Department of the Nicolaus Copernicus Provincial Hospital. This allowed him to continue his professional development and obtain the level 2 specialisation degree in the field of internal medicine, to which he added a level 2 specialisation degree in industrial medicine as well. In subsequent years, he became the head of the Municipal Peripheral Clinic on Kajki Street, and later the manager of the Industrial Clinic on Kętrzyńska Street. He was an active member of the Polish Society of Internal Medicine and the Polish Association of Occupational Medicine, as well as an activist in the Society of Former Political Prisoners of Lublin Castle and the Gestapo in Lublin [3].

For his selfless and irreproachable service, he was awarded the Cavalier Cross of the Order of Restitution of Poland, the Golden Cross of Merit, a badge "For exemplary work in the Health Service", and numerous military medals, including the medal "For Odra, Nysa and the Baltic Sea", a Grunwald Badge, and a Silver Medal of Merit on the Field of Glory. In his spare time, he enjoyed hunting and playing bridge. He belonged to "Ryś", a hunting club in Żary. He adored the poetry of Juliusz Slowacki and knew several of his poems by heart. He admired the works of Henryk Sienkiewicz, especially the Trilogy. In his private life, he was a husband and a proud father of two: Marta and Marek.

Lt. Col. Stanislaw Andrzej Bonikowski died of cancer on 29 June 1977 in Olsztyn, and was buried in the municipal cemetery [2].

His life story shows him to have been a medical practitioner persevering in his vocation despite extremely traumatic war experiences, which left him full of empathy, willing to help, respectful towards the dignity of every human being, regardless of the circumstances. He maintained this attitude as the first president of the GWKL in Żary, which was not a simple and obvious task during the time of Stalinist terror.

On 23 October 2015, on the initiative of the co-authors of this publication, a commemoration plaque (designed by Zbigniew Kopociński) was unveiled in Żary to honour all officers to have ever performed this function at the Medical Military Board in Żary on the 70th anniversary of its creation. Below the Latin inscription "Sic itur ad astra" by Virgil, it is possible to see the name of Lieutenant Colonel Stanislaw A. Bonikowski, who left part of his heart and soul in the capital of Polish Łużyce, which is worthy of remembering on the 40th anniversary of his death.

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