LEKARZ WOJSKOWY
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- Primary hyperoxaluria type 1 – clinical characteristics and new therapeutic options
- Application of selected biochemical parameters in the prediction of acute kidney injury risk at the early stage of burn disease
- Kidney abscess as a rare complication of the urinary tract infections in children – 20 years of single-center observations
- Hypercalcemia in the course of long-term lithium treatment

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INSTYTUT MEDYCZNY
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Letter from the Editor-in-Chief

Welcome to Military Physician!

I would like to present this year's second issue of “Military Physician”, which as promised earlier is devoted almost entirely to urinary tract diseases.

Inside you can find review papers, including one concerning the ultra-rare disease, hyperoxaluria type I, along with an analysis of new therapeutic options in its management. The issue also contains several original papers from the field of adult and pediatric nephrology, case reports in nephrology, which are very important in teaching, as well as reports from congresses.

The current comprehensive issue is crowned with an interview with the rector of the University of Warsaw, Prof. Alojzy Z. Nowak, who talks about the establishment of the Faculty of Medicine at the University of Warsaw. Referring to the tradition of the University of Warsaw in teaching future medics, we need to mention the links between military doctors and this university.

So, in the holiday spirit, enjoy reading Issue 2 of Volume 101 of the “Military Physician”.

Prof. Bolesław Kalicki MD, PhD

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Contents

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MALE HYPOGONADISM – PRACTICAL GUIDELINES

Hipogonadyzm męski – zalecenia praktyczne

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Abstract: Male hypogonadism is a medical condition associated with disorders of sperm production or testicular hormone function. Endocrine disorders related to a deficiency in testosterone secretion can lead to various systemic complications, which can be alleviated by appropriate hormone supplementation. The key to successful treatment lies in an accurate diagnosis based on thorough diagnostic procedures. Studies have shown that testosterone supplementation provides real benefits only for patients with genuine hypogonadism. During the diagnostic process, it is also necessary to exclude secondary causes of hypogonadism. In Poland, healthcare professionals have access not only to various testosterone preparations but also to medications that act on the gonadotropic axis. These individually dosed treatments allow for therapeutic success. The widespread availability of laboratory tests and literature (not always of a professional nature) may encourage patients to self-diagnose and self-administer subjective hypogonadism treatment, leading to numerous complications. Doctors should alert patients to this potential issue and refer them to specialists to ensure that such therapy is conducted according to medical indications and with patient safety in mind.

Keywords: hypogonadism, male, testosterone, gonadotropins.

Streszczenie: Hipogonadyzm męski jest jednostką chorobową związaną z zaburzeniami funkcji plemnikotwórczej lub hormonalnej jąder. Zaburzenia endokrynologiczne związane z niedoborem wydzielanego przez jądra testosteronu prowadzą do wielu powikłań ogólnoustrojowych, które mogą być ograniczane prawidłową suplementacją hormonalną. Podstawą dobrego leczenia jest prawidłowo postawione rozpoznanie po rzetelnie przeprowadzonej diagnostyce. Badania wykazały, że suplementacja testosteronem przynosi realne korzyści jedynie u pacjentów z rzeczywistym hipogonadyzmem. W toku diagnostyki konieczne jest wykluczenie wtórnych przyczyn hipogonadyzmu. W Polsce lekarze dysponują nie tylko różnymi preparatami testosteronu, ale również lekami działającymi na całą oś gonadotropową, które dawkowane indywidualnie, pozwalają osiągnąć sukces terapeutyczny. Powszechna dostępność badań laboratoryjnych i literatury (nie zawsze fachowej) skłaniają pacjentów do samodzielnej diagnostyki i samodzielnego leczenia subiektywnego hipogonadyzmu, co prowadzi do licznych powikłań. Lekarze powinni zwracać uwagę pacjentów na możliwy problem i kierować ich do specjalistów, aby taka terapia była prowadzona zgodnie ze wskazaniami medycznymi i zachowaniem bezpieczeństwa pacjenta.

Słowa kluczowe: hipogonadyzm, męski, testosteron, gonadotropiny.

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Introduction

Due to the media-promoted fashion for perfect musculature, as well as greater awareness of possible endocrine disorders, in increasing numbers of men leads to initiate a diagnostic process for "testosterone deficiency". Greater availability of private tests, often requested by patients themselves, leads to false-positive or negative results (mainly resulting from their unfounded or incorrect performance). Not only a diagnostic process, but also treatment is not always carried out in accordance with the principles of good medical practice and with the actual indications. The patient who is suspected to abuse doping substances should receive knowledge-based information from their physician of the possible complications resulting from such behavior.

Definition and clinical manifestations of hypogonadism

Male hypogonadism includes both hormonal disorders (abnormal production of testosterone) and infertility (abnormal sperm production). These disorders may co-exist, or only one of them may be present. The main symptoms of hormonal hypogonadism addressed in this paper are reduced libido, erectile dysfunction, fatigue, depressive disorders, sleep disorders, lack of motivation, infertility, reduced body hair, gynecomastia, obesity, or metabolic syndrome/insulin resistance [1, 2]. These are non-specific symptoms – they may also occur in other endocrine (e.g., hypothyroidism) and non-endocrine diseases (e.g., anemia), which should be excluded first.

Types of hypogonadism

Hypogonadism is divided into:

- primary – originating from testicle disorders,
- secondary – indicating disorders of the hypothalamic-pituitary axis,
- peripheral – related to receptor dysfunction and tissue response.
- Some men are also affected by so-called functional hypogonadism, not directly related to the hypothalamic-pituitary-gonadal axis, but resulting from other diseases and conditions that may affect testicular function [3].

Diagnostics

The diagnosis of hypogonadism is primarily established by laboratory determination of total serum testosterone. A disorder is diagnosed in case of reaching a cut-off point of less than 12 nmol/l (such a result is considered "low likelihood of hypogonadism"), while less than 8 nmol/l is considered "high likelihood of hypogonadism") [1]. It should be remembered that the hypogonadism diagnosis is based on manifested symptoms of androgen deficiency and consistently lowered serum testosterone levels, so the testosterone test should be performed twice with an interval of about 1-2 weeks. Blood should be collected in the morning (before 11.00), preferably on an empty stomach. The patient should be informed to get enough sleep, avoid excessive exertion and night work before the testing. If total testosterone levels are within the range of 8–12 nmol/l, a sex hormone binding globulin (SHBG) test should be performed. Free testosterone [fT] testing is not recommended due to the lack of standardization of the test. fT calculators (e.g., http://www.pctag.uk/testosterone-calculator/) should be used instead [3]. According to European guidelines, the fT concentration, suggested as a cut-off point for the hypogonadism diagnosis, should be less than 225 pmol/l.

Due to the above diagnostic information, and the fact that meta-analyses have shown a clinical benefit for hypogonadal patients only when treated with an administration of testosterone, then treatment with anabolic-androgenic steroids should not be offered to those patients with "subjectively low" testosterone levels, which, however, stays within the norms [4]. We should also bear in mind the factors and diseases that affect the physiological testosterone decrease. Obesity, metabolic syndrome, type 2 diabetes mellitus, treatment with certain groups of medications (including antipsychotics, antidepressants, opioids), excessive exercise, and poor-diet should be treated and optimized first [5, 6, 7, 8]. Elderly patients are also more likely to suffer from the physiological decline in testosterone levels (so-called late onset hypogonadism – LOH). Differential diagnosis should include hypothyroidism (TSH, fT4) and hyperprolactinemia associated with a pituitary adenoma or the intake of drugs affecting the dopaminergic system (differentiation based on history, prolactin levels, magnetic resonance imaging of the pituitary with contrast) – testosterone administration in such cases may exacerbate the underlying disease [2, 9].

Indications for treatment

Indisputable indications to testosterone treatment include:

- delayed puberty (secondary hypogonadism, Kallmann syndrome),
- Klinefelter syndrome with hypogonadism,
- hypogonadotropic hypogonadism,
- low bone density with associated hypogonadism.

Two further indications must be met simultaneously:

- adult men with reduced testosterone levels (< 12 nmol/l), persistent and multiple hypogonadism symptoms after unsuccessful treatment of obesity and comorbidities,
- sexual dysfunctions with reduced testosterone levels unresponsive to phosphodiesterase 5 inhibitors (e.g., Tadalafil, Sildenafil, which are first-line medications) [2].

Contraindications to treatment

Treatment with an administration of exogenous testosterone is contraindicated in patients planning to have children, with locally advanced or metastatic prostate cancer, breast cancer, haematocrit > 54% and severe chronic heart failure (NYHA IV) [2].

Complications of inappropriate treatment or treatment without indications

Possible complications of the use of testosterone and its derivatives include acne, headaches, increased haematocrit, mood disorders, libido disorders, aggression, decreased testicular volume, infertility, weight gain, alopecia, gynecomastia [1]. These symptoms are particularly exacerbated when the patient uses large, uncontrolled doses of drugs (e.g., products of unknown or uncertain chemical composition).

Treatment

Testosterone preparations

Hypogonadism is primarily treated with testosterone with individualised dosage to achieve values within the age-appropriate range. It must be remembered that maintaining testosterone levels above the upper limit of normal is associated with an increased risk of complications.

The following testosterone preparations can be found on the Polish market:

- Testosterone heptanoate/enanthate (Testosteronum prolongatum® 100 mg/ml) – dosage: 1 ampoule intramuscularly (i.m.) every 1–4 weeks.
- Mixed testosterone esters (decanoate, isocaproate, phenylpropionate, propionate) (Omnadren 250®) – dosage: 1-amp i.m. every 1–4 weeks.
- Testosterone Undecylate (Nebido® 250 mg/ml) – dosage: 1 amp. i.m. every 10–14 weeks.
- Testosterone (Androtop®, Testavan®), in a pump applicator – for daily application to the skin (gels rubbed into arms, shoulders).

Thanks to transdermal application, testosterone concentrations remain on a more physiological levels throughout the whole period of use and are more convenient. In case of side effects, discontinuation of these preparations leads to quicker resolution of the complaints. Their disadvantages, compared to injectable preparations, are higher price, daily application and possible hormone contamination of children and women.

Blood testosterone levels should be controlled:

- in the case of gel preparations – after approx. 14–28 days of use, 2–4 hours after application to the skin,
- in the case of testosterone enanthate – one week after injection,
- in the case of testosterone undecylate – before the subsequent injection [8].

It should be remembered (and patients should be informed) that testosterone preparations are contraindicated in men planning to have children due to potential blocking of the gonadotropic axis and inhibition of endogenous gonadotropins, which may reduce fertility.

Gonadotropins

Chorionic gonadotropin acts in a similar way to luteinizing hormone (and has weak thyroid-stimulating activity). When administered to males, the substance stimulates Leydig cells to produce endogenous testosterone. Currently, there is one product of chorionic gonadotropin produced by recombinant DNA techniques (Ovitrelle®) and one of purified chorionic gonadotropin (Zivafert®) available on the Polish market, both registered for use in women only. Until recently, there was one more product available for treatment of hypogonadotropic hypogonadism in men, named Pregnyl®. It is periodically replaced by products from other companies (Eutrig®, Cho-ragon®, Chorapur®, Biogonadyl®) and is available in some pharmacies. It is administered by intramuscular injection at a dose of 1,000–2,000 jm 2–3 x weekly. It is mainly used in hypogonadotropic hypogonadism or in functional hypogonadism in patients planning to have children. The product is also used to unblock the gonadotropic axis after the use of testosterone and other anabolic-androgen preparations.

Selective Estrogen Receptor Modulators (SERMs)

Clomiphene and tamoxifen belong to the group of selective estrogen receptor modulators (SERMs). Their registered indications in Poland are ovulation induction in the case of clomiphene and treatment of breast cancer in the case of tamoxifen. These substances exert their actions by modulating (both ago- and antagonistically) the estrogen receptors. By blocking the above-mentioned receptors in the pituitary and hypothalamus in men, they stimulate endogenous testosterone production through a feedback mechanism. By increasing intranuclear testosterone concentrations, SERMs improve semen quality. The medications are dosed individually (in the case of clomiphene, usually 25–50 mg every 1–2 days). Since they are not registered for treatment in men and the need for off-label use, the medications should be used under the supervision of an endocrinologist, urologist or andrologist.

Aromatase inhibitors (AIs)

As far as legal aspects are concerned, the use of aromatase inhibitors (letrozole and anastrozole) seems similar. The registered indications are the same as for SERMs in women, whereas these drugs are not registered in Poland for the treatment of male hypogonadism. They are used off-label in justified cases to reduce aromatization (conversion of androgens to estrogens) and to regulate the gonadotropic axis.

Abuse and doping

With greater availability of doping agents, a temptation to achieve better sporting results often leads to pharmacological abuse. Athletes and amateurs of achieving rapid effects related to muscle mass and body build use products from all the groups mentioned above (testosterone derivatives, SERMs, IA), but also new and unspecified pharmacological substances [11]. One of them is selective androgen receptor modulators (SARMs) [12,13]. Representative of this group is ostarine – currently increasingly used as in the doping area due to its availability and the alleged lack of complications during use. SARMs are relatively new substances, and it should be noted at the outset that none of them have been authorized by the FDA, nor has their full safety profile been proven, so the spectrum of complications of these substances can be very broad and unclear. Frequent patients are officers from various services who, apart from the obvious need to maintain a high level of physical fitness and mandatory physical education examinations, may be inclined by peer pressure to include supplementation with anabolic steroids. They should be informed about the high risks of such treatment without medical supervision and the possible complications.

Iatrogenic hypogonadism

Hypogonadism induced by pharmacological agents (both legal and with unknown composition) is treated individually with all the groups of drugs mentioned in the article. Treatment depends on how long the patients used the drugs, what drugs he took and in what dosage. Another important aspect is the clinical and laboratory findings. Great caution needs to be exercised in such treatment and awareness of the addictive potential of anabolic-androgen steroids is advisable. Such treatment often consists in switching to pharmacy preparations and gradually reducing the dose until it can be safely discontinued.

Summary

Treatment of hypogonadism may bring many metabolic and non-metabolic benefits to the patients with actual and confirmed hypogonadism. In other cases, the initial drug-induced euphoria phase may be followed by a series of unpleasant and often irreversible disorders. A physician involved in such “treatment” should exercise caution in making a diagnosis and applying treatment, and, in the case of doubt, should refer patients to the specialists: endocrinologists, urologists or andrologists. It can reduce the number of complications and helps determine a group who will enjoy real clinical benefit from the treatment.

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LEVETIRACETAM – KNOWN AND POSSIBLE APPLICATIONS

Lewetiracetam – znane i możliwe zastosowania

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Abstract: The use of levetiracetam in treatment of epileptic seizures is well established in the literature. The article reviews uses of the drug in the treatment of neurological disorders and potential research directions for it. The literature available in the PubMed database was reviewed using the following keywords: “levetiracetam”; “epilepsy”; “status epilepticus”; “Alzheimer’s disease”; “migraine”; “neuropathic pain”.

Results

Levetiracetam is an antiepileptic drug. It has been approved by the FDA (Food and Drug Administration) for adjuvant treatment of focal, myoclonic and tonic-clonic seizures. The literature indicates that it is also effective for off-label uses – treatment of migraine, a mania episode in the course of bipolar affective disorder. Single studies imply its efficacy in the treatment of Alzheimer’s disease. The most common adverse effects occurring during treatment with the drug are mild and resolve quickly. They include, among others: drowsiness, dizziness, irritability, anxiety or nasopharyngitis. Levetiracetam can be used for both pediatric population and adults.

The use of levetiracetam represents an interesting direction in the treatment of many neurological disorders. Drug uses described in the literature require additional research on a larger group of patients.

Keywords: levetiracetam, epilepsy, status epilepticus, Alzheimer’s disease.

Streszczenie: Zastosowanie lewetiracetamu w leczeniu napadów padaczkowych jest dobrze znane w literaturze. W tym artykule dokonano przeglądu zastosowań danego leku w leczeniu schorzeń neurologicznych oraz potencjalnych kierunków badań nad tym lekiem a także literatury dostępnej w bazie PubMed, używając następujących słów kluczy: „lewetiracetam”, „padaczka”, „stan padaczkowy”, „choroba Alzheimera”, „migrena”, „ból neuropatyczny”.

Wyniki

Lewetiracetam jest lekiem przeciwpadaczkowym. Został zatwierdzony przez FDA (Food and Drug Administration) do leczenia adjuwantowego ogniskowych, mioklonicznych oraz toniczno-klonicznych napadów padaczkowych. Z literatury wynika, że jest także skuteczny w niezarejestrowanych wskazaniach: terapii migreny, epizodu manii w przebiegu choroby efektywnej dwubiegunowej. Pojedyncze badania wskazują na jego skuteczność w leczeniu choroby Alzheimera. Najczęstsze działania niepożądane występujące podczas leczenia lekiem są łagodne i szybko ustępują. Możemy zaliczyć do nich m.in.: senność, zawroty głowy, drażliwość, lęk czy zapalenia nosogardła. Lewetiracetam może być stosowany zarówno w populacji pediatrycznej, jak i u osób dorosłych.

Zastosowanie lewetiracetamu stanowi interesujący kierunek w leczeniu wielu schorzeń z zakresu neurologii. Opisane w literaturze zastosowania leku wymagają przeprowadzenia dodatkowych badań na większej grupie pacjentów.

Słowa kluczowe: lewetiracetam, padaczka, stan padaczkowy, choroba Alzheimera.

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Introduction

Levetiracetam is an anti-epileptic drug sold under the brand name KEPPRA. It was approved by the Food and Drug Administration (FDA) in 1999 for the adjuvant treatment of partial epileptic seizures in patients aged 1 month and older. Additionally, it can be used for the treatment of myoclonic seizures in adults and children over 12 years of age with juvenile myoclonic epilepsy. It is also approved for the treatment of primary generalized tonic-clonic seizures in adults and children over 6 years of age with idiopathic generalized epilepsy [1]. The exact mechanism of action of this drug is not known. It is assumed that levetiracetam affects the concentration of Ca2+ ions in neurons. It leads to inhibition of N-type Ca2+ currents, resulting in a reduced release of calcium ions into the synaptic gap. In addition, it has been shown to bind to synaptic vesicle protein 2A, which affects neurotransmitter release, enhancing GABAergic neurotransmission [2]. Due to the main drug interactions, it should not be used with, among other things: buprenorphine, cinnarizine, flunarizine, dihydrocodeine and cannabidiol. Used together, they may exacerbate such adverse effects as excessive daytime sleepiness and consciousness disorders. Respiratory distress and coma may also occur. The drug should also not be combined with methotrexate, as this can cause a large drop in erythrocyte, white blood cell and platelet count. In addition, kidney and liver damage may occur [1]. In some patients, especially pregnant women, monitoring of serum drug levels is recommended [3].

Aim

This paper aims at reviewing the current applications of levetiracetam for the treatment of various medical conditions and guiding the course towards potential scientific research.

Materials and methods

The literature available in the PubMed database was reviewed using the following keywords: “levetiracetam”; “epilepsy”; “status epilepticus”; “Alzheimer’s disease”; “migraine”; “neuropathic pain”.

Results

Use of levetiracetam in prevention of focal and generalized epileptic seizures

Around 50 million people worldwide suffers from epilepsy - one of the most common neurological diseases. It is caused by synchronous and excessive neuronal discharges [4]. We can distinguish two peaks in the incidence of the disease. The first one occurs in children around the age of one, when it is usually caused by genetic factors. The second incidence peak is around 65 years of age. In that case, the main causes may include vascular diseases, metabolic diseases, and brain tumors [5]. It has been shown that people with epilepsy face a greater risk of physical injury in the form of fractures and bleeding episodes, the occurrence of psychiatric disorders – mainly depression and anxiety [4]. One third of patients have drug-resistant epilepsy. Adverse effects after antiepileptic medications occur in 20–30% of patients [6].

Numerous clinical studies and meta-analyses show that levetiracetam can be used to prevent both focal and generalized epileptic seizures.

In their clinical study, Manrez et al. have assessed the efficacy and safety of levetiracetam therapy in the prevention of focal epileptic seizures in a group of children and adults. The study included 114 persons. Inclusion criteria were as follows: the presence of epileptic seizures for a minimum of two years with at least 12 epileptic seizures in the 12 weeks preceding the study and no documented brain damage. In addition, the subjects had to take up to three anti-epileptic drugs regularly for at least one month. Women had to also have a negative pregnancy test prior to inclusion in the study and take contraceptives during the study. The study lasted for 30 weeks and consisted of three parts. For the first 8 weeks, patients continued their previous antiepileptic treatment. Next, the subjects were randomly allocated to the levetiracetam and placebo groups for 16 weeks. At the start of the study, the pediatric group received the medication at a dose of 20 mg/kg/day and the adult group at a dose of 1,000 mg/day. The dose was increased every 2 weeks until reaching a dose of 60 mg/kg/day in the pediatric group and 3,000 mg/day in the adult group. If the subject did not tolerate a higher dose, the lowest effective dose was used. In the third part

of the study, treatment with an appropriately adjusted dose was maintained for 6 weeks. It was shown that in 38.7% of patients from the group receiving levetiracetam the average number of focal seizures occurring per week dropped by a half. The incidence of adverse effects and the safety profile of the medication were similar to the placebo group. Levetiracetam was shown to be an effective and safe drug in both children and adult patients with refractory focal epilepsy [4].

A meta-analysis of 3205 participants also showed that levetiracetam is an effective antiepileptic drug in the prevention and treatment of seizures which are classified as partial, generalized, and refractory to other drugs. The effective dose of levetiracetam for adults is 1000–3000 mg/day and in pediatric patients 60 mg/kg/day. Side effects are mild and resolve quickly: they manifest as drowsiness, dizziness, irritability, anxiety or nasopharyngitis. Compared to the placebo, the medication reduces the incidence of epileptic seizures by 50% and shortens their duration [6].

Numerous studies and meta-analyses have compared the efficacy and safety of levetiracetam to other antiepileptic drugs.

In a meta-analysis of 574 individuals, Kharel et al. have shown that levetiracetam has similar efficacy to oxcarbamazepine in preventing focal epilepsy [7].

The SANAD II study has also compared the efficacy of levetiracetam with other antiepileptic drugs. The study included patients over the age of five with a history of a minimum two epileptic seizures and who additionally require regular antiepileptic medication. The study involved 990 participants with focal epilepsy. The subjects were randomly allocated to a group receiving levetiracetam (332 subjects), lamotrigine (330 subjects) and zonisamide (328 subjects). It was shown that the use of levetiracetam and zonisamide was associated with higher treatment costs and lower efficacy in preventing focal epileptic seizures compared to lamotrigine. Adverse effects occurred in 33% of subjects taking lamotrigine, 44% taking levetiracetam and 45% of those treated with zonisamide.

In a group of patients with generalized and unclassified epilepsy, 260 individuals were randomly allocated to the valproate-treated group, with the remaining 260 taking levetiracetam. 397 patients suffered from generalized epilepsy and 123 patients – from unclassified epilepsy. Valproate appeared to be more effective in the prevention of generalized and unclassified epileptic seizures, and the cost of therapy with this medication was lower. Adverse effects occurred in 37.4% of participants taking valproate and in 41.5% receiving levetiracetam [8].

Use of levetiracetam in the interruption of status epilepticus

By definition status epilepticus is uninterrupted, persistent epileptic seizures lasting at least 30 minutes, or repeated seizure episodes between which the person does not fully regain consciousness. The first-line drugs used to terminate status epilepticus are intravenous (iv) benzodiazepines. It has been shown that 80% of patients respond to the first-line treatment if they receive the medication within 30 minutes of the seizure onset. The mortality rate due to status epilepticus is approximately 26% [5]. It is therefore important to apply appropriate treatment and to introduce new forms of therapy and drugs in the patient's refractory to the first-line treatment.

It has been shown that levetiracetam can be used to interrupt status epilepticus.

In their meta-analysis, Yasiry et al. have evaluated the efficacy of different antiepileptic drugs in the treatment of status epilepticus in patients unresponsive to the first-line treatment with benzodiazepines. It was shown that the use of phenobarbital, valproate and levetiracetam can effectively interrupt the epileptic seizure. The first-line therapy with levetiracetam was effective in 68.5% of patients [9].

In contrast, the EcLiPSE study by Appleton et al. on 286 subjects have assessed the efficacy of levetiracetam 40 mg/kg i.v. and phenytoin 20 mg/kg i.v. in interrupting epileptic seizures in children and adolescents aged from 6 months to 17 years 11 months who did not respond to the first-line treatment. It was shown that the use of levetiracetam was of little benefit in terms of the number of interrupted epileptic seizures and the time between medication intake and seizure termination, as well as the number of side effects compared with the use of phenytoin [10].

More clinical trials must be conducted on larger groups to validate levetiracetam as an effective form of the first-line therapy for the interruption of epileptic seizures in patients.

Use of levetiracetam in the treatment of neonatal seizures

Neonatal seizures occur with a frequency of 1 to 3 per 1,000 live births. They are most often caused by intraventricular hemorrhage (IVH) or hypoxic ischemic encephalopathy (HIE) [11]. Phenobarbital and phenytoin are often administered to patients to interrupt neonatal seizures. Clinical practice suggests that the use of phenobarbital and phenytoin in the treatment of this disease in neonates is not very effective [12]. The FDA has approved levetiracetam as adjunctive therapy for the treatment of focal seizures in infants over 1 month of age. The medication is often used off-label in the first-line treatment of a given condition [13].

In their clinical trial, Gowda et al. have compared the efficacy of levetiracetam with phenobarbital in the treatment of neonatal seizures. If the seizure did not stop after compensation by hypoglycemia or hypocalcemia, the study subjects were randomly assigned to groups receiving levetiracetam 20 mg/kg or phenobarbital at the same dose. When seizures persisted, a dose of the same drug was

repeated. Seizures were shown to resolve in 86% of neonates treated with levetiracetam and in 62% of those treated with phenobarbital. In addition, the phenobarbital-treated group developed adverse effects in the form of hypotension and bradycardia, whereas the levetiracetam-treated group did not. It was observed that neonates born at term and with a birth weight between 2.5–2.7 kg responded best to levetiracetam therapy [14].

In their clinical study, Sharpe et al. have also shown that levetiracetam treatment was associated with a lower incidence of adverse effects than phenobarbital therapy. In addition, it was shown that increasing the dose of levetiracetam from 40 to 60 mg/ kg bw increase its efficacy in treating a given disease [12]. Another study indicates that a safe dose of levetiracetam in this group of patients is up to 100 mg/kg bw [15].

In addition, clinical studies in animals confirm that levetiracetam causes fewer neurotoxic effects than phenobarbital. In their study, Kaushal et al. have assessed the effects of antiepileptic medications, including levetiracetam, on neuronal apoptosis within the white matter in rodents. The use of phenobarbital and phenytoin was shown to lead to a significant increase in neuronal apoptosis, whereas the use of levetiracetam did not increase it [11].

Numerous clinical studies have demonstrated the superior efficacy of levetiracetam compared to phenobarbital in the treatment of neonatal seizures. Further studies are needed to obtain FDA approval of levetiracetam for the treatment of the condition in the first-line therapy.

Use of levetiracetam in the treatment of epilepsy in pregnant women

The European Registry of Antiepileptic Drugs and Pregnancy (EURAP) reports that the frequency of epileptic seizures during pregnancy remains unchanged in 63.6% of patients, increases in 17.3% and decreases in 15.9% of pregnant women [16]. Conventional antiepileptic drugs have shown teratogenic effects in the fetus. They increase the risk of major birth defects from 1–2% to 4–9% [17].

In their clinical trial, Tabrizi et al. have found that levetiracetam should be used as a replacement for valproate, especially in women of childbearing age and planning to become pregnant [18]. Several international registries, such as EURAP, NAAPR or the UK and Ireland Pregnancy Register, have shown that the use of levetiracetam is associated with a lower risk of major congenital disorders in the fetus. In their retrospective study, Marini et al. and Sharma et al. have shown a reduction in epileptic seizure frequency in case of applying levetiracetam monotherapy to pregnant women [16, 17]. The Polish Society of Gynaecologists and Obstetricians (PSGO) recommends the use of levetiracetam in pregnant women with epilepsy. Due to changes in pharmacokinetics, the serum drug concentration may decrease by 30-50%, which may contribute to the severity of the symptoms. Which is why PSGO recommends monitoring the blood concentration of this medication both before pregnancy and at least once during each trimester [3].

Use of levetiracetam in the treatment of migraine

Around 1 billion people worldwide suffer from migraine headaches. The efficacy of antiepileptic drugs, including levetiracetam, in the treatment of migraine headache is due to the fact that both migraine and epilepsy share the same pathophysiology. They are both related to a hyperactivity of neurons in the cerebral cortex. FDA has approved only valproic acid and topiramate for the prevention of migraine headache attacks. However, valproic acid is now rarely used in the treatment of the disease due to its side effects [2].

In their meta-analysis, Po-Hua et al. have assessed the efficacy of levetiracetam for migraine. The medication was shown to cause a significant reduction in the frequency and severity of headaches compared to the placebo. It brings similar effects in both pediatric and adult populations. In some patients, after the treatment with levetiracetam, migraine headache attacks did not recur [2].

In their clinical study, Montazerlotfelahi et al. have assessed the safety and efficacy of levetiracetam in the prevention of migraine headaches in children. 31 study subjects were randomly allocated to the levetiracetam group and 31 subjects – to the placebo-controlled group. The study included patients between the ages of 4 and 17 with a minimum of four episodes of migraine headache per month or suffering from severe pain during an episode, which prevents them from daily functioning. It was shown that levetiracetam is effective and can be used for the prevention of migraine headaches by decreasing the frequency and intensity of attacks. Adverse effects in the form of irritability, daytime sleepiness and mild nervous twitches were rare [19].

Also, in a clinical study on 65 adults, Verma et al. have shown that the use of levetiracetam reduces the frequency and severity of migraine headache episodes in adults. Patients also reported the need to take fewer medications compared to the placebo group to control migraine headache symptoms [20].

The results of the study raise hopes for an effective treatment of migraine headache with a drug that does not cause bothersome side effects.

Use of levetiracetam in the treatment of neuropathic pain

Chronic neuropathic pain is usually caused by diabetic neuropathy and postoperative pain. Its prevalence is estimated to be around 10% of patients. It has been shown that patients with chronic neuropathic pain experience a reduced quality of life and are more likely to require medical consultations and hospitalization, resulting in higher healthcare costs. Currently available treatment methods have been shown to help reduce the neuropathic pain in

approximately 30% of patients with diabetic neuropathy [21].

In their clinical study, Ling et al. have shown that levetiracetam should not be used for relief of neuropathic pain since it is ineffective in that case [22].

Also, in their meta-analysis based on six clinical trials conducted on 344 patients, Crawford-Faucher et al. have shown that levetiracetam therapy brings no relief to patients with neuropathic pain. In addition, 67% of study subjects experienced adverse effects in the form of fatigue, headache, dizziness, nausea, and constipation [21].

Use of levetiracetam in the treatment of a manic episode

The treatment of a manic episode is based mainly on mood stabilizers, which include lithium, lamotrigine, carbamazepine, sodium valproate and second-generation antipsychotics, which include olanzapine, aripiprazole, risperidion and quetiapine. The main reason why patients stop therapy with the above-mentioned drugs are the adverse side effects occurring during their use [23].

In their clinical trial, Keshavarzi et al. have assessed the effect of levatiracetam on the course of bipolar affective disorder in patients with a manic episode. The study subjects were divided into two groups. Group one received levetiracetam in addition to lithium therapy at a dose of 250 to 1,500 mg, group two was treated with lithium alone. The patients completed self-assessment and sleep assessment questionnaires at baseline and day 12 of the study. In addition, the severity of the manic episode was assessed using the Young Mania Rating Scale (YMRS) at baseline, day 12 and day 24 of the study. It was proven that the use of levatiracetam with lithium reduces the severity of the manic episode and improves the sleep quality of the patients [23].

In their clinical study, Zarezadeh et al. have assessed the safety, efficacy, and tolerability of levetiracetam and quetiapine in patients in the acute manic phase. 44 patients with YMRS scores ≥ 20 were included in the study. The subjects were randomly allocated to a group receiving levetiracetam and quetiapine or to a placebo-controlled group taking quetiapine alone for 6 weeks. It was shown that the addition of levetiracetam alleviate the course of a manic episode to a greater extent than the placebo. The number of side effects was similar in both groups. Levetiracetam is safe, effective, and well tolerated in patients with a manic episode [24].

Further studies must be conducted on larger groups to validate levetiracetam for the treatment of manic episode in bipolar disorder.

Use of levetiracetam in the treatment of Alzheimer's disease

Epileptic seizures in patients with Alzheimer's disease over 80 years of age are three times more common than in people without dementia: in their case a risk of having an epileptic seizure is between 10 and 20%. Patients show neuronal hyperactivity in the hippocampus and medial temporal lobe [25].

In their clinical trial called LEV-AD, Vossel et al. have evaluated the effect of low-dose levetiracetam administered for 4 weeks on cognitive function in people with Alzheimer's disease (AD). It was shown that the low-dose use of the medication improves patients' spatial and executive memory [26].

The study by Shi et al. has involved administering antiepileptic medications, including levetiracetam at a dose of 50 mg/kg body weight, to mice with overexpression of the amyloid β precursor gene and presenilin 1 for 30 days. Levetiracetam was shown to inhibit the production of amyloid β and increase its degradation by autophagy [27].

These results suggest that additional clinical trials are needed to better understand the effect of levetiracetam on slowing the progression of Alzheimer's disease.

Summary

FDA has approved levetiracetam for the adjuvant treatment of focal, myoclonic, and tonic-clonic epileptic seizures. The drug is also effective in off-label indications: the management of migraine, a manic episode in the course of bipolar affective disorder. Single studies indicate its positive effect on the course of Alzheimer's disease. Adverse effects occurring during treatment with this medication are rare and mild. They can include, among other things, drowsiness, dizziness, irritability, anxiety or nasopharyngitis. Further research is needed into the use of levetiracetam, which will help expand its use in medical practice.

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PRIMARY HYPEROXALURIA TYPE 1 – CLINICAL CHARACTERISTICS AND NEW THERAPEUTIC OPTIONS

Pierwotna hiperoksaluria typu 1 – charakterystyka kliniczna i nowe opcje terapeutyczne

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Abstract: Primary hyperoxaluria type 1 (PH1) is an ultra-rare, autosomal recessive metabolic disorder caused by mutations of the AGXT gene, encoding the liver specific peroxisomal enzyme, alanine: glyoxalate aminotransferase (AGT). It disturbs the glyoxalate metabolism and leads to hepatic overproduction of oxalate and its increased urinary excretion (hyperoxaluria). In majority of cases, first symptoms are observed during childhood as recurrent calcium – oxalate (CaOx) urolithiasis and/or nephrocalcinosis causing oxalate nephropathy, progressive chronic kidney disease (CKD) and end stage renal failure. Decreased renal clearance leads to oxalosis – systemic disease caused by multiorgan CaOx deposition. Until recently, the liver transplantation (LT) was the only causative therapy, performed usually parallel with the kidney transplantation in patients who reached CKD stage 4-5. Unfortunately, symptomatic treatment (hyperhydration, alkali citrate, low oxalate diet) as well as pyridoxine therapy are not satisfactory in majority of patients. The approval of lumasiran, the new orphan drug based on the RNA interference, seems to be a breakthrough in PH1 treatment. It silences glycolate oxidase- the key enzyme of glyoxalate metabolism and therefore decreases hepatic oxalate synthesis. This innovative strategy gives a reasonable hope for an effective treatment and may replace the necessity of the LT in patients with PH1.

Keywords: primary hyperoxaluria type 1, clinical course, treatment, innovative therapies.

Streszczenie: Pierwotna hiperoksaluria typu 1 (PH1) to genetycznie uwarunkowana, ultrarzadka choroba metaboliczna o dziedziczeniu autosomalnym recesywnym. Jej powodem są mutacje genu AGXT kodującego specyficzny dla hepatocytów peroksysomalny enzym – aminotransferazę alaninowo-glioksalanową (AGT). Skutkiem jest zaburzenie metabolizmu glioksalanu prowadzące do wątrobowej nadprodukcji szczawianu i jego nadmiernego wydalania z moczem (hiperoksalurii). W większości przypadków choroba ujawnia się w okresie dzieciństwa jako nawracająca kamica moczowa szczawianowo-wapniowa (CaOx) i/lub nefrokalcynoza. W następstwie prowadzi do rozwoju nefropatii szczawianowej, postępującej przewlekłej choroby nerek (PChN) i ostatecznie ich schyłkowej niewydolności. Obniżenie klirensu nerkowego skutkuje oksalozą – układową chorobą spowodowaną wielonarządowym gromadzeniem CaOx. Do niedawna jedyną metodą leczenia przyczynowego był przeszczep wątroby, zazwyczaj wykonywany równocześnie z przeszczepem nerki u pacjentów, którzy osiągnęli stadium 4-5 PChN. Stosowane metody leczenia zachowawczego (obfite pojenie, zasadowe cytryniany, dieta ubogoszczawianowa), jak również terapia pirydoksyną, są niestety mało skuteczne u większości chorych. Dlatego przełomem stało się dopuszczenie do leczenia lymazyranu – leku opartego na technologii interferencji RNA. Celem jego działania jest wyłączenie kluczowego enzymu metabolizmu glioksalanu – oksydazy glikolanowej, a w efekcie zmniejszenie wątrobowej syntezy szczawianu. Ta innowacyjna terapia daje uzasadnioną nadzieję na skuteczne leczenie, a w szczególności może zastąpić potrzebę przeszczepu wątroby u pacjentów z PH1.

Słowa kluczowe: pierwotna hiperoksaluria typu 1, obraz kliniczny, leczenie, innowacyjne terapie.

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Primary hyperoxaluria type 1 (PH1) (MIM #259900) is an autosomal recessive monogenic metabolic disease with increased endogenous production of oxalate and subsequent urinary oxalate excretion, i.e., hyperoxaluria. The cause of PH1 is mutations in the AGXT gene (2p37.3), encoding the liver specific peroxisomal enzyme, alanine: glyoxalate aminotransferase (AGT) [1-3]. Depending on the type of mutation, of which more than 200 have been identified to date, there is a complete or partial absence of AGT activity. In the latter case, it may be due to enzyme

mistargeting. The resulting enzymopathy disturbs the glyoxalate metabolism in the liver and leads to overproduction of oxalate in this organ [4]. Two other types of primary hyperoxaluria known so far (PH2 and PH3) also lead to similar metabolic sequelae, but they result from mutations of other genes: GRHPR and HOGA1, respectively, encoding their specific enzyme proteins glyoxalate reductase/hydroxypyruvate reductase (GRHPR) and 4-hydroxy-2-oxoglutarate aldolase (HOGA) [1-3].

PH1 is an ultra-rare disease with a geographically diverse epidemiology. It is the most common type among primary hyperoxalurias, accounting for approximately 80% of cases [1, 2, 5]. PH1 in Western European countries and the USA has the estimated incidence of approximately 1:120,000 live births and prevalence of 1-3 cases per 1 million population. The disease appears to be more prevalent in some Middle Eastern and North African countries [1, 2, 5]. In Poland, 15 patients with PH1 have been diagnosed in the last 25 years, suggesting a much lower incidence of the disease compared to the above statistics. However, undiagnosed cases cannot be excluded [6].

Clinical picture

The disease usually manifests in childhood in the form of recurrent, often bilateral calcium oxalate urolithiasis and/or nephrocalcinosis (NC), which are direct consequences of hyperoxaluria. Symptoms thus include episodes of renal colic accompanied by hematuria, less commonly sterile leukocyturia or urinary tract infections. The accumulation of calcium oxalate crystals in the interstitium of the kidneys leads to the development of oxalate nephropathy, chronic kidney disease (CKD) and ultimately end-stage renal disease (ESRD), which usually occurs in the second or third decade of life. Sometimes this dramatic scenario may be observed in infants (infantile oxalosis) or only in late adulthood [1, 2, 7]. It is estimated that PH1 is responsible for approximately 1% of pediatric cases managed by renal replacement therapy in Western countries. A decrease in glomerular filtration rate < 30-45 ml/min/1.73 m2 body surface (b.s.) results in a significant decrease in oxalate clearance, saturation of plasma with oxalate, crystallization of calcium oxalate and its extra-renal deposition, mainly in the bones, joints, skin, cardiovascular system, retina, and peripheral and central nervous system. It leads to multi-organ damage, making PH1 a systemic disease (oxalosis). The condition is mainly manifested by severe bone and joint pain, pathological fractures, erythropoietin-resistant anemia, skin ulcerations due to vasculopathy, peripheral neuropathy, retinopathy, cardiomyopathy, cardiac arrhythmias, and circulatory failure, which can be fatal [1, 2, 7].

Diagnostics

PH1 may be suspected when test results reveal elevated daily urinary oxalate excretion, i.e., > 0.5 mmol/1.73 m2 b.s. /24 h (> 45 mg/1.73 m2 b.s./24 h), but usually oxaluria exceeds 1 mmol/1.73 m2 b.s./24 h (> 90 mg/1.73 m2 b.s./24 h) [8, 9]. Therefore, assessment of urinary oxalate excretion should be a part of the metabolic evaluation of all pediatric cases of urolithiasis and NC and recurrent adult urolithiasis of unclear etiology, especially with concomitant CKD. Initial assessment of urinary oxalate excretion, especially in the youngest children, can be based on so-called creatinine indices (oxalate to creatinine ratio) determined in single morning urine portions, taking into account age norms [8, 9]. It should be remembered that in patients with PH1 and stage > 3-4 CKD, urinary oxalate excretion may be normal due to the aforementioned, significantly reduced renal clearance. In such cases, it may be helpful to determine plasma oxalate levels, which usually exceed 50 µmol/l during SNN [8, 9]. In contrast to most patients with urolithiasis, a frequent characteristic manifestation in PH1 patients is the low urinary calcium excretion resulting from excessive crystallization of calcium oxalate. Unfortunately, also in our country, PH1 is sometimes diagnosed only after the loss of the transplanted kidney as a result of "recurrence" of the underlying disease [6]. Currently, the diagnosis of PH1 is based on genetic test, and the most common mutation revealed in approximately 30% of alleles of the AGXT gene is the c.508G>A mutation (p.Gly170Arg) [10].

Treatment

Early diagnosis of PH1 is crucial for appropriate disease management and increasing the chances of improved prognosis [8, 9]. In patients with adequate diuresis, the cornerstones of treatment are abundant fluid supply (> 2500-3000 ml/1.73 m2 b.s.) evenly distributed throughout the day and intake of potassium citrate (0.5-2 mEq/kg/24h; 50-200 mg/kg/24 h; 3-4 x/day), since they reduce the crystallization of calcium oxalate in the urine. In carriers of certain mutation types, including the already mentioned c.508G>A (p.Gly170Arg) and additionally c.454T>A (p.Phe152Ile), a significant reduction in oxaluria can be achieved by administration of pyridoxine (vitamin B6) at a usual dose of 5 mg/kg/24 h (2 x/day) [9, 10]. It is due to the catalytic effect of pyridoxine on AGT activity, especially when this enzyme is dislocated into the mitochondria. It must be remembered that in patients with PH1 minimally invasive endoscopic methods are preferred in the surgical treatment of urolithiasis. Extracorporeal shock wave lithotripsy (ESWL) should be avoided, as it increases the risk of damage to the renal parenchyma [11].

Patients who have reached stage 4 CKD are recommended to start renal replacement therapy, which is much earlier than for other diseases leading to SNN, in order to slow down the development of systemic oxalosis. Unfortunately, classical dialysis management does not sufficiently eliminate excess oxalate, with hemodialysis being slightly more effective than peritoneal dialysis. Therefore, patients are advised to increase their session frequency and time, preferably with control of plasma oxalate levels, whose pre-dialysis level should not exceed 30-45 µmol/l. However, in specific clinical situations, continuous renal replacement therapy (CRRT) techniques are recommended [8, 9]. Until recently, the treatment of choice in patients with PH1 with stage 4 CKD was simultaneous combined liver/kidney

transplantation or, exceptionally, isolated liver transplantation in patients with well-preserved own kidney function. Removing patient's own liver and replacing it with a transplant restores normal glyoxalate metabolism and inhibits progression of systemic oxalosis, including the potential recurrence of oxalate nephropathy in the renal graft. However, there is still a threat relate to the tissue oxalate pool, which needs to be cleared with CRRT, especially in the peri-transplant period.

Thanks to recent advances in biotechnology, new therapeutic options for the PH1 treatment have emerged, resulting in modifications to existing recommendations [9].

New therapeutic options

Technologies based on RNA interference (RNAi) seem to be a breakthrough in the PH1 treatment [12]. RNAi means post-transcriptionally gene silencing, which is induced by short interfering RNAs (siRNAs). They act as a probe that recognizes the target mRNA sequence for a specific protein, recognizes the target mRNA sequence for a specific protein, allowing the associated RISC (RNA induced silencing complex) to enzymatically degrade the mRNA. This gene expression regulation mechanism, discovered over two decades ago, has led to development of innovative therapies for many diseases [13].

In the case of PH1, this technology was used to study the inhibition of the expression of selected enzymes of glyoxalate metabolism, ultimately reducing endogenous oxalate formation. It resulted in creation of lumasirane and nodazirane – substances with high affinity for the hepatic cell, which degrade the mRNA for a specific enzyme [14, 15].

Lumasirane targets mRNA of the HAO1 gene, which encodes the peroxisomal liver enzyme, glycolate oxidase (GO). After experimental studies in an animal model and subsequent clinical trials allowed the drug was approved in November 2020 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of PH1 patients [16].

Lumasirane (Oxlumo®) can be used in all age groups. It is administered subcutaneously in a dose and schedule dependent on body weight. In children weighing < 10 kg, the injection is administered once a month, while in children > 10 kg and adults it is initially administered monthly for 4 months as a saturation dose, followed by maintenance doses every 3 months. Clinical trials have shown that in over 60% of PH1 patients with eGFR >30 ml/ min/1.73 m2 (stage 1–3 CKD) treatment brings oxaluria reduction, as well as a significant reduction in plasma oxalate concentrations in PH1 patients with advanced renal failure, including end-stage renal disease, undergoing dialysis. At the same time, no significant side effects were found [17-19].

In Poland, lumasiran treatment has been available via the Medical Fund since 2022 under a dedicated drug program for patients with PH1 and stage 1–3 CKD. Currently, five patients are being treated, including two children.

On the other hand, nedosiran targets the mRNA of lactate dehydrogenase A (LDHA), the cytosolic enzyme that influences conversion of glyoxalate to oxalate. The drug is in the final phase of clinical trials and registration can be expected soon. Previous observations indicate, among other things, that after 6 months of treatment in 81% of patients with PH1 and stage 1 - 3 CKD urinary oxalate excretion is reduced < 1.5 times the upper limit of normal and a significant reduction in plasma oxalate levels in dialysis patients with PH1 [20, 21]. Since glyoxalate has as a different target than lumazirane in the metabolic pathway, nedosiran could theoretically also be effective in the treatment of the other two types of PH, but the current results of clinical trials for PH2 are inconclusive [21].

Another promising medicament in the clinical treatment of PH1 is styripentol [22]. It is widely-used in the treatment of Dravet syndrome, a severe drug-resistant form of myoclonic epilepsy of infancy (SMEI). In addition to controlling seizures, mainly due to an increase in gamma-aminobutyric acid (GABA) levels, styripentol appears to inhibit the activity of the previously mentioned lactate dehydrogenase isoenzyme (LDHA), thanks to which, like nedosiran, it may be useful in the treatment of all types of PH. Although single observations are promising, at least in patients with PH1 in the early stages of CKD, ongoing clinical trials need to confirm this effect [23]. Undoubtedly, given the high cost of RNAi medications, treatment with styripentol could be an interesting therapeutic option.

Summary

Primary hyperoxaluria type 1 is an ultra-rare disorder of hepatic glyoxalate metabolism leading to severe multi-organ complications, most notably renal damage. The ultra-rare occurrence and non-specific course of the disease hinders timely diagnosis, and the specific pathomechanism makes effective treatment difficult. New therapeutic options hold out hope for improving patient prognosis and, above all, avoiding the need for liver transplantation – currently the only effective causal treatment option.

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URINARY TRACT INFECTIONS IN CHILDREN – DIAGNOSTICS, TREATMENT AND THE PROPHYLAXIS OF RECURRENCES

Zakażenia układu moczowego u dzieci – diagnostyka, leczenie i profilaktyka nawrotów

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Abstract: Urinary tract infections (UTIs) are among the most common bacterial infections in children. Early diagnosis, although important, can be a problem for physicians of all specialties. The manuscript presents the latest guidelines for diagnosis (methods of urine collection and interpretation of the results), treatment of lower and upper urinary tract infections with a typical as well as atypical course, prevention of recurrent urinary tract infections, and management of special conditions such as UTI in pregnant teenagers. In addition, the article discusses the dosage of medications recommended for urinary tract infections, methods of prophylaxis of recurrent infections (including non-pharmacological methods) and presents indications for imaging studies in children with UTI. The study is based mainly on the 2021 Guidelines of Polish Society of Pediatric Nephrology.

Keywords: urinary tract infections, children, acute pyelonephritis, cystitis, prophylaxis.

Streszczenie: Zakażenie układu moczowego (ZUM) jest jednym z najczęstszych zakażeń bakteryjnych u dzieci. Wczesne rozpoznanie, choć jest istotne, może stanowić problem dla lekarzy wszystkich specjalności. Prezentowana praca przedstawia najnowsze wytyczne w zakresie diagnostyki (metody pobierania moczu i interpretacja wyników badań), leczenia zakażeń dolnych i górnych dróg moczowych o typowym, jak i o nietypowym przebiegu, profilaktyki nawracających zakażeń układu moczowego oraz postępowania w stanach szczególnych, np. u nastolatek w ciąży. W artykule omówiono ponadto dawkowanie leków rekomendowanych w zakażeniach układu moczowego, metody profilaktyki nawrotów zakażeń (w tym metody niefarmakologiczne) oraz przedstawiono wskazania do badań obrazowych u dzieci z ZUM. Opracowanie jest oparte głównie na wytycznych Polskiego Towarzystwa Nefrologii Dziecięcej z 2021 r.

Słowa kluczowe: zakażenia układu moczowego, dzieci, ostre odmiedniczkowe zapalenie nerek, zapalenie pęcherza moczowego, profilaktyka.

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Definitions

The definitions used in this article are based on the recommendations of the Polish Society of Paediatric Nephrology (PTNFD), also considering the recommendations of other scientific societies [1-5]:

- **Lower urinary tract infection (cystitis):** inflammation of the bladder, dysuric symptoms, frequent urination, urgency, wetting, pain in the suprapubic area, strong smelling urine, sometimes hematuria.
- **Upper urinary tract infection (acute pyelonephritis, acute infectious tubulointerstitial nephritis (AITIN):** infection involving the renal pelvis and renal interstitium, body temperature > 38°C, abdominal pain or tenderness in the lumbar region (positive Goldflam's sign), usually with high inflammatory markers.
- **Asymptomatic bacteriuria:** presence of bacteria in the urine at a symptomatic titer without clinical symptoms and without changes in the urinalysis.
- **Urinary tract infection with an atypical course:** UTI characterized by (one of the following): severe general condition (symptoms of generalized infection), impaired urinary outflow (urinary tract abnormalities), impaired glomerular filtration rate, sepsis, no response to antimicrobial treatment within 48 hours, or infection caused by a bacterium other than *Escherichia coli*.
- **Recurrent urinary tract infections:** 2 or more episodes of pyelonephritis or 1 episode of pyelonephritis plus 1 episode of cystitis or 3 or more episodes of cystitis.

Pathophysiology

Above the bladder sphincter, the urinary system is sterile. Certain mechanisms in the human body prevent the proliferation of bacteria in the urinary tract – properly functioning bladder emptying, and urinary tract peristalsis prevent urinary stasis and backflow; a functional immune system and the presence of endogenous antimicrobial substances also play a protective role [6].

Risk factors for urinary tract infections and recurrent urinary tract infections are the history of UTIs, congenital anomalies of the urinary tract, positive family history of UTIs and/or congenital anomalies of the urinary tract, bladder catheterization, neurogenic and non-neurogenic micturition disorders, constipation, sexual activity and urinary tract stones and conditions predisposing to them. Some studies indicate a reduced risk of infection in boys after circumcision [4-6].

UTI is usually an ascending infection, descending (blood-borne) pathway occurs rarely, mainly in neonates and immunocompromised patients [6, 7].

The most common cause of UTI in children is *Escherichia coli*. Urinary tract infections can also be caused by other Gram-negative bacilli, e.g., *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis* (causes cystitis in boys), Gram-positive bacteria (*Enterococcus faecalis*, *Streptococcus agalactiae or Staphylococcus spp*) in neonates, *Pseudomonas aeruginosa* (in children with severe abnormalities of the urinary tract or neurogenic bladder, and the biofilm produced protects the microbe from antibiotics, making eradication difficult or impossible). Neonates, immunocompromised patients, or individuals after prolonged antibiotic therapy may develop a fungal UTI. Viral infections caused, for example, by adenoviruses (hemorrhagic cystitis) are rare [5, 6, 8].

How to recognize a urinary tract infection in children

The younger the child, the less specific the symptoms of UTI are. The most constant symptom of UTI in younger children is the presence of a—fever, which may be accompanied by lack of weight gain, excessive sleepiness, loose stools, prolonged jaundice. Older children usually develop abdominal pain and dysuria. In all age groups, an alarming sign is a change in the smell or color of the urine. Due to the difficulty in differentiating between upper and lower infections in younger children (< 2 years of age), all infections should be treated as acute pyelonephritis [4, 5, 9].

While collecting medical history, attention should be paid to symptoms and conditions that predispose to UTI. Episodes of fevers of unknown cause in the past (possible unrecognized pyelonephritis) may be relevant. The history should additionally include urinary and fecal disorders. The HCP should ask about previous treatment, as even a single dose of medication can alter the results of the urinalysis and urine culture [5, 6].

On physical examination, the general condition should be assessed. A febrile child should be examined for a developing generalized infection (capillary return, symptoms of centralized circulation, meningeal symptoms). Masses palpable in the abdominal cavity may suggest urinary tract abnormalities. A positive Goldflam's sign indicates an upper urinary tract infection. A thorough examination of the genitourinary tract is necessary in search of abnormalities (phimosis, labial adhesions). Incorrect urine collection or vulvitis can sometimes be the cause of an abnormal result of a general urine test or a false-positive urine culture [5].

Abnormalities in the lumbosacral region (excessive skin pigmentation, lipoma, hemangioma, hair tuft) may indicate a dysraphism and neurogenic bladder. Height and weight deficiency or hypertension suggest unrecognized chronic kidney disease.

According to PTNFD recommendations, a general urine test should be performed in all children under 5 years of age with a fever without an identifiable cause and in children with symptoms suggestive of UTI, and regardless of age in children with a–fever, who have risk factors for UTI. According to the above recommendations, a urine culture should be performed in infants and children with suspected acute pyelonephritis, in infants and children with abnormal general urine test results and when clinical symptoms do not correlate with a general urine test result [5].

According to the PTNFD recommendations, a general urine test can be collected by any method, while a urine culture test must not be collected using a bag attached to the perineal area [5].

The most common method of collecting urine for testing is to collect it–from the midstream. For proper collection, thorough hygiene of the genitourinary area should be performed with pulling back the foreskin or spreading the labia. The child should then do free micturition. If urine collection with this method is not possible, if the urine test result is doubtful and in children where a rapid urine result is needed, diagnostic bladder catheterization or suprapubic puncture is recommended [5].

The urine sample must be forwarded to the laboratory within one hour of collection or stored prior to testing in a refrigerator for a maximum of 4 hours at 4°C.

Suspicion of urinary tract infection should be based on clinical symptoms and an abnormal urinalysis. A positive result for leukocyte esterase and nitrite in dipsticks suggests urinary tract infection. Dipsticks have limited specificity and sensitivity, with 79% and 88% for leukocyte esterase and 98% and 49% for nitrite [3]. According to the PTNFD recommendations, an abnormal dipstick result should be verified by performing a urine sediment examination. In the urine sediment, the primary abnormality suggestive of URI is leukocyturia, defined as: the presence of more than 5 leukocytes in the field of view

(lpf) of the microscope in uncentrifuged urine or 10 or more leukocytes/lpf in centrifuged urine, or a leukocyte count above the reference value when examined by automated microscopy or flow cytometry. The urinalysis may reveal other abnormalities, e.g., hematuria or proteinuria. Hematuria and high proteinuria are common in cystitis. Leukocyturia is sometimes present in non-infectious kidney disease (so-called sterile leukocyturia) [5].

UTI is confirmed by a positive urine culture. According to Polish recommendations, the significant bacteriuria for midstream urine collection is 10^5 colonies of uropathogenic bacteria in 1 ml of urine, 10^4 in catheterized urine and 10^3 in urine from a suprapubic puncture. Lower bacterial titers can be found in infections caused by non- *E. coli* pathogens with symptoms characteristic for UTI. An increase of two different bacteria in a urine culture suggests a false-positive result and incorrect collection of a urine sample. According to PTNFD, in adolescent girls with a first cystitis, a urine culture may be waived [5, 6].

In cases of hospitalized children and a severe infection course, blood tests are performed. Evaluation of inflammatory markers (leukocytosis, elevated C-reactive protein [CRP] and especially procalcitonin [PCT]) can be helpful in differentiating between upper and lower urinary tract infections. In hospitalized children, renal function parameters (serum urea and creatinine levels) and ionogram (sodium, potassium, calcium) should be assessed. UTI may be accompanied by transient pseudohypoaldosteronism (resolves after treatment) presenting with hyponatremia, hyperkaliemia and metabolic acidosis. Hypercalcemia and hypercalciuria (e.g., as a result of vitamin D overdose or hypersensitivity) may promote urinary tract infections.

Indications for hospitalization

Inpatient treatment is required for children in the first 3 months of age, in severe clinical condition, with suspected generalized infection, immunodeficiency, vomiting, in case of unresponsiveness to outpatient treatment or when outpatient treatment is impossible, e.g., due to social reasons [5].

Acute pyelonephritis treatment

Treatment of uncomplicated upper urinary tract infections include oral, intravenous, or sequential antibiotic administration for 7–14 days. Current studies and the authors' own experience indicate that most children can be treated for 7-10 days. In the case of complicated acute pyelonephritis, treatment may be extended to 14 days, which is also recommended in the case of urosepsis [1, 4, 5].

Treatment begins with empirical antibiotic administration, which is planned on the basis of recommendations from scientific societies and local microbiological analyses. In children in the first 3 months of age, PTNFD recommends intravenous treatment with a third-generation cephalosporin (cefotaxime, ceftriaxone) or ampicillin with an aminoglycoside antibiotic. It is due to the high risk of developing generalized infection in this age group. Based on our experience, in patients under 3 months of age who are in good general condition and the risk of generalized infection is low, cefuroxime i.v. or another antibiotic can be used according to the antibiogram result [5].

In older children, PTNFD recommends the use of a second- or third-generation cephalosporin, amoxicillin with clavulanic acid or ciprofloxacin for empirical treatment. In sequential therapy, the antibiotic should be given intravenously for a minimum of 48 hours; the antibiotic may be changed when switching to the oral route (e.g., ceftriaxone/cefotaxime to cefixime or cefuroxime). Local medication susceptibility is crucial when choosing an empirically used antibiotic. In many centers, cefuroxime is recommended as the first-choice medication. Due to the high resistance of *E. coli* (25-50%) to amoxicillin with clavulanic acid, its use should be limited to situations where sensitivity is confirmed in the antibiogram. The use of amoxicillin, cotrimoxazole or furasidine alone is not recommended in children for the treatment of acute pyelonephritis. In severe infections, ceftriaxone or cefotaxime (in exceptional situations with an aminoglycoside antibiotic) is recommended as a first-line treatment [5, 10].

In neonates in whom, in addition to Gram-negative bacilli, UTIs are often caused by bacteria typical of other infections (e.g., *Enterococcus spp.* with natural resistance to aminoglycosides), combination treatment with ampicillin and an aminoglycoside is recommended [11].

When using an aminoglycoside antibiotic, renal function should be monitored (before, during and after treatment). Administration once daily reduces the risk of complications without reducing efficacy. Blood levels of aminoglycosides should be checked in children with impaired renal function, in severe clinical condition and when treatment is prolonged beyond 7 days [12]. Antibiotics used in the treatment of pyelonephritis are shown in Table 1.

Lower urinary tract infection (cystitis) treatment

The treatment of lower urinary tract infection includes an antibiotic or chemotherapeutic agent given over 3–5 days. Empirical treatment should be planned based on recommendations from scientific societies and local microbiological charts. The first-line treatment according to PTNFD includes furasidine, cotrimoxazole, trimethroprim and fosfomycin (Table 2). In practice, the widely available furasidine is most commonly used. It is well tolerated, has low bacterial resistance (although there are some microbes naturally resistant to it, e.g., *Proteus mirabilis*, *Klebsiella pneumoniae or Pseudomonas aeruginosa*). In Poland, furasidine preparations are available in both tablets (registered for use in children aged > 2 years) and syrup (registered for use in children aged > 3 months). The antimicrobial sensitivity test kits do not contain furasidine, but nitrofurantoin, a chemotherapeutic agent with the same mechanism of action and similar chemical structure.

Table 1. Medications used in acute pyelonephritis (upper urinary tract infection) according to PTNFD recommendations with self-modification.

Pharmacological name	Daily dose	Route of administration	Acceptable age and other restrictions
Cefuroxime axetil Cefuroxime	30 mg/kg b.w. 500–1000 mg[1] 50–100 mg/kg b.w. 2.25–4.5 g[1]	*P.O. b.i.d* *i.v. t.i.d*	> 3 months of age (orally)
Cefotaxime	100–200 mg/kg b.w. 3–6 g[1]	*i.v., i.m. b.i.d-t.i.d*	
Ceftriaxone	50-80 mg/kg b.w. 1–2 g[1]	*i.v., i.m. q.d.*	
Ceftazidime	100–150 mg/kg b.w. 2–6 g[1]	*i.v., i.m. t.i.d*	Preparation for the treatment of *Pseudomonas aeruginosa* infections
Cefxime	8 mg/kg b.w. 400 mg[1]	*P.O. q.d.-b.i.d*	> 6 months of age, oral 3rd generation Cephalosporin
Ceftibuten	9 mg/kg b.w. 400 mg[1]	*P.O. q.d.*	> 6 months of age, oral 3rd generation Cephalosporin
Cefepim	100 mg/kg b.w. 4.0 g[1]	*i.v. b.i.d.*	Treatment of infections caused by cephalosporinase-producing microbes AmpC
Cephalexin	25–50 mg/kg b.w. 1–4 g[1]	*i.v. b.i.d*	> 1 months of age
Ampicillin	100–200 mg/kg b.w.	*i.v., i.m. t.i.d*	Usually in combination with a third-generation cephalosporin or aminoglycoside, not recommended in monotherapy
Amoxicillin/clavulanic acid	45–60 mg/kg b.w. 1875–3000 mg[1] 90 mg/kg b.w. 3600 mg[1]	*P.O. b.i.d-t.i.d* *i.v. t.i.d*	> 2 months of age (orally)
Amikacin	15 mg/kg b.w. (max. 1.5 g)	*i.v. q.d-b.i.d* (recommended administration q.d.)	
Gentamicin	Infants: 4.5–7.5 mg/kg b.w. Older children: 3–6 mg/kg b.w. (max. 0.4 g)	*i.v. q.d.-t.i.d* (recommended administration q.d.	
Ciprofloxacin	20–40 mg/kg b.w. 1000 mg[1] 20–30 mg/kg b.w. (max. 0.4 g/dose)	*P.O. b.i.d* *i.v. t.i.d*	If other medications are not available, after consideration of the risks, in accordance with the restrictions in the summary of product characteristics
[1] > 12 years of age			

In general conditions, sensitivity to nitrofurantoin can be assumed to coincide with sensitivity to furasidine [5]. A convenient therapeutic option is fosfomycin, an oral medication used in a single evening dose, registered for the treatment of cystitis in children over five years of age (two-gram product). Another option could be antibiotics recommended for the treatment of upper urinary tract infections administered orally.

Special situations in the treatment of urinary tract infections

UTI in a pregnant teenager is a risk factor for miscarriage, fetal hypotrophy, and preterm birth. A medication should be chosen according to the summary of product characteristics. The website: http://www.e--lactancia.org contains up-to-date information on medicines that are safe for pregnant and breastfeeding women. In pregnant adolescents with acute pyelonephritis, PTNFD recommends hospitalization and empirical therapy with intravenous second-generation cephalosporin for 7–14 days. Cystitis treatment can be administered orally for 5–7 days. Pregnancy is also one of the few situations where treatment of asymptomatic bacteriuria needs to be implemented [5, 13].

Renal abscess is a rare but severe urinary tract infection that can present in an atypical manner. No changes in the urine test are necessary to diagnose an abscess.

According to authors' experience, abscesses often require long (several-week) individualised pharmacological

Table 2. Medications used in the treatment of cystitis (lower urinary tract infection) according to PTNFD recommendations with self-modification.

Pharmacological name	Daily dose	Route of administration	Acceptable age and other restrictions
Furasidine	5–7 mg/kg b.w. 300 mg[1]	*P.O. b.i.d-t.i.d*	Only when eGFR ≥ 45 ml/min/1.73 m^2 > 3 months old as a suspension > 2 years old as a tablet Usually on day 1 of treatment q.i.d 4-x 100 mg[1]
Trimethoprim	4 mg/kg b.w. 200–400 mg[1]	*P.O. b.i.d*	> 3 months old. Only at low risk of resistance
Trimethoprim/sulfamethoxazole	36 mg/kg b.w. 960–1920 mg[1]	*P.O. b.i.d*	> 6 weeks old
Cefaclor	20–40 mg/kg b.w. 1.5 g[1]	*P.O. b.i.d-t.i.d*	
Cefadroxil	30 mg/kg b.w. 1–2 g[1]	*P.O. b.i.d*	
Cephalexin	25–50 mg/kg b.w. 1 g[1]	*P.O. b.i.d-t.i.d*	
Cefuroxime axetil	30 mg/kg b.w. 500–1000 mg[1]	*P.O. b.i.d*	> 3 months old
Cefxime	8 mg/kg b.w. 400 mg[1]	*P.O. q.i.d-b.i.d*	> 6 months old
Ceftibuten	9 mg/kg b.w. 400 mg[1]	*P.O. q.i.d*	> 3 months old
Amoxicillin	50–90 mg/kg b.w. 1.5–3.0 g[1]	*P.O. b.i.d-t.i.d*	Only with confirmed sensitivity
Amoxicillin/clavulanic acid	45–60 mg/kg b.w. 1500–1750 mg[1]	*P.O. b.i.d-t.i.d*	> 2 months old
Phosphomycin	2 g (> 5 years of age) 3 g (> 12 years of age)	*p.o.* once	
Ciprofloxacin	20–40 mg/kg b.w. 500–1,000 mg[1]	*P.O. b.i.d*	If other medications are not available, after consideration of the risks, in accordance with the restrictions in the summary of product characteristics
[1] > 12 years of age			

treatment. Surgical treatment is usually not necessary. Similarly, fungal infections usually require prolonged treatment, and occasionally patients require surgical treatment or local administration of antifungal medications. Surgical treatment is also absolutely necessary in the case of so-called infectious stones – from struvite (magnesium ammonium phosphate) deposits, which are formed in patients colonized with urease-producing bacteria. Even a small fragment of deposit left behind poses a risk of recurrent infection and re-growth of the deposit [5, 6].

For infections with atypical etiology other than *Escherichia coli*, a targeted antibiotic therapy often needs to be introduced, taking into account the natural microbe resistance (Table 3). Resistance in bacteria causing UTIs can

Table 3. Special situations in the treatment of urinary tract infections.

Microbe	Comments
Pseudomonas aeruginosa	First-line treatment – ceftazidime. Other antibiotics have activity against *Pseudomonas aeruginosa*: piperacillin with tazobactam, cefepime, meropenem, imipenem, aminoglycoside antibiotics. No indication for eradication in children with neurogenic bladder in the absence of clinical manifestations.
Proteus spp.	Usually sensitive to cefuroxime and amoxicillin with clavulanic acid. Natural resistance to furasidine and nitrofurantoin
Enterobacter cloacae	Natural resistance to first and second generation cephalosporins, treatment; third generation cephalosporins in monotherapy are dissuaded (risk of AmpC cephalosporinase induction).
Enterococcus spp.	Recommended treatment with amoxicillin/ampicillin (*Enterococcus faecalis*) or a glycopeptide antibiotic (*Enterococcus faecium).*

be divided into natural resistance (e.g., cephalosporin resistance in *Enterococcus sp.*) and acquired resistance, which is a major problem and usually involves degradation of the antibiotic molecule (e.g., by beta-lactamases or carbapenemases) or modification of the antibiotic molecule (e.g., resistance to high concentrations of aminoglycosides). It presents difficulties in the treatment of children with recurrent UTIs, urinary tract abnormalities, and neurogenic bladder. Management aimed at reducing drug resistance consists in avoiding unnecessary and prolonged antibiotic therapy, a sensible hospital antibiotic policy, using antibiotics with the narrowest possible spectrum in the targeted treatment of UTI, limiting the length of antibiotic therapy and limiting the indications for chronic prophylaxis of UTI [5, 14].

Asymptomatic bacteriuria

Asymptomatic bacteriuria (bacteriuria) is the presence of bacteria in the urine in a significant titer in the absence of clinical manifestations and abnormalities on urinalysis (leukocyturia). Asymptomatic bacteriuria occurs in 1–3% of children, is transient and is not associated with adverse long-term effects [15]. The treatment of asymptomatic bacteriuria is only recommended in pregnant adolescents and in children before planned procedures with urinary tract instrumentation. When medical indications require it, asymptomatic bacteriuria is treated like cystitis [5]. In the case of urinary tract instrumentation (cystoscopy, cystometry, micturition cystourethrography), a 1–3 day chemotherapeutic or antibiotic cover is recommended; diagnostic catheterization does not require prophylaxis [16, 17].

In catheterized patients with a neurogenic bladder, bacteriuria is sometimes accompanied by leukocyturia, which is not conclusive for the diagnosis of UTI and may result, for example, from irritation of the bladder mucosa by the–catheter. The treatment is indicated only in the co-occurring abnormal general examination, a positive urine culture and clinical symptoms – primarily a fever [5, 18, 19].

Imaging examinations in children with urinary tract infections

Ultrasound (USG) is a routinely used examination and is recommended for most patients with a first episode of UTI. The examination may give rise to a suspicion of urinary tract abnormalities, a diagnosis of a renal abscess. The urinary system should be assessed with a full bladder. The tissue flow option allows assessment of inflammatory involvement of the renal parenchyma. According to Italian recommendations, the examination should be performed within 2-4 weeks after a history of UTI and as soon as possible for atypical infections [5, 20].

Currently, the indications for micturating cystourethrography are significantly limited. PTNFD recommends cystourethrography in cases of septic UTIs, recurrent UTIs with a fever, atypical etiology and suspected urinary tract abnormalities on ultrasound. In micturating cystourethrography, a thorough assessment of the urethra is important, especially in boys for the presence of posterior urethral valve [3, 5].

Static scintigraphy of the kidney with dimercaptosuccinic acid is the method of choice for imaging renal parenchymal scarring. However, the examination is associated with a rather high radiation dose. A loss of tracer accumulation may indicate current inflammation or an established post-inflammatory scarring. According to PTNFD, the examination should be performed at least 3 months after the last infection. The indications for imaging examinations in children after a history of UTIs according to the PTNFD recommendations with self-modification are presented in Table 4 [3, 5].

Table 4. Urinary tract imaging examinations in children with urinary tract infections according to the recommendations of the Polish Society of Paediatric Nephrology with self-modification

Indications for urinary tract ultrasound examination
First UTI in a child < 24 months of age
First febrile UTI in a child > 24 months of age
First UTI in a child > 24 months of age with atypical course
First UTI in a child > 24 months of age with risk factors for recurrence
Recurrent UTI
Indications for micturating cystourethrography
History of UTI and ultrasound findings suggestive of vesicoureteral reflux or other urinary tract abnormalities
Recurrent UTI
Past history of septic UTI
Indications for renal scintigraphy with dimercaptosuccinic acid
Recurrent febrile UTI
Recognized grade III-V vesicoureteral reflux
Ultrasound or clinical symptoms suggestive of renal scarring

Prophylaxis in urinary tract infections

The indications for pharmacological prophylaxis of recurrent UTI in children are currently limited. Predisposing factors for recurrent UTI are primarily urinary tract abnormalities and bladder dysfunction. Usually, recurrent UTIs have uncommon etiology and are frequently caused by drug-resistant strains. Numerous studies have shown little or no benefit from the use of long-term prophylaxis for UTI [6, 21]. Prophylaxis significantly reduced the frequency of recurrent UTIs but had no effect on the number of scars in the renal parenchyma and generated selection of resistant strains [14, 20, 22, 23]. Indications for pharmacological prophylaxis of UTI are determined on an individual basis. Prophylaxis can be used in children after a first episode of UTI until a micturating cystourethrography is performed, in children with ≥ grade III vesicoureteral reflux, complex urinary tract abnormalities, bladder dysfunction with urine retention after micturition, urinary

Table 5. Pharmacological prophylaxis of urinary tract infections according to the PTNFD recommendations with self-modification.

Pharmacological name	Daily dose (usually given as 1 evening dose)	Acceptable age and other restrictions
Furasidine	1–2 mg/kg b.w.	Only when eGFR ≥ 45 ml/min/1.73m2 > 3 months of age as a suspension > 2 years of age as tablets
Trimethoprim	1–2 mg/kg b.w.	> 3 months of age
Trimethoprim/sulfamethoxazole	6–12 mg/kg b.w.	> 6 weeks of age
Amoxicillin	10 mg/kg b.w.	From birth
Cefuroxime axetil	5 mg/kg b.w.	> 3 months of age

tract abnormalities impeding urine outflow and recurrent UTIs. Suggested duration of prophylactic treatment is 6–12 months (possible extension to 24 months in girls). The appropriateness of prophylaxis should be reviewed every 6 months. Pharmacological prophylaxis is based low-dose drugs, usually chemotherapeutics: furasidine, trimethroprim or cotrimoxazole. In the youngest children, beta-lactam antibiotics can be used (Table 5) [5].

Other methods of preventing recurrent urinary tract infections

A functional disorder of urinary and fecal excretion must be excluded. In children with urinary disorders (daytime incontinence, urgency), a 2-day urinary diary must be carried out and urine backflow after micturition must be assessed in the ultrasound. Another test for bladder function is uroflowmetry (urethral flow). In case of abnormalities, urotherapy (behavioral training) is implemented and, if ineffective, pharmacotherapy is used. In all patients with recurrent UTIs, the rhythm of bowel movements and the consistency of the stool should be assessed (within a week) with the Bristol Stool Scale. In constipations diet must be modified and macrogol preparations must frequently be introduced [5, 24].

Probiotics or cranberry juice can be used in children with recurrent UTIs. Studies show a small (but statistically significant) benefit connected with the use of probiotics. Cranberry preparations prevent recurrent UTIs in multiple ways: they inhibit *Escherichia coli* adhesion to the epithelium of the urinary tract, reduce urine pH, modify the microbiota and induce the synthesis of the antimicrobial uromodulin [25]. Cranberry extracts used in children have been shown to reduce the frequency of recurrent UTIs with efficacy similar to antibiotic prophylaxis [26]. Vitamin C, which increases the risk of calcium oxalate stones, is not recommended [5].

Consequences of urinary tract infections in children

Undiagnosed, too late, or inadequately treated urinary tract infection, especially in newborns and infants, is a significant risk factor for generalized infection and septic shock. In addition, it also poses the risk of post-inflammatory renal parenchymal scarring. Patients with recurrent UTIs who develop end-stage renal failure most often suffer from complex urinary tract abnormalities and congenital renal hypodysplasia. Swedish authors have shown that a risk factor for reduced glomerular filtration rate in adult women after childhood-onset UTI is increased bilateral scintigraphic lesions performed after the first episode of infection [5, 27]. However, it does not exempt the physician from giving the prompt diagnosis and introducing the appropriate treatment of all urinary tract infections in children.

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APPLICATION OF SELECTED BIOCHEMICAL PARAMETERS IN THE PREDICTION OF ACUTE KIDNEY INJURY RISK AT AN EARLY STAGE OF BURN DISEASE

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Abstract:

Introduction and objective

Acute kidney injury (AKI) is a common, severe complication of burn disease, developing in the first days after a massive thermal injury and worsening the prognosis of patients. Early diagnosis of AKI plays a crucial role in improving health of patients and therapeutic results. Detection of AKI based on the standard parameters of renal function is insufficient due to too late changes in their values. The aim of the study is to evaluate the relationship between the selected non-renal biochemical parameters and the risk of AKI in this group of patients.

Material and methods

The prospective study involved a group of 33 adult patients (22 men, 11 women) hospitalized after massive burns. The patients were intensively monitored for the first 7 days after the injury, daily assessing the parameters of renal function. The selected parameters were also measured: platelet count (PLT), sodium (Na), potassium (K), albumin (ALB), aspartate aminotransferase (AST), creatine kinase (CK), arterial blood pH, arterial blood bicarbonate (HCO3-), 24-hour urinary sodium excretion (24hUNa) and fractional excretion of sodium (FENa).

Results

AKI was diagnosed in 15 (45.5%) patients. Statistical differences in the obtained average values of selected parameters between the AKI and non-AKI groups were confirmed. A significant univariate relationship was found between CK, AST and ALB in the blood serum and an increased risk of developing AKI in the following days. However, after adjustment for The Abbreviated Burn Severity Index score, only CK remained significant.

Conclusions

The potential clinical benefit of monitoring AST and ALB in blood serum and especially CK was confirmed. The other routine parameters did not seem to be related to the risk of AKI and require further analysis.

Keywords: burn, rhabdomyolysis, renal failure, acute renal injury, thermal injury.

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Background

Burn disease is a group of organ complications developing in response to massive thermal, chemical or electrical trauma, that damages a large area of the skin and mucous membranes. As a result of the disease development, homeostasis of the organism is deeply disturbed, with particular emphasis on the water-electrolyte and acid-base balance. The degree of damage of individual organs and systems depends directly on the strength of the injury as well as on the area and depth of skin and mucous membrane damage and the involvement of respiratory tract. Thermal trauma covering more than 20-30% of the total body surface area (TBSA) dramatically increases the risk of developing multiorgan damage resulting in the simultaneous dysfunction of various physiological systems called multiple organ dysfunction system (MODS), which may occur at any stage of the course of a massive burn, significantly increasing the risk of death. As a consequence of distant organs damage and impairment of their functions, a number of substances are released into the bloodstream. Their increased concentrations exceed the limits of laboratory norms and can be detected, confirming the diagnosis of the development of a burn disease [1].

Acute kidney injury (AKI) and subsequent acute renal failure (ARF) constitute one of the most serious complications of burn disease, significantly worsening its clinical course. Most authors agree that after a massive burn approximately 1/3 of patients develop AKI. 30% of AKI patients have the biochemical and clinical features of ARF, which require renal replacement therapy (RRT) procedures in 5–10% of patients. The transition of AKI renal complications to ARF and/or RRT significantly increases the risk of death in this group of patients, reaching 50–100% in the RRT group [2].

The etiology of AKI in burn patients is multifactorial and depends on the time elapsed since the thermal injury. Basically, the course of burn disease can be divided into two periods, early and late, extending before and after the seventh day since the burn. The early period is associated with the post-traumatic shock phase, the release of pro-inflammatory cytokines from the cells, and increased protein catabolism. At this time acute, non-inflammatory kidney injury predominates. The late period is characterized by a gradual regeneration of damaged tissues and organs, anergy of the immune system and an increased risk of infectious complications, which at this time are the main cause of AKI [3, 4].

There are not fully sensitive and specific AKI prognostic markers in the course of burn disease so far. Diagnosis based on standard changes in serum creatinine and urea concentration values or fluctuations of the estimated glomerular filtration rate (eGFR) seems to have a number of significant limitations. The time inertia of changes in values may significantly delay the diagnosis time. Changes in parameters can also result from non-renal causes, such as the state of protein hypercatabolism characteristic for the early stage of post-burn shock, affecting the correct interpretation of biochemical results. In addition, there is not uniformly adopted optimal eGFR assessment formula for patients with AKI after massive burns, many different ones are used: Cockroft-Gault (C-G), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [5]. The measurement of the volume of produced urine is also a subject to the risk of subjective error due to incorrect reading and writing. Especially in patients in a serious clinical condition, who require frequent transport between various elements of the health care system, the analysis of diuresis is often inadequate and insufficient.

According to scientific reports, a change in the values of additional biochemical parameters resulting from damage to other organs in the course of MODS and not directly related to the physiology of the urinary system, may suggest AKI dysfunction in the early stages of its development. These substances can be measured both in blood serum and urine [6].

Undoubtedly, the crucial element in improving the prognosis in this group of patients is the diagnosis of AKI at the earliest stage of development. The implementation of properly targeted therapy can have a beneficial effect in reducing mortality and improving the survival of patients. The aim of the study is to identify selected, routinely measured after burn injury biochemical parameters, which can have a relationship with the occurrence of AKI in the early stages of burn disease.

Material and Methods

The study included patients hospitalized in the Clinical Department of Burns, Plastic and Reconstructive Surgery of a specialized multi-profile hospital. The project and all experimental protocols were approved by the Committee for Bioethics in Medicine at Military Institute of Medicine (resolution number 36/WIM/2015 of 20 May 2015). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects. All adult patients treated for massive thermal burns between March 2017 and May 2019 were pre-qualified for the project.

Criteria for inclusion in the study group were:

- Age over 18 years
- 2nd and 3rd degree burns including at least 30% TBSA or at least 20% TBSA with accompanying respiratory tract burn
- No terminal diseases (e.g., generalized neoplastic process) or severe infectious diseases (e.g., sepsis) at the time of hospitalization
- The time from burn injury to hospitalization of less than 72 hours

Assessment of Clinical Condition

In accordance with the project guidelines, a uniform diagnostic and therapeutic procedure was adopted for each qualified patient. After thermal injury the patient was immediately hospitalized and transferred from the hospital Emergency Department (ED) to the target department. At the time of admission, a detailed interview was collected regarding the circumstances of the thermal injury, the condition of the patient and comorbidities. A thorough

physical examination was performed, with particular emphasis on the extent and depth of the burn wounds. Basic vital parameters (including blood pressure, heart rate, body temperature) were measured. Consciousness was assessed using the normalized Glasgow Coma Scale (GCS). The burn injury status was evaluated with the use of the Abbreviated Burn Severity Index (ABSI). Each patient was treated with a unified fluid resuscitation procedure (Parkland formula) in accordance with the applicable standards. They recommend an administration of 4 ml of Ringer's lactate/kg weight/% burn skin during the first 24 hours – half of this should be given in the first 8 hours and the other half in the subsequent 16 hours after the burn. The correct volume status was strictly maintained by the whole time-period of the observation and monitored using clinic examinations and measurement of life-basic parameters (central venous pressure, hematocrit etc.).

Every day, from admission to the clinic until the seventh day of hospitalization, the basic vital parameters of the patient were intensively monitored, with particular emphasis on the fluid balance and the amount of daily urine collection (DUC). In accordance with the research protocol, selected laboratory parameters in blood serum were determined every day in order to assess the damage to systems essential for maintaining homeostasis and their dysfunctions: platelet count (PLT), serum sodium concentration (Na), serum potassium (K) concentration, serum creatinine concentration (sCr), serum urea concentration (U), serum albumin concentration (ALB), serum aspartate aminotransferase activity (AST), serum creatine kinase activity (CK), arterial blood bicarbonate concentration (HC03-), 24-hour urinary sodium excretion (24hUNa), fractional excretion of sodium (FENa).

They were performed in the certified hospital laboratory. In the case of death of the patient, the exact date and time as well as the suggested cause were recorded.

AKI Diagnostics

The diagnosis of acute kidney injury was made based on the AKIN (Acute Kidney Injury Network) and RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease) classification criteria [5].

It was assumed that it is enough to meet at least one criterion in order to qualify for a specific category. The eGFR value was calculated based on 3 variants: the C-G formula, the abbreviated MDRD formula and the CKD-EPI equation based on the sCr.

sCr and eGFR values at the time of hospitalization were accepted as baseline and the results in the following days were referred to them accordingly. Analysis of the difference between the current day value and the baseline value provided the basis for the diagnosis of the appropriate AKI stage. A uniform assumption was made that meeting at least one criterion confirmed the diagnosis of AKI. Based on the diagnosis of AKI, the entire group of patients was divided into two: AKI and non-AKI group.

The DUC values were analyzed starting from the 1st day of hospitalization. The assessment on admission to the hospital was considered unreliable due to the admission of the patient and the commencement of the DUC measurement at different times of the day. Similarly, the determinations of urinary excretion of selected substances were performed from the first day.

Assessment of AKI Prediction

The relation between the selected biochemical parameters, the score in ABSI scale and the risk of AKI occurrence was analyzed. The values were evaluated in the following days of observation, starting from the moment of admitting the patient to the ED. Then, the relationship between the parameter value and the occurrence of AKI on the next day was compared. The analyses concerned both the non-normative values of the parameter as well as the dynamics of changes in the values within and outside the norms.

Statistical Analysis

All obtained information available in medical records was archived in specially prepared, proprietary spreadsheets in the Windows EXCEL format. The distribution of the obtained values of each biochemical parameter in the studied population of patients was examined in individual days after the injury. Parameter value subject to subsequent analysis is presented as mean with standard deviation (SD) in the case of the distribution of normal-type variables or as median considering the interquartile range (IQR) between quartile 3 and 1 for non-normal distribution type. The analyses of the association of each selected biochemical parameter with the risk of AKI occurrence were conducted uniformly for every selected parameter. On each day of observation (days 0 - 7 of hospitalization), the current, average value of a given parameter in both group of patients was compared using t-Student test or Mann-Whitney test, when appropriate. Additionally, the relationship between the value of a given parameter on a previous day and the risk of AKI was analyzed using the chi2 test and forward logistic regression. The results were presented also in the form of relative risk (RR) value with a 95% confidence interval (CI). The p-value <0.05 was considered statistically significant. Statistical analyses were performed with the use of computer software (IBM SPSS ver. 25).

Results

33 patients were qualified for the project finally, including 11 (33.3%) women and 22 (66.7%) men. The exact characteristics of the study group are presented in table 1.

All 33 patients suffered a severe thermal injury in an outpatient setting. 24 (72.7%) patients were transported directly from the scene of the incident to the ED of the destination hospital, and in the case of 9 (27.3%) patients there was a temporary stay in the ED of regional hospitals. The average time from the moment of injury to hospitalization in the ED of the target hospital was usually approximately 1 hour, with a maximum of 24 hours for one patient. Almost 2/3 of the patients presented severe disturbances of consciousness (< 8 GCS points) or required tracheal intubation and mechanical ventilation. More than 63% of patients presented symptoms of hemodynamic instability and required support of the circulatory system with intravenous infusion of pressor amines.

Table 1. Characteristics of the study group.

Number of patients		n = 33
Age (years), mean (±SD)		48.0 (±18.6)
Men, n (%)		22 (66.7 %)
BMI (kg/m2), mean (±SD)		25.8 (±5.4)
Percentage of body surface area burned (%), mean(±SD)		42.2 (±18.1)
3rd degree burns, n (%)		21 (63.6 %)
Respiratory tract burns, n (%)		23 (69.7 %)
Time from injury to admission (hours), median (IQR)		1 (1–24)
Admission directly from the scene of the incident, n (%)		24 (72.7 %)
Consciousness disturbances (GCS) n (%)	Mild	10 (30.3 %)
	Moderate	1 (3.0 %)
	Severe or intubation	22 (66.7 %)
The administration of pressor amines, n (%)		21 (63.6 %)
Hospitalization time (days), median (IQR)		23 (2–95)
AKI (According to the criterion of dieresis), n (%)		15 (45.5 %)
Renal replacement therapy, n (%)		5 (15.2 %)
Day of hospitalization at death, median (IQR)		16 (2–48)

The severity of burn injury according to ABSI scale was shown in the table 2.

Ultimately, the diagnosis of AKI was based solely on laboratory criteria: a reduction in eGFR values or an increase in sCr concentration. During the first 7 days of hospitalization, the biochemical features of AKI were diagnosed in a total of 15 (45.5%) patients finally qualified for the project. AKI was first observed in 10 (30.3%) patients on the first day of hospitalization, in 4 (12.1%) patients on the second day, and in 1 (3.0%) patient on the fifth day. A total of 5 (15.2%) patients required renal replacement therapy during the observation. The time to start dialysis therapy was the first day in 2 (6.1%) patients, the third day in 1 (3.0%) patient, and the fifth day in 2 (6.1%) patients.

In the course of 7-day intensive monitoring, death occurred in 3 (9.1%) patients, on the second, fourth and sixth day, respectively. During this time, no patients (0%) were discharged home. During the entire hospital stay, death was recorded in 16 (48.5%) patients, on day 16 (range 2–48) on average. 17 (51.5%) patients were discharged home, the mean duration of hospitalization ended with discharge (convalescence) was 27 (range 10–95) days. Overall, the average length of stay in hospital from the moment of injury to discharge or death of the patient was 24 (range 2–95) days.

Dynamics of selected parameters in the early period after thermal injury

The obtained mean values of daily diuresis and laboratory determinations divided into two groups according to the presence of AKI (AKI and non-AKI) are presented in Fig. 1A-1J.

The mean value of noticed daily diuresis tended to increase during the observation period, with the lowest values of 0.65 (IQR 0.42 ischemia 1.3) liters initially observed on admission to the hospital. However, in only 25 (75.8%) patients any information on the amount of urine excreted on that day was obtained. In line with the adopted assumptions, the daily diuresis values obtained on admission to the hospital were disregarded as inadequate. On the first day of hospitalization, the mean daily diuresis was 0.94 (IQR 0.46–1.71) liters with a significantly lower amount in the AKI group 0.58 (IQR 0.29–0.98) vs 1.16 (IQR 0.69–2.4) (p=0.003). The tendency to stabilize the average amount of urine produced at the level of over 1.5 liters per day was observed for more than 48 hours of observation with a maximum point of 2.02 (IQR 1.39–2.88) liters on day five with the accompanying blurring of differences between the groups, 1.93 (IQR 1.14–2.65) vs 2.04 (IQR 1.57–3.07) (p = 0.330) respectively.

Unfortunately, during the study the problems with adequate measurement of diuresis volume were observed. Due to technical problems with verifying the accuracy and uniformity of diuresis measurement in the first days of hospitalization, this component of AKI diagnosis was excluded from the analyses.

The greatest intensity of disturbances in the values of the analyzed biochemical parameters was observed in the first 2–3 days after the thermal injury, as in the case of AKI biochemical parameters. This concerned both the enzymatic activity in the blood serum, elements of blood count, plasma proteins and the concentrations of other bioactive substances.

Table 2. ABSI score.

ABSI score	Number of patients	Threats to life	Probability of survival (%)
2–3	4(12.1%)	Very low	>99
4–5	11 (33.3%)	Moderate	98
6–7	10 (30.3%)	Moderately severe	80–90
8–9	6 (18.2%)	Serious	50–70
10–11	2 (6.1%)	Severe	20–40
12–13	0 (0%)	Maximum	<10

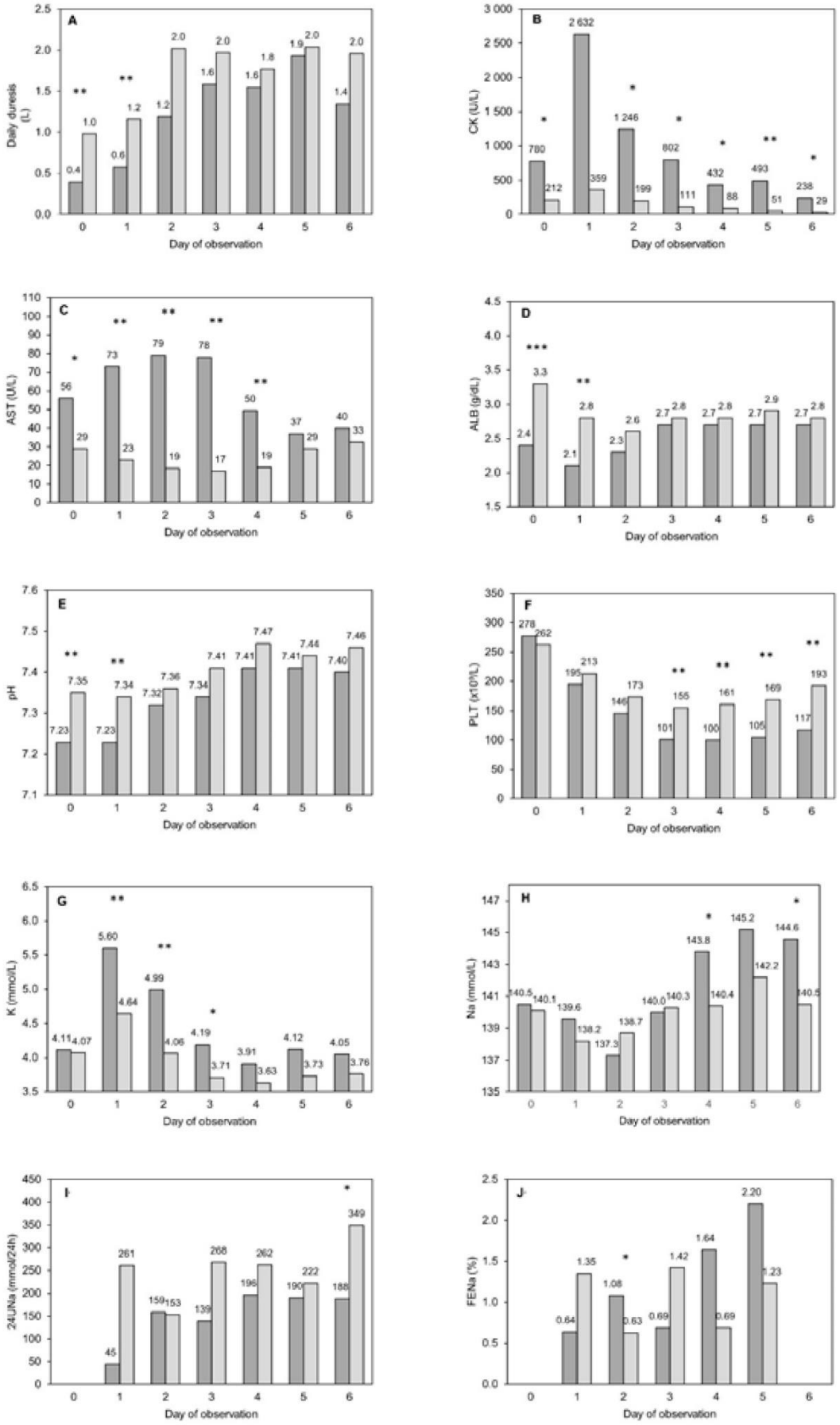

Figure 1. Candidate prognostic parameters in patients with AKI and without AKI in the first 7 days after burn injury. AKI group – dark grey, non-AKI group – light grey. Daily diuresis, CK, AST, 24UNa, FENa. – medians; ALB, pH, PLT, K, Na – means. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Serum enzymatic activity (CK, AST) was highest in the first 3 days after injury. The mean CK values recorded the peak of activity and variability of results during the second day, amounting to an average of 772.0 (IQR 212.5–4952.0) U/L in the whole group with a subsequent gradual reduction to 50.0 (IQR 24.8–245) U/L on the seventh day. During the entire observation period, the values changed simultaneously in both groups, but in the AKI group they reached significantly higher maximum values of 2632 (IQR 389–5661) U/L vs 358 (IQR 170.5–3459.5) U/L in the non-AKI group (p < 0, 05).

Fluctuations in AST activity for the whole group were two-phase: the first peak was recorded in the first two days of hospitalization – 38.0 (IQR 23.0–58.0) U/L and 30.0 (IQR 21.0–73.5) U/L, respectively, with a subsequent decrease to 24.0 (IQR 16.3–82.0) U/L and the re-escalation of the value to 39.0 (IQR 23.0–60.0) U/L on the sixth day. The analyses of the curves in groups divided for the occurrence of AKI revealed a significantly different dynamics of changes in the compared groups during the first 4 days. In the AKI group, the values initially showed a tendency to increase with a maximum point of 79 (IQR 28–185) U/L on the second day and a subsequent decrease in the following days. In the non-AKI group, the AST values gradually decreased from the moment of the injury, reaching the value of 17 (IQR 14–28.5) U/L on the third day, significantly differing from the values measured in the AKI group (p < 0.001). Differences in both groups were blurred in the following days, getting closer to each other at the end of the observation period, with 48 (IQR 19–79) U/L in the AKI group vs 30 (IQR 27–45) U/L in the non-AKI group (p = 0.421).

ALB concentrations in the whole group showed a tendency to decrease on the second day to a minimum of 2.4 (± 0.7) g/dL with a subsequent increase and stabilization from the fifth day at an average level of 2.8 (± 0.4) g/dL. In both groups, the course of changes in the values was parallel, but in the AKI group, the hypoalbuminemia developed earlier, already on the first day and the disturbances were deeper, respectively 2.1 (± 0.5) g/dL vs 2.8 (± 0.7) g/ dL (p=0.005). In the final phase of observation, the values found in both groups were similar, respectively 2.7 (± 0.5) g/dL vs 2.9 (± 0.5) g/dL (p = 0.326).

The tendency to metabolic acidosis continued during the first 24 hours of the observation with the lowest pH values at 7.28 (± 0.1). At the same time, disturbances in blood gas tests were clearly more marked in the AKI group compared to the non-AKI group: 7.23 (± 0.08) vs 7.34 (± 0.05) (p=0.001). In the course of further observation, the pH values tended to increase, normalize and stabilize the pH at an average level of 7.42 (± 0.09) with the simultaneous blurring of differences between the groups, respectively 7.41 (± 0.1) vs 7.46 (± 0.04) (p=0.102) on the sixth day.

The mean PLT value during hospitalization gradually decreased, reaching the minimum point of 130.5 (± 51.2) x 109/L on the third day, simultaneously narrowing the spread of results. In the following days, a tendency for the value to increase again and normalize at the average value of 178.6 (± 91.7) x 109/L with increasing scattering of results was observed. Thrombocytopenia was more pronounced in the AKI group, respectively 100.5 (± 51.6) x 109/L vs. 155.1 (± 36.4) x 109/L (p = 0.002).

The tendency to electrolyte imbalance was found mainly in the initial period of observation. The mean value of potassium tended to increase on the first and second day to 5.08 (± 1.0) mmol/L and 4.48 (± 0.89) mmol/L respectively, with the subsequent normalization of the value at an average level of approximately 4.0 mmol/L in the following days, with this feature being more pronounced in the AKI group compared to the non-AKI group, 4.99 (± 0.88) mmol/L vs 4.06 (± 0.65) mmol/L, respectively (p = 0.001).

The average values of Na were within the limits of laboratory norms. The sodium balance curve showed a slight reduction in value and an increase in the scattering of the results to 138.8 (± 5.4) mmol/L and 138.0 (± 4.5) mmol/L on the second and third day, respectively. In both groups, the graphs of the curves were arranged in parallel, the average values obtained usually showed no significant differences (p > 0.05). On the other hand, the average values of 24hUNa gradually increased during the observation, with the threshold value exceeded on the third day, reaching the maximum point of 280.5 (IQR 182.5–392.0) mmol/24 h on the sixth day. The sodium excretion values were higher in the non-AKI group, but the threshold statistical significance was achieved only on the sixth day of observation with 349 (IQR 215.3–444.3) mmol/24 h vs 188 (136.3–320.6) mmol/24 h in the AKI group (p = 0.035).

The values of FENa AKI in the whole group remained below 1% from day 1 to day 3 and slightly above 1% on day 4 and 5 of hospitalization, not reaching the 2% threshold characteristic for nephrogenic etiology of sodium excretion imbalance. No significant differences between the groups were also observed, except for day 2, in which a significant dominance of the FENa value in the AKI group 1.08 (IQR 0.71–2.54)% vs 0.63 (0.12–0.88)% (p=0.011) was found. In the AKI group on day 5, the mean value of FENa was 2.2%, but this result cannot be considered representative (p = 1.0).

The association between selected biochemical parameters and the risk of AKI in the early stage of burn disease development. The results of statistical analyses of AKI predictors are presented collectively in table 3.

The following predictors of AKI determined in the blood serum before its occurrence were identified as statistically significant: high activity of creatine kinase (CK) and aspartate aminotransferase (AST) as well as low concentration of albumin (ALB).

Three - and more than three times the upper limit of the normal CK activity, was related to almost two- and threefold increase in the risk of developing AKI on the next day, respectively (ptrend = 0.047; RR = 1.6 and 2.86). The increase in AST activity was associated with a nearly three-fold increase in the risk of AKI (ptrend = 0.034; RR = 2.72). Hypoalbuminemia in the range between 2.5 and 3.5 g/dL increased the risk of AKI almost twice (RR = 1.57), and in

Table 3. Selected biochemical parameters and the risk of developing AKI on the next day.

Parameter			AKI		p-value*	RR (95% CI)
			Yes % (n)	No % (n)		
CK	Normal		25.0% (1)	75.0% (3)	0.047	Ref.
	2 times the upper limit of normal		14.3% (1)	85.7% (6)		0.57 (0.05–6.86)
	3 times the upper limit of normal		40.0% (2)	60.0% (3)		1.60 (0.21–11.92)
	>3 times the upper limit of normal		71.4% (5)	28.6% (2)		2.86 (0.49–16.62)
AST	Normal		28.6% (4)	71.4% (10)	0.034	Ref.
	2 times the upper limit of normal		40.0% (4)	60.0% (6)		1.40 (0.46–4.31)
	> 2 times the upper limit of normal		77.8% (7)	22.2% (2)		2.72 (1.11–6.69)
ALB	≥ 3.9 g/Dl		0.0% (0)	100.0% (1)	0.012	Ref.
	3.5–3.9 g/Dl		0.0% (0)	100.0% (4)		0.40 (0.01–14.07)
	2.5–3.5 g/Dl		38.5% (5)	61.5% (8)		1.57 (0.13–18.90)
	< 2.5 g/Dl		66.7% (10)	33.3% (5)		2.63 (0.23–29.71)
Metabolic acidosis Yes		No	22.2% (2)	77.8% (7)	0.090	Ref.
		66.7% (12)	33.3% (6)		3.0 (0.85–10.63)	
PLT	≥150x109/L		44.8% (13)	55.2% (16)	1.000	Ref.
	<150x109/L		50.0% (2)	50.0% (2)		1.12 (0.39–3.22)
Na	<135 mmol/L		33.3% (1)	66.7% (2)	0.692	0.75 (0.14–3.92)
	135–145 mmol/L		44.4% (12)	55.6% (15)		Ref.
	>145 mmol/L		66.7% (2)	33.3% (1)		1.50 (0.61–3.71)
F	<5 mmol/L		48.0% (12)	52.0% (13)	0.699	Ref.
	≥ 5 mmol/L		37.5% (3)	62.5% (5)		0.78 (0.29–2.09)

*) **chi2** *test for trend*.

the range below 2.5 g/dL it almost tripled (RR = 2.72) (ptrend = 0.012).

Parameters increasing the risk of AKI occurrence, but not reaching the statistical significance criterion, are: decreased PLT values below 150,000 /mL in blood count (RR = 1.12; p = 1.0), metabolic acidosis with pH below 7.35 (RR = 3.0; p = 0.09), increase in K concentration above 5 mmol/L (RR = 0.78; p = 0.699), increase in Na concentration above 145 mmol/L (RR = 1.5; ptrend = 0.692).

In a forward logistic regression analysis, when the values of CK, AST or ALB separately were adjusted for ABSI score, only CK was not excluded from the model and remained statistically significant. In case of AST or ALB these parameters were excluded from the model.

The parameters of the sodium excretion (24hUNa, FENa) required evaluation in a 24-hour urine collection. The first meaningful results obtained, which, according to the assumptions of the project, were to be treated as baseline, were obtained only on the first or second day of hospitalization (Fig.1I-J) in which some patients already presented the laboratory features of AKI. Therefore, further analysis of sodium excretion parameters in terms of the potential impact on the risk of AKI development was abandoned.

Discussion

The current criteria for the diagnosis of AKI after massive thermal injuries do not differ from those used routinely in other clinical conditions and are based on the observation of hourly and daily diuresis and changes in classic parameters of renal function, i.e., an increase in serum creatinine concentration or a reduction in the value of eGFR. World reports suggest that this leads to a too late diagnosis, already at the stage of developed ARF.

Identification of measurable, non-renal biochemical parameters that precede the appearance of classic AKI markers may positively affect the course of this serious complication of burn disease in the initial stages of its development. The parameters presented above are biochemical substances that can be routinely marked in the blood and urine of each patient after a thermal injury.

The aim of the presented prospective research project involving 33 severely burned patients was an attempt to identify statistically significant parameters predicting the increasing risk of AKI occurrence in the early period (≤ 7 days) after a thermal injury. Initially a number of biochemical parameters were tested, and after in-depth mathematical analyses, the ones directly related to the occurrence of AKI were selected.

Increase in creatine kinase and rhabdomyolysis

Creatine kinase (CK), also called phosphocreatine kinase, catalyses the translocation reaction of phosphate groups to regenerate ATP in order to mobilize energy sources in tissues with high energy needs, such as striated muscle. Increased CK activity in the blood serum occurs in the case of massive disintegration of skeletal muscle cells, especially as a result of extensive crush injuries. One of the most serious complications of rhabdomyolysis is acute kidney injury. Acute lysis of myocytes accompanied by high CK concentration may cause AKI mainly by the mechanism of excessive accumulation of glomerular-filtered myoglobin. Impaired renal function occurs because of blockage of the renal tubules, secondary to protein precipitation, intratubular inflammation, contraction of renal vessels and direct destruction of tubular cells by locally released oxygen free radicals. Apart from myoglobinuria, renal dysfunction results from the usually accompanying low blood pressure leading to ischemia of the renal parenchyma, and the crystallization of uric acid molecules in the tubular lumen, accompanying myoglobin complexes [7].

Thermal injury causes an increase in CK activity as a result of the disintegration of muscle tissue under the influence of thermal energy and mechanical damage to myocytes in the crushing mechanism. The mechanism of damage to kidney function is similar to that of other causes of rhabdomyolysis [8]. The incidence of this complication is estimated at approximately 1% in the population of patients with severely burned TBSA above 25%. Rhabdomyolysis increases the risk of AKI occurrence by 70-75% and death by approximately 50%, and the risk of AKI increases with increasing CK activity [9, 10]. During the implementation of the project, it was found that CK activity is highest during the first 72 hours after the thermal injury. This was especially observed in the AKI group, where the values were significantly higher compared to the non-AKI group almost throughout the observation period, until the seventh day after the injury. Exceeding the upper limit of normal for CK by more than 3 times also significantly increases the risk of AKI by 3 times. Moreover, this effect remained independent on ABSI score after adjustment in forward logistic regression. This is consistent with the conclusions contained in the above--cited works. The close association between the increase in CK activity and the risk of developing AKI confirms the clinical usefulness of CK determination in this group of patients. This should be a base to postulate routine, early and intensive measurement of CK activity during the first hours after thermal injury. Tendency to abnormal CK results should induce intensive and strict control of renal function, even in case of the normal results of standard parameters.

Elevated aminotransferase level

Aspartate aminotransferase (AST) is an enzyme from the group of transaminases involved in the metabolism of amino acids that catalyse the transamination of α-amino groups from α-amino acids to α-keto acids, thus allowing the synthesis of amino acids from carboxylic ketoacids and the removal of excess nitrogen from the body. Increased concentrations of serum transaminases are most frequently observed in the course of liver diseases and in rare cases of damage to the heart muscle, kidneys, striated muscles, as well as during intense physical exercise and hemolysis. They indicate damage to the cytoplasm and mitochondria of cells [11].

Acute liver failure (ALF) with elevated AST level is a rare but serious complication of massive thermal trauma causing liver dysfunction, impaired synthesis of plasma proteins, including albumin, and disorders of the blood coagulation cascade [12]. The development of ALF is caused by a "cytokine storm" in the form of a series of inflammatory mediators released in response to a thermal stimulus [13]. At the cellular level, it is the result of damage to the structure and function of the endoplasmic reticulum and mitochondrion inside hepatocytes, causing dysfunction of their functions [14]. The etiology of AKI in the course of ALF is complex, and the main causes are renal tubular hypoperfusion due to rapid vasodilation of the celiac visceral bed (similar to hepatorenal syndrome), increased rhabdomyolysis, vascular endothelial dysfunction and septic complications [15].

The dynamics of changes in AST activity was significantly different in both studied groups. AST activity in the AKI group tended to double: for the first time right after the thermal injury and again after 5–7 days. The observed early aminotransferase elevated level is consistent with the previous reports confirming the occurrence of significant liver damage in the first several hours after the burn. Liver enzyme hyperactivation is most likely due to rapid hepatocyte necroptosis caused by massive infiltration of immunocompetent cells secreting several pro-inflammatory cytokines, such as IL-6, IL-1beta and TNF. Further escalation of the inflammatory process and generalization of the cytokine release syndrome beyond the hepatic area can lead to the subsequent sudden development of MODS, including AKI [16].

It was shown that an increase in activity of liver enzymes in the serum can be significantly associated with an increased risk of developing AKI. However, after adjustment for ABSI score, AST was excluded from the logistic regression model. The thing worth to mention is, that the non-AKI group tended to maintain the average AST values within the laboratory norms at the time of observation, and even to reduce during the first 4 days, in contrast to the AKI group. This tendency can suggest a close association between the activity of liver enzymes and the scale of damage to the renal parenchyma, and the usefulness of intensive monitoring the dynamics of their value changes, especially in the early post-trauma period, which is indicative of the risk of AKI. However, the negative result in logistic regression can indicate, that this parameter can be less important than previously described CK activity. The association between the liver enzymes and renal function can be indirect and can require further, advanced studies.

Hypoalbuminemia

Pathological reduction in serum protein concentration, including albumin, may be due to two main causes: impaired synthesis or increased loss. The process of synthesizing plasma proteins takes place in the liver. Severe and chronic

dysfunction of this organ may cause hypoproteinemia, and its severity is usually correlated with the degree of damage to this organ. Loss of proteins can take place through many metabolic pathways: with urine – as a component of the nephrotic syndrome, with feces - through the damaged wall of the gastrointestinal tract, and with serous fluid and lymph through damaged layers of the skin. In the course of burn disease, the latter element has a major influence, and the degree of deviation in protein resources is closely correlated with the extent and severity of burn wounds. Hypoproteinemia, and in particular hypoalbuminemia, is associated with the risk of developing AKI, which was observed, inter alia, in patients after surgical procedures complicated with a significant loss of plasma proteins. The cause of this phenomenon is not entirely clear, but attention is drawn to the role of impaired renal flow, the effect on the disturbance of the structure and function of the renal proximal tubules, modification of binding of endogenous toxins by plasma proteins, escalation of oxidative stress and interaction via the lysophosphatidic acid pathway [17].

In severely burned patients, a relationship between low serum albumin and an increased risk of AKI has been suggested. In the case of burns covering more than 20% of TBSA, there is a massive loss of extracellular fluid containing a significant number of proteins, leading to destabilization of intravascular oncotic pressure, development of hemodynamic disturbances and the phase of hypovolemic shock. Extensive thermal trauma induces an immediate, intense, generalized inflammatory response increasing the permeability of vessels, especially capillaries, to albumin and larger proteins. In addition, hypoproteinemia impairs the healing process of traumatic wounds, prolonging the time of damage to the skin layers, increasing the risk of hypovolemia and septic complications [18].

Observations during the implementation of the research project confirmed the earlier findings of other authors. During the first 3 days of hospitalization in the entire study group, the tendency to reduce ALB was clearly visible, more intense and earlier in the AKI group. Hypoalbuminemia in the first days after the injury is an expression of the disproportion between the amount of their loss through damaged skin layers and the impaired synthesis in the multi-organ failure syndrome as well as insufficient supplementation of external proteins. Normalization of ALB values observed at an approximately similar level in both study groups only above the fifth day should be treated as an expression of too late or too economical compensation of already existing protein deficiencies in the previous days.

The analyses showed a significant relationship between hypoalbuminemia and the risk of AKI in the first days of hospitalization. However, after adjustment for ABSI score, ALB was excluded from the logistic regression model. It confirms that ALB, similar to AST, can play rather minor role in early AKI diagnostic. Both parameters are depended on liver function. As was previously mentioned, the association between liver and renal dysfunctions can be not obvious and needs more studies.

This indicates the importance of strictly maintaining the correct level of protein metabolism parameters as important components of the therapeutic process of thermal injuries, already at an early stage of the disease development. Prophylactic and adequate supplementation of colloid solutions, which is an integral part of the fluid resuscitation system immediately after a thermal injury, may also significantly reduce the AKI/ARF percentage and improve patient survival. Consideration of implementing prophylactic protein supplementation should take place at the earliest stage of the disease development, without waiting for a decrease of their values in laboratory tests. Additionally, intensive, daily monitoring of the protein concentration in the blood serum would allow for a precise assessment of the adequate demand for their preparations in the following days.

Metabolic acidosis

Metabolic acidosis is a disorder of the acid-base balance characterized by an excessive accumulation of acidic substances (H+ ions) in the blood serum or a deficiency of alkaline substances (HCO3- bicarbonate anions). The diagnosis is based on the analysis of the arterial blood gas test showing a simultaneous decrease in the pH value with the accompanying low concentration of HCO3- ions. Acute systemic acidosis is a common complication in patients after massive burns, especially in a severe clinical condition, contributing to the deterioration of the clinical course [19]. The main causes are acute renal failure with impaired excretion of non-volatile acids, as well as hypovolemic and septic shock. A particular, non-renal, cause of acidosis is intoxication with substances released from specialized antibacterial dressings, widely used in severely burned patients, containing silver preparations as well as propylene and ethylene glycol. The risk of developing acidosis for this reason is proportional to the area of damaged skin layers, the depth of the injury and the length of the period of applying toxic compounds, thus it usually develops only in the distant day of hospitalization [20, 21].

In patients qualified for the project, the occurrence of metabolic acidosis was observed already during the first day after thermal injury, much more pronounced in the AKI group. Although all patients were treated with extensive dressings containing potentially nephrotoxic substances, the early incidence of acid-base disturbances contradicts this etiology. Therefore, developing AKI may be considered a cause of acidosis. The project showed a relationship between the decrease in serum pH and the occurrence of AKI, but without reaching the adopted threshold of statistical significance, which concerned both the same and the next day. In addition, it should be emphasized that the cases of acidosis of purely metabolic etiology were analyzed. Blood gas disturbances of other etiology, such as pulmonary pathologies, were not analyzed. The above observations can lead to the conclusion that although the occurrence of systemic acidosis is a consequence of AKI, its laboratory parameters may change earlier than the classical markers of renal function. Changes in pH occur at a very early stage in the development of burn disease, which additionally increases the potential predictive value of intensive determination of blood gas parameters in this

group of patients. Unfortunately, there is currently no available literature that extensively describes the occurrence of this disorder.

Thrombocytopenia

Platelets are formed from the progenitor cells of the megakaryocytic system located within the bone marrow. Circulating in the blood, they play several important roles in maintaining proper homeostasis of the body. They are cells of the immune response, participate in the initiation of the inflammatory process and the formation of the hemostatic plug. The survival time of platelets in peripheral blood ranges from 7 to 14 days, and their number is the resultant between bone marrow synthesis and loss through bleeding or autoimmune degradation [22].

Hemostatic disorders, resulting from fluctuations in serum PLT concentration, often occur in the course of burn disease, especially in the early stages of its development. Their intensification usually correlates with the severity of the injury and suggests the possibility of organ complications during the clinical course. As a result of extensive thermal trauma, there is often mechanical and thermal damage to the surrounding tissues, disruption of the continuity of the walls in large vascular trunks and massive bleeding from damaged vessels with the loss of a significant part of circulating blood, leading to the rapid development of post-hemorrhagic shock. Additionally, because of the implementation of anti-shock treatment based on the principle of fluid resuscitation and the transfusion of large amounts of crystalloids, generalized hemodilution and a decrease in the PLT value occur. Burn shock already at an early stage leads to the development of an acute, generalized inflammatory response with the activation of a number of immunocompetent cells. Numerous pro-inflammatory and pro-aggregating cytokines, such as: platelet-activating factor (PAF) P, prostaglandin G2 (PGG2) and H2 (PGH2) and thromboxane A2 (TXA2) are released. The effect of their action is a rapid increase in the prothrombotic state with increased adhesion and aggregation of PLT, disseminated intravascular coagulation (DIC) and the formation of numerous blood cell conglomerates. The immobilization of a significant portion of the platelets in the aggregation plugs results in a decrease in the number of free circulating platelets. A rapid decrease in the value of PLT causes a reflex stimulation of their synthesis in the bone marrow. However, in the case of massive burns and the advanced stage of burn disease accompanied by MODS, the level of platelet loss often exceeds the compensatory capacity, reducing the total number of PLT. The intensity of thrombocytopenia corresponds to the existing organ disorders and may be an indicator of the severity of the disease, as well as a poor prognostic factor for the survival of patients [23].

During the implementation of the project, the tendency for a significant decrease in the average value of PLT, most marked during the third day of hospitalization, was confirmed, which is consistent with the observations of other authors. The study by Shou B. et al. also showed a tendency to develop thrombocytopenia in the first days after a thermal injury, additionally emphasizing its negative impact on the survival of patients. Thrombocytopenia, as an indicator of an increased process of inflammatory response and intravascular coagulation, may also be a very early marker of the risk of septic shock, which usually develops fully only in the second or third week after thermal trauma. In this work, immediate administration of anti-infective treatment in all burn patients with thrombocytopenia was postulated [24].

During the implementation of the project, a trend for the occurrence of significantly deeper thrombocytopenia in the AKI group was observed, which is consistent with the conclusions of the study by Chen et al. [25]. An association between low PLT values and the risk of AKI was found both on the day of the test and on the following days of observation, but without reaching statistical significance. The most likely explanation for this relationship is the presentation of thrombocytopenia as one of the early elements of the developing MODS. Thus, thrombocytopenia should be regarded as a direct predictor of ARF development and as one of the components of the multi--organ failure syndrome.

Hyperkalemia

Elevated potassium concentration in the blood serum may result from excessive supplementation of this ion, its release from disintegrated cells or dysfunction of its excretion through the kidneys. It is a relatively common symptom accompanying acute renal disorders, and its underlying cause is a dysfunction of ion transmission at the level of the renal tubules. Elevated values of potassium concentration, especially above 6.5 mmol/L, pose a significant threat to the life of patients as they increase the risk of ventricular arrhythmia.

Massive burn may contribute to the occurrence of hyperkalemia in the course of metabolic acidosis, hemolysis and erythrocyte breakdown, rhabdomyolysis and the development of acute kidney injury [26]. Which of the above-mentioned metabolic pathways is most marked depends on the type and strength of thermal injury, complications and the choice of treatment. A relatively high risk of hyperkalemia in this group of patients exists in the case of the coexistence of the crush syndrome with the destruction of numerous organs, tissues and cell disintegration, rhabdomyolysis with damage to a significant mass of striated muscles, and the development of ARF. Importantly, hyperkalemia in the course of burn disease may result from AKI and is one of its early symptoms.

In the course of the project, it was shown that hyperkalemia occurs early in the development of burn disease, non-normative values were observed already in the first 48 hours after the injury with a clear tendency to higher values in the AKI group. It was found that hyperkalemia may precede the occurrence of standard laboratory symptoms of AKI and correlate with an increased AKI risk in the following days. Taking into account the potential diversity of the etiology of the increased potassium concentration in the blood serum, it should be emphasized that monitoring of potassium can be a beneficial element in the early

diagnosis of AKI development in this group of patients, but after excluding non-renal causes.

Sodium disturbances

Sodium disturbances are common in patients in a serious clinical condition usually as a consequence of the underlying disease development or an iatrogenic error in the composition of administered fluids and medications. Abnormal blood sodium levels are associated with increased mortality in this group of patients. Patients after massive burns often develop disturbances in blood sodium concentration. Hypernatremia is more common (in approximately 10% of patients) than hyponatremia (in approximately 7% of patients) [27]. The main cause of hypernatremia is profound hypovolemia, resulting from rapid fluid loss through damaged skin layers or insufficient control of the negative fluid balance [28]. Hypernatremia in this group of patients is associated with prolonged hospitalization, worse prognosis and increased mortality [29].

The causes of hyponatremia are usually: excessive intake of electrolyte-free fluids, the development of ARF with damage to renal tubules and salt loss syndrome, or hormonal disorders [30].

During the observation, the average Na values remained within the accepted laboratory norms, both in the profile of the entire study group and in the AKI and non-AKI groups. It was most likely related to the adoption and strict implementation of a uniform procedure for the management of a severely burned patient, based on the principles of dynamic, high-volume fluid resuscitation, significantly minimizing the risk of dehydration and electrolyte imbalance. However, from the fourth day of observation a slight tendency to increase the average sodium values, especially in the AKI group, was observed. This is consistent with the information contained in the above-cited study by Lam et al., in which the mean time of occurrence was estimated at approximately 8.3 (± 4.3) days, and the lack of exceeding the laboratory norms was perhaps due to the limitation of the observation time to 7 days.

During analyses, a correlation between the non-normative increase in sodium and the risk of AKI was found, but without obtaining the threshold of statistical significance.

Hypernatremia physiologically causes a reflex increase in the excretion of sodium ions in the urine in order to get rid of their excess and regulate electrolyte disorders. In addition, increased values of sodium excretion may indicate damage to sodium ions reabsorption in renal tubules as part of renal interstitial dysfunction. The above findings were not confirmed during the observation. It is true that after the third day of hospitalization a tendency for an extra-normative increase in the average 24-hour urinary sodium (24hUNa) excretion is observed, but it applies only to patients from the non-AKI group and the results mostly do not meet the statistical significance criterion. On the other hand, values of fractional sodium excretion (FENa) above 2%, which could potentially indicate an intrarenal etiology of disorders, were found in the AKI group, but also without statistical significance. Additionally, due to incomplete data, reliable analyses of sodium excretion disorders as the predictors of AKI proved to be impossible to perform.

In conclusion, despite the insignificant association between hypernatremia and the risk of AKI development, the obtained results of sodium metabolism elements do not clearly indicate their potential use in the early diagnosis of AKI in patients after burns.

Limitations

The main limitation of the project was the relatively small size of the study group. The main reasons for disqualifying patients were too low percentage of damage to layers, too long time from injury to hospitalization, changing the place of hospitalization during the project, and a limited number of stations for intensive burn treatment.

In some patients, especially in the first hours after the injury, technical problems with the adequate measurement of daily urine output occurred, which prevented a reliable assessment of daily diuresis and the analysis of biochemical parameters in the excreted urine.

The significant clinic problem was to keep the correct euvolemic status during fluid resuscitation. To minimize the risk of water-balance disorders we use the same fluid protocol according to Parkland's formula for each patient and the treatment was carried out by the same medical team in one burn department. The current volemic status was strictly monitored and corrected during all time of observation.

Conclusions

AKI is a common, serious complication after massive thermal injuries. Intensive monitoring of renal function parameters as well as a detailed and systematic analysis of the dynamics of their value changes can improve the diagnosis of AKI in this group of patients.

Selected biochemical parameters, such as increased CK and AST values and decreased serum ALB concentration can be considered early markers of increased risk of AKI development. The increased CK activity, especially in the rhabdomyolysis range, seems to be the most important parameter and can play the crucial role in the early AKI diagnosis. It seems important to add routine, daily determinations of the above-mentioned parameters to the current treatment regimens immediately after thermal injuries in order to early diagnose AKI, implement adequate therapy and reduce the percentage of ARF and RRT significantly worsening the prognosis of patients.

Other investigated parameters, such as metabolic acidosis, thrombocytopenia and hyperkalemia, can have a potential diagnostic benefit, but require further in-depth analyses involving larger groups of patients.

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KIDNEY ABSCESS AS A RARE COMPLICATION OF URINARY TRACT INFECTIONS IN CHILDREN – 20 YEARS OF SINGLE-CENTRE OBSERVATIONS

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Abstract:

Introduction and objective

Kidney abscess is one of the complications of the urinary tract infection. Gram (-) intestinal flora is considered the most common etiological factor in development of kidney abscess. The spreading of bacteria usually occurs via an ascending route. Currently, in the era of antibiotic therapies, the kidney abscess is a relatively rare complication. Material and methods

The study aimed to analyze the prevalence, risk factors, clinical course of the disease, results of treatment, and the long-term consequences in pediatric patients with kidney abscess diagnosis.

Results

The renal abscess was diagnosed in 8 out of 32,000 hospitalized children (0.00025%) (5 girls, 3 boys, average age 6 years). In 7 cases, the association with urinary tract infection was confirmed (87.5%). In all patients, the abscess was limited to the renal parenchyma and its diameter was below 50 mm; two patients had multiple abscesses. Three children (37.5%) had a history of urinary tract disease. All patients had increased levels of the inflammation markers but the renal function parameters were within the reference values. Five children (62.5%) presented clinical symptoms (fever, pain, dysuria); in 2 children (25%) the clinical course was chronic and oligosymptomatic. The sensitivity and specificity of ultrasound examinations (US) were 100% accurate in the diagnosis and monitoring of treatment. In all cases, antibiotic therapy was effective. Post-antibiotic treatment renoscintigraphy showed persistent post-inflammatory scars in 62.5% of cases.

Conclusions

During 20 years of observations, kidney abscess was a rare complication of urinary tract infection. Most patients did not have any underlying risk factors. Ultrasound examination had high sensitivity and specificity in the diagnosis and monitoring of the treatment. Broad-spectrum, prolonged antibiotic therapy proved to be an effective treatment in all patients. However, after the abscess has been successfully healed, most patients required permanent nephrology care due to the presence of the post-inflammatory scars.

Keywords: kidney abscess, children, urinary tract infection, ultrasound examination, renoscintigraphy.

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Introduction

occurs with a frequency of about 1–10: 10,000 hospitalized patients [1, 2]. It is one of the complications of urinary tract infections. Bacterial spread and abscess formation usually occur via the ascending route [2, 3]. In such cases, Gram (-) bacteria of the intestinal flora such as *Escherichia coli*, *Klebsiella sp.*, and *Proteus sp.* are the etiological factor [2-4]. Urinary tract obstruction is one of the risk factors contributing to kidney abscess formation [5]. In the pre-antibiotics era, a lot of renal abscesses formed as a result of

secondary, hematogenous spread of Gram (+) bacteria, most often from the infections located in the skin, bones or endocardium. In such cases, multiple abscesses located in the renal cortex were observed. Currently, drug addiction, diabetes mellitus, and dialysis are the main risk factors for the development of renal abscesses [4, 6].

Abscesses classification by the location:

- an intrarenal abscess (located in the renal parenchyma, single or multiple abscesses),
- a perinephric abscess (purulent material outside the renal capsule but within the renal fascia),
- a paranephric abscess (extends out of the renal fascia – may spread under the skin to the iliopsoas, to the groin, and even to the scrotum) [3].

Perinephric and paranephric abscesses are a serious complication of acute tubulointerstitial nephritis. They are caused by extension of the intrarenal abscess to the perirenal space. Occasionally, they are complications of some urological procedures [3].

Clinical symptoms of kidney abscess are usually the same as symptoms of acute tubulointerstitial nephritis. Patients present fever, lumbar pain, and dysuria [2]. Making an accurate diagnosis can be difficult at the beginning of the abscess formation. For this reason, as well as due to insufficient access to imaging examination in the past, the incidence of delayed diagnosis, uncontrolled spread of infection, and death as a consequence of sepsis, have been relatively common [2]. Therefore, in the presence of symptoms of severe urinary tract infection, and poor response to standard therapy, imaging tests of kidneys and urinary tract should be performed [2, 6]. Although currently, access to ultrasound examination (US) is good, the subjective interpretation of the ultrasound, in the case of renal abscess suspicion, requires the confirmation of diagnosis by computed tomography (CT) or magnetic resonance imaging (MRI) [2, 3, 6].

Successful treatments for kidney abscess are still being researched and discussed. Usually, the treatment begins with a broad-spectrum intravenous antibiotic therapy. Only in the case of the lack of no improvement after such a therapy, and in case of patients with large or perinephric abscess, it is necessary to perform surgery. The most commonly used treatment among surgical techniques is percutaneous drainage. Major surgical procedures such as surgical drainage (open surgery), heminephrectomy, or nephrectomy are reserved only for large abscesses causing permanent renal insufficiency, or the severe general condition of the patient [2, 6, 7].

Aim of the study

The aim of the study was analysis of demographic data, risk factors, clinical course, treatment results, and long-term consequences of the disease in children with a kidney abscess, treated in our department during the last 20 years.

Material and methods

We performed retrospective analysis of the medical records of all children hospitalized at the Department of Paediatrics, Paediatric Nephrology, and Allergology in Military Institute of Medicine in Warsaw between 2000 and 2019, and identified the data of children hospitalized due to urinary tract infection.

Data of children with kidney abscess diagnosis were analyzed in detail. Age, gender, risk factors, clinical symptoms, course of infection, laboratory results (white blood cells – WBC, C-reactive protein – CRP, erythrocyte sedimentation rate – ESR, urea, creatinine, urinalysis, urine culture), imaging results (ultrasonography – US, computed tomography – CT, magnetic resonance imaging – MRI), type and duration of treatment, as well as long--term consequences of the disease were analyzed.

The abscess size was determined by measuring its largest dimension.

All patients after recovery remained under the care of a nephrologist Blood pressure was regularly measured, parameters of renal function and urinalysis were periodically assessed, and abdominal ultrasound, as well as renoscintigraphy, were performed in order to recognize possible consequences of the disease.

The results of the analyses are presented as the average and percentage value. Data were analyzed using Microsoft Excel.

Results

Between 2000 and 2019 32,000 patients at the age of 0-18 years were hospitalized at the Department. Urinary tract infection was the reason for the hospitalization of 2148 (6.71%) children. In 8 patients (5 girls and 3 boys) kidney abscess was diagnosed, which constituted 0.00025% of all hospitalizations. In 7 cases, this diagnosis was associated with urinary tract infection (0.032% of all diagnosed urinary infections). In one patient, the abscess was a complication of peritonitis. The average age of patients with kidney abscess diagnosis was 6 years. In three cases, the pathology was localized in the left (37.5%), and in five cases in the right (62.5%) kidney. In all patients, parenchymal abscesses were diagnosed: in 6 cases single, in 2 cases – multiple abscesses. The size (diameter) of abscesses in the analyzed material ranged from 10 to 33 mm, an average 21.6 mm (Table 1).

A history of urinary tract diseases was recorded in 3 patients (37.5%). One patient had urolithiasis, the second had recurrent urinary tract infections and a complex kidney cyst, and the third had recurrent urinary tract infections and vesicoureteral reflux. Appendicitis complicated by perforation and peritonitis was also an important pathology outside the urinary tract, contributing to kidney abscess.

All observed patients had increased inflammatory markers (WBC: range 7.0–21.94 x 109/l, average 14.31 x 109/l; CRP: range 1.2–22.5 mg/dl, average 9.7 mg/dl, ESR: range 14–109 mm/h, average 71.5 mm/h). In 7 children (87.5%) in urinalysis the features of urinary tract infection were found (leukocyturia). In all children, the parameters of renal function were normal (creatinine: range 0.3–0.7 mg/dl, average 0.4 mg/dl; urea: range 17–32 mg/ dl, average 22.4 mg/dl) (Table 1).

Table 1. Summary of analyzed variables: characteristic of a group, risk factors, course of the disease.

Variable	Value
Sex	
Girl	5 (62.5%)
Boy	3 (37.5%)
Age	
< 1 year old	0 (0%)
2–6 years old	6 (75%)
> 6 years old	2 (25%)
Location	
Right kidney	5 (62.5%)
Left kidney	3 (37.5%)
Multiplicity	
Abscess of kidney parenchyma	8 (100%)
Single abscess	6 (75%)
Multiple abscesses	2 (25%)
Size	
<30 mm	6 (75%)
30–50 mm	1 (12.5%)
No data	1 (12.5%)
Risk factors	
Positive history of urinary tract diseases	3 (37.5%)
Other (peritonitis)	1 (12.5%)
Course of illness	
Severe (sepsis, multi-organ failure)	1 (12.5%)
Moderate-severe (urosepsis, dehydration)	1 (12.5%)
Moderate (fever, pain, dysuria)	3 (37.5%)
Mild (no clinical symptoms, chronic course)	2 (25%)
No data	1 (12.5%)
Laboratory test results	
Elevated inflammation markers	8 (100%)
Leukocyturia in urinalysis	7 (87.5%)
Elevated kidney function parameters	0 (0%)
Urine culture	
Escherichia coli	3 (37.5%)
Enterococcus faecalis	2 (25%)
Proteus mirabilis	1 (12.5%)
Sterile culture	1 (12.5%)
No data	1 (12.5%)

In urine culture, the most common isolated pathogen was *E. coli* (37.5%). Table 1 presents the results of the urine culture.

Five children presented clinical symptoms of urinary tract infection, such as fever, chills, vomiting, lumbar pain, and dysuria. In two children, clinical symptoms were not observed at the time of diagnosis (chronic course – asymptomatic) (Table 1). These were patients under constant nephrological care due to recurrent urinary tract infections. In one of them, a complex kidney cyst had been observed for several years.

In each case, ultrasound examination was performed in the diagnostic process, and during monitoring of the treatment. To confirm the diagnosis, magnetic resonance imaging was used in four cases, and computed tomography in three. In one case, due to the patient's severe condition and multi-organ failure, all three imaging methods were used for diagnosis and monitoring (Table 2).

In each case, at the beginning of the treatment, a combination of broad-spectrum, intravenous antibiotic therapy was used, followed by an oral antibiotic therapy. The average duration of intravenous antibiotic therapy was 18 days and the average duration of total antimicrobial treatment – 45 days. The duration of treatment was chosen individually, depending on the severity of the disease and the degree of recovery. In the acute phase of the disease satisfactory treatment results were obtained in all patients. None of the patients required surgical treatment. Detailed data on the used antibiotics are presented in Table 3.

Table 3. Antibiotic therapy.

Patient	Before and during hospitalization	After discharge from the Department
1.	cefuroxime axetil p.o. (6 days) -> amikacin i.v. (10 days) -> metronidazole i.v. (10 days) - > ceftriaxone i.v. (21 days)	sulfamethoxazole/ trimethoprim p.o. (21 days) -> trimethoprim p.o. (5 weeks)
2.	ceftazidime i.v. (10 days), ampicillin i.v. (10 days) - > amikacin i.v. (10 days), ceftriaxone i.v. (14 days), linezolid i.v. (10 days)	no antibacterial treatment was used
3.	ceftriaxone i.v. (21 days) netromycin i.v. (10 days)	ciprofloxacin p.o. (10 days)
4.	ceftriaxone i.v. (16 days)	sulfamethoxazole/ trimethoprim p.o. (5 weeks)
5.	cefuroxime i.v. (14 days) amikacin i.v. (10 days)	cefuroxime axetil (7 days)
6.	ceftazidime i.v. (21 days) amikacin i.v. (10 days) -> metronidazole i.v. (10 days)	clindamycin p.o. (5 weeks)
7.	cefuroxime axetil (6 days) -> ceftazidime i.v. (14 days)	sulfamethoxazole/ trimethoprim p.o. (6 weeks)
8.	No data	No data

i.v. – intravenously, p.o. – orally

Table 2. Diagnostic imaging.

Method	Number of cases in which an examination was performed to diagnose or confirm a diagnosis	Number of cases in which a kidney abscess was visualized	Number of cases in which the course of the disease was monitored
USG	8	8	8
MRI	5	5	2
CT	4	4	1

During nephrological follow-up, five patients (62.5%) were found to have persistent post-inflammatory renal scars visualized by ultrasound and renoscintigraphy. The other 3 patients had normal renal parenchyma. Deterioration of kidney function and chronic kidney disease were not observed in any of the children.

Discussion

Our study analyzed etiology, risk factors, clinical course, and results of treatment of kidney abscess in the pediatric population.

Kidney abscess was a rare complication in the examined material. The prevalence was 8 out of 32,000 of all hospitalized patients, and 7 out of 2148 patients with urinary tract infections, which is consistent with the published data [1, 2]. In 87.5% of analyzed cases, an association between the formation of an abscess and urinary tract infection was confirmed. In the literature, this correlation was estimated to be above 75% [6]. Our study showed that the pathology was slightly more common in girls (62.5%). This observation can be explained by the fact that urinary tract infections are more common in female population, but the small number of analyzed cases makes it impossible to draw definite conclusions. Similar results were obtained by Lee et al. [8]. In their study, which analyzed the course of the disease in 56 adults, women constituted 75% of patients. However, Willard et al. [1] found that kidney abscesses occurred with the same frequency in both sexes.

In our study, the abscesses were more often diagnosed in younger children (<6 years of age).

In the studied group of patients, the coexisting urinary tract pathologies (recurrent urinary tract infections, vesicoureteral reflux, urolithiasis) were the main risk factor for renal abscess. This association was found in 37.5% of patients. According to the literature, other risk factors for the formation of renal abscesses are urinary tract defects, diabetes, liver cirrhosis, cancer, and congenital or acquired immunodeficiency [2, 4, 8]. Yen et al. [9] and Hung et al. [10] described the risk factors for poor prognosis and increased mortality among adults with renal abscesses. Poor prognosis positively correlated with the high values of C-reactive protein [10] and urea nitrogen [9] in blood serum, and with the advanced age of patients [10]. According to various studies, mortality in renal abscesses was between 0-7% in adults [8, 11, 12]. In our observations of pediatric patients, no impairment of renal function was found in any child. However, elevated inflammatory markers were observed in all of them. In two children with a septic level of markers of inflammation, the use of antibiotic therapy normalized the parameters. In our observation, high WBC, CRP, and ESR values did not correlate with worse prognosis. None of the studied children were found to have a serious chronic disease, including immunodeficiencies.

As already mentioned, in studies analyzing patients before 1960, most of the renal and perirenal abscesses were the result of hematogenous spread of S. aureus from other foci of infection. Currently, the widespread use of antimicrobial drugs has almost completely eliminated this phenomenon. Today, most of the renal abscesses are caused by Gram (-) bacilli originating from the urinary tract, which is confirmed by the results of our study, as well as the results from other centers. E.coli is the main pathogen causing the abscesses [8, 13, 14].

In all cases of patients with abscess of renal parenchyma described in our study early diagnoses and implementation of broad-spectrum antibiotic therapy prevented serious complications, such as perinephric abscess or extension out of the renal fascia. However, in the study of Lee et al. [8] of the population of adults with many coexisting chronic diseases, the percentage of abscesses extending beyond the renal parenchyma was 45% [8].

According to our observations attention should be paid to the usefulness of ultrasound examinations in initial diagnostics and in monitoring the course of the disease. US is a widely available and non-invasive test. According to the literature, its sensitivity in abscess detection ranges from 70 to 86% [9, 15]. In our study sensitivity and specificity of ultrasound imaging were 100%. Computed tomography and magnetic resonance imaging were used to confirm the diagnosis. Computed tomography enables the diagnosis of a kidney abscess with accuracy at 90-100% [9]. This method is particularly useful in the case of equivocal US results. It is also useful in accurate assessment of the abscess size, its extension, and renal parenchyma failure [2]. Magnetic resonance imaging has the highest sensitivity and specificity. However, due to limited availability and high cost, it is primarily used to differentiate abscesses with malignant tumors [2, 8, 16]. In our observations, CT and MRI were used with the same frequency to confirm the diagnosis. In one of the cases, both imaging tests were performed because of the atypical course of the disease and severe general condition of the patient. To monitor the treatment, the ultrasound examination has been used in all children, while MRI scans were performed in 2 patients, and CT scan in one patient. Radiological protection should be the key aspect in the choice of imaging methods in pediatric population [2, 16].

In empirical treatment, combined broad-spectrum antibiotic therapy was used, such as second and third-generation cephalosporins, aminoglycosides, and metronidazole. Similar drugs were used in many other studies described in the literature [2, 8, 17]. Adult patients were also treated with fluoroquinolones [2, 17]. In all examined children a good therapeutic effect of antibiotic therapy was observed, none of the patients required surgical intervention. In all cases, the abscess size did not exceed 50 mm. The size of the abscess which is a definite indication for surgical treatment, is still the subject of discussion. In 1996, Siegel et al. proposed an algorithm for the treatment of renal abscesses depending on their size. Renal abscesses were divided into small (<3 cm), medium (3–5 cm) and large (>5 cm) [17]. Broad-spectrum intravenous antibiotic therapy was recommended for small abscesses, whereas a more invasive treatment was the preferred option for large abscesses. In the case of medium abscesses, the indication for surgical interventions depended on the response to antimicrobial treatment and

the patient's clinical condition [2, 17, 18]. This scheme was accepted in the majority of studies, which described the positive outcome [2, 7, 8, 15, 19]. In the case of perinephric abscesses, their size is less important. In most of these cases, conservative treatment was ineffective [19].

After recovery, each of the patients analyzed by us remained under nephrological care. In the available literature, there are no results of long-term observations on possible renal dysfunction or other long-term consequences after recovery in adults [8, 15, 16]. In our observations in 62.5% of cases, persistent post-inflammatory scars were found by renoscintigraphy. Therefore, continuous nephrological care seems to be justified in this group of patients.

The limitation of research presented here is the small study group, which does not allow statistical analyses and definitive conclusions. However, in the available literature, there are no sufficient descriptions and analyses of kidney abscesses in pediatric population. Thus, further observations are necessary to make recommendations for the management of renal abscesses in pediatric patients. Due to the rare occurrence of such a complication, the thorough analysis will require the multi-center studies.

Conclusions

1. During 20 years of observation of our patients, renal abscess was a rare complication of urinary tract infection.
2. Most patients did not have any underlying risk factors.
3. The clinical course in the majority of children was mild, they mostly demonstrated fever and elevated inflammatory markers.
4. Ultrasound examination showed high sensitivity and specificity for the diagnosis and monitoring of treatment.
5. Broad-spectrum prolonged antibiotic therapy proved to be a sufficient method of treatment in all patients.
6. Due to the presence of post-inflammatory scars in the majority of observed patients, they required constant nephrological care after the abscess has been healed.

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ANALYSIS OF DIETARY SUPPLEMENTS AND OVER-THE-COUNTER ANALGESICS USE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Ocena stosowania suplementów diety oraz leków przeciwbólowych dostępnych bez recepty przez chorych z przewlekłą chorobą nerek

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Abstract:

Introduction and objective

Popularity of dietary supplements and over-the-counter analgesics is constantly increasing. Patients diagnosed with CKD (chronic kidney disease) are more exposed to consequences of unreasonable usage of these kinds of preparations. The reasons are electrolytes disorders and polypharmacy resulting from many comorbidities. Research aim is the analysis of dietary supplements and OCT analgesics usage frequency among CKD patients with an attempt of dietary errors assessment.

Material and methods

Questionnaire research was conducted on patients diagnosed with chronic kidney disease treated conservatively and dialyzed. 120 patients were included in the study – 46 treated conservatively (16 women and 30 men) and 74 receiving dialysis (30 women and 44 men).

Results

87.5% of respondents declared dietary supplements and over-the-counter analgesics use. 82% of man and 96% of woman (p = 0.028). It was 93% among dialysis patients, and 78% among treated conservatively (p = 0.018). 48% of patients take over-the-counter analgesics, 52% calcium, 21% magnesium.

Conclusions

The research results indicate overuse of dietary supplements and OCT analgesics among patients with CKD, especially among women and dialysis patients. The most frequent taken preparations are analgesics, calcium, and magnesium.

Keywords: vitamins, chronic kidney disease, dietary supplements, dialysis therapy, non-steroidal anti-inflammatory drugs.

Streszczenie:

Popularność suplementów diety i leków dostępnych bez recepty stale rośnie. Pacjenci z PChN w większym stopniu narażeni są na skutki nieprzemyślanej podaży tego typu preparatów z powodu zaburzeń gospodarki jonowej i polipragmazji wynikającej z wielu chorób współtowarzyszących. Celem pracy jest analiza częstości przyjmowania suplementów diety i leków dostępnych bez recepty w populacji osób z przewlekłą chorobą nerek z próbą ustalenia błędów dietetycznych. Przeprowadzono badanie ankietowe na grupie pacjentów z rozpoznaną przewlekłą chorobą nerek leczonych zachowawczo oraz dializowanych. Do badania włączono 120 pacjentów, w tym 46 leczonych zachowawczo (16 kobiet i 30 mężczyzn) oraz 74 chorych hemodializowanych (30 kobiet i 44 mężczyzn). W badanej grupie 87,5% osób zadeklarowało przyjmowanie suplementów i/lub leków przeciwbólowych dostępnych bez recepty. Przyjmowanie zgłosiło 82% mężczyzn i 96% kobiet (p = 0,028). W grupie dializowanych przyjmowanie dotyczyło 93%, a wśród leczonych zachowawczo 78% (p = 0,018). 48% pacjentów przyjmowała leki przeciwbólowe dostępne bez recepty, 52% wapń, a 21% magnez.

Wnioski

Wyniki analizy wskazują na nadużywanie suplementów i leków dostępnych bez recepty przez chorych z wywiadem przewlekłej choroby nerek, szczególnie przez kobiety i pacjentów dializowanych. Najczęściej nadużywane są leki przeciwbólowe, preparaty wapnia i magnezu.

Słowa kluczowe: witaminy, przewlekła choroba nerek, suplementy diety, dializoterapia, niesteroidowe leki przeciwzapalne.

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Introduction

Chronic kidney disease (CKD) is diagnosed in approximately 10-13% of the population [1]. It is defined as the presence of each abnormality in the kidney structure or function persisting for more than 3 months. The leading causes of CKD are glomerulonephritis and diabetes mellitus as well as hypertension, the latter two being classified as civilization diseases. Kidney function deterioration – along with disease progression – affects many organs and systems. Derangements include, among other things, water-electrolyte, and acid-base metabolism, while a reduced number of functional nephrons results in abnormal concentrations of ions, vitamins and medicaments and their metabolites [2]. Over the years, both the popularity of dietary supplements and the value of the global market for such products have been increasing [3, 4]. However, the Internet and advertising, which contribute to the increase of such phenomena, do not lead to the formation of correct convictions in this regard [5]. The group of patients with CKD requires an individualised attitude towards the supplementation aspect. It should be in line with the patient's changed needs, and recommendations should depend on disease severity, the treatment applied and documented or anticipated deficiencies.

Aim of the study

The analysis of dietary supplements and OCT drug usage frequency among CKD patients with identification of abnormal dietary trends.

Material and methods

A paper-based survey, consisting of 19 questions, was conducted to assess trends in the intake of dietary supplements and OTC medications. The questionnaire was completed by 120 patients treated at the nephrology outpatient clinic and Dialysis Unit of the Military Institute of Medicine in Warsaw (WIM) with a diagnosis of chronic kidney disease. Questions included age, gender, duration of disease and therapy, type of treatment, supplements and OCT analgesics usage, reason for taking them, well-being improvement, awareness of the harmful effects and interactions with other medicaments. The study was conducted in accordance with the requirements of the Declaration of Helsinki. All patients gave their informed consent to participate in the study. The study was approved by the WIM Bioethics Committee.

A total of 120 patients (aged 23 to 91 years, mean 65.6 ±14.0 years) were studied, including 74 dialysis patients (aged 23 to 89 years, mean 64.6 ±14.9 years of age, including 44 men and 30 women) and 46 patients managed with conservative treatment (aged 36 to 91 years, mean 67.2 ±12.4 years of age, including 30 men and 16 women). Among the subjects, there were both patients with recently diagnosed kidney disease and patients with a long-time diagnosis (6 months to 60 years, mean 11.3 ±11.2). The conservative treatment group was significantly larger than the dialysis group. The groups did not differ in terms of gender and age categories ≥ 65 and < 65 years of age (Table 1).

Statistical analysis

The results were presented as mean with outliers and standard deviation and, for nominal variables – as number and incidence. In order to assess the significance of differences in the studied trait prevalence between groups, the Chi2 test or Fisher's exact test was performed, depending on the size of the analyzed groups. The significance level for a two-sided $p < 0.05$ was considered statistically significant. The statistical analysis was performed with Statistica software version 12.0 (StatSoft, Krakow, Poland).

Results

In the study group, 105 subjects (87.5% of respondents) declared using dietary supplements and OCT analgesics: 69 dialysis patients and 36 managed with conservative treatment, 61 men aged 24 to 91 years and 44 women aged 23 to 89 years.

Supplementary products were taken by 96% of women and 82% of men. In the dialysis group, supplements were taken

Table 1. Characteristics of the study group.

Type of treatment	All (n=120)	Male (n=74)	Female (n=46)	<65 years of age (n=49)	≥65 years of age (n=71)
Dialysis therapy (n=74)	74 (62%)	44 (60%)	30 (40%)	31 (42%)	43 (58%)
Conservative (n=46)	46 (38%)	30 (65%)	16 (35%)	18 (39%)	28 (61%)
Significance of differences - p	<0.001	0.528		0.765	

by 93% and in the conservative treatment group by 78% of patients. As many as 84% of patients under 65 years of age and 90% above this age reach for OCT products.

Only 15 patients (12.5%) denied taking supplements – five dialysis patients and 10 patients managed with conservative treatment, including 13 men aged 47 to 83 years and two women aged 64 to 70 years (Table 2).

Table 2. OCT supplements usage in different groups.

Supplements	All (n=120)	Male (n=74)	Female (n=46)	<65 years of age (n=49)	≥65 years of age (n=71)	Dialysis therapy (n=74)	CT (n=46)
YES (n=105)	105 (87.5%)	61 (82%)	44 (96%)	41 (84%)	64 (90%)	69 (93%)	36 (78%)
NO (n=15)	15 (12.5%)	13 (18%)	2 (4%)	8 (16%)	7 (10%)	5 (7%)	10 (22%)
Significance – p	<0.001	0.028		0.621		0.018	

CT – *Conservative treatment*

Supplements included, among other things, calcium, magnesium, vitamins A, D, E, K, C and B, folic acid, fish oil, potassium, iodine, and zinc. The taking of any analgesic medication was reported by as many as 58 (48%) patients. The most commonly used medication was paracetamol (37%), but the respondents also mentioned non-steroidal anti-inflammatory drugs (21%), opioids, metamizole and others (Table 3).

Table 3. Types of OCT products used.

Type of supplement	All (n=120)	Dialysis (n=74)	CT (n=46)	Significance – p
Calcium	62 (52%)	58 (78%)	4 (9%)	<0.001
Magnesium	25 (21%)	11 (15%)	14 (30%)	0.103
Vitamin D (cholecalciferol)	16 (13%)	8 (11%) 8 (17%)		0.421
B-group vitamins	16 (13%)	10 (14%)	6 (13%)	1.000
Vitamin A	3 (2.5%)	2 (3%)	1 (2%)	1.000
Vitamin C	3 (2.5%)	2 (3%)	1 (2%)	1.000
Fish oil	3 (2.5%)	1 (1%)	2 (4%)	0.560
Folic acid	2 (2%)	2 (3%)	0	0.526
Potassium	2 (2%)	0	2 (4%)	0.153
Vitamin K	2 (2%)	1 (1%)	1 (2%)	1.000
Vitamin E	1 (1%)	1 (1%)	0	1.000
Iodine	1 (1%)	0	1 (2%)	0.388
Zinc	1 (1%)	1 (1%)	0	1.000
Paracetamol	44 (37%)	35 (47%)	9 (20%)	0.040
NSAIDs	25 (21%)	15 (20%)	10 (22%)	0.876
Metamizole	6 (5%)	5 (7%)	1 (2%)	0.410
Opioids	3 (2.5%)	1 (1%)	2 (4%)	0.560
Other	2 (2%)	0	2 (4%)	0.153

CT – *Conservative Treatment*

Table 4. Comparison of different NSAIDs.

Analgesic	Number of users	Significance – p				
		Paracetamol	NSAIDs	Metamizole	Opioids	Other
Paracetamol	44 (37%)	-	0.043	<0.001	<0.001	<0.001
NSAIDs	25 (21%)	0.043	-	0.002	<0.001	0.001
Metamizole	6 (5%)	<0.001	0.002	-	0.500	0.282
Opioids	3 (2.5%)	<0.001	<0.001	0.500	-	1.000
Other	2 (2%)	<0.001	<0.001	0.282	1.000	-

In the study group, taking supplements did not significantly improve patients' well-being and, at the same time, was not associated with an increase in information provided to the nephrologist about the usage of these substances (Table 5).

Table 5. Other data related to the OCT products usage.

	YES	NO	Significance – p
Improvement in well-being associated with product usage (n=105)	55 (46%)	50 (42%)	0.690
Informing nephrologist about taking the products (n=109)	53 (44%)	56 (47%)	0.815
Self-discontinuation of the product (n=118)	30 (25%)	88 (73%)	<0.001
Occasional unplanned purchase of the product (n=102)	8 (7%)	94 (78%)	<0.001
Reading books/magazines/websites dedicated to health (n=120)	48 (40%)	72 (60%)	0.002
Awareness of potential negative effects of taking the products (n=117)	77 (64%)	40 (33%)	0.005
Awareness of interactions of the products with other medicaments (n=118)	93 (78%)	25 (21%)	<0.001
Reading the product leaflet or consulting a physician or pharmacist (n=117)	84 (70%)	33 (28%)	<0.001

Despite awareness of possible interactions and potential negative consequences of supplements, the majority of users did not discontinue the product they were using. There were no significant differences between men and women in terms of the analyzed issues, except for significantly more frequent reading of the product leaflet or discussing the supplement usage with a physician or pharmacist (Table 6).

Table 6. Other data related to the OCT products usage among women and men.

	YES		NO		Significance – p
	Male (n=74)	Female (n=46)	Male (n=74)	Female (n=46)	
Improvement in well-being associated with product usage (n=105)	31 (42%)	24 (52%)	33 (45%)	17 (37%)	0.312
Informing nephrologist about taking the products (n=109)	31 (42%)	22 (48%)	35 (47%)	21 (46%)	0.669
Self-discontinuation of the product (n=118)	20 (27%)	10 (22%)	52 (70%)	36 (78%)	0.463
Occasional unplanned purchase of the product (n=102)	3 (4%)	5 (11%)	61 (82%)	33 (72%)	0.145
Reading books/magazines/websites dedicated to health (n=120)	28 (38%)	20 (43%)	46 (62%)	26 (57%)	0.540
Awareness of potential negative effects of taking the products (n=117)	46 (62%)	31 (67%)	25 (34%)	15 (33%)	0.772
Awareness of interactions of the products with other medicaments (n=118)	56 (76%)	37 (80%)	16 (22%)	9 (20%)	0.820
Reading the product leaflet or consulting a physician or pharmacist (n=117)	43 (58%)	41 (89%)	28 (38%)	5 (11%)	<0.001

Table 7. Other data related to the OCT products usage among dialysis patients and those managed with conservative treatment.

	YES		NO		Significance – p
	Dialysis (n=74)	CT (n=46)	Dialysis (n=74)	CT (n=46)	
Improvement in well-being associated with product usage (n=105)	36 (49%)	19 (41%)	30 (41%)	20 (43%)	0.564
Informing nephrologist about taking the products (n=109)	33 (45%)	20 (43%)	33 (45%)	22 (48%)	0.809
Self-discontinuation of the product (n=118)	19 (26%)	11 (24%)	54 (73%)	34 (74%)	0.848
Occasional unplanned purchase of the product (n=102)	6 (8%)	2 (4%)	51(69%)	43 (93%)	0.461
Reading books/magazines/websites dedicated to health (n=120)	28 (38%)	20 (43%)	46 (62%)	26 (57%)	0.540
Awareness of potential negative effects of taking the products (n=117)	48 (65%)	29 (63%)	23 (31%)	17 (37%)	0.611
Awareness of interactions of the products with other medicaments (n=118)	58 (78%)	35 (76%)	14(19%)	11 (24%)	0.562
Reading the product leaflet or consulting a physician or pharmacist (n=117)	53 (72%)	31 (67%)	20 (27%)	13 (28%)	0.803

CT – *Conservative treatment*

There were no significant differences in the issues discussed above, including well-being, between dialysis and conservative treatment patients (Table 7).

Discussion

The vast majority of patients diagnosed with CKD report taking OTC products, with as many as 47% not informing their nephrologist. In addition, one third of the patients admit to being unaware of potential side effects. It poses a significant problem that requires increased awareness among both patients and physicians who are in contact with CKD patients.

Women are significantly more likely than men to use OTC products. The dialysis group was also superior to the group managed with conservative treatment. Compared to the patients managed with a conservative treatment, the dialysis patients were significantly more likely to use calcium supplements and less likely magnesium supplements – which, given the frequent hypocalcemia in the course of secondary hyperparathyroidism and magnesium retention, partly coincides with current recommendations [6].

Below, we outline the relationship of disorders occurring in patients with CKD to the possible consequences of inadequate supplementation with the most common products.

Calcium

In case of patients with CKD, both negative and positive calcium balance are unfavorable phenomena. A deficiency may result, among other things, in pathological fractures, while an excess – in vascular calcification, progression of renal damage and escalation of cardiovascular problems [7]. In patients with chronic kidney disease, it is very important to determine levels of parathormone (it is usually elevated; a parathormone level for patients receiving dialysis should be 2–9 times of the upper limit of normal), phosphate (usually elevated) and calcium (usually reduced), and on the basis of their results, recommendations for dietary and supplemental calcium supply should be adjusted. Calcium-phosphate imbalance appears from the early stages of the disease (from around eGFR < 50 ml/min/1.73 m2). Studies have shown that a neutral calcium balance can be achieved in patients with stage 3 and 4 CKD in the case of a total elemental calcium intake of 800-1,000 per day [8]. In individual cases, recommendations for early stages of the disease follow a standard dose for healthy individuals (1000-1200 mg per day) [9]. It should be remembered that calcium is usually contained in phosphate binders (calcium carbonate, calcium acetate) often taken by patients with hyperphosphatemia. A decision to supplement calcium and to include calcium-based phosphate binders should be made on an individual basis, depending on the patient's current test results and initial dietary calcium content [10]. In cases of normal calcium concentrations or hypercalcemia, calcium-free compounds such as sevelamer hydrochloride or lanthanum carbonate may be used. In advanced stages of the disease, the calcium balance may become positive, which should be kept in mind and calcium levels and dosage should be regularly monitored. In our study, 62/120 patients (52%) reported taking calcium

supplements. Calcium compounds were taken significantly more often by patients receiving dialyses than by patients managed by conservative treatment (78% vs. 9%; $p < 0.001$). On the one hand, there are no universal recommendations for taking calcium supplements. On the other hand, a daily total dose of 6.0 g of calcium carbonate should not be exceeded. In any case, calcium supplementation should be adjusted to the existing demand since blood calcium concentration is one of the most important parameters to be monitored in the course of CKD.

Vitamin D

Vitamin D deficiency is associated, among other things, with insufficient sunlight necessary for adequate cutaneous synthesis. In patients with CKD, this phenomenon is also reinforced by a reduced synthesis of the active form in the kidneys, as well as difficulties in leaving the house. Reduced vitamin D levels are observed in more than 80% of patients with CKD [9]. Vitamin D intake should be recommended to every CKD patient in order to reduce PTH concentrations and maintain calcium-phosphate metabolism as close to normal as possible [11]. At the early stages, up to an eGFR ≥ 45 ml/min/1.73 m2, the recommended cholecalciferol intake is the same as in the general population, while at the later stages of CKD, active derivatives are used, including: alfacalcidol, calcifediol and calcitriol. However, the dose of the vitamin D supplement should be adjusted according to existing demand, calcium and parathormone concentrations [12, 13]. The results of recent studies suggest a significantly lower risk of developing a severe form and the mortality of COVID19 in patients supplementing with-calcitriol [14].

In the presented study, 16/120 patients (13%) listed vitamin D among the OTC products they were taking. This is probably due to the fact that the respondents are mostly patients with advanced forms of CKD, taking active forms of the vitamin available with a-prescription.

Magnesium

Magnesium is responsible for, among other things, normal bone structure, it regulates the normal function of the nervous and circulatory systems. Magnesium concentrations should be maintained within the normal range or even closer to the higher limit, which, according to some studies, may be beneficial for the prevention of cardiovascular disease and is associated with a lower risk of CKD progression [15-19]. The kidneys play a major role in maintaining appropriate magnesium levels, and consequently, impaired kidney function in patients with chronic kidney disease leads to disorders in this regard. In CKD stages 1–3, an increase in fractional magnesium excretion compensates and maintenance of normal concentrations, whereas in stages 4-5, these compensatory mechanisms become inadequate, leading to an increased risk of hypermagnesemia, which may be further reinforced by the intake of magnesium supplements [20]. On the other hand, dialysis patients face the risk of hypomagnesaemia. It may result from the use of dialysates with low magnesium concentrations. Hypomagnesaemia may also result from the use of such medications, as thiazide diuretics or proton pump inhibitors and from the fact that intestinal absorption of magnesium is significantly reduced in patients with CKD (possibly related to active vitamin D deficiency). Hence, regular measurement of magnesium levels and appropriate dialysate selection to maintain the desired magnesium concentration are recommended in dialysis patients [21]. The data collected during the study show that magnesium is the second most commonly used supplement after calcium, with as many as 21% of the patients surveyed taking oral magnesium supplements, of which 14 (56%) are patients managed by conservative treatment and 11 (44%) are dialysis patients. Similarly, in the Polish general population, magnesium is one of the most common dietary supplements. The popularity of magnesium supplementation is due to the belief that it effectively resolves problems with the muscular system (muscle cramps) and improves the functioning of the nervous system (eliminates fatigue, improves concentration). The widespread intake of magnesium supplements is both due to the numerous advertisements and the fact that magnesium supplements are also sometimes recommended by physicians for the ailments mentioned above. It should be noted, however, that in people with CKD, difficulties in maintaining normal magnesium concentrations combined with uncontrolled magnesium supply may lead to deterioration of renal function. It is therefore worth paying attention to whether there is clinical justification for patient's intake of such supplements.

Analgesics

The prevalence of chronic kidney disease increases with age [22]. A number of comorbidities also increases with age, and patients are often under the care of multiple specialists, as evidenced by the survey data (43% cardiologist, 27% diabetologist, 7% oncologist). In view of the increased number of pain complaints, symptomatic treatment is increasingly used. In the context of CKD, particular attention should be paid to the use of NSAIDs. They are considered to be nephrotoxic medications, causing renal damage via various mechanisms. One of them is reduced prostaglandin production as a result of blocking cyclooxygenase synthesis. Reduction of PGI2 synthesis results in impaired diastole of the afferent glomerular ~~nephron supply~~ arteriole, thereby reducing blood flow to the glomerulus. Weaker renal perfusion may result in hypoxia, damage to the tubular epithelium and further lead to interstitial fibrosis [23]. In addition, PGE2 deficiency increases sodium and water retention, causing increased blood pressure and further glomerular damage [24]. In addition, NSAIDs can induce acute immune mediated interstitial nephropathy. The changes usually regress when the medications are discontinued, but in the case of chronic use, renal papillary necrosis and progressive deterioration of renal function may occur [25].

In the presented analysis, 48% of patients reported taking analgesics. As many as 21% mentioned NSAIDs in the products taken, 37% indicated paracetamol and 9% other drugs. The choice of NSAIDs in patients with CKD is a significant clinical problem. Patients should be informed about the potential effects of taking this type of analgesics and should always try to avoid it. Paracetamol should be

recommended as a first-line medicament for management of pain with an intensity of the first step of the analgesic ladder. For more severe pain, opioids addition would be a good option.

Conclusions

Dietary supplements and OTCs are often used by patients with chronic kidney disease, especially women and dialysis patients, without adequate control, which may exacerbate symptoms and lead to disease progression. This patient population most commonly takes analgesics and calcium and magnesium supplements in an uncontrolled manner. Patients should be widely educated about the possible adverse effects of dietary supplements and OTCs. At the same time, awareness should be raised in the nephrology community about the problem of hidden polypragmasy, which should increase the safety of therapy for patients with chronic kidney disease.

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ECHOCARDIOGRAPHIC ASSESSMENT OF PATIENTS WITH DILATED CARDIOMYOPATHY (DCM) DEPENDING ON THE SYSTOLIC FUNCTION OF THE RIGHT VENTRICLE ASSESSED BY CARDIOVASCULAR MAGNETIC RESONANCE IMAGING (CMR)

Ocena echokardiograficzna chorych z kardiomiopatią rozstrzeniową w zależności od funkcji skurczowej prawej komory serca ocenianej metodą rezonansu magnetycznego

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Abstract:

Introduction and objective

Dilated cardiomyopathy (DCM) is a primary disease of the myocardium, which is one of the three main causes of heart failure and the most common reason for qualifying for transplantation. The criteria for diagnosing left ventricular dysfunction in DCM are quite specific, but there are no clear guidelines regarding right ventricular dysfunction. The objective of the paper was to compare the echocardiographic image of patients with DCM, with special consideration to the function of the right and left ventricles depending on the function of the right ventricle assessed by cardiovascular magnetic resonance imaging (CMR).

The study involved 29 patients with DCM hospitalized at the Department of Cardiology and Internal Medicine of the Military Institute of Medicine in 2018–2021, in whom other causes of heart failure i.e., advanced coronary artery disease, significant heart defects, pulmonary embolism, and lung pathology were excluded. The right ventricular ejection fraction (RVEF) assessed in CMR was used as the indicator of the reference right ventricular function. Echocardiography was used to determine, among others: right ventricular end diastolic diameter (RVEDd), right ventricular global longitudinal strain (RVGLS), right ventricular fractional area change (RVFAC), left ventricular global longitudinal strain (LVGLS), left ventricular ejection fraction (LVEF).

The right ventricular dysfunction defined as RVEF <45% in CMR, was found in over 50% of patients. Statistically significant correlations were observed between reduced RVEF assessed in CMR and echocardiographic measurements of the right and left ventricle RVEDd (p=0.006), RVGLS (p=0.007), RVFAC (p=0.005) and between-group differences by RVEF for LVGLS (p=0.034) and LVEF (p=0.056).

Decreased right ventricular ejection fraction in cardiovascular magnetic resonance imaging revealed correlations with worse right ventricular systolic function and dilatation in echocardiographic evaluation. Right ventricular dysfunction is also associated with impaired left ventricular systolic function expressed as worse longitudinal strain and lower ejection fraction.

Keywords: dilated cardiomyopathy, heart failure, right ventricular dysfunction.

Streszczenie:

Kardiomiopatia rozstrzeniowa (DCM) to pierwotna choroba mięśnia serca będąca jedną z trzech głównych przyczyn niewydolności serca. Jest również najczęstszą przyczyną kwalifikacji do transplantacji. Kryteria rozpoznania dysfunkcji lewej komory w DCM są dość ściśle określone, ale brakuje jednoznacznych wytycznych dotyczących dysfunkcji prawej komory serca. Celem pracy było porównanie obrazu echokardiograficznego chorych z DCM, ze szczególnym

uwzględnieniem funkcji prawej i lewej komory serca, w zależności od funkcji prawej komory ocenionej metodą rezonansu magnetycznego (CMR).

Do badania włączono 29 pacjentów z DCM hospitalizowanych w Klinice Kardiologii i Chorób Wewnętrznych WIM w latach 2018-2021, u których wykluczono inne przyczyny niewydolności serca, tj: zaawansowana choroba wieńcowa, istotne wady serca, zatorowość płucna, istotna patologia płuc. Jako wskaźnik referencyjny funkcji prawej komory przyjęto frakcję wyrzutową prawej komory (RVEF) ocenianą w CMR. Za pomocą echokardiografii określono między innymi: wymiar końcowo-rozkurczowy prawej komory (RVEDd), globalne odkształcenie podłużne prawej komory (RVGLS), zmianę pola powierzchni prawej komory (RVFAC), globalne odkształcenie podłużne lewej komory (LVGLS) oraz frakcję wyrzutową lewej komory (LVEF).

Dysfunkcję prawej komory określoną jako RVEF < 45% w CMR stwierdzono u ponad 50% badanych. Wykazano istotne statystycznie korelacje miedzy obniżoną RVEF ocenioną w CMR a RVEDd (p=0,006), RVGLS (p=0,007), RVFAC (p=0,005) oraz różnice międzygrupowe w zależności od RVEF w zakresie LVGLS (p=0,034) i LVEF (p=0,056). Obniżona frakcja wyrzutowa prawej komory w ocenie rezonansu magnetycznego wykazuje związek z gorszą funkcją skurczową prawej komory i jej rozstrzenią w ocenie echokardiograficznej. Dysfunkcja prawej komory wiąże się również z upośledzoną funkcją skurczową lewej komory wyrażoną jako gorsze odkształcenie podłużne i niższa frakcja wyrzutowa.

Słowa kluczowe: kardiomiopatia rozstrzeniowa, niewydolność serca, dysfunkcja prawej komory serca.

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Introduction

Heart failure (HF) occurs in 1–2% of adults, and the prevalence increases significantly with age – to over 10% in the population over the seventh decade of age [1, 2]. The incidence of HF in Europe is 3/1000 person/year in all age groups and 5/1000 person/year in adults. Despite recent advances in the diagnosis and treatment of HF, mortality in this patient population is still high, reaching almost 70% within 5 years of diagnosis.

Dilated cardiomyopathy (DCM) is a primary myocardial disease in which the left heart ventricle or both ventricles are enlarged, and its/their systolic function is impairment without concomitant coronary artery disease, hypertension, congenital or acquired valvular abnormality in such an extensive stage that they cause significant myocardial damage [3, 4]. It is one of the three main causes of HF and the most common reason for qualifying patients for transplantation. The etiopathogenesis of DCM is very complex, involving genetic disorders as well as inflammatory, autoimmune, metabolic, and toxic causes [5, 6].

While the diagnostic criteria for left ventricular dysfunction are currently quite well defined [1, 2], in the case of the right ventricle they are not so clear. Right ventricular dysfunction assessed by MRI can be defined as a reduction in right ventricular ejection fraction (RVEF) ≤ 45%, e.g., based on the result published by Gulati et al., who found it in 34% of 250 DCM patients involved in the study [7].

The right ventricle has a complex anatomic structure formed in a D shape. It consists of an inflow portion (from the tricuspid valve annulus to the distal attachment of the valve to the papillary muscles), the main cavity (known as the beaded part) and the outflow part [8]. Detailed echocardiographic evaluation is quite difficult, and a patient often requires MRI, which is still of limited availability. This is one of the reasons why reports on the association between right ventricular function and left ventricular dysfunction are still scarce in patients with DCM.

Aim of the study

The study aims at comparing echocardiographic images of patients with dilated cardiomyopathy, with special consideration to the right and left ventricles depending on their function in relation to right ventricle function assessed by cardiovascular magnetic resonance imaging.

MATERIAL AND METHODS

Study group

The study involved 29 patients of both sexes admitted to the Department of Cardiology and Internal Medicine of the Military Institute of Medicine between 2018 and 2021 meeting the following inclusion criteria: age > 18 years of age, diagnosis of HF based on an interview and physical examination, diagnosis of dilated cardiomyopathy based on the following echocardiography criteria: LVEF (left ventricular ejection fraction) < 45% and/or LVEDd (left ventricular end diastolic diameter) > 58 mm for men and > 52 mm for women or LVEDV (left ventricular end diastolic volume) / BSA (body surface area) > 74 ml/m2 for men and > 61 ml/m2 for women. Exclusion criteria included: advanced coronary artery disease (defined as > 50%

coronary artery narrowing in coronary angiography or CT angiography), cardiac defects not resulting from cardiomyopathy (i.e. moderate or severe aortic stenosis or regurgitation, moderate or severe mitral stenosis or regurgitation, severe tricuspid regurgitation), cardiac shunt defects, pulmonary embolism, pulmonary arterial hypertension, interstitial lung diseases with DLCO (*diffusing capacity for carbon monoxide)* below 60% of the reference value, obstructive lung diseases with FEV1 *[forced expiratory volume in one second)* below 60% of the reference value, advanced liver disease, uncompensated endocrine disorders.

The study protocol was approved by the Bioethics Committee of the Military Institute of Medicine (approval no. 59/WIM/2017). All patients involved in the study expressed their written informed consent for participation.

Clinical evaluation

Recruited patients underwent an interview and physical examination for the purpose of obtaining information on the circumstances and timing of the heart failure diagnosis, the occurrence of infection preceding the onset of heart failure symptoms and the severity of heart failure symptoms. It was followed by a physical examination including assessment of the following: presence of pulmonary circulation stasis, arrhythmia and murmurs over the heart, hepatomegaly, jugular vein distention, peripheral oedema, and measurement of blood pressure and pulse.

Echocardiography

Echocardiography was performed, using the Vivid E95 device (General Electric, United States), then analyzed off-line on the Echo PAC workstation (General Electric, United States). All measurements were taken in accordance with the current standards of the European Association of Echocardiography (EAE), currently EACVI (European Association of Cardiovascular Imaging). During the examination, an electrocardiogram from the limb leads was recorded simultaneously [9]. At the beginning of the examination, the size of the cardiac cavities was measured in the parasternal long axis (LAX) view. To assess the left ventricle, left ventricular end-systolic diameter (LVESd) and left ventricular end-diastolic diameter (LVEDd) were measured in one-dimensional view (M-mode) and two-dimensional (2D) view, including the parasternal short axis (SAX) view. Left ventricular ejection fraction (LVEF) was calculated based on the apical four-chamber and two-chamber views with a modified Simpson's rule algorithm. Segmental left ventricular wall motion abnormalities were assessed visually using 17-segment division. Cardiac defects were assessed using Doppler techniques (continuous wave Doppler, pulsed wave Doppler and color Doppler). The left atrium size was assessed by measuring the left atrial area (LAa) and the left atrial volume index (LAVI), and the size of the right atrium by measuring its right atrial area (RAa). To assess left ventricular diastolic function, we used the measurement of the E/E' ratio (the ratio of the mitral early-diastolic inflow peak velocity to the early diastolic mitral annular velocity), as one of the recognized determinants of high left ventricular filling pressure.

Right ventricular morphology was assessed in the parasternal long-axis view and the apical four-chamber view, in which RVEDd was measured in the basal segment area, i.e., at the level of the closed tricuspid valve leaflets. Right ventricular systolic function was estimated by measuring in the apical four-chamber view: percentage right ventricular fractional area change (RV FAC), measurement of tricuspid annular systolic velocity (S') using tissue Doppler and measurement of tricuspid annular plane systolic excursion (TAPSE) in M-mode. The right ventricular systolic pressure (RVSP) was calculated according to the formula: RVSP = TRPG + RAP, in which the tricuspid regurgitation gadobutrol peak gradient (TRPG) was assessed using continuous wave Doppler, and right atrial pressure (RAP) was assessed based on the size and respiratory collapse of the vena cava inferior (VCI) assessed based on the substernal planes.

Left ventricular myocardial global longitudinal strain (LV GLS) was assessed using speckle tracking echocardiography (STE) in the apical 2- and 4-chamber planes. Right ventricular global longitudinal myocardial strain (RV GLS) was assessed using STE in the four-chamber plane targeting the right ventricle. According to the EACVI guidelines, the RV GLS value is the obtained right ventricular free wall longitudinal strain (RV FWLS) [9, 10]. Longitudinal strain values for both ventricles were given as absolute numbers (without negative sign).

Cardiac magnetic resonance examination

Cardiac magnetic resonance (CMR) was performed with GE Discovery MR 750 in 3.0T (General Electric, United States) using the paramagnetic contrast agent, gadobutrol (Gadovist from Bayer AG) administered at a dose of 0.1 ml/kg body weight, after the patients had completed a questionnaire excluding any contraindications to electromagnetic field and/or contrast agent administration.

During imaging, simultaneous electrocardiography recording was performed, allowing prospective gating using R wave detection during image acquisition performed in diastole. Therefore, a prerequisite for the study was the presence of sinus rhythm, while arrhythmia (e.g., extrasystoles) made image acquisition difficult or impossible (e.g., atrial fibrillation). Just like echocardiography, MRI was also performed in the 2-chamber plane (so-called long vertical axis), 4-chamber plane (so-called long horizontal axis), 3-chamber plane, short-axis sections and myocardium division into 17 segments.

The first part of the examination involved the assessment of cardiac and large vessel morphology using spin echo (SE) sequences (so-called black blood), which allowed for the assessment of T1-weighed images used to plan subsequent sequences. The second part of the examination concerned

a functional (cine) CMR, allowing for imaging of the heart in motion, with particular emphasis on a sequence called steady-state free precision (SSFP) with the assessment of: end-systolic volume (ESV), end-diastolic volume (EDV), septal and ventricular wall thickness, stroke volume (SV) and ejection fraction (EF) of both ventricles [11, 12]. The measurements were made using the following formulas according to Simpson's rule algorithm:

SV (ml) = EDV – ESV EF (%) = (SV/ EDV) x 100%.

Laboratory tests

In accordance with the ESC (European Society of Cardiology) recommendations regarding the diagnosis of heart failure [2], laboratory tests were performed in the study group, including peripheral blood count, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and renal function parameters (creatinine, urea), and estimated glomerular filtration rate (eGFR) was calculated using the Cockroft-Gault formula.

Statistical analysis

Statistical analysis was performed using Statistica 12.0 software (StatSoft Inc., Tulsa, OK, USA). The distribution and normality of the data were assessed visually and using the Kolmogorov-Smirnov test. Continuous variables were presented as mean and standard deviation (SD) and median with interquartile range (between the 25th and 75th percentile), while nominal variables as counts and percentages. Analysis of differences for continuous variables was performed using the t-test with a normal distribution and the Mann-Whiney U test with a non-normal distribution. Relationships between data were assessed using the Spearman correlation test. A p-value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

29 patients were included in the study, including 4 women and 25 men. The mean age of the patients was 44.2 ± 10.6 years. The etiology of dilated cardiomyopathy was mostly unknown, although 4 (14%) patients (men only) reported alcohol abuse, and in 12 patients (41%) the first symptoms of heart failure were preceded by an infection (predominantly of the respiratory tract). The time from first diagnosis of HF to inclusion in the study ranged from 2 weeks to 96 months.

The majority of patients presented with NYHA class II symptoms (55%), there were no patients in class IV. Patients received pharmacotherapy in accordance with current ESC guidelines [2]. Among them, 25 (86%) received angiotensin-converting enzyme inhibitor (ACE-I), one patient (3%) had angiotensin- receptor blocker), two patients (7%) had ARB and an angiotensin receptor – neprilysin inhibitor (ARNI), 27 patients (93%) a mineralocorticoid receptor antagonist (MRA), 26 patients (90%) a loop diuretic, 1 patient (3%) a thiazide diuretic, 28 patients (97%) a β-blocker. Almost all study subjects gave a history of comorbidities, including: 35% hypertension, and 14% chronic kidney disease grade ≥ 3 according to the KDIGO classification [13]. The mean eGFR value was 77.1 ± 16.9 ml/min/1.73m2 and the mean hemoglobin concentration was 14.8 ± 1.4 g/dl. The NT-proBNP value of 2527 ± 2956 pg/ml was significantly high. Detailed data are shown in Table 1.

Table 1. Baseline characteristics of the study group.

Parameter/clinical data	Whole group mean (SD); median (IQR) or n (%)
Age in years	44.2 (10.6); 42 (35-51)
BMI in kg/m2	27.5 (4.2); 27.6 (24.1–30.8)
Sex (male)	25 (86.2%)
NYHA	2.2 (0.7); 2 (2-3)
NYHA class I	4 (13.8%)
NYHA class II	16 (55.2%)
NYHA class III	9 (31.0%)
PHARMACOTHERAPY	
Loop diuretic	26 (89.7)
Thiazide diuretic	1 (3.4%)
MRA	27 (93.1%)
Beta-blocker	28 (96.6%)
ACEI	25 (86.2%)
ARB	1 (3.4%)
ARNI	2 (6.9%)
Ca-blocker	0 (0%)
Ivabradine	7 (24.1%)
Digoxin	1 (3.4%)
Amiodarone	2 (6.9%)
COMORBIDITIES	
Paroxysmal AF	5 (17.2%)
Persistent AF	0 (0%)
Long-term AF	0 (0%)
CKD ≥ 3 according to KDIGO	4 (13.8%)
COPD	0 (0%)
Diabetes	1 (3.4%)
Arterial hypertension	10 (34.5%)
Nicotinism	1 (37.9%)
Stroke CNS/TIA	1 (3.4%)
LABORATORY TESTS	
HGB (g/dl)	14.8 (1.4); 14.9 (13.9–15.9)
NT-proBNP (pg/ml)	25274 (2956.1); 1422.5 (809.4–2943)
CREATININE (mg/dl)	1.0 (0.2); 1.1 (0.9–1.1)
eGFR (ml/min/1,73m2)	77.1 (16.9); 74.5 (70.3–81.9)

Abbreviations:
BMI – body mass index, NYHA – New York Heart Association, MRA – mineralocorticoid receptor antagonist, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin-receptor blocker, ARNI – angiotensin receptor-neprilysin inhibitor, Ca-blocker – calcium blocker, AF – atrial fibrillation, CKD - chronic kidney disease, KDIGO – Kidney Disease: Improving Global Outcomes, COPD – chronic obstructive pulmonary disease, CNS – central nervous system, TIA – transient ischemic attack, HGB – hemoglobin, NT-proBNP – N-terminal fragment of natriuretic peptide, eGFR – estimated glomerular filtration rate

The majority of subjects presented with NYHA class II symptoms (55%); there were no patients in class IV. Patients received pharmacotherapy treatment according to current ESC guidelines [2], of which 25 (86%) took an angiotensin-converting enzyme inhibitor (ACE-I), 1 patient (3%) an angiotensin-receptor blocker (ARB), 2 patients (7%) an angiotensin receptor-neprilysin inhibitor (ARNI), 27

Table 2. Echocardiographic and magnetic resonance imaging assessment of the study group.

Parameter	Whole group mean (SD); median (IQR) or n (%)
ECHOCARDIOGRAPHY	
RVEDd (mm)	34.1 (4.3); 34 (32-35)
LVEDd (mm)	67.1 (6.5); 68 (61-71)
LA (mm)	46.7 (5); 48 (42-50)
LVEF (%)	27.2 (8.8); 26 (21-34)
LVEF < 40%	26 (89.7%)
LV GLS (%)	7.9 (3); 7.3 (6.2-9.7)
E/A	1.6 (1); 1.33 (0.83-2.14)
E' m (cm/s	4.9 (1.6); 5 (4-6)
E' l (cm/s)	5.3 (2.4); 5 (3-7)
E/E'	15.3 (7.7); 12 (9-20.5)
LAa (cm2)	29 (6.3); 29.3 (23.5-32.6)
LAVI (ml/m2)	52.8 (17.4); 50.8 (38.44-64.9)
RV GLS (%)	14.8 (5.5); 15 (10.1-17.3)
RV FAC (%)	37.2 (11.1); 36.05 (28.05-46.15)
S' RV (cm/s)	10.1 (2.2); 10 (9-11)
TAPSE (mm)	19.2 (4.1); 20 (16-22)
RAa (cm2)	20 (5); 19.4 (16.7-22.4)
TRPG (mmHg)	30.3 (7.4); 30 (26-32)
RVSP (mmHg)	36.7 (10.5); 34 (31-40)
MAGNETIC RESONANCE	
LVEF (%)	28.4 (10.5); 29.5 (18.5-36)
RVEF (%)	42.5 (13.8); 43.5 (34.5-53)
RVEF < 45%	13 (54.2%)
LVEDV/BSA (ml/m2)	148.4 (40.3); 142 (124.5-171.5)
RVEDV/BSA (ml/m2)	86.9 (25.7); 81.5 (71-100)

Abbreviations:
RVEDd – right ventricular end diastolic diameter, LVEDd – left ventricular end diastolic diameter, LA – left atrium, LVEF – left ventricular ejection fraction, LV GLS – left ventricular global longitudinal strain, E/A – ratio of mitral peak flow velocity of early filling (E) to peak flow velocity caused by atrial contraction (A), E'm – early diastolic mitral annular velocity (e'), E'l – early diastolic velocity of lateral wall velocity, LAa – left atrial area, LAVI – left atrial volume index, RV GLS – right ventricular global longitudinal strain, RV FAC – right ventricular area change, S' RV – S'-tissue Doppler imaging-derived tricuspid lateral annular systolic velocity, TAPSE – tricuspid annulus plane systolic excursion, RAa – right atrial area, TRPG – tricuspid regurgitation peak gradient, RVSP – right ventricular systolic pressure, LVEF – left ventricular ejection fraction, RVEF – right ventricular ejection fraction, LVEDV/BSA – left ventricular end diastolic volume/body surface area, RVEDV/ BSA – right ventricular end diastolic volume/body surface area

Echocardiography showed significant left ventricular dysfunction (LVEF 27.2 ± 8.8%) and significantly enlarged left ventricular dimension (LVEDd 67.1 ± 6.5 mm) in all study subjects. LV GLS was also significantly reduced (7.9 ± 2.9%). In the assessment of left ventricular diastolic function, the mean E/E' value was 15.3 ± 7.7. Right ventricular systolic dysfunction assessed using longitudinal strain measurement was significantly reduced, with a mean RV GLS value of 14.8 ± 5.5% in the entire study group. Detailed data are shown in Table 2.

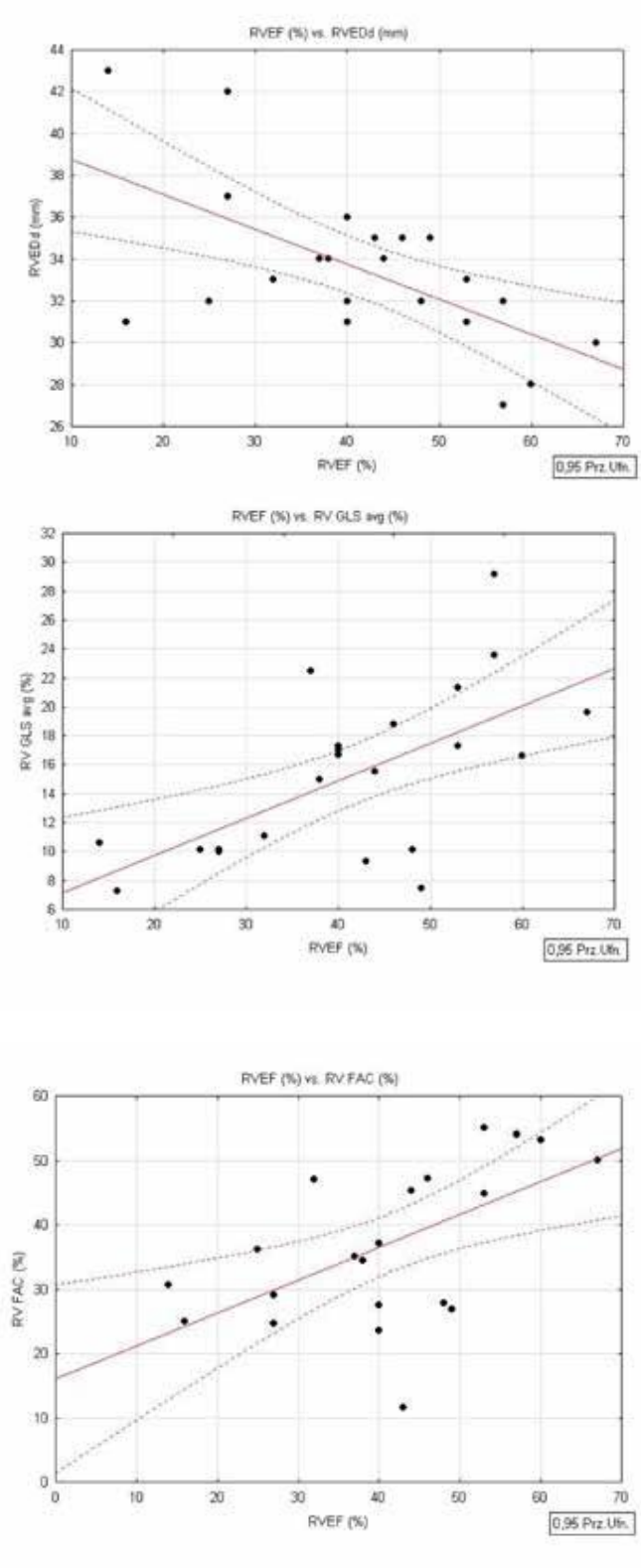
MRI was performed in 24 patients. In one patient, the examination was performed but all measurements could not be taken due to cardiac arrhythmias and artefacts, in 4 patients the examination was not performed due to arrhythmias potentially preventing measurements, and one patient did not consent to the examination due to back pain. The study group was characterized by significant left ventricular dysfunction expressed as LVEF 28.4 ± 10.5% and its significant LVEDV/BSA 148.4 ± 40.3 ml/m2. The analogous parameters for the right ventricle were respectively: RVEF 42.5 ± 13.8% and RVEDV/BSA 86.9 ± 25.7ml/m2. RVEF was reduced in 54% of the study subjects (Table 2).

Correlation of selected echocardiography parameters with reduced right ventricular systolic function as assessed by magnetic resonance imaging.

In the correlative assessment of the selected echocardiography parameters of right ventricular morphology and function with RVEF, as assessed by magnetic resonance imaging, statistically significant correlations were found with RVEDd (R = 0.54; p = 0.006), RV GLS (R = 0.56; p = 0.007) and

RV FAC (R = 0.57; p = 0.005). The correlations are illustrated in Figure 1.

Figure 1. Correlation plots of RVEF with RVEDd (top graph), RV GLS (middle graph), RV FAC (bottom graph) – assessed by MRI.



We also assessed the discriminative role of RVEF by magnetic resonance imaging in terms of echocardiography parameters of the left ventricle: LVEF, LV GLS, LAVI and E/E' (Figures 2 and 3), as well as the NT-proBNP (Figure 4), finding statistically significant differences for measures of

its systolic function: LVEF (borderline p = 0.056) and LV GLS (p = 0.034) (Figures 2 and 3). The difference in NT-proBNP levels was also clear, although not statistically significant in the study group: 2174 pg/ml in patients with normal RVEF vs. 2572 pg/ml in patients with impaired RVEF.

Figure 2. Comparison of differences between groups with abnormal (< 45%) and normal (≥ 45%) RVEF as assessed by magnetic resonance imaging of LVEF (top graph), LV GLS (middle graph) and LAVI (bottom graph).

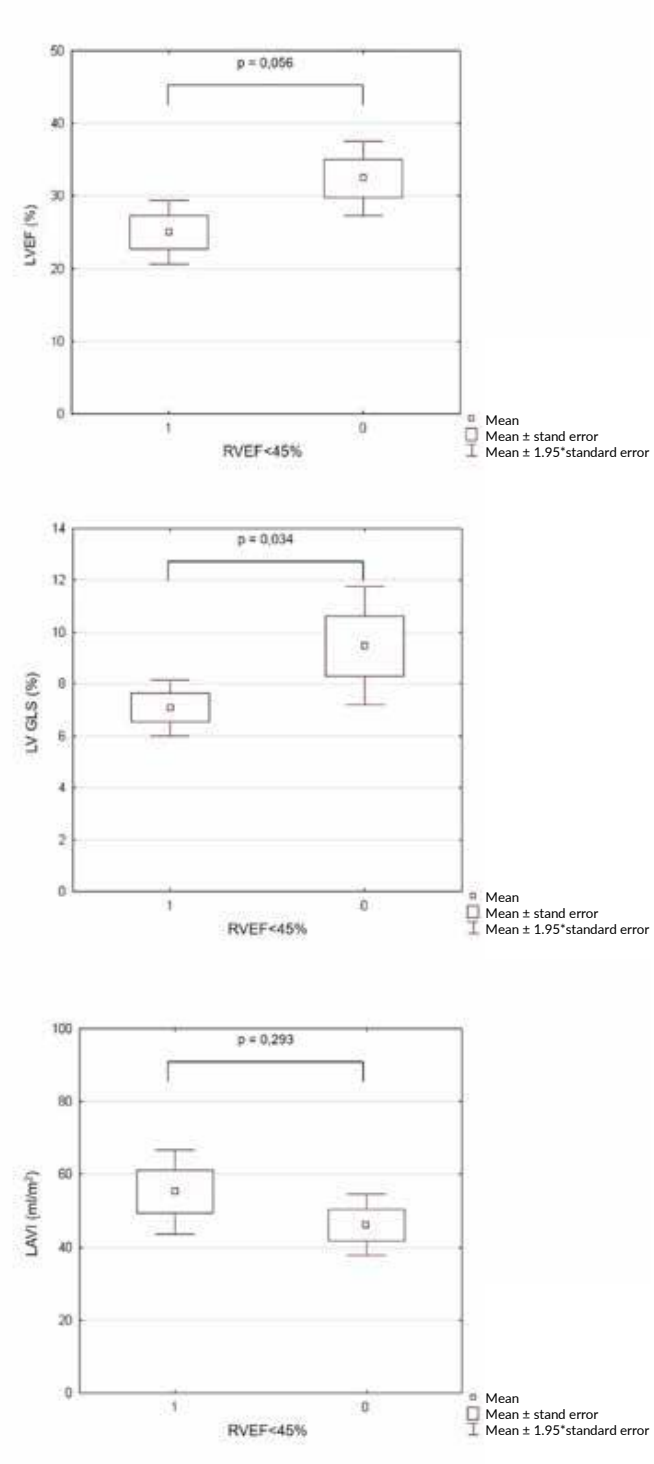
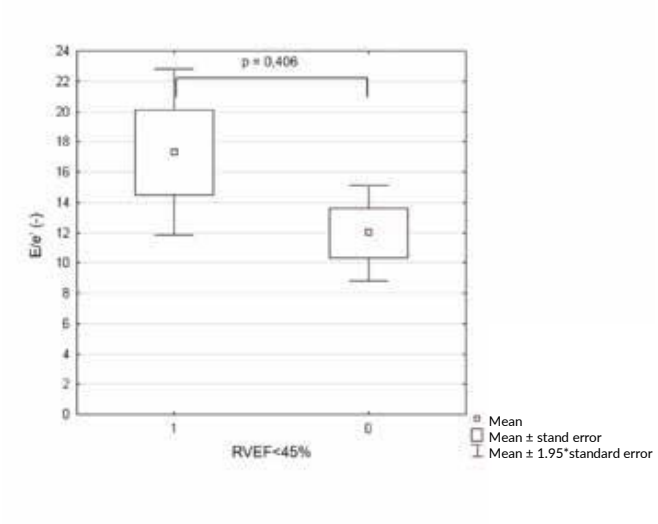
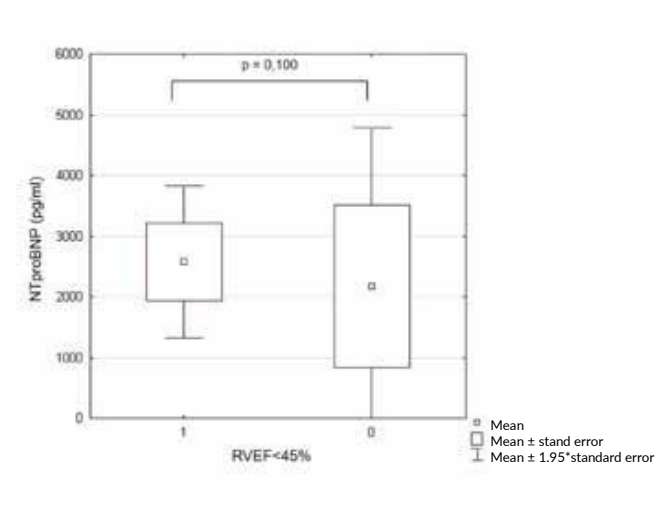


Figure 3. Comparison of differences between groups with abnormal (< 45%) and normal (≥ 45%) RVEF as assessed by magnetic resonance imaging of LVEF (upper left graph),



LV GLS (upper right graph), LAVI (lower left graph) and E/e' (lower right graph).

Figure 4. Comparison of differences between groups with abnormal (< 45%) and normal (≥ 45%) RVEF as assessed by magnetic resonance imaging for NT-proBNP.



Discussion

The results obtained confirmed the usefulness and complementarity of echocardiography and MRI in the assessment of patients with DCM. Reduced RVEF was also shown to be associated with impaired left ventricular systolic function.

According to current knowledge of HF pathophysiology, deterioration of right ventricular function may occur secondary to left ventricular dysfunction as a consequence of increased afterload in the pulmonary circulation or left ventricular dilatation and dyssynchronous septal motion impeding right ventricular diastole [14]. On the other hand,

right ventricular failure leads to a reduction in left ventricular preload, which, with reduced LVEF, results in a further decrease in cardiac ejection capacity. Additionally, poorer right ventricular systolic function results in reduced pulmonary perfusion, causing poorer oxygenation of circulating blood and secondarily tissue hypoxia [14]. The ESC guidelines for HF, as well as numerous publications mention right ventricular dysfunction as an unfavorable prognostic factor [1, 15, 16, 17].

The majority of the subjects in the study group presented with NYHA class II symptoms (55%). It was, therefore, a clinically stable group. In other populations comprising patients with HF, the functional status of recruited patients was similar, e.g., in the AMULET study, conducted at our center, 65%, and in the PARADIGM-HF study, 69.3% of subjects presented symptoms in NYHA class II [18, 19]. Mean LVEF was 27.2 ± 8.8%, comparable to that found in other studies of patients with DCM: Julliere et al. (30 ± 10%), La Vecchia et al. (28.8 ± 9.1%), Venner et al. (27.5 ± 8.71%) [20, 21, 22], but higher than the study by Kawata et al. (17.9 ± 5.5%) [23] and Ishiwata et al. (18.9 ± 7.5%) [24]. The patients generally received pharmacotherapy according to the current heart failure treatment guidelines at the time of the study: 90% took an ACE-I or ARB, 93% an MRA, 97% a β-blocker and 90% a loop diuretic. Only 2 patients (7%) took the currently recommended sacubitril/valsartan, and none took the newest group of drugs, sodium-glucose co-transporter-2 (SGLT2) inhibitors.

The prevalence of right ventricular dysfunction in dilated cardiomyopathy presented in the world literature varies widely, ranging from 34 to 65% [7, 21, 25, 26]. Using angiographic methods to measure RVEF, La Vecchia et al. showed in a group of 92 patients with idiopathic DCM that up to 65% had right ventricular dysfunction defined as RVEF < 35% [21]. In our study, RVEF < 45% assessed by magnetic resonance imaging was found in more than 50% of the subjects.

In the study group, RVEF assessed by CMR correlated significantly with echocardiography parameters of morphology (RVEDd) and right ventricular systolic function (RV GLS, RV FAC). In particular, the latter two parameters are less well known but have a significant clinical value. In the study involving 40 patients with DCM, Zairi I et al. showed that impaired right ventricular longitudinal strain (absolute value less than 12%) is, like TAPSE, less than 12.5 mm and S' less than 8.5 cm/s, an independent factor for cardiac events [27]. In the work of Seo J et al., this rate was independently associated with a higher risk of adverse events, such as death, hospitalization, sudden cardiac arrest, or malignant ventricular arrhythmia, with a cut-off point of 16.5% [28]. It should be noted that in their study, neither TAPSE nor S' were statistically significant factors in detecting the occurrence of cardiovascular events [27]. Ishiwata et al. analyzed the clinical course of 109 patients with DCM and LVEF < 40%, considering *right ventricular longitudinal strain* (RV LS) worse than 17.8% as right ventricular dysfunction. They showed that patients with a concomitant reduced RV FAC of less than 27% and RV LS of less than 8.6% had the highest risk of death or need for LVAD (left ventricular assist device) implantation during the first year of follow-up [24].

Based on an evaluation of 68 DCM patients eligible for heart transplantation, Kawata et al. found RV FAC to be a better prognostic factor than TAPSE and S', and considered the RV FAC value < 26.7% to be the best cut-off point for identifying patients at high risk of cardiac events (defined in the study as cardiac death or the need for left ventricular assist device (LVAD) implantation within the first year of follow-up) [23]. In a 6-year follow-up of 512 patients with DCM, Merlo et al. showed that successful treatment and improvement in left ventricular function can be associated with RV FAC normalization (this phenomenon was observed in 86% of patients with reduced baseline value of that indicator). On this basis, the authors conclude that the originally diagnosed right ventricular dysfunction was most likely due to its 'hemodynamic collapse' due to a dysfunctional left ventricle, rather than structural damage [29].

The close relationship between the function of both ventricles is confirmed by our observations of lower LVEF and LV GLS values in patients with RVEF < 45% at CMR. Given the strong prognostic value of these parameters of left ventricular systolic function [2], it should be presumed that patients with biventricular dysfunction face a particularly high risk. Although in terms of the NT-proBNP concentration in our study, a difference between groups did not show the assumed statistical significance, 20% higher value in the group with reduced RVEF is consistent with the above argument. Particularly in the context of the prognostic value of this indicator [1, 30] or the work of Li et al. who, in their study involving 622 DCM patients hospitalized for HF, showed an almost threefold higher mortality rate in the group of patients with NT-proBNP > 2247 pmol/l [31].

A limitation of the presented study is undoubtedly a small size of the study group, especially low representation of women in the study group, who accounted for only 13.8% of the study population. The analyses also did not cover any history of COVID-19 (the study was partly conducted during the pandemic period), a disease that could potentially affect right ventricular performance. The unavoidable time lag between clinical assessment, echocardiography, and laboratory tests and CMR examination (median 14 days), due to organizational reasons, should also be taken into account. It may have affected the results of the analyses confronting two methods with each other and with other assessed variables.

Conclusions

Decreased right ventricular ejection fraction in cardiovascular magnetic resonance imaging revealed correlations with worse right ventricular systolic function and dilatation in echocardiographic evaluation. Right ventricular dysfunction is also associated with impaired left

ventricular systolic function, expressed as its worse longitudinal strain and lower ejection fraction.

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CHALLENGES AND THREATS FOR WHO AS THE GUARDIAN OF HEALTH SECURITY OF THE INTERNATIONAL COMMUNITY

Wyzwania i zagrożenia dla WHO jako piastuna bezpieczeństwa zdrowotnego wspólnoty międzynarodowej

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Abstract:

The aim of the work is to answer the question whether in the current legal order and in the current international conditions it is possible to make the World Health Organization more effective in the sphere of combating global threats? Criticism of this organization, present in the doctrine, speaks in favor of such a definition of the research problem. Understanding these criticisms, as well as the legal basis, will help to define the factors that undermine the effectiveness of health security management at the supranational level, as well as inform about possible solutions. The author focuses on the analysis of the position of representatives of the doctrine – especially in the field of international law and security sciences. In addition, an exegesis of normative acts is carried out, in particular Constitution of the World Health Organization, and a critical analysis of previous publications on the subject.

Conclusions

It has been shown that the center of gravity of the WHO effectiveness during the COVID-19 pandemic shifts from medical challenges to legal challenges and political issues. It was pointed out that the effectiveness of international security regulations and procedures, including health security, resulting from the adopted international conventions, is a direct consequence of the extent to which the authorities of the United Nations Member States are willing to transfer the competences to act both to the UN itself and its specialized organizations. In selected cases, particular interests and an etatist approach to security prevailed over the responsibility for health security in the global dimension.

Keywords: WHO, health security, UN, COVID-19, pandemic.

Streszczenie:

Celem pracy jest udzielenie odpowiedzi na pytanie, czy w obecnym porządku prawnym i w obecnych uwarunkowaniach międzynarodowych możliwe jest uczynienie Światowej Organizacji Zdrowia (WHO) bardziej efektywną w sferze zwalczania globalnych zagrożeń? Za takim określeniem problemu badawczego przemawia wielokrotnie obecna w doktrynie krytyka tej organizacji. Zrozumienie owej krytyki i podstaw prawnych pomoże zdefiniować czynniki osłabiające skuteczność zarządzania bezpieczeństwem zdrowotnym na szczeblu ponadnarodowym oraz dostarczy informacji o możliwych rozwiązaniach.

Autor koncentruje się na analizie stanowiska przedstawicieli doktryny, zwłaszcza w zakresie prawa międzynarodowego oraz nauk o bezpieczeństwie. Nie bez znaczenia będzie również egzegeza aktów normatywnych, w szczególności Konstytucji Światowej Organizacji Zdrowia oraz krytyczna analiza dotychczasowych publikacji przedmiotowych. Wykazano, że środek ciężkości problemu efektywności działań WHO w okresie pandemii COVID-19 przesuwa się od wyzwań medycznych do wyzwań prawnych i kwestii politycznych. Wskazano, że skuteczność międzynarodowych regulacji i procedur bezpieczeństwa, w tym zdrowotnego, wynikająca z przyjętych konwencji międzynarodowych stanowi wprost pochodną stopnia, w jakim władze państw członkowskich Organizacji Narodów Zjednoczonych skłonne są przekazać zarówno samej ONZ, jak i jej wyspecjalizowanym organizacjom kompetencje do działania. W wybranych przypadkach partykularne interesy i etatystyczne ujmowanie bezpieczeństwa przeważyły nad odpowiedzialnością za bezpieczeństwo zdrowotne w wymiarze globalnym.

Słowa kluczowe: WHO, bezpieczeństwo zdrowotne, ONZ, COVID-19, pandemia.

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Introduction

March 2023 will mark three years since the outbreak of the SARS-CoV-2 pandemic. According to the official data released by the World Health Organisation (WHO), it claimed lives of 6,850,594 people (as of 2022-02-21), while a total of 757,264,511 individuals became ill [1]. The pandemic became a kind of caesura, separating the time and events "before" and "after" its outbreak. An impressive number of scientific papers have been devoted to the issue of COVID-19's impact on almost all spheres of our lives, analyzing its effects on all areas of both collective and individual security. Researchers refer to its implications, among other things, on a sociological, economic, legal, or psychological level. David W. Steward emphasizes that "the COVID-19 pandemic is a generational phenomenon" [2]. While Lauren J. Beesley and other authors point out that "The ongoing novel coronavirus pandemic [...] and associated economic crisis have impacted every corner of the earth, pushing millions of people into poverty, disrupting governments, and leading to socioeconomic instability around the globe" [3]. Finally, the SARS-CoV-2 pandemic has also become a kind of probe to assess both the effectiveness of health security management and the efficiency of the World Health Organization in its efforts.
Another caesura that impacted the effectiveness of the tasks performed by the World Health Organization and permanently remodeled the hitherto existing reality of international security is the date of 24 February 2022, the day of Russian invasion on Ukraine. The unlawful and unjustified aggression against Ukraine highlighted the inadequacies of the United Nations, the world's most important collective security organization. With regard to the aforementioned perception of the United Nations as a collective security system, we need to note that doctrinal definition of collective security usually includes "a situation based on the idea that the members of a given security system – be it a united nation or a regional group – renounce the use of force against each other and commit themselves to coming to the aid of any member attacked by an aggressor who has violated that system" [4]. In contrast, as Boubacar Sidi Diallo emphasizes, collective security "[...] refers to the collective actions taken by states in time of peace in order to maintain lasting peace and ensure mutual defense" [5].

An inglorious symbol of the above-mentioned shortcomings of the UN is, among other things, the outcome of the 30 October 2022 Security Council vote on a draft resolution condemning Russian Federation's attempted annexation of four Ukrainian regions on the basis of illegal referenda. At the time, Russia, as a permanent member of the Council, vetoed the draft, while four members of this main body, namely China, India, Brazil and Gabon, abstained (sic!) [6]. On the other hand, the United Nations security system has not undergone complete atrophy after all, as evidenced by the results of the 13 October 2022 vote in the UN General Assembly to adopt a resolution condemning Russia's attempted annexation of part of Ukraine's territory – as many as 143 states condemned Russian operations. Although the General Assembly resolutions, unlike the ones of the Security Council, have no binding force, they demonstrate a noticeable trend indicating that the majority of the international community does not accept the behavior of a specific axis of illiberal states centered around Russia in the United Nations. These events are only seemingly unrelated to health security, since the effectiveness of WHO partly derives from a degree of cooperation of the states within the United Nations, and WHO itself is a UN specialized organization.

This paper aims at answering the question of whether it is possible, in the current legal order and international context, to make the World Health Organization more effective in the area of combating global threats. Criticism of this organization, present in the doctrine, speaks in favor of such a definition of the research problem. Having understood these criticisms and the legal basis, we will be able to define the factors undermining the effectiveness of health security management at supranational level and to work out possible solutions. Due to the format of the article, the author will focus on analyzing the position of representatives of the doctrine, especially in the field of international law and security sciences. In addition, an exegesis of normative acts is carried out, in particular Constitution of the World Health Organization, and a critical analysis of previous publications on the subject.

The special role of WHO in the United Nations system

In the collective security system of the United Nations an important role is played by the specialized organization - World Health Organization, which has functioned since 1948. The Constitution of the World Health Organization, opened for signature in 1946, defined 22 functions of the organization, of which the first was to act "[...] as the directing and coordinating authority on international health work" [7]. Researchers have distinguished different periods of reform, during which the organization sought to adapt to the present-day challenges. For example, according to Charles Clift, there has been a clear process of "fragmentation" of the health security arena in recent years due to the engagement of other structures also dealing with this area of security, such as UNAIDS or Unitaid. We need to note that, according to this researcher, it was already

apparent in 2013 that the current reform process "does not ask fundamental questions about WHO's place in the international system" [8]. The organization itself is, according to Article 3 of its Constitution, "open to all States". Particular importance of WHO and, indirectly, the relevance of health security issues for the states, is evidenced by the fact that it currently consists of as many as 194 countries (sic!) [9].

The WHO operates on the basis of the 1948 Constitution of the World Health Organization. However, we cannot ignore the important role of other normative acts crucial in pandemic prevention, preparedness, and response, in particular the International Health Regulations, first published in 1971 and then periodically revised. On their basis "Public Health Emergency of International Concern" was identified, which, according to the International Health Regulations, requires a coordinated international response and poses a threat to public health in other countries through the international spread of disease. As is commonly known, such a threat linked to the SARS-CoV-2 virus, was announced by WHO on 30 January 2020. [10]. And on 11 March 2020, WHO declared a COVID-19 infectious disease pandemic [11].

Analyzing the perception of WHO and its actions on the international arena, we need to recall in particular, spectacular, and willingly broadcast criticism of this organization expressed by the former US President Donald Trump. He pointed out that "Through the middle of January [2020 – author's note] it parroted [WHO – author's note] ... the idea that there was no human-to-human transmission happening despite... clear evidence to the contrary" [12]. The specific accusations levelled by the US President against the World Health Organization were verbalized in Donald Trump's famous letter to the organization's Director-General, T. A. Ghebreyesus, announcing the suspension of US contributions to the World Health Organization. Many accusations included therein referred to ignoring credible reports of the virus spreading in Wuhan, failing to investigate the reports that conflicted directly with the Chinese government's official accounts, the WHO's failing to apply pressure on the Chinese authorities to allow for a visit of an international team of researchers, or providing inaccurate or misleading information [13]. Reservations against the WHO were also articulated by members of the Japanese government at the time, emphasizing the need for a "fair, independent and comprehensive verification" of the organization's efforts to address the coronavirus pandemic [14]. Japanese Deputy Prime Minister, Taro Aso, even suggested changing the name of the organization to the "Chinese Health Organization" [15].

The above quoted criticism of WHO is only an example illustrating the broad spectrum of accusations levelled at the organization. Their common denominator was most often a delayed response to the threat posed by SARS-CoV-2, inability to send experts without the consent of the concerned country, a flawed warning system, or the need to ask a relevant government for confirmation of any information on a disease outbreak obtained from a non-state source [16]. Another accusation concerned the fact that the organization uncritically repeated information from the Chinese authorities [16]. The significance of the problem is evidenced by the fact that, in May 2020, over 100 member states agreed to set up an independent inquiry into whether WHO had taken appropriate steps in relation to the pandemic threat [17]. One of the scholars, Elizabeth Good, in her analysis, accuses the organization of declaring a public health emergency of international concern (PHEIC) too late and providing insufficient support to strengthen cooperation between the states. Moreover, contacts with the Government of the People's Republic of China were dominated by the approach based on the desire to maintain friendly relations with Beijing at all costs, which was reflected in excessive and undeserved praise for the state of actual cooperation. E. Good points out that "[...] unflinching support of the Health Commission of the People's Republic of China unsettled much of the West, potentially sacrificing global cooperation as a result" [18].

At the same time, it must be noted that the organization had to take actions in a media environment filled with fake news and conspiracy theories. Michael A. Peters, Stephanie Hollings and other researchers explicitly indicate the significance of the politicization of the virus by the then US president, adding that "this deliberate misinformation has done incalculable damage and fed into the other major source – the nationalist populist and far-right insistence on individual freedoms or rights sparking a constitutional debate just when the US and the world required an international collective approach to the management of public world health" [19].

At this point, one might say *nihil novi sub sole*, as already in 2015 WHO was criticized for too indecisive actions towards the Ebola virus outbreak. The researchers even pointed at "a crisis of confidence" towards the organization [20]. Margaret Chan, the director general of the World Health Organization, was criticized for WHO's declarations that the epidemic was under control, while Doctors Without Borders warned of the threat.

At the time, independent experts claimed that WHO that "does not currently possess the capacity or organizational culture to deliver a full emergency public health response" [21]. There were numerous experts claiming that the Ebola outbreak "[...] illustrates the Organization's institutional weakness as well as the failure of states to comply with their obligations" [22]. The literature includes positions whose authors analyze the World Health Organization's response to the pandemic threat as a product of the relationship between science and policy. According to Łukasz Gruszczyński and Margherita Melillo, criticism of the organization should be toned down. "From the point of view of WHO's Members, any shortcomings or even mistakes in WHO's work [...], should therefore not be seen as a failure of the organization or a kind of atrophy, but rather as part of the normal policy-making process in an emergency situation" [23].

It must be stipulated that the described events, in particular the noticeable criticism of the United Nations and its specialized organization, the World Health Organization,

are part of a multi-dimensional process of progressive deterioration of the collective security system based on the United Nations. The polarization of the UN, unprecedented since the so-called Cold War, the aforementioned dividing lines that are noticeable both within the Security Council, the UN General Assembly or within the individual organs of the United Nations all point to the increasingly apparent need to undertake reforms of the decision-making system in the Security Council as well as the UN Charter itself. A qualitative change is becoming a reality. Here, we need to emphasize, among other things, the suspension of Russia from the Human Rights Council [24].

The identified problems related to the effectiveness of the World Health Organization's bodies actually echo in part the problems of the founding organization itself, the UN, for WHO. It was the United Nations that convened the International Health Conference in 1946, during which 61 countries ratified the WHO Convention. The UN's problems affect the specialized organization, which, after all, operates in its shadow. Showing the operational realities of the largest and most important collective security organization in the world, Wojciech Stankiewicz emphasizes that "[...] The UN does not act independently, it is dependent on the will of states to which it cannot impose its point of view. [...] The problems arising in the world: nationalisms, conflicts between states and ideologies, are UN problems. [...] The UN assumes cooperation between the states that distrusted each other and had different interests. The frequent use of the veto and the lack of independence from the military forces of member states meant that the UN could not fulfil its statutory goals. After the end of the Cold War, the national interest of the member states still comes first" [25].

Relevant are the words of David Steward, quoted above, who points out that "the COVID-19 pandemic has also made clear that policy is not made at one level – it occurs at many levels ranging from the individual organization to local government, to state government, to the federal government, to international agencies" [2]. It may seem a truism to say that the global challenge that was and still is the COVID-19 pandemic has a multi-dimensional impact on different areas of security: from the individual security to the security of the entire international community, economic security, or food security [26]. Some researchers, such as Edward Newman, rightly point out that because Covid-19 has had an overwhelming impact upon states with the most advanced institutional capacity, it raises questions of efficacy of the paradigm regarding the method of "how security is conceptualized and practiced" [27]

From a deteriorating health security system to an anti-pandemic treaty

It should be noted that since its creation, it has been the first time that WHO as a health security guardian has faced such a serious challenge – nothing like that happened even during the period of threats generated by the viruses like SARS, EBOLA and A/H1N1. Such a position is supported not only by the nature of this medical threat, but also by the unprecedented scale of the mediatization of modern societies. Perhaps at this point we should ask an important question whether and what the chances are in the near future to make the World Health Organization more effective by improving coordination between WHO and its member states? It seems that the answer to the question formed in this way must be negative. The current global security system centered within the United Nations is undergoing a deep structural crisis. The fundamental nature of the threats that we see today is reflected by the partial atrophy of the security system culminating in the Security Council. The erosion of international law, degeneration of the international security law system, particularistic politics of states affecting even the functioning of international organizations that act as the global health security guardian (sic!), exemplified by Donald Trump's decision to suspend US contributions to this organization, are clear and worrying examples that demonstrate the scale of threats to health security.

At the same time, they are a kind of memento that health security of the international community, which has been assigned special significance, is not separated from the ubiquitous rivalry of states. The problems of the United Nations are partly those of the World Health Organization. As demonstrated by the experience of the COVID-19 pandemic, despite declarations WHO has not become a unifying factor for the international community, but another platform for the clashing interests of the superpowers. Thus, criticism of WHO is also partly political in nature.

Regarding both the multifaceted security threat generated by the pandemic and a different way of perceiving the measures and approaches to ensuring systemic resilience to COVID-19 by national governments, it must be stressed that the essence of the challenges cannot be simply reduced to medical security or the race to develop an effective vaccine, which is of particular interest to societies. Attempts to limit the pandemic on both a national and international level are not only medical efforts aimed at guaranteeing health security. It is also, and perhaps above all, a sphere of political cooperation and competition. Obviously, this phenomenon cannot be described as a new factor affecting the fulfilment of the tasks assigned WHO under its Constitution. However, the pandemic has dynamized the process and made it distinct. Furthermore, health security should be seen in a broader, even global context – as a system of international relations based on cooperation and rivalry, connected on a scale that most people have not yet realized. Different political systems also mean different ways in which governments perceive remedies, which, depending on a degree of democratization and adherence to the rule of law, may be considered either permissible or incompatible with national law and unconstitutional.

Therefore, it seems reasonable to ask whether the elected members of the international community, in criticizing WHO's indecisive attitude towards the growing COVID-19 pandemic, expected too much from the organization? If we juxtapose the competencies determined in the WHO Constitution of 1948, now 75 years old (sic!), in particular entrusting the organization with the role of global health

guardian *vide* acting "as the directing and coordinating authority" with the current challenges faced by the UN, we may reach the conclusion that the problems and criticisms concern – at least not fully – not so much WHO, but the essence of international relations and the realities of contemporary national security.

It is important to note that there is now an institutionalized crisis of international order and, as Mary Elise Sarotte points out, a "new Cold War" [28].

It seems that the progressive deterioration of the UN guarantee system today and the increasingly noticeable polarization of the current international arena into a group of democratic countries and their opposite in the form of illiberal states, will hinder the implementation of new structural reforms of WHO in the coming years. Nonetheless, WHO, and indirectly its members, cannot be denied legislative actions aimed at implementing a legislative act that would make collective efforts to address health crises more effective. Indeed, the importance of evaluating actions taken to reduce and counteract COVID-19 is recognized. The WHO Constitution explicitly equips the organization with powers broader than simply proposing "conventions, agreements and regulations", see Article 2(k) [7]. We should not forget Articles 19 and 21 of the WHO Constitution granting quasi-legislative powers to the World Health Assembly, which constitute an important contribution to the development of a normative basis for countering pandemic threats.

In November 2020, the President of the European Council, Charles Michel proposed developing an international treaty on pandemics and opening it for signature. The need for such an international agreement was also emphasized by members of the Independent Panel for Pandemic Preparedness and Response [29]. This body evaluated WHO's actions during the pandemic. And in May 2020, 73rd session of the World Health Assembly adopted resolution WHA73.1, which established the Independent Panel on Pandemic Preparedness and Response. The result of its work was presented during the subsequent 74th session. Key recommendations included the proposal to establish a high-level Global Health Threat Council to be headed by Heads of State and Government, and the idea of adopting a Pandemic Framework Convention within the next six months, which is important in the light of WHO's efficiency issues. To make our considerations complementary, we should also mention the interesting concept of "[...] establishing a new global system for surveillance, based on full transparency by all parties, using state-of-the-art digital tools" [30]. Leaving aside the actual feasibility of the latter postulate, the verbalization of the recommendations of the Independent Panel on Pandemic Preparedness and Response resounded during the second Special Session of the World Health Assembly, which on 1 December 2021 adopted the document "The World Together: Establishment of an intergovernmental negotiating body to strengthen pandemic prevention, preparedness and response" [11]. The Assembly decided that a "negotiating body open to all Member States and Associate Members [...] to draft and negotiate a WHO convention, agreement or other international instrument on pandemic prevention, preparedness and response [...]" [11]. It should be appreciated that the body to develop a future pandemic convention was created unanimously (sic!), reflecting the importance of the proposed international agreement. The draft anti-pandemic treaty is planned to be ready in 2024. Although there is currently no comprehensive draft – only a so-called "working draft" – the guidelines published by the Intergovernmental Negotiating Body (INB) have several common features: strengthening the role of WHO as the leading authority responsible for coordinating health issues at supranational level; striving after the establishment of a greater number of alert levels that would better reflect the severity of the health threat, which explicitly translates into faster warning; and imposing an obligation on the states being parties to the future convention to "facilitate WHO with rapid access to outbreak areas within the Party's jurisdiction or control" [31]. According to reports prepared by the INB, the planned treaty will conceptualize postulates previously expressed by national governments and experts to rectify perceived deficiencies in the World Health Organization's operations.

While we should welcome the beginning of works on an undoubtedly needed convention, there are still some important issues to be addressed. Firstly, the mere completion of the draft anti-pandemic treaty by the special body is *de iure* and *de facto* only the finalization of the first stage of work. It is known that the treaty will then be opened for signature and later subjected to ratification by further states. The implementation of the postulates and guidelines identified by the INB experts is linked to the need for relevant changes not only at the level of international law, but also at the national level of the individual signatories. It should be recalled that as early as 1998, David Fidler indicated that WHO should "take leadership in building legal capacities at both these levels of law" [32]. Secondly, it should be noted with concern, but also with caution, that according to some views the multitude of problems and challenges for which the future treaty is supposed to be a miraculous remedy will in fact make it impossible to achieve consensus among states. In the doctrine, Clare Wenham, Mark Eccleston-Turner and Maike Voss argue that "[...] the content of the pandemic treaty currently being proposed is at its heart a globalist project, seeking to improve health for all, allow equity in preparedness for and response to future pandemics, and asserting at its core the universality of human populations. [...] the defense of solidarity and equity requires states to depart from state-centric policy-making and focus on the global, something states have been unable or unwilling to do in global health governance to date, and indeed during the COVID-19 pandemic" [33]. Finally, it is appropriate to express doubts of a praxeological nature, i.e., whether the elaboration of such an important international agreement for health security can be achieved in such a short time and during a still ongoing pandemic.

Summary

However long it may take to put the anti-pandemic treaty into force, it is legitimate at this point to ask a key question:

will the new international agreement streamline WHO's operating procedures and make countries' cooperation more flexible? At the moment, there are two answers to this question. In formal terms – it certainly will. Implementation of case-based solutions relating to the various areas of prevention, control, or cooperation between states in the works on different forms of countermeasures and vaccines will undoubtedly facilitate this cooperation. In practical terms, on the other hand, optimism should be tempered, as the degree of cooperation between the states depends on the ability to go beyond the national interests.

In summary, the center of gravity of the discussed problem shifts from medical to legal challenges and political issues. We must not forget a seemingly trivial fact, which accurately illustrates the relationship between the will of states and their vested interests and the effectiveness of WHO's work. The effectiveness of international security (including health) regulations and procedures arising from accepted international conventions directly depends on the extent to which the authorities of the United Nations member states are willing to delegate to both the UN itself and its specialized organizations the competence to take actions. While it sounds like a truism to say that speed of response is crucial in pandemic threats, we need to remember the peculiar lesson taught by the conduct of certain states related to communicating the actual impact caused by SARS-CoV-2. In selected cases, particular interests and an etatist approach to security prevailed over the responsibility for health security in the global dimension.

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DE NOVO BIOPSY-NEGATIVE ALPORT SYNDROME: A NOVEL MUTATION VARIANT

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Abstract:

Alport syndrome (AS) is an inherited disease caused by a mutation in type IV collagen genes, including the COL4A3 COL4A4 and COL4A5 genes. X-linked Alport syndrome associated with a mutation in COL4A5 gene is the most commonly observed type of AS. The clinical symptoms of AS include renal, hearing and vision impairments. The diagnosis is based on the manifestation of these symptoms and either specific kidney biopsy lesions or positive genetic tests. We present a case of a de novo biopsy negative Alport syndrome. The patient's diagnosis was delayed because the biopsy did not show specific findings for AS. Genetic tests (Next-Gen Sequencing, NGS) made it possible to establish the final correct diagnosis. A c.2441G>A variant of COL4A5 gene detected in probant has not been described in the literature yet. In the past years a significance of NGS in AS diagnosis has increased. The new pathogenic variants are still being reported including de novo mutations having an incidence rate of around 12%. Early diagnosis is crucial for the effective treatment of patients with AS.

Keywords: Alport syndrome, molecular pathology, whole exome sequencing, chronic renal insufficiency, genetic testing.

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Introduction

Alport syndrome (AS) is a hereditary disease in which collagen network defects in the basement membranes cause glomerular, cochlear and ocular abnormalities that manifest clinically as kidney failure, hearing and vision impairments [1]. It is described that Alport syndrome is most frequently associated with an X-linked transmission, with mutation being seen in the COL4A5 gene, while pathogenic mutations in COL4A3 and COL4A4 can cause Alport syndrome via an autosomal transmission with either a recessive or dominant inheritance [2]. The phenotype of AS has been observed to vary depending on the mutation, ranging from a nonprogressive disorder limited to the kidneys to a progressive one with multisystem involvement [3]. The most common renal symptom of AS is persistent hematuria, observed in all male patients. Other clinical features include proteinuria in early childhood, hearing loss in late childhood and renal failure before 40 years of age in 90% of males [4]. To diagnose AS then a patient's suggestive clinical picture and either sufficient kidney biopsy findings or a positive genetic test are needed [5]. Sometimes, however, especially in early stages of AS the biopsy results are not specific, which can be misleading [4]. Before the widespread utilization of Next-Generation Sequencing (NGS), genetic tests were expensive and inaccessible. We describe the case of a de novo, biopsy-negative Alport Syndrome with a novel mutation variant that was successfully diagnosed because of NGS.

Case report

A 39-year-old man with a history of chronic kidney disease, microhaematuria, proteinuria and hearing impairment was admitted in 2018 to the nephrology clinic in order to modify his treatment. He underwent a kidney biopsy in 2006, in which focal segmental glomerulosclerosis was discovered, with no findings suggestive of AS. Long-term immunosuppressive therapy (cyclosporine and oral steroids) introduced after the biopsy resulted in clinical remission, however a relapse of proteinuria was observed. On admission the patient denied dysuria and fever, but reported swelling of the lower limbs. His cardiovascular parameters were stable, with a heart rate of 80 BPM and blood pressure of 145/90 mmHg. Laboratory studies showed elevated levels of creatinine (2,3 mg/ dl) and urea (82 mg/dl), and the estimated glomerular filtration rate was 34 ml/min (using short MDRD formula). Urinalysis revealed proteinuria (100 mg/dl) and microhaematuria. In a 24-hour urine collection 3,43 mg of protein was detected.

Methylprednisolone pulse therapy, with three 500 mg intravenous doses administered every 3 months, was introduced and subsequently the patient was treated with oral steroids, with a starting dose of 30 mg Prednisone every two days. After 3 months the dose was adjusted to 20 mg every two days. Two months later the dose was decreased to 15 mg every two days, but after the next two months eventually changed to 15 mg daily. The patient was observed over the following months, his renal function parameters were stable with no significant deterioration and onset of new symptoms. In 2020, considering the patient's medical history and his symptoms, as well as the accessibility of genetic testing the decision about returning to the diagnostic process of Alport syndrome was made, despite a non-suggestive family history of kidney disease. The previous kidney biopsy did not show the findings characteristic for AS, so Whole Exome Sequencing (WES) of COL4A3-5 genes in the patient, his parents and his daughter was conducted. A ClinVar database, which includes the information about pathogenic variants of the COL4A5 gene was applied. The analysis exposed the presence of a c.2441G>A variant of COL4A5 gene in the probant, whereas his parents were shown to exhibit no such mutation. The absence of the c.2441G>A variant in COL4A5 gene in the patient's parents indicates de novo mutation. This mutation was also detected in the patient's daughter, who has recently developed hematuria. What is noteworthy, the c.2442G>A variant has not been described in literature, however the ClinVar database classifies it as possibly pathogenic – of unknown clinical significance.

Discussion

Renal biopsy findings suggestive of Alport syndrome have been described to vary in patients with different models of inheritance, with male X-linked AS and autosomal recessive AS cases often showing nephritis progression and lesions specific to AS, and female X-linked AS and autosomal dominant AS cases linked to electron microscopy findings, frequently limited to thinned glomerular basement membranes (GBM) [4]. AS-characteristic lesions found in fully-developed AS include irregular, focal alternation of thinning and thickening of the GBM with lamination and splitting of the lamina densa [6]. In a study from 2014, which described 7 families with genetically confirmed Alport syndrome mistakenly diagnosed for hereditary focal segmental glomerulosclerosis (FSGS) after kidney biopsies, four families had biopsy findings not suggestive of AS, despite showing specific symptoms [7]. These families had mutations in the COL4A3 and COL4A4 genes, not COL4A5, yet had a similar diagnostic pathway to our patient - they were diagnosed with FSGS after an electron biopsy. That study also highlights the importance of NGS in evaluating renal phenotypes of AS. In the newest consensus regarding the diagnostic process of AS, molecular studies in the form of comprehensive parallel testing of COL4A3, COL4A4 and COL4A5 genes are suggested as the primary, most accurate option, while kidney biopsy is regarded as not necessary in causative cases, especially considering the risk of such a procedure [8]. There are two options for molecular genetic testing. The recommended approach includes using a multigene panel, which identifies genes most frequently associated with specific phenotype or focuses on the particular genes chosen for analysis [9]. A multigene panel is the most effective in finding the mutation responsible for the disease. Sequence analysis and other non-sequencing based tests are techniques used in a panel. The second option for finding the pathogenic variants in genes is comprehensive genomic testing using exome sequencing or genome sequencing. This method does not require to choose which genes are most likely to be the cause of the medical condition and is used commonly in individuals with atypical symptoms. A potentially pathogenic variant may be connected with the development of a particular disease, but proving this relation is not possible due to lack of data at the moment of its discovery. Confirming the link between a variant and the condition requires additional tests and scientific evidence – it cannot be said that further research will disprove the clinical significance of the finding. As of now, over 3,000 pathogenic variants of the COL4A3, COL4A4 and COL4A5 genes have been reported [10]. The general consensus in literature is that numerous mutations of aforementioned genes are still to be described and have their phenotype and clinical significance determined to ensure adequate introduction of treatment and assessment of prognosis [11]. The exact prevalence of pathogenic variants is unknown, however a recent population-based study using the data from the gnomAD cohort has shown a frequency of 1/2320 individuals with an incidence of a predicted pathogenic mutation in the COL4A5 gene, while 1/106 individuals had a heterozygous predicted pathogenic mutation in the COL4A3 or COL4A4 genes, and 1/88,866 subjects that had two heterozygous predicted pathogenic mutations [12]. The variant of our patient - the c.2441G>A variant of the COL4A5 gene - prior to his genetic test had not been described in literature, and was considered to be of unknown clinical significance, or potentially pathogenic. Since the patient's daughter exhibits symptoms of Alport syndrome, it is possible to presume that this variant is among the pathogenic ones. One study of 195 families with COL4A5 mutations described the incidence of de novo mutations in this gene as approximately 12% [13], so it is possible that even the cases with negative family history or biopsy, but exhibiting clinical symptoms of AS, should be assessed for de novo mutations. There are articles that demonstrate a need for widely accessible and cost-effective molecular diagnostic methods, since the significance of genetic testing in AS diagnosis has been increasing over the recent years [14]. New, emerging variants are being discovered [15] – confirming their relationship with pathogenicity and plausible clinical implications or phenotype variations are important to develop knowledge of this condition and its future management.

The current management of renal AS manifestations targets mainly the renin-angiotensin-aldosterone system, using ACE-inhibitors to slow down the progression of the disease, which are especially effective in delaying end-stage disease in males with X-linked AS, even if introduced before the onset of proteinuria [5], but novel treatment options are pursued as well [16]. With the recent FDA Complete Response Letter rejecting the New Drug

Application for bardoxolone for AS treatment due to unsatisfactory performance [17] the USA registration process of one of the more promising AS drugs was effectively closed. Other emerging therapeutic options employ genetics and include nonsense read-through therapy and exon skipping therapy [4]. A podocyte-lineage cell genetic therapy using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is being studied in pre-clinical models with COL4A3 and COL4A5 genes [18]. Genetic therapies are described to be the target of future therapeutic interventions and are a promising option whose importance can be greatly increased.

The advancements reached in availability and quality of genetic testing can improve the patient's chance of quick and accurate diagnosis, enabling introduction of adequate management in early stages of the disease, which has been shown to delay the onset of end-stage disease and improve prognosis [8, 19].

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TUBULOINTERSTITIAL NEPHRITIS – A CASE REPORT SERIES FROM ONE CENTRE

Cewkowo-śródmiąższowe zapalenie nerek – seria przypadków z jednego ośrodka

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Abstract: Tubulointerstitial nephritis (TIN) is a disease that affects a wide range of age groups – from young patients without comorbidities to elderly with multiple burdens of the disease. It is a diagnostic and therapeutic challenge due to its non-specific course and etiology that's often difficult to define. The aim of the study was to analyze the 3-year frequency of TIN and to assess the diagnostic difficulties, methods and effects of treatment based on the analysis of hospitalizations in the Department of Internal Medicine, Nephrology and Dialysis Military Institute of Medicine. The paper presents descriptions of fourteen patients diagnosed with TIN with their symptoms, treatments, and results. Four patients had a kidney biopsy. Three patients needed temporary dialysis. In more than half of the discussed patients the kidney functions had not returned to normal or to the values from before the onset of the disease.

Keywords: acute kidney injury, chronic kidney disease, tubulointerstitial nephritis, renal biopsy, drug-induced kidney injury

Streszczenie: Cewkowo-śródmiąższowe zapalenie nerek (CŚZN) jest chorobą dotykającą osoby w szerokim przedziale wiekowym, od ludzi młodych bez chorób współistniejących po osoby starsze z licznymi obciążeniami chorobowymi. Ze względu na niespecyficzny przebieg i niejednokrotnie trudną do uchwycenia etiologię stanowi wyzwanie diagnostyczne i terapeutyczne. Celem pracy była analiza 3-letniej częstości CŚZN oraz ocena trudności diagnostycznych, sposobów i efektów leczenia na podstawie analizy hospitalizacji w Klinice Chorób Wewnętrznych, Nefrologii i Dializoterapii WIM. Zaprezentowano opisy 14 pacjentów ze zdiagnozowanym CŚZN. Przedstawiono objawy, sposoby leczenia i wyniki. Czterech chorych miało biopsję nerki. U trzech osób konieczne było czasowe prowadzenie leczenia nerkozastępczego. U ponad połowy chorych funkcja nerek nie powróciła do normy lub do stanu sprzed choroby.

Słowa kluczowe: ostre uszkodzenie nerek, przewlekła choroba nerek, cewkowo-śródmiąższowe zapalenie nerek, biopsja nerki, polekowe uszkodzenie nerek

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Introduction

The tubules and interstitium make up over 95% of the renal volume. Therefore, we need to better understand the physiology and pathology of these parts of kidneys. TIN is caused by a primary tubular and parenchymal injury that leads to impaired renal function. Acute TIN most often results from toxic, allergic, or infectious reactions. Chronic forms of the disease are usually associated with genetics, metabolic disorders, or exposure to toxic environmental factors. Originally, it was believed that the main cause of TIN was infectious agents, but more recently the increasing attention has been paid to the immune factors induced by xenobiotics, e.g., antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs) in the TIN etiology [1]. Identification of the etiological factors of TIN is essential for both the treatment and prevention of the disease. The frequency of TIN in biopsy material is variable and depends primarily on the age of the patients, the ratio of acute kidney injury to chronic kidney disease in the study population and the adopted methodology [2, 3, 4, 5].

Aims of the paper

Evaluation of the incidence of TIN and assessment of diagnostic difficulties, treatment methods and outcomes based on an analysis of hospitalizations in the Department of Internal Medicine, Nephrology and Dialysis at the Military Institute of Medicine over a 3-year period.

Methodology

Below is an overview of the 14 TIN patients diagnosed and treated in the Department of Internal Medicine, Nephrology and Dialysis between 2020 and 2022. During

this period, there were 2,902 hospitalizations involving 1,613 patients. It represents 0.48% of hospitalizations and 0.87% of patients. They were selected with the search engine of the AMMS (Asseco Medical Management Solutions) system, using the option to search by ICD-10 diagnosis code. The inclusion criteria were at least one of the N10-12 range in the final diagnoses. 16 results were obtained, of which 2 were discarded due to an incorrectly assigned ICD-10 code (validation was done on the basis of available medical records). The following data were checked in the records: possible causative agent, clinical and demographic data, renal function parameters at baseline and at discharge from the Department and applied therapeutic management. The data are presented in Table 1. The potential causative agent of the disease was determined on the basis of the history collected by the admitting and attending physicians. Brief case descriptions are presented below.

Case reports

Patient No. 1

A 64-year-old female in a fairly good general condition, admitted to hospital with a diagnosis of acute kidney injury. Data indicating TIN: urinary tract infection (UTI) one month prior to hospitalization treated with azithromycin and deterioration of general condition since then, abdominal, and low back pain. On admission: creatinine 4 mg/dl, eGFR 11 ml/min/1.73 m2, urea 62 mg/dl, CRP 3.4 mg/dl, erythrocyturia, leukocyturia, proteinuria 30 mg/dl. Probable causes of TIN: drug-induced (azithromycin)/infection (UTI). Treatment applied: corticosteroids. Treatment effects: a decrease in creatinine level to 1.6 mg/dl, urea level to 23 mg/dl and CRP level to 3 mg/dl, an increase in eGFR level to 32 ml/min/1.73 m2.

Patient No. 2

A 67-year-old male in a good general condition, admitted to hospital with suspected tubulointerstitial nephritis. Data indicating TIN: taking ciprofloxacin with metronidazole for 10 days (after cholecystectomy) one month before hospitalization, abdominal pain. On admission: creatinine 4.2 mg/dl, eGFR 14 ml/min/1.73 m2, urea 128 mg/dl, hyperkaliemia 5.8 mmol/l. Probable cause of TIN: drug-induced (ciprofloxacin). Treatment applied: corticosteroids. Treatment effects: a decrease in creatinine level to 2 mg/dl and urea level to 80 mg/dl, an increase in eGFR level to 33 ml/min/1.73 m2, normokalaemia, a decrease in CRP level to normal values.

Patient No. 3

A 31-year-old female in a good general condition, admitted initially to the Department of Surgery for suspected appendicitis, then redirected to the Department of Nephrology due to elevated renal parameters. Data indicating TIN: taking ciprofloxacin and ad hoc ketoprofen with drotaverine approximately 6 days prior to hospitalization due to right intra-abdominal pain and frequent urination and temperature up to 38°C. On admission: creatinine 2.6 mg/dl, eGFR 21 ml/min/1.73 m2, urea 46 mg/dl, CRP 13.6 mg/dl, proteinuria 15 mg/dl. Probable cause of TIN: drug-induced (ciprofloxacin, ketoprofen). Treatment applied: intravenous fluid therapy, furosemide. Treatment effects: an improvement in renal function – at discharge creatinine 1.5 mg/dl, eGFR 41 ml/min/1.73 m2, urea 22 mg/dl; a decrease in CRP level to 0.2 mg/dl.

Patient No. 4

A 21-year-old male admitted to hospital in an average general condition due to acute kidney injury. Data indicating TIN: low back pain approximately 4 days prior to hospitalization, treated with ad hoc ibuprofen and ketoprofen, less frequent urination and slight foaming, and the bilaterally positive Goldflam sign. On admission: creatinine 2.4 mg/dl, eGFR 34 ml/ min/1.73 m2, proteinuria 100 mg/dl, in 24-hour urine collection 551 mg/dl. Probable cause of TIN: drug-induced (ibuprofen, ketoprofen). Treatment applied: with corticosteroid drugs. Treatment applied: corticosteroids. Treatment effects: a decrease in creatinine level to 1.1 mg/dl, a normalization of eGFR, resolution of pain.

Patient No. 5

A 63-year-old female in a fairly good general condition, admitted to hospital due to fainting. Data indicating TIN: taking levofloxacin and clarithromycin for SARS-CoV-2 infection approximately two months prior to hospitalization. On admission: creatinine 1.8 mg/ dl, eGFR 28 ml/min/1.73 m2, urea 104 mg/dl, leukocytosis 15,000/µl, eosinophilia 1.08,000/µl (N: 0.05-0.5), leukocyturia. Probable cause of TIN: drug-induced (levofloxacin, clarithromycin)/ post-infectious (SARS-CoV-2 infection). Treatment applied: fluid therapy. Treatment effects: a decrease in creatinine level to 1.1 mg/ dl, a normalization of eGFR level and a decrease in urea concentration to 32 mg/dl.

Patient No. 6

A 21-year-old male admitted to hospital due to acute kidney injury. Data indicating TIN: low back pain a few days before hospitalization. On admission: creatinine 6.3 mg/dl, eGFR 11 ml/ min/1.73 m2, urea 86 mg/dl, CRP 3.0 mg/dl, proteinuria 5.1 mg/dl (in 24-hour urine collection: 306 mg/24 h). On ultrasound: thickening of the renal parenchyma, increased echogenicity of the cortex of both kidneys, abnormal corticomedullar differentiation – lesions indicating nephritis. Confirmation of TIN in diagnostic renal biopsy (DRB) performed due to the lack of improvement in renal function despite conservative treatment – acute tubular epithelial injury with inflammatory reaction in the interstitium. Probable cause of TIN: unknown. Treatment applied: ciprofloxacin (due to suspected UTI), followed by steroid therapy. Treatment effects: a decrease in creatinine level to 1 mg/dl, urea 37 mg/dl, a normalization of eGFR, a decrease in CRP level to normal values, resolution of pain.

Table 1. Summary of key clinical data in the patients described.

Patient (no.)	Age (years)	Baseline test results						Triad of symptoms (rash, fever, pain)	Treatment (without corticosteroid drugs/ treatment with corticosterois / hemodialysis)	DRB	Possible cause	Response to treatment
		Creatinine (mg/dl) N: 0.5–0.9	Urea (mg/dl) N: 15–43	CRP (mg/dl) N: 0–0.8	Urinalysis							
					erythrocyturia	leukocyturia	Proteinuria					
1	64	4	62	3.4	+	+	30 mg/dl	Lumbosacral pain	treatment with corticosteroids	-	infection (UTI), drug-induced (azithromycin)	Cr 1.6 Urea N CRP: 3
2	61	4.2	128	1.2	-	-	-	Abdominal pain	treatment with corticosteroids	-	drug-induced (ciprofloxacin)	Cr: 2 Urea: 80 CRP: N
3	31	2.6	46	13.6	-	-	15 mg/dl	Abdominal pain, low-grade fever (37.6˚)	without corticosteroid	-	drug-induced (ciprofloxacin. ketoprofen)	Cr: 1.5 Urea: N CRP: N
4	21	2.4	N	N	-	-	100 mg/dl (24-hour urine collection: 551	Lumbosacral pain	treatment with corticosteroids	-	drug-induced (ibuprofen)	Cr: 1.1
5	63	1.8	104	N	-	+	-	-	without corticosteroid	-	drug-induced (levofloxacin)	Cr: 1.5 Urea: 54
6	21	6.3	86	3	-	-	5.1 mg/dl (24-hour urine collection: 306	Lumbosacral pain	treatment with corticosteroids	TIN	unknown	Cr: 1.0 Urea: N CRP: N
7	20	8.7	180	9	+	-	-	-	hemodialysis, treatment with corticosteroids	TIN	infection, drug-induced (amoxicillin, ciprofloxacin)	Cr: 2.0 Urea: 88 CRP: N
8	20	11.4	179	1	+	-	100 mg/dl (24-hour urine collection:	-	hemodialysis, treatment with corticosteroids	-	unknown	Cr: 2 Urea: 88 CRP: N
9	62	1.8	56	N	-	+	-	-	without corticosteroid	TIN	drug-induced (mesalazine)	No change
10	71	6	113	1.2	+	-	-	-	treatment with corticosteroids	-	unknown	Cr: 3.8 Urea: 192 CRP: N
11	71	2.6	103	N	+	-	9.6 mg/dl (24-hour urine collection: 347	-	treatment with corticosteroids	-	infection	No change
12	57	3.3	136	N	-	+	-	Lumbosacral pain, rash	treatment with corticosteroids	-	drug-induced (ibuprofen), infection	Cr: 1.5 Urea: 98
13	61	4.72	96	N	+	+	33.2 mg/dl (24-hour urine collection: 978	-	treatment with corticosteroids	TIN	drug-induced (azathioprine)	Cr: 2.5 Urea: 77
14	57	5.4	273	1.4	+	+	100 mg/dl	-	hemodialysis, without corticosteroid	-	drug-induced (ibuprofen)	Cr: 2.5 Urea: 77 CRP: N

Legend Cr – creatinine, Urea – urea, CRP – C-reactive protein, DRB – diagnostic renal biopsy, DUC– daily urine collection, N – normal range for a parameter.

Patient No. 7

A 20-year-old female in an average general condition admitted to the Department of Nephrology due to suspected sepsis and acute kidney injury. Data indicating TIN: taking antibiotics approximately 1 week prior to hospitalization (amoxicillin-clavulanate, clindamycin, ciprofloxacin) due to a systemic infection. On admission: creatinine 8.7 mg/dl, eGFR 6 ml/min/1.73 m2, urea 180 mg/dl, CRP 9.0 mg/dl leukocytosis 14,000/µl, metabolic acidosis with pH 7.3, hyperphosphatemia, hypocalcemia, hypoproteinemia with hypoalbuminemia, oliguria 150 ml/day, erythrocyturia. Confirmation of TIN on renal biopsy (lymphocyte infiltration in the interstitium with the presence of eosinophilia indicating a hypersensitivity reaction). The biopsy was performed due to lack of improvement despite conservative treatment. Probable cause of TIN: drug-induced (amoxicillin-clavulanate, clindamycin, ciprofloxacin)/systemic infection. Treatment applied: hemodialysis (2 procedures in total), treatment with corticosteroids, antibiotic therapy (meropenem with vancomycin deescalated subsequently to levofloxacin with cloxacillin according to cultures obtained). Treatment effects: resolution of inflammation and acidosis, improvement in renal function (at discharge, creatinine 1.9 mg/dl, urea 77 mg/dl, eGFR 34 ml/min/1.73 m2), diuresis returned.

Patient No. 8

A 62-year-old male in a good general condition, admitted to hospital due to acute kidney injury. Data indicating TIN: CKD; history of AKI on a background of acute TIN about 4 years earlier, treated with ad hoc hemodialysis; significantly reduced urine output noted by the patient 3 days before hospitalization, slight oedema of lower limbs. On admission: creatinine 11.4 mg/dl, eGFR 5 ml/min/1.73 m2, urea 179 mg/dl, hyperkaliemia 6.3 mmol/l, metabolic acidosis with pH 7.29, erythrocyturia, proteinuria 100 mg/dl (in 24-hour urine collection: 1,305 mg/24h). Probable cause of TIN: unknown. Treatment applied: 1 hemodialysis procedure followed by treatment with corticosteroids. Treatment effects: rapid return of diuresis (3-4 l/day), improvement in renal function (at discharge, creatinine 2 mg/dl, urea 88 mg/dl, eGFR 34 ml/ min/1.73 m2), resolution of metabolic acidosis, normokalaemia.

Patient No. 9

A 33-years-old female in a good general condition, admitted to hospital due to an increase in creatinine level on follow-up tests, to be qualified for diagnostic renal biopsy. Data indicating TIN: taking mesalazine due to ulcerative colitis (UC) diagnosed 2 years before. On admission: creatinine 1.8 mg/dl, urea 56 mg/dl, eGFR 32 ml/min/1.73 m2, leukocyturia; confirmation of TIN in the DRB (extensive lymphocyte infiltration in the interstitium and tubular epithelium). Probable cause of TIN: drug-induced (mesalazine)/autoimmune (UC). Treatment applied: discontinuation of mesalazine. Treatment effects: stably impaired renal function. In the future, further observation of the patient to control the course of TIN after mesalazine discontinuation.

Patient No. 10

A 71-year-old male in average general condition, admitted to hospital due to an increase in creatinine level on follow-up tests. Data indicating TIN: CKD. On admission: creatinine 6 mg/dl, urea 113 mg/ dl, eGFR 9 ml/min/1.73 m2, erythrocyturia. The patient was qualified for a long-term dialysis program at another center for 3 months. Probable cause of TIN: unknown. Treatment applied: corticosteroids. Treatment effects: a steady decrease in creatinine level to 2.6-3 mg/dl, eGFR 21-24 ml/min/1.73 m2, urea concentration around 150 mg/dl. Three months after hospital discharge, a re-exacerbation of renal failure was noted following a reduction in the prednisone dose to 2.5 mg/day, which resolved when the corticosteroid dose was increased again. Does not require dialysis.

Patient No. 11

A 71-year-old male in a fairly good general condition, admitted to the Department of Nephrology for assessment of renal function and implementation of further diagnostics. Data indicating TIN: history of AKI about one month before in the course of SARS-CoV-2 infection with an increase in creatinine level then to 8.8 mg/dl, eGFR 6 ml/min/1.73 m2, since then, treatment with prednisone with dose reduction to 5 mg/day until further discontinuation. On admission: creatinine 2.6 mg/dl, eGFR 24 ml/min/1.73 m2, urea 103 mg/dl, erythrocyturia, proteinuria 9.6 mg/dl (in 24-hour urine collection: 347 mg/24 h). Creatinine concentration remained elevated. Probable cause of TIN: post-infectious.

Patient No. 12

A 57-year-old female in a fairly good general condition, admitted to the Department of Nephrology due to elevated creatinine levels. Data indicating TIN: a history of a catarrhal infection about 3 months before, since when the patient suffered from recurrent lumbar pain radiating to the perineum and frequent urination; a fine-spotted rash on the abdomen skin. Due to the pain, the patient took ibuprofen 400 mg on a long-term basis. On admission: creatinine 3.3 mg/dl, eGFR 14 ml/ min/1.73 m2, urea 136 mg/dl, leukocytosis 12,000/µl, leukocyturia. Probable cause of TIN: drug induced (NSAIDs), post-infectious. Treatment applied: corticosteroids. Treatment effect: a decrease in creatinine level to 1.5 mg/dl and urea level to 98 mg/dl, an increase in eGFR level to 36 ml/min/1.73 m2, resolution of pain.

Patient No. 13

A 61-year-old female in an average general condition, admitted to the Department of Nephrology for treatment of tubulointerstitial nephritis diagnosed 4 months before, after performing a DRB, which confirmed the diagnosis. Data indicating TIN: CKD, taking azathioprine (discontinued 4 months prior to hospitalization) due to UC diagnosed 2 years before; increasing fatigue and weakness for about 4 months. On admission: creatinine 4.72 mg/dl, eGFR 9 ml/min/1.73 m2, urea 96 mg/dl, metabolic acidosis with pH 7.21, erythrocyturia, leukocyturia, proteinuria 33.2 mg/dl (in 24-hour urine collection: 978 mg/24h). Additional burdens: suspected SLE (due to positive result on an ANA test). Probable cause of TIN: drug-induced (azathioprine).

Treatment applied: corticosteroids. Treatment effects: a decrease in creatinine to 2.5 mg/dl and urea to 77 mg/dl, an increase in eGFR to 20 ml/min/1.73 m2. Due to persistently low creatinine levels at follow-up, the prednisone dose was reduced to 10 mg/dl after one month.

Patient No. 14

A 57-year-old male in a quite severe general condition, admitted to the Department of Nephrology due to acute kidney injury, for urgent hemodialysis due to severe hyperkaliemia. Data indicating TIN: taking large amounts of ibuprofen (6 tablets per day) due to increasing for two weeks, lumbosacral back pain (probably being the result of discopathy found on CT scan). On admission: creatinine 5.4 mg/dl, eGFR 11 ml/min/1.73 m2, urea 273 mg/dl, CRP 1.4 mg/dl, leukocytosis 15,000/µl, hyperkaliemia 8.5 mmol/l, hyponatremia 130 mmol/l, metabolic acidosis with pH 7.09, erythrocyturia, leukocyturia, proteinuria 100 mg/dl. Probable cause of TIN: drug-induced (ibuprofen). Treatment applied: 2 hemodialysis procedures, empirical antibiotic therapy (ciprofloxacin, ceftriaxone). Treatment effects: a decrease in creatinine level to 1.1 mg/dl and urea to 66 mg/dl, a normalization of eGFR, normalization of sodium and potassium concentrations and inflammatory markers, resolution of metabolic acidosis.

Discussion

Form and etiology of TIN

Acute TIN is characterized by the presence of inflammatory infiltrates and local oedema within the renal parenchyma. Inflammatory infiltrates contain T cells, monocytes, and acidophilic granulocytes. A renal biopsy typically shows inflammation and injury to the tubular and parenchymal structure of the kidney without glomerular or vascular involvement [6]. The term “interstitial nephritis” was first used in 1898 by Councilman, who described the histopathological picture of the kidneys in autopsy material from individuals who died of diphtheria or scarlet fever [7]. A characteristic feature of the disease is an abrupt onset, less typical feature is a chronic course leading progressively to end-stage renal failure. Symptoms include nausea, vomiting, malaise, fever, abdominal or lumbar pain, joint pain, and often a rash. None of the symptoms listed are pathognomonic; rather, we mean a triad or tetrad of symptoms that together may indicate TIN. Eosinophilia in the peripheral blood smear may indicate a drug-induced etiology of the disease.

Drugs are the most common cause of TIN (over 70–80% of cases) [2, 8]. Practice shows that any drug can cause TIN, but the most common inducers of TIN are non-steroidal anti-inflammatory drugs and antibiotics. TIN can also be induced by proton pump inhibitors, furosemide, phenytopin, lithium salts, acyclovir, allopurinol [2]. We found a similar situation in our patients.

In patients with drug-induced TIN, the average time between the start of the drug intake and the onset of renal injury symptoms is 10 days [9]. However, we need to remember that symptoms of injury can occur even on the first day of intake of certain antibiotics or after several months in the case of non-steroidal anti-inflammatory drugs.

In the other-cases, TIN may be caused by infectious agents, either bacterial (e.g., streptococcus, staphylococcus, legionella, yersinia) or viral ones (e.g., CMV, HCV, EBV, mumps virus). They may also be a complication of systemic diseases (e.g., SLE, Sjögren's disease, sarcoidosis). In a certain percentage of cases, the cause of the disease remains unknown [2].

A diagnostic renal biopsy allows for establishing a definite TIN diagnosis, but due to its invasive nature, it is used only in specific clinical situations:

- ambiguous clinical picture,
- progressive deterioration of renal function,
- lack of improvement despite discontinuation of the drug suspected to be the cause of the disease.

In our patients, biopsy was performed in 4 out of 14 patients. The main reason was the unclear clinical picture and prolonged renal failure.

TIN treatment

The literature mentions removal of the causative agent and standard management of acute kidney injury or chronic kidney disease as the primary interventions in the treatment of TIN. The role of glucocorticosteroids remains unclear. They are recommended in recognized clinical textbooks, but there are no randomized clinical trials confirming the validity of such treatment, and the available literature does not provide clear data on the choice of a specific drug and its dose [10, 11].

71% of the cases presented were related to the use of medications with the well-known potential to induce TIN, which seems to be consistent with the literature. Most often, development of the disease was associated with NSAIDs and fluoroquinolones, known as the frequent causes of TIN. It should be noted that in 21% of cases, a possible cause of the disease was not identified. 36% of the group are young people (under 40 years of age), in 40% of whom the causative agent of the disease could not be identified, indicating a great difficulty in diagnosis and treatment of this group of patients. 14% of patients had an additional burden of autoimmune disease, which may have contributed to the development of TIN. The course of the disease varied from a form accompanied by very few symptoms with a slow increase in creatinine concentration to a dynamic form accompanied by severe non-respiratory acidosis and serious ionic disturbances that required urgent renal replacement therapy. Compared to the data in Table 2, erythrocyturia, leukocyturia and non-renal proteinuria occurred in 50%, 43% and 57% respectively. None of the patients developed nephrotic proteinuria and 7% had normal results of general urinalysis. It means that, although TIN typically presents with abnormalities in the urinalysis, the characteristic pattern of abnormal parameters cannot be clearly defined. Eosinophilia was found in 7% of patients; it also represents 10% of patients with drug-induced TIN. It confirms that, irrespective of the etiology, this symptom is rare in the course of TIN. Other symptoms included in Table 2. were present in 7% of patients (fever and exanthema) or

not present at all (joint pain). In 87% of patients, treatment had a satisfactory outcome, with significant improvement in renal function. 21% of patients required urgent initiation of hemodialysis, but because of the undertaken treatment all of them were able to give up renal replacement therapy. Glucocorticosteroids were used in 71% of patients: initially methylprednisolone infusions, modified to prednisone at a gradually reduced dose. Glucocorticosteroids were not used in 29% of patients – this management related to patients in good general condition with moderately elevated renal function parameters.

Table 2. Symptoms and their incidence in 121 patients with TIN of predominantly drug-related etiology (91%), including those induced by NSAIDs (41%) [2].

Acute kidney injury	100%
Acute kidney injury requiring dialysis	40%
Joint pains	45%
Fever	36%
Rash	22%
Eosinophilia (>500 eosinophils in mm3 of peripheral blood)	35%
Erythrocyturia	67%
Hematuria	5%
Leukocyturia	82%
Non-nephrotic proteinuria	93%
Nephrotic proteinuria	2.5%
Nephrotic syndrome	0.8%

Summary

Tubulointerstitial nephritis is a disease with a heterogeneous clinical picture, causing dangerous complications. It requires prompt treatment implementation. Its prevalence is higher in the older population (> 65 years of age) and in patients with acute kidney injury, but it should also be considered in the differential diagnosis of chronic kidney disease in young people [12]. The course of the disease usually differs from a typical one described in the literature, so it is important to take a thorough medical history, especially regarding medication taken (also occasionally), past infections. Diagnostic renal biopsy is conclusive, but subject to the risk of complications and not available outside large nephrology centers. The prognosis is usually good; it worsens in the event of a prolonged course of the disease associated with interstitial fibrosis, prolonged exposure to the causative agent and, according to some reports, delayed implementation of corticosteroids [13, 14]. Treatment is mainly based on glucocorticosteroids, which seems reasonable due to the inflammatory basis of the disease, but mild forms of the disease may regress spontaneously. Patients with a history of TIN should receive ongoing nephrology care due to the risk of recurrence.

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SEVERE MANIFESTATION OF ACUTE TUBULOINTERSTITIAL NEPHRITIS

Ostre cewkowo-śródmiąższowe zapalenia nerek o ciężkim przebiegu

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Abstract: Acute tubulointerstitial nephritis (TIN) can cause acute kidney failure. It is characterized by presence of inflammatory cells in the renal interstitium, interstitial oedema and renal tubules damage. Among many causes of TIN, the most important seems the drug-induced immune response, especially associated with antibiotics or non-steroidal anti-inflammatory drugs. Treatment of TIN is based on removal of causative agent and on anti-inflammatory treatment with steroids. The paper presents the case report of TIN. A kidney biopsy was performed for prolonged anuria. The patient required a transient 11-day renal replacement therapy and steroid course. Kidney function was restored.

Keywords: hemodialysis, acute kidney injury, kidney biopsy, acute tubulointerstitial nephritis, steroid therapy.

Streszczenie: Ostre cewkowo-śródmiąższowe zapalenie nerek (OCŚZN) może być przyczyną ostrej niewydolności nerek. Charakteryzuje się obecnością komórek zapalnych w śródmiąższu nerki z towarzyszącym obrzękiem oraz uszkodzeniem cewek nerkowych. Wśród wielu przyczyn OCŚZN najważniejszą wydaje się reakcja immunologiczna na przyjmowane leki, w szczególności na antybiotyki i niesteroidowe leki przeciwzapalne. Leczenie OCŚZN opiera się na usunięciu czynnika wywołującego chorobę i stosowaniu leczenia przeciwzapalnego w postaci sterydoterapii. W niniejszej pracy przedstawiono opis przypadku OCŚZN. Diagnostyczną biopsję nerki wykonano z powodu przedłużającego się bezmoczu. Chora wymagała przejściowego 11-dniowego leczenia nerkozastępczego i sterydoterapii. Uzyskano powrót prawidłowej funkcji nerek.

Słowa kluczowe: hemodializa, ostre uszkodzenie nerek, biopsja nerki, ostre cewkowo-śródmiąższowe zapalenie nerek, sterydoterapia.

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Introduction

The interstitium and the renal tubules, make up the large part of ~~the~~ renal volume, hence any inflammation in these structures can impair renal function. Initially, infectious agents were considered to be the most common cause of TIN, but nowadays researchers attribute the greatest role in the development of this condition to immune reactions related to medication, particularly non-steroidal anti-inflammatory drugs and certain antibiotics [1, 2]. TIN may also have an autoimmune origin [3]. The histopathological picture of the kidneys in patients with TIN is characterized by damage to the renal interstitium and tubules with inflammatory infiltration within these structures and accompanying oedema, but without tubular injury to the glomeruli or vessels. The infiltrate is particularly composed of lymphocytes and monocytes, but also eosinophils, which may indicate a drug-induced background of the disease [4, 5, 6].

Case report

A 50-year-old woman was admitted to the Department of Internal Medicine, Nephrology and Dialysis of the Military Institute of Medicine due to the signs of acute kidney injury. The patient experienced a burning sensation in her lower abdomen and a headache persisting for a few days before her admission, for which she had taken several ibuprofen tablets and acetylsalicylic acid. After two days, the patient had developed nausea and vomiting, weakness, swelling of the lower extremities, anuria and deterioration of effort tolerance. The patient had a history of deep vein thrombosis of the right lower limb on two occasions, otherwise with no burden history.

On admission, the patient was in an average general condition, with good cardiovascular and respiratory function (BP 130/70 mmHg, ASM 70/min, SpO2 97%, no signs of pulmonary circulation stasis). Notable symptoms were oedema of the face, lower abdomen and lower extremities.

Performed laboratory tests revealed elevated renal function parameters (creatinine 6.9 mg/dl [N: 0.5–0.9], urea 97 mg/dl [N: 15–43]), elevated CRP (6.9 mg/dl [N: 0–0.8]) without leukocytosis, thrombocytopenia (137,000/µl [N: 150–400]), lymphopenia (0.55 thousand/µl [N: 0.9–4.5]), hyponatremia (124 mmol/l [N: 136–145]), non-respiratory acidosis with a pH of 7.33. In addition, hypoalbuminemia (3.2 g/dl [N: 3.9–4.9]), hyperphosphatemia (6.1 mg/dl [N: 2.6–4.5]) and elevated parathormone levels (122.4 pg/ml [N: 15–65]), the ionized calcium concentration was 1.11 mmol/l [N: 1.15–1.35]. Hepatotropic virus screening (HBsAg, anti-HBs, anti-HCV, anti-HIV) and an autoimmune panel were performed (antibodies: ANA, cANCA, pANCA, anti-GBM and cardiolipin) – the results were negative. In addition, reduced concentrations of complement components were revealed: C3 (24 mg/dl [N: 90–180]) and C4 (2 mg/dl [N: 10–40]), no monoclonal protein was found in the proteinogram. Due to persistent anuria during the initial period of hospitalization, a general urinalysis was not possible.

Urinary ultrasound showed increased echogenicity of the parenchyma of both kidneys with increased corticomedullary differentiation and hyperechoic, linear inclusions within the renal pyramids. The pelvicalyceal systems were distally slightly dilated, without deposits. High flow resistance was noted in the segmental arteries of both kidneys. The overall picture could correspond to tubulointerstitial lesions or acute tubular necrosis.

A chest X-ray revealed signs of moderately severe pulmonary circulation stasis and suspected pleural fluid.

Initially, conservative treatment of acute kidney injury was attempted, but due to the persisting anuria and increasing nitrogen retention parameters, hemodialysis therapy was implemented on the third day of hospitalization. Due to suspected acute tubulointerstitial nephritis, steroid therapy was initiated: five intravenous infusions of methylprednisolone 500 mg/day, followed by oral prednisone 40 mg/day in gradually reduced doses. From the 10th day of hospitalization, after two weeks of anuria, a gradual return of diuresis was observed. Dialysis therapy was continued until the 13th day of hospital stay (11 days in total). After the return of diuresis, a general urinalysis showed: proteinuria of 15 mg/dl, hematuria and reduced urine specific gravity (1.005 g/l [N: 1.016-1.035]), with no other abnormalities. Daily proteinuria was 857 mg.

In addition, due to the suspected infectious origin of the acute kidney injury, the empirical antibiotic therapy was initiated (with ciprofloxacin, ceftriaxone) and blood (sterile) culture test was performed.

The treatment resulted in an improvement in the patient's condition: a reduction in oedema, inflammatory markers, and renal function parameters (on the day of discharge, creatinine 1.1 mg/dl, urea 33 mg/dl, CRP 0.8 mg/dl).

A diagnostic renal biopsy was performed to clarify the cause of acute kidney injury with prolonged anuria and low complement component levels. The result corresponded to tubulointerstitial inflammation with a non-specific picture, which, however, raised the suspicion of a drug-related etiology (infiltration of numerous eosinophils and plasma cells).

During hospitalization, the patient developed normocytic anemia (hemoglobin 8.5 g/dl) with associated thrombocytopenia and lymphopenia, which, in combination with mononuclear cell infiltration in the renal biopsy, gave suspicion of a proliferative process from the hematopoietic system. A fine-needle aspiration biopsy of the bone marrow was performed, and hematologist was consulted, without confirming proliferative disease. The diagnostics for anemia was extended, iron deficiency, vitamin B12 deficiency and hemolysis were ruled out, folic acid deficiency was diagnosed, and folic acid supplementation was implemented.

The patient stayed in hospital for 21 days. She was discharged in a good general condition with the recommendation to take prednisone in a gradually reduced dose (from 30 to withdrawal in outpatient follow-up).

After 9 months, the patient was admitted electively to the Department for evaluation of the ongoing treatment. The interview, physical examination and additional tests did not reveal any significant abnormalities.

Discussion

The clinical picture of TIN is non-specific, ranging from asymptomatic forms to those with multiple symptoms, such as abdominal or lumbar pain, nausea and vomiting, weakness, fever, skin rash and arthralgia. The vast majority of patients develop kidney injury with impaired kidney function, but only exceptionally requiring the introduction of dialysis therapy. The disease is diagnosed based on the whole clinical picture and the history of potential causes of TIN. The most indicative tool in TIN is a diagnostic renal biopsy, but in most cases, especially in patients with co-morbidities, the diagnosis of TIN is based on clinical picture due to the risks associated with the renal biopsy [6, 7].

Treatment of TIN is based on discontinuing exposure to the causative agent. In addition, due to the inflammatory

Table 1. Profile of serum creatinine, urea concentrations and CRP values during hospitalisation.

Day of hospitalisation	1	2	3	4	6	8	10	11	12	15	18	19	21
Creatinine (mg/dl)	6.9	7.8	10.2	9.5	10.4	9.1	5.1	4.9	3.4	2.7	1.6	1.4	1.1
Urea (mg/dl)	97	115	139	111	125	180	122	156	116	92	76	52	33
CRP (mg/dl)	6.5	8.3	11.5	13.9	9.9	3	-	0.8	0.9	-	0.8	-	-

background of this condition, immunosuppressive treatment, usually in the form of steroid therapy, is very often necessary, although no strict guidelines have been established so far for the treatment regimen of this disease [8,9].

This case report of a patient with acute tubulointerstitial nephritis proves that the clinical picture of this disease may be non-specific. In the described case, there were no symptoms considered most characteristic, such as fever, skin rashes and eosinophilia, but we could note the development of severe renal failure accompanied by anuria and peripheral oedema, as well as abnormalities in the morphological picture of the peripheral blood, resembling proliferative processes within the hematopoietic system [6]. Despite her relatively young age and few comorbidities, the patient developed severe acute kidney injury requiring renal replacement treatment and steroid therapy. Although the patient stayed in hospital for a prolonged period, the effects of the applied treatment were satisfactory, as illustrated by a significant decrease in renal parameters and inflammatory exponents (Table 1). The therapy results were sustained, as confirmed by examinations performed during the follow-up hospitalization.

Summary

The presented case of a patient with acute tubulointerstitial nephritis shows that this disease may occur in a relatively young person without an extensive history of comorbidities. Moreover, even small doses of such easily available and frequently used non-steroidal anti-inflammatory drugs (NSAIDs) can, in the short-term, lead to severe renal failure, even requiring the implementation of renal replacement therapy, which demonstrates how severe the clinical course of TIN can be. From a practical perspective, these observations lead to the conclusion that TIN may develop in patients of any age group and that symptoms can be varied. Therefore, increased diagnostic vigilance is extremely important to avoid the serious health consequences of TIN resulting from a lack of diagnosis or its significant delay.

In the described case, the patient fully recovered. However, it is important to remember that the patients with a history of TIN must be followed-up regularly due to the increased risk of disease recurrence.

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ACUTE AND DELAYED CONSEQUENCES OF VITAMIN D INTOXICATION: TWO CASE REPORTS

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Abstract:

Background

Vitamin D intoxication (VDI) is a rare cause of kidney injury, but it can have fatal consequences. We would like to present two cases of patients in whom high doses of vitamin D intake led to significant health problems

Case Presentation

The first case is a 68-year-old woman taking approximately 20,000 IU of vitamin D daily. On admission, laboratory tests showed elevated renal function parameters, hypercalcemia, and elevated serum vitamin D concentration. The second case was a 71-year-old man intoxicated with vitamin D two and a half years earlier, as a consequence the patient was included in the chronic hemodialysis program. Because of a potentially reversible cause of kidney disease – signs of tubulointerstitial nephritis and persistent high serum vitamin D concentration, attempt of hemodialysis withdrawal was made, steroid therapy was administered, without expected effect.

Discussion

A persistent problem is supplementing with high doses of vitamin D without medical supervision. It is estimated that a significant number of people in the U.S. population takes more than 4,000 IU of vitamin D per day. These are the doses that have been linked to numerous health benefits by unverified sources, even though in recent years scientific studies have been able to refute some of these claims. Based on the two cases we have presented, we want to emphasize how serious the consequences of vitamin D intoxication can be.

Conclusions

Vitamin D intoxication may cause acute kidney injury, and in some cases may lead to end-stage renal failure and require renal replacement therapy.

Keywords: hemodialysis, hypercalcemia, renal failure, vitamin d intoxication.

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Background

Vitamin D intoxication (VDI) is a rare cause of kidney injury even though taking higher-than-recommended doses of vitamin D supplementation is common in the general community. This is due to easy accessibility of supplements and high prevalence of unverified data on health benefits of taking these products. It is worth to ask patients carefully about the dietary supplements they are taking, especially when kidney injury is combined with hypercalcemia, because of the potentially fatal consequences of VDI [1].

We describe cases of two patients who suffered from VDI caused by excessive long-term intake of over-the-counter vitamin D supplements. Patient A presents acute consequences of VDI, while patient B presents effects of VDI years after the last oral intake of vitamin D.

Case presentation

Patient A

A 68-year-old female patient previously treated only for hypertension presented to the emergency room with a history of progressive weakness and anemia on laboratory tests performed by a primary care physician. Laboratory tests showed elevated ionized calcium concentration of 1.75 mmol/l (normal range 1.15–1.35 mmol/l) and elevated total serum calcium concentration 13.5 mg/dl (8.6–10.2 mg/dl), significantly elevated creatinine concentration 5.4 mg/dl (0.5–0.9 mg/dl), urea concentration 98 mg/dl (15–43 mg/dl) and anemia with hemoglobin of 9.3 g/dl (11–18 g/dl). Parathyroid hormone concentration was normal. The patient was admitted to the nephrology department for further diagnostics and treatment.

On admission, the patient's main complaints were: pruritus of the whole body (persistent for six months), unintended weight loss of 4 kg in the last 8 months, abdominal pain and constipation. On physical examination: blood pressure and pulse rate were within normal limits. Lung auscultation revealed normal symmetric vesicular sound. The patient's skin presented numerous excoriations on the back. The abdomen was soft, non-tender, without peritoneal signs or pathological masses, with numerous pale striae and a small umbilical hernia. Peripheral oedema was absent.

During hospitalization the patient admitted to long-term intake of high doses of vitamin D (approximately 20,000 IU per day) and calcium supplements. 25-hydroxyvitamin D serum concentration was 279.5 ng/ml (20–80 ng/ml). Hypercalcemia was treated with intensive fluid therapy, diuretics, and glucocorticosteroids. Antihistamines were used in the treatment of severe pruritus. Intravenous iron was given because of decreased serum iron concentration and anemia.

Because of suspicion of multiple myeloma, x-rays of the skull and pelvis were performed, as well as serum protein electrophoresis, urine and blood immunofixation tests and concentration of light chains of immunoglobulins, showing a kappa/lambda serum ratio of 2.171 and finding no osteolytic lesions in radiological studies. Bone marrow biopsy was not performed as indicated by a consultant hematologist.

During hospitalization abdominal ultrasound was performed with findings as follows: a few benign lesions and calcium deposits, as well as reduced parenchymal layer with a loss of corticomedullary differentiation in the right kidney. Gastroscopy was performed finding several elevated erosions in the antrum. The urease test was negative. No abnormalities were found in a colonoscopy apart from melanosis in the colon.

After 12 days of hospitalization there was an improvement in renal function, blood creatinine concentration decreased to 3.2 mg/dl, and urea concentration decreased to 82 mg/dl. We observed a consistent decrease in total serum calcium concentration to 10.9 mg/dl and ionized calcium with a final day result of 1.47 mmol/l. Despite a further drop in hemoglobin concentration, blood was not transfused due to a lack of patient consent.

We observed a significant reduction in pruritus. The patient was released home with a recommendation of withdrawal of vitamin D and calcium supplementation.

Patient B

A 71-year-old male patient with a history of end-stage chronic kidney disease secondary to VDI was admitted to the hospital for a re-assessment of the purposefulness of further hemodialysis. The patient had become intoxicated with vitamin D two and a half years earlier, at which time intermittent hemodialysis was initiated. With stable renal function parameter results and normal diuresis, it was possible to discontinue hemodialysis for six months. About a year and a half earlier, the patient was put back on a chronic hemodialysis program because of increasing symptoms of chronic kidney disease.

The patient also presented a history of hypertension, permanent atrial fibrillation, dilated cardiomyopathy, hypertensive retinopathy, spondylosis, obesity, restless legs syndrome, benign prostatic hyperplasia and hemodialysis-catheter-related sepsis five months earlier. The patient denied kidney disease before the VDI episode.

On the initial examination the patient presented with irregular heartbeat, hypertension, and pain in the shoulders, lumbar and cervical spine but denied any abdominal tenderness, muscle weakness or signs of infection.

The patient was admitted to the hospital to start treatment - findings of tubulointerstitial nephritis with nephrocalcinosis on kidney biopsy indicated a potentially reversible cause of the disease. Persistently high blood concentration of vitamin D were noted, even though the patient had not taken vitamin D supplementation for more than two and a half years.

Initially hemodialysis was discontinued and the patient received intravenous diuretic therapy. He had a serum total calcium concentration in the normal range of 9.1 mg/ dl (8.6–10.2 mg/dl), with a parathyroid hormone concentration of 78.7 pg/ml (15–65 pg/ml) and elevated 25OHD serum concentration of 91.3 ng/ml (20–80 ng/ml). A test for active vitamin D (1,25 (OH)2) was also taken, and its concentration was low: 19.2 pg/ml (20–63 pg/ml).

The patient received 125 mg of methylprednisolone on days 6–8. Steroid therapy was continued orally with prednisone. Due to low diuresis despite high dose intravenous diuretic therapy and increasing peripheral edema, hyperkalemia and increasing creatinine and urea concentration, the patient underwent hemodialysis on day 7 of hospitalization. Tests were performed for other possible causes of tubulointerstitial nephritis: tuberculosis, syphilis and multiple myeloma, all turned out to be negative.

After 11 days of hospitalization, the patient was released from the hospital with recommendations for further renal replacement therapy and steroid therapy. A date has been set for another hospitalization to assess the effects of implemented treatment, at which the patient did not appear.

Discussion

Various non-medical sources attribute remarkable health benefits as an effect of taking high doses of vitamin D. In recent years, many randomized controlled clinical trials and meta-analyses have been published that do not support some of these claims. Increasing serum 25 OHD concentration does not significantly affect the risk of cancer, cardiovascular incidents, type 2 diabetes, falls or fractures. While taking doses above 4,000 IU daily is associated with a risk of hypercalcemia and hypercalciuria [2]. Due to widespread access to unverified medical knowledge on the internet and easy access to vitamin D supplements, many people take supplements on their own without medical supervision. It is estimated that in 2013–2014, more than 3% of the U.S. adult population took supplements containing 4,000 IU (100 µg) or more vitamin D [3]. There are over-the-counter preparations on the market that contain very high unit doses of cholecalciferol up to as much as 50,000 IU (1,250 µg) per capsule. A significant problem is also the content of vitamin D in unlicensed supplements, in many reports exceeding many times the dose declared on the package [4].

Symptoms of VDI depend on vitamin D metabolism and function. Vitamin D is lipophilic, in the body it is stored in adipose tissue with an elimination half-life of approximately 2 months. Both 25OHD and 1,25 (OH)2D circulate bound to vitamin D binding protein (DBP), while the free form of 1,25 (OH)2D is considered the metabolically active form. Although it is 1,25OH2D that is the active form of vitamin D, toxicity may also result from the high concentration of circulating 25OHD through direct activation of vitamin D receptors and dissociation of 1,25OH2D from DBP associated with excess circulating 25OHD [5, 6].

Vitamin D is involved in the regulation of more than 1000 genes [7]. The clinical manifestations of VDI can be varied but are closely related to hypercalcemia and include weakness, nausea, vomiting, polyuria, dehydration, abdominal pain and anorexia [8]. Hypercalcemia is the leading cause of AKI in VDI. There are three potential causes of AKI in hypercalcemia: spasm of the afferent arteries resulting in decreased glomerular filtration rate, decreased antidiuretic hormone reactivity resulting in dehydration and tubular damage, and fibrosis due to long-term calcium deposition in the kidney [9].

Further complications of VDI can be serious. Patients with chronic kidney disease are much more prone to complications [10]. Elevated vitamin D concentrations may persist long after supplementation is discontinued due to its long half-life [11]. This may be partly related to the accumulation of fat-soluble vitamin D in adipose tissue, as well as to the effect of parathormone itself, prolonging the half-life of vitamin D, as has both been reported in the past [12, 13].

Patient A, although she originally arrived at the hospital due to anemia, presented with symptoms of hypercalcemia, such as abdominal pain, constipation, fatigue, as well as worsening renal function and nephrolithiasis in ultrasonography. Due to taking high doses of vitamin D supplements, her serum 25OHD concentration was as high as 279.5 ng/ml (698.75 nmol/l) while concentrations above 150 ng/ml (375 nmol/l) are already a sign of VDI [14]. However, it is worth mentioning that high vitamin D concentrations correlate neither with serum calcium concentration nor with clinical symptoms [15]. The applied treatment of hypercalcemia had the expected effect, the symptoms reported by the patient significantly decreased. The blood calcium concentration decreased, and a reduction in creatinine and urea concentration was achieved.

Patient B presents with renal failure associated with hyperparathyroidism as well as VDI years ago. Despite ending supplementation of vitamin D two and a half years earlier, the patient presented with high serum 25OHD concentration at the time. Also, despite the long time since the cessation of vitamin D supplementation, steroid treatment was attempted. Immediately in the hospital, the expected effect was not obtained, and it was necessary to continue intermittent hemodialysis. There are no data on the patient's further course of the disease because he did not appear for a scheduled visit.

Conclusion

Vitamin D intoxication can cause both acute and delayed health problems so, due to the prevalence of patient use of dietary supplements, it is worth to remember VDI as a possible cause of hypercalcemia and renal failure.

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CASE STUDY

INFECTIVE ENDOCARDITIS WITH NEGATIVE BLOOD CULTURES IN PATIENTS WITH END-STAGE RENAL DISEASE TREATED WITH PERITONEAL DIALYSIS

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Abstract: Infective endocarditis (IE) is an inflammatory disease involving a proliferative-destructive processes, usually of streptococcal or staphylococcal etiology. It may also be caused by the physiological flora of the oral cavity, mainly gram-negative bacteria from the HACEK group. IE typically develops in damaged areas of the endocardium. Bacterial vegetations are found in majority on valves but they may be as well visualized in blood vessels, ventricles, on mechanical valves, electrodes and intracardiac catheters. Risk factors for endocarditis concern the growing population of adults with congenital heart disease and patients with frequent healthcare contact for other comorbidities, also patients who are immunocompromised, treated with hemodialysis or use intravenous drugs. The diagnosis of IE is made by the use of transthoracic or transesophageal echocardiography, also other imaging techniques are used. Blood cultures also should be taken. However, it was estimated that approximately 10% of patients have cultures and serologic tests negative for IE. In our study we present a case of a 51-year-old man with end-stage renal disease treated with peritoneal dialysis for 3 weeks prior to hospital admission with an acute infection of unknown origin. Infective endocarditis was suspected based on echocardiography examination. In this case PET-CT (positron emission tomography/computed tomography) was performed for verification. Its result as well as sterile blood cultures did not fully confirm the diagnosis of IE. Despite the access to highly specialized diagnostic methods and broad-spectrum antibiotics the diagnosis and treatment were not easy. This story of patient's disease can be the confirmation that IE is heterogeneous in etiology, clinical manifestations, and course.

Keywords: peritoneal dialysis, echocardiography, infective endocarditis, blood cultures.

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Introduction

Infective endocarditis develops as a result of an endocardial infection, most often of bacterial – staphylococcal etiology [1]. Risk factors include heart defects, previous endocarditis, medical procedures that disturb the continuity of heart tissue and frequent contact with health care [2, 3]. Despite the use of antibiotic prophylaxis in the highest-risk patients, preventive procedures and improvement of diagnostic methods it is still a disease that not only is a diagnostic challenge but is also associated with mortality up to 30% and serious complications [4, 5]. It can have a different course, from a mild infection to septic shock and multiorgan failure [6]. Early clinical suspicion and a rapid diagnosis are essential to enable the correct treatment pathways to be accessed and to reduce complication and mortality rates [7]. The clinical indications of IE rely on the Duke criteria which are presented in Table 1.

Case report

A 51-year-old man with a history of type 2 diabetes complicated by end-stage renal disease, diabetic retinopathy, bilateral diabetic foot syndrome, peripheral polyneuropathy, hypertension, atherosclerosis, after implantation of stents into the left femoral superficial artery, secondary hyperparathyroidism, hyperuricemia, history of nicotine addiction, qualified to renal replacement therapy that started 3 weeks earlier with peritoneal dialysis, after implantation of the Tenckhoff catheter 1.5 months earlier, was applied to the Hospital Emergency Department because of worsening of his general condition and intensification of pain of the lumbosacral and thoracic spine. These symptoms were accompanied by a low-grade fever and a decrease of blood pressure. Symptoms began four days prior to hospitalization. Patient was admitted to the Department of Nephrology.

Table 1. Modified Duke Clinical Diagnostic Criteria for Infective Endocarditis [13]

Major criteria	**Positive blood cultures for infective endocarditis** Typical microorganisms consistent with IE from 2 separate blood cultures: • Viridans streptococci, Streptococcus bovis, HACEK group (Hemophilus spp, Actinobacillus acti-nomycetemcomitans, Cardiobacterium hominis, Eikenella spp, and Kingella kingae), S. aureus; or community-acquired enterococci, in the absence of a primary focus; or • Microorganisms consistent with IE from persistently positive blood culture results, defined as follows: • At least 2 positive culture results of blood samples drawn 12 h apart; or • All of 3 or most of ≥4 separate culture samples of blood (with first and last samples drawn at least 1 h apart) • Single positive blood culture result for Coxiella burnetii or antiphase I IgG antibody titer > 1:800
	Evidence of endocardial involvement • positive echocardiogram for infective endocarditis: oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or on implanted material in the absence of an alternative anatomical explanation or abscess or new partial dehiscence of prosthetic valve • new valvular regurgitation
Minor criteria	**Predisposition,** predisposing heart disorder, or IV illicit drug use
	Fever ≥ 38.0°C
	Vascular phenomena: arterial embolism, septic pulmonary embolism, mycotic aneurysm, intracranial hemorrhage, conjunctival petechiae, Janeway lesions
	Immunologic phenomena: glomerulonephritis, Osier nodes, Roth spots, Rheumatoid factor
	Microbiologic evidence of infection consistent with but not meeting major criteria
	Serologic evidence of infection with organisms consistent with endocarditis

On admission to the Department of Nephrology detailed medical history was taken. Patient denied typical symptoms of respiratory or urinary tract infections. Physical examination revealed regular heart rate, clear and correctly accentuated heart tones, correct blood pressure values. Lung fields were normal on auscultation. There was a skin lesion on the surface of the right heel. In biochemical tests normocytic anemia (hemoglobin 11.1 g/dL, mean corpuscular volume of red cells 93 fl), leukocytosis (10.54x10^9/L) with neutrophilia (75.7%), increased inflammatory parameters – C-reactive protein (CRP) (2.7 mg/dL) and procalcitonin (PCT) (0.9 ng/L) were found. Slight leukocyturia was researched in the analysis of urine, but there were no bacteria in the sample. What is more no evidence of peritonitis was detected during assessment of dialysis fluid morphology. Blood and urine cultures also were tested. Considering the health state of patient (weakness, fever) empiric antibiotics were initiated (ciprofloxacin and ceftriaxone). Despite wide range of examinations trigger of infection was not revealed. As part of the search a surgical consultation was made to assess the skin change on patient's right heel. A second--degree thermal burn was diagnosed. It was unlikely to be the source of suspected bacteremia. In connection with persistent pain of the lumbosacral and thoracic spine computed tomography and magnetic resonance were performed. Imaging showed degenerative changes of the spine and excluded the presence of abscesses in the thoracic and lumbosacral spine. The ultrasound examination of the abdomen apart from the increased echogenicity of both kidneys was correct. Blood and urine cultures were sterile. Due to the persistently high values of inflammatory parameters and the lack of clinical improvement, antibiotic therapy was modified. Meropenem and vancomycin were started. In the course of further diagnostics, the echocardiography examination was performed, which visualized the 6mm x 9 mm lesion connected to the edge of the non-coronary aortic valve cusp (Figure 1). Infective endocarditis was suspected. Firstly a transesophageal echocardiography was made for verification. It revealed small degenerative changes in the coronary aortic valve cusp and also small, thin, airy threadlike echo, connected with coronary aortic valve cusp, 7 mm long, which was diagnosed as a Lambla thread for possible differentiation with bacteria vegetation in the course of IE. The patient was qualified for PET/CT examination and increased accumulation of 18-fluorodeoxyglucose in a delayed phase in left ventricle was shown. However, no definite diagnosis of IE was made after all these examinations. On completion the treatment the patient's condition improved significantly. Inflammatory markers were finally decreased (CRP 0.4 mg/dL, PCT 0.21 ng/mL). Peritoneal dialysis was correct, without peritonitis in clinical examination and in peritoneal effluent examination. Although the diagnosis was not clear, patient was discharged with the intention of another echocardiographic examination in two weeks during the planned visit at the Dialysis Center.

As recommended, the patient applied for a follow-up. In transthoracic echocardiography examination a hypoechogenic lesion associated with the margin of the

non-coronal aortic valve cusp, measuring 12 mm x 4 mm, was visualized (Figure 2). Unfortunately, second time the progressive weakening and a dynamic rise of inflammatory parameters (CRP 28 mg/dL, PCT 0,9ng/dL) were noticed. Decision was made to use another empiric antibiotic therapy (biseptol and fluconazole) and to admit the patient to the hospital for further diagnostics.

On admission patient reported weakness, fatigue, dizziness and pain of the lumbar spine making it difficult to move. As previously, the physical examination found no significant pathologies. The heel area of the right foot showed no signs of inflammation, the burn was in the process of healing. Blood cultures were negative. During hospitalization an echocardiographic examination was performed. The reduction of the lesion associated with the edge of the non-coronary aortic valve cusp to 5 mm x 2 mm was noticed. More of the same diagnostics were performed to identify different sources of infection. Even skin and rectum swabs remain negative. Patient was consulted by otolaryngologist and dentist – no potential foci of infection were detected. As well as no inflammatory changes were visualized on the chest X-ray. Based on the overall clinical picture, echocardiography examination, PET-CT examination and by exclusion of other active foci of infection, the diagnosis of infectious endocarditis of the aortic valve was made. Empirical antibiotic therapy was started – ampicillin, cloxacillin and gentamicin. During further treatment, considering a slight decrease of inflammatory markers after 7 days of full antibiotherapy (CRP 28 -> 23.8mg/dL, PCT 0.9 -> 0.86 ng/mL), a decision was made to replace cloxacillin with vancomycin. After this modification, the patient's condition improved quickly. Control laboratory tests showed the significant decrease of inflammatory markers (CRP 0.7 mg/dL and PCT 0.2 ng/mL). The patient, in fairly good general condition, was discharged with instructions to continue antibiotic therapy during outpatient treatment.

Figure 1. Transthoracic echocardiography visualizing lesion connected with aortic valve. Modified parasternal long-axis view.

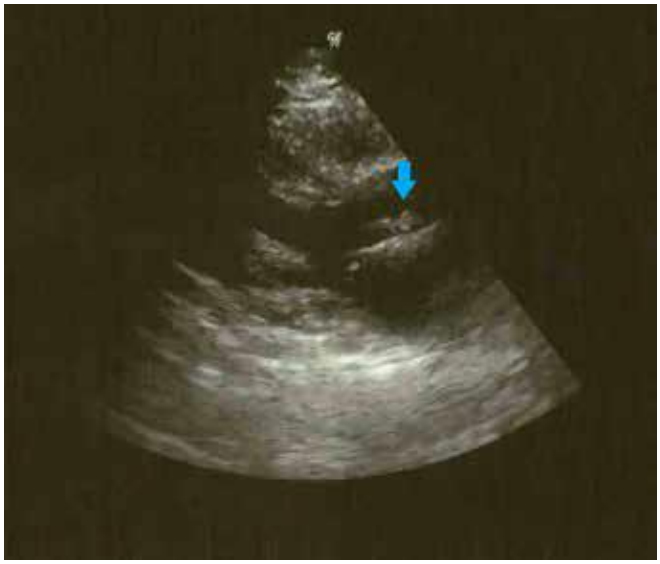
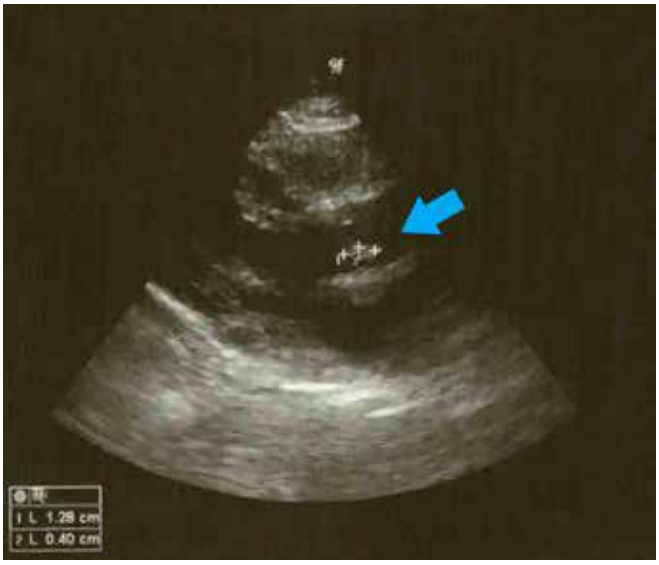


Figure 2. Transthoracic echocardiography visualizing the dimensions of the lesion connected with aortic valve. Modified parasternal long-axis view.



Discussion

Infective endocarditis is a diagnostic challenge due to the numerous possibilities of clinical manifestation and the serious consequences of late diagnosis. The course may differ depending on the etiology and the presence of risk factors [9]. It is also quite rare disease so definitive studies of IE have been limited [10]. Because of a non-specific character of inflammatory parameters such as CRP and PCT they cannot be used as a basis for the diagnosis of infective endocarditis. It is recommended to use the algorithm according to the modified Duke criteria in which the result of transthoracic and transesophageal echocardiography, positive blood culture results, and the presence of clinical symptoms are crucial for the diagnosis [11]. In the discussed case numerous comorbidities including type 2 diabetes and end-stage renal disease treated with peritoneal dialysis program made the diagnosis of IE difficult and challenging. It was very important to find the solution quickly because infection is a significant cause of morbidity in patients with end-stage renal disease undergoing maintenance dialysis [12]. One of the most common localizations of infection in this group of patients is peritonitis. New onset of abdominal pain, fever, or the appearance of cloudy peritoneal effluent need immediate response [13]. However also the incidence of IE is higher in dialysis patients compared to the general population [14]. The frequency of IE in patients treated with hemodialysis compared with those receiving peritoneal dialysis differ widely, but in both groups it is raised [15]. The difficulty in the case of described patient was that he did not present typical symptoms as well as examinations were incoherent. Fever, weakness, osteomuscular pains occur in almost every cold and lots of different infections. Thereupon sometimes they do not seem to be serious. Doctor's problem is to distinguish when fast diagnostic is needed. Based on this case we can also draw a conclusion that staying broadminded and searching for new, nonobvious solutions is very important.

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HYPERCALCEMIA IN THE COURSE OF LONG-TERM LITHIUM THERAPY

Hiperkalcemia w przebiegu długotrwałego leczenia litem

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Abstract: Lithium salts are a commonly used mood stabiliser with a narrow therapeutic index. Changes in dosage and long-term treatment bring the risk of acute and chronic complications from the cardiovascular, gastrointestinal, urinary, and endocrine systems. One of the most frequently occurring complication is hypercalcemia, which can be an independent cause of systemic signs.

The article analyses the case of a 66-year-old long-term lithium user with bipolar affective disorder, who presented with neuropsychiatric symptoms and accompanying markers of acute kidney injury. In the course of diagnosis, hypercalcemia and lithium overdose were identified. In addition, the patient presented with multiple disorders that might have resulted from acute lithium intoxication as well as chronic toxicity, including hypothyroidism, bradycardia, and parkinsonian syndrome. After lithium withdrawal and conservative treatment of hypercalcemia and acute kidney injury, significant clinical improvement was achieved, while renal parameters and serum calcium levels did not return to normal until six months after hospital discharge.

The paper aims at outlining the profile of possible adverse effects of lithium treatment, which create a complex clinical picture. It presents diagnostic and therapeutic management in hypercalcemia and lithium intoxication, as well as methods of preventing their occurrence.

Keywords: bipolar disease, acute kidney injury, hypercalcemia, lithium intoxication, lithium carbonate.

Streszczenie: Sole litu są powszechnie stosowanym stabilizatorem nastroju o wąskim zakresie terapeutycznym. Jego przekroczenie oraz długotrwała terapia obarczone są ryzykiem wystąpienia ostrych i przewlekłych powikłań ze strony układów: sercowo-naczyniowego, pokarmowego, moczowego oraz dokrewnego. Do najczęstszych zaliczana jest hiperkalcemia mogąca stanowić niezależną przyczynę objawów układowych. Omówiono przypadek 66-letniej chorej długotrwale stosującej lit z powodu choroby afektywnej dwubiegunowej, u której wystąpiły objawy neuropsychiatryczne z towarzyszącymi wykładnikami ostrego uszkodzenia nerek. W toku diagnostyki stwierdzono hiperkalcemię oraz przedawkowanie litu. Dodatkowo pacjentka prezentowała liczne zaburzenia mogące wynikać z ostrego zatrucia litem, ale także toksyczności przewlekłej w tym: niedoczynność tarczycy, bradykardię, zespół parkinsonowski. Po odstawieniu litu i zastosowaniu leczenia zachowawczego hiperkalcemii oraz ostrego uszkodzenia nerek uzyskano znaczną poprawę kliniczną. Natomiast parametry nerkowe oraz stężenie wapnia w surowicy krwi powróciły do normy dopiero po upływie sześciu miesięcy od wypisu ze szpitala. Celem pracy było nakreślenie profilu możliwych działań niepożądanych leczenia litem, które składają się na złożony obraz kliniczny. Przedstawiono postępowanie diagnostyczno-terapeutyczne w hiperkalcemii i zatruciu litem oraz sposoby zapobiegania ich wystąpieniu.

Słowa kluczowe: choroba afektywna dwubiegunowa, ostre uszkodzenie nerek, hiperkalcemia, zatrucie litem, węglan litu.

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Introduction

Lithium salts are one of the longest-used mood stabilizers, as their efficacy in the prevention of bipolar affective disorder (BAD) was demonstrated already in the 1960s [1, 2]. Despite the introduction of new types of mood stabilizers, lithium salts are the primary and most effective long-term BAD prophylaxis [3].

Lithium has a narrow therapeutic range. Treatment requires control of serum drug levels and taking into consideration such factors as age, medication taken or water-electrolyte disturbances [3, 4].

Both exceeding the permitted serum lithium concentration and long-term lithium treatment can lead to acute and chronic cardiovascular, gastrointestinal, urinary, endocrine, and nervous system complications [5-7]. One of the most common complications is hypercalcemia (3-30%), which can cause acute kidney injury [5, 8].

This study aims at presenting a case of lithium intoxication as a rare cause of hypercalcemia.

Case report

A 66-year-old patient treated with levothyroxine due to hypothyroidism and, additionally, with lithium and mianserin due to bipolar affective disorder, and in the course of vitamin D supplementation at a dose of 4,000 IU/day – presented to the Hospital Emergency Department (ED) in early May 2022 due to consciousness disturbances that had lasted for about two weeks and abnormal renal parameters. Based on the medical history it was determined that after the onset of speech and gait disturbances, the patient consulted a neurologist who raised the suspicion of Parkinson's disease and prescribed the following medications: biperiden, propranolol. The treatment was unsuccessful and, moreover, the balance impairment intensified just before he reported to hospital. The patient fell over, suffering a head injury. Laboratory tests performed on an outpatient basis showed an elevated serum creatinine level of 4.5 mg/dl.

Laboratory tests were performed in the ED (results in Table 1). Physicians paid special attention to the elevated creatinine 5.1 mg/dl, urea 145 mg/dl, ionized calcium 1.85 mmol/l and a reduced estimated glomerular filtration rate of 9 ml/min/1.73 m2. A determined lithium concentration of 2.0 mmol/l was above the therapeutic range. In order to exclude post-traumatic lesions of the nervous system, a CT scan of the head was performed. It did not reveal fresh ischemic lesions, signs of intracranial bleeding or visible fracture fissures of the cranial bones. Due to the abnormal results of the renal function indices, an abdominal ultrasound examination was performed. The only revealed abnormality was a 21 x 25 mm deposit in the gallbladder.

Due to the reported symptoms, the patient was consulted by a neurologist, who diagnosed the signs of extrapyramidal syndrome requiring further diagnosis on an outpatient basis.

Since the laboratory tests revealed the acute kidney injury and hypercalcemia, the patient was urgently admitted to the Department of Nephrology. On admission, the patient reported: fatigue, sleepiness, difficulty with articulating and walking, muscle pain and cramps, diarrhoea, reluctance to take liquids and food.

Table 1. Results of laboratory tests performed on admission to hospital.

Parameter	Result	Normal
Creatinine	5.1 mg/dl	0.45–1.10 mg/dl
Urea	145 mg/dl	15–43 mg/dl
eGFR *	9 ml/min/1.73 m2	>90ml/min/1.73 m2
Hemoglobin	10.8 g/dl	12.0–15.1 g/dl
Leukocytes	16.08 thousand/ul	4.4–9.64 thousand/ul
Lymphocytes	11.0 %	18.9–47.1%
Neutrophils	79.1 %	39.2–71.5%
Activated partial thromboplastin time (aPTT)	21.5 sec	23.0–35.0 sec
Ionized calcium	>1.85 mmol/l	1.19–1.33 mmol/l
Lithium	>2.0 mmol/l	0.6–1.2 mmol/l
Sodium	>136 mmol/l	136–145 mmol/l
Potassium	>4.7 mmol/l	3.5–5.1 mmol/l
Venous blood pH	7.383	7.350–7.450

* estimated Glomerular Filtration Rate (eGFR)

Abnormalities on physical examination included full-body tremor, dysarthria, and a slowed gait. Based on the overall clinical picture, lithium toxicity was suspected. Tests performed during hospitalization confirmed hypercalcemia with a total serum calcium concentration of 12.6 mg/ dl. In addition, the tests revealed an elevated inorganic phosphate concentration of 4.6 mg/dl and an increased free triiodothyronine concentration of 2.58 pmol/l. Parathormone, thyrotropin and free thyroxine concentrations were normal. Detailed results of the tests performed during hospitalization are shown in Table 2. The urinalysis showed the following deviations: low specific gravity of 1.009 g/l (N: 1.016 - 1.035 g/l) and leukocyturia, without the signs of any urinary tract infection.

Table 2. Serum concentrations of selected hormones and electrolytes.

Parameter	Result	Normal
Total calcium	12.6 mg/dl	8.6–10.2 mg/dl
Inorganic phosphates	4.6 mg/dl	2.6–4.5 mg/dl
Parathormone (PTH)	22.5 pg/ml	15–65 pg/ml
Thyrotropin (TSH)	0.624 ulU/ml	0.27–4.2 ulU/ml
Free thyroxine (FT4)	>16.98 pmol/l	12–22 pmol/l
Free triiodothyronine (FT3)	>2.58 pmol/l	3.2–6.9 pmol/l

Protein electrophoresis performed in differential diagnosis of hypercalcemia showed no abnormalities. The chest X-ray showed a micronodular approx. 3-millimetre-long outline located peripherally in the upper field of the right lung in the posterior projection of the fifth rib. Otherwise, no abnormalities were found.

The patient displayed a tendency to bradycardia, especially at night, therefore diagnostics was extended with a holter monitor test, which detected sinus bradycardia without pauses. A performed echocardiogram showed no significant abnormalities. A rectal swab was taken due to diarrhea. However, no pathogens were cultured that could affect the patient's clinical condition.

After reviewing the results of all diagnostic tests, acute kidney injury was diagnosed in the course of hypercalcemia in the patient with lithium poisoning. Lithium and vitamin D products were discontinued and conservative treatment of acute kidney injury with control of body fluid balance was applied. This treatment resulted in an improvement in the patient's general condition, a gradual resolution of nervous system symptoms and an improvement in renal function. On the day of discharge, a serum creatinine level was 1.6 mg/dl, total calcium 10.7 mg/dl. After psychiatric consultation, sodium valproate with valproic acid and mianserin were introduced in order to stabilize the mood. The hospitalization proceeded without complications. The patient was discharged for further psychiatric and neurological care on an outpatient basis. Approximately 6 months after discharge from hospital, serum calcium and creatinine levels returned to normal. The patient feels well and is in a balanced mood.

Discussion

In the presented case, the first neurological symptoms resulted most likely from a complication of chronic lithium neurotoxicity. Subsequently, further factors favoring lithium accumulation were added, such as the inclusion of propranolol, which reduces lithium clearance, and progressive dehydration, which in combination led to toxic serum lithium concentrations and induced hypercalcemia. The diagnosed acute kidney injury in the course of hypercalcemia induced further lithium accumulation, leading to exacerbating symptoms of lithium poisoning. The diagnostic process was complicated due to neurological symptoms and renal injury, which could result from both chronic lithium treatment, acute lithium toxicity or hypercalcemia.

Neurological symptoms of moderate to severe lithium toxicity include impaired consciousness, gait disturbances, muscle fasciculations and extrapyramidal disorders. These symptoms occur when the serum concentration of the drug exceeds 1.6 mmol/l [9]. On the other hand, the long-term lithium therapy may cause the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). In patients on long-term lithium treatment, SILENT may occur even at the therapeutic serum lithium concentrations [5, 10]. Typical manifestations of the syndrome include persistent cerebellar disorders, extrapyramidal symptoms, brainstem dysfunction and dementia with associated psychoorganic disorders of varying severity. The differentiating criterion between acute lithium toxicity and SILENT is the persistence of neurological symptoms despite discontinuation of lithium therapy and normalization of serum lithium levels [10, 11].

Although all the neurological symptoms presented by the patient could correspond to the picture of SILENT, only the symptoms of Parkinson's syndrome that did not resolve as a result of the applied treatment were suggestive of their potential association with this syndrome, while the remaining neurological symptoms most likely resulted from the acute lithium toxicity and accompanying hypercalcemia.

Hypercalcemia may occur during lithium treatment as a result of acute lithium toxicity or permanent parathyroid lesions. Acute disorders are potentially reversible and result from lithium antagonizing calcium-sensitive receptors in the parathyroid glands and kidneys, leading to disorders resembling familial hypocalciuria with hypercalcemia. In contrast, in patients treated with lithium for a long time, the most common cause of hypercalcemia is primary hyperparathyroidism, which may result from lithium-induced increased proliferation of the gland or disclosure of pre-existing parathyroid disorders, such as subclinical adenoma [12, 13]. The literature reports the case of a patient receiving the long-term lithium treatment with recurrent hypercalcemia despite maintaining normal serum PTH concentrations [14].

In the described case, the values of serum PTH and phosphate concentrations, no history of renal disease and the acute onset of symptoms speak against long-term lithium treatment as the cause of hypercalcemia. The clinical history and serum lithium levels suggest acute lithium toxicity as the most likely cause of the patient's hypercalcemia.

When hypercalcemia occurs in a patient treated with lithium, a diagnostician should exclude neoplastic and granulomatous diseases as well as side effects of other drugs, including thiazide diuretics, aminophylline, tamoxifen, vitamins A and D [15].

Renal damage during lithium treatment may be acute or may be a complication of the long-time treatment. Acute kidney injury in the course of lithium treatment may result not only from the toxic effects of lithium exceeding the therapeutic range, but also from hypercalcemia [16]. The nephrotoxic effects of lithium during long-term treatment led to chronic tubulointerstitial nephropathy, whereas the progression of the disease and the degree of renal parenchymal fibrosis depend on the medication dose and the total duration of lithium treatment [17–19].

Monitoring the patient's serum lithium and calcium levels are crucial for maintaining the safety of long-term lithium therapy. The second important element is controlling serum renal function indices, which are reported to be inadequately monitored during lithium salt use [16, 20]. The literature suggests frequent, at least annual, checks of lithium levels [21–23].

Treatment for lithium poisoning should follow two tracks, addressing both electrolyte imbalance and high serum lithium concentrations. Treatment of mild hypercalcemia

may be limited to discontinuation of vitamin D and lithium preparations and hydration to regain electrolyte balance. In cases of hypercalcemia due to primary hyperparathyroidism, adequate calcium control can be achieved with cinacalcet or the patient can be qualified for parathyroidectomy [24]. If the therapeutic range of lithium serum levels is significantly exceeded or if severe symptoms of lithium toxicity occur, especially in patients with significantly impaired renal function, renal replacement therapy with hemodialysis procedures should be considered [4]. If complications of the long-term lithium treatment occur, the benefits and risks of discontinuing lithium and including another mood stabilizer should be considered [5].

The symptoms presented by the patient and multimorbidity started with a bipolar affective disorder and the lithium used in its treatment. Hypothyroidism, bradycardia, parkinsonian syndrome, as well as hyperleukocytosis and urine thickening disorders are characteristic complications of the long-term lithium treatment [5, 21]. What also drew attention was patient's restricted food and fluid intake. Although these symptoms may have been due to hypercalcemia, food and fluid aversion may also be associated with chronic lithium treatment.

Summary

This paper highlights the problems of diagnosis and treatment of hypercalcemia caused by inadequately controlled lithium treatment of bipolar disease.

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CASE STUDY

DENT DISEASE AS A RARE CAUSE OF PROTEINURIA

Choroba Denta jako rzadka przyczyna białkomoczu

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Abstract: Dent disease is a rare, genetically determined tubulopathy associated with a mutation on the X chromosome, characterized by the occurrence of low molecular weight proteinuria (LMWP), hypercalciuria, and at least one of the following symptoms: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia or renal failure. In the early stages of the disease, the only symptom may be proteinuria. We present a case of a 5-year-old boy admitted to the clinic due to proteinuria, which was detected during a follow-up examination after an upper-airways infection. Further diagnostics also showed signs of hypercalciuria. The family history revealed the death of the mother's relative at the age of 32, probably due to renal failure, and kidney diseases in relatives on the father's side. Due to persistent nephrotic-range proteinuria, a kidney biopsy was performed, which revealed focal segmental glomerulosclerosis (FSGS). Genetic testing was performed due to the increased presence of low-molecular-weight proteins in the urine and hypercalciuria. It confirmed a de novo mutation in the CLCN5 gene, indicating Dent disease. Treatment included the use of an angiotensin-converting enzyme inhibitor and a thiazide diuretic. The above case confirms that the rare occurrence of Dent disease presents diagnostic difficulties in patients with proteinuria. However, proper diagnosis, including the evaluation of low-molecular-weight proteins, calcium levels in urine, and genetic testing, can avoid immunosuppressive treatment, which is ineffective and associated with adverse side effects.

Keywords: Dent~~'s~~ disease, proteinuria, hypercalciuria, low molecular weight proteinuria (LMWP).

Streszczenie: Choroba Denta należy do rzadkich, genetycznie uwarunkowanych tubulopatii związanych z mutacją na chromosomie X, która charakteryzuje się występowaniem białkomoczu drobnocząsteczkowego (low molecular weight proteinuria, LMVP), hiperkalciurii oraz przynajmniej jednego z poniższych objawów: nefrokalcynozy, kamicy, hematurii, hipofosfatemii lub niewydolności nerek. W początkowym okresie choroby jedynym objawem może być białkomocz. Przedstawiamy przypadek 5-letniego chłopca, przyjętego do kliniki z powodu białkomoczu stwierdzonego w badaniu kontrolnym po przebyciu infekcji górnych dróg oddechowych. Dalsza diagnostyka uwidoczniła również hiperkalciurię. Wywiad rodzinny obciążony zgonem krewnego matki w wieku 32 lat, prawdopodobnie z powodu niewydolności nerek oraz chorobami nerek u krewnych ze strony ojca. Z powodu utrzymującego się białkomoczu nerczycowego wykonano biopsję nerki, na podstawie której rozpoznano ogniskowe, segmentalne szkliwienie kłębuszków (FSGS). Ze względu na zwiększoną zawartość w moczu białek o niskiej masie cząsteczkowej oraz hiperkalciurię - wykonano badanie genetyczne. Rozpoznano mutację de novo w genie CLCN5, potwierdzającą chorobę Denta. W leczeniu zastosowano inhibitor konwertazy angiotensyny i diuretyk tiazydowy. Powyższy przypadek potwierdza, że rzadkie występowanie choroby Denta rodzi trudności diagnostyczne u pacjentów z białkomoczem, jednak prawidłowa diagnostyka zawierająca ocenę białek o niskiej masie cząsteczkowej, ocenę kalciurii oraz badanie genetyczne pozwala uniknąć leczenia immunosupresyjnego, które jest w tej chorobie nieskuteczne i wiąże się z wystąpieniem obciążających działań niepożądanych.

Słowa kluczowe: choroba Denta, białkomocz, hiperkalciuria, niskocząsteczkowy białkomocz (LMWP).

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Introduction

Dent disease is a rare, genetically determined tubulopathy. It is caused by a mutation on the X chromosome, leading to symptoms of Fanconi syndrome with increased loss of low molecular weight (LMW) proteins [1]. The disease usually develops in boys and can start in early childhood. Women sometimes have a mild disease phenotype [2]. The diagnosis of Dent disease is based on the presence of three symptoms: LMVP (low molecular weight proteinuria), hypercalciuria and one of the following: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia or renal failure [3, 4]. Dent disease has so far been reported in around 250 families worldwide [3].

The pathomechanism of the disease is associated with defective CIC-5 chloride channel located in the cellular membranes of the proximal tubules, the thick ascending limb of Henle's loop and in the collecting tubule [5]. This channel interacts with vacuolar H+ -ATPase (V--ATP) [6], which is responsible for the reabsorption of albumin and LMW proteins by tubule cell endosomes. Activation of V-ATPase in endosomes, which enables protein transport, results in the release of hydrogen ions into the endosome. The action of the CIC-5 chloride channel through H+/Cl- exchange enables the removal of excess positive charges from within the endosome and maintaining V-ATP-ase production. Mutation of the CLCN5 gene blocks the CIC-5 channel function, resulting in proximal tubular cell dysfunction and symptoms of Fanconi syndrome. The disease has a genetically varied nature. 50-60% of patients present with a CLCN5 mutation (Dent Disease 1), about 15% have an OCRL1 mutation (Dent Disease 2, Lowe syndrome) and the remaining 25-35% have none of the above mutations but are likely to have a defect in other genes [7-10]. Dent disease as a congenital genetic disorder is still incurable. The only possible symptomatic treatment focuses on the management of hypercalciuria and the prevention of kidney stones. It has been shown that the use of thiazides at doses similar to those used to treat idiopathic hypercalciuria can partially reduce urinary calcium excretion [11-12]. The prognosis in most patients is good, although chronic kidney disease develops between 30 and 50 years of age in 30-80% of men [3].

Case report

We present the case of a 5-year-old previously healthy boy referred to the nephrology clinic because of proteinuria first found on examination after an upper respiratory tract infection. A boy was born from the second pregnancy in natural labor and rated 10 points on the Apgar scale. Family history included death of a maternal relative at the age of 32 years, probably due to renal failure, as well as renal disease in relatives on the father's side. A physical examination on admission revealed low weight in relation to height (10c) with height remaining at 25c, dental caries. No hypertension or oedema was found. Additional investigations showed nephrotic proteinuria 60-80 mg/kg/day, without hematuria, the presence of hypercalciuria 7 mg/kg/day with normal concentrations of: total serum protein, albumin, cholesterol, calcium, and phosphate. However, a decrease in the C4 complement component of 11 mg/dl [normal 16-47 mg/dl] was noted. The peripheral blood count, coagulation system exponents, blood gasometry, ionogram, immunoglobulins, complement component C3 and serum vitamin D levels were normal. Antibody testing for systemic diseases (ANA, ANCA, and dsDNA) were all negative. In a further diagnostic process, the Pak test showed hypercalciuria of renal origin; other renal parameters were within normal limits. Orthostatic proteinuria was also excluded. Urinary tract ultrasound showed no abnormalities.

A renal biopsy was performed after approx. one-year follow-up of proteinuria, ranging from 40–60 mg/kg/day. It revealed glomerulosclerosis in six glomeruli out of 20 assessed, as well as stromal fibrosis, tubular atrophy, and the absence of deposits on immunofluorescence. Renal biopsy findings led to establishing a diagnosis of FSGS (focal segmental glomerulosclerosis). Due to a burdened family history, the variable nature of proteinuria and the lesions in the renal biopsy, and a suspicion of a genetic basis for the condition, an angiotensin-converting enzyme inhibitor was included in the treatment.

After about 2 years of symptomatic treatment, proteinuria gradually increased to a value of approximately 70 mg/kg/day. At the same time, hypercalciuria of 6.7 mg/kg/day persisted without other abnormalities on additional tests. In addition, from the age of 7, the patient showed a decrease in growth rate (3-10c), and later even < 3c, as well as in body weight (3-10c). Searching for the cause of the disease, a urine protein test was performed. It revealed a significantly elevated alpha-1-microglobulin level of 123 mg/dl (normal < 20 mg/dl). Due to the presence of LMWP and hypercalciuria, diagnosticians started suspecting Dent disease. Treatment with hydrochlorothiazide at a dose of 0.4 mg/kg/day was initiated. The diagnosis was confirmed by genetic testing, which identified a mutation in the CLCN5 gene. Since this abnormality was found neither in the mother nor in the sisters, the mutation could be a de novo mutation.

After 6 years of treatment, the boy was diagnosed with somatotropic hypopituitarism and rhGH treatment was started. After 7 years of disease, renal ultrasound showed early features of nephrocalcinosis. Currently, the 18-year-old patient has proteinuria of 95 mg/kg/day, without hematuria, hypercalciuria of 13 mg/kg/day, normal renal function markers: creatinine 0.8 mg/dl (GFR 92 ml/min according to Schwartz), urea 23 mg/dl, normal serum Ca levels. Body weight is maintained at 3c, while attention is drawn to the body height between 25-50c. Lumbar spine and whole-body bone densitometry results are below the range of the broad age standard. The boy's intellectual development is normal.

Discussion

The first description of two boys with Dent disease dates to 1964 [13]. Since then, although case reports with genetic

testing are quite numerous, renal biopsies are still not performed in patients with the CLCN5 mutation. One of the few studies showing correlations between glomerular lesions and Dent disease revealed that the renal biopsy performed in patients diagnosed with Dent disease (30) showed FGGS (focal global glomerular glomerulosclerosis) in 83.3% of cases, while FSGS was found in only 6.6% of the patients [14]. It also must be noted that there have been reports of patients presenting with isolated proteinuria whose renal biopsy showed FSGS or FGGS lesions [15]. Solanki et al. report that a mutation in the CLCN5 gene may be directly linked to the occurrence of glomerulosclerosis in patients with Dent disease, irrespective of the presence of hypercalciuria or nephrolithiasis [16]. It results from damage to the tubules and podocytes, forming a histological picture of FSGS. The patients with Dent disease and FSGS-type lesions do not develop rapid progression to renal failure [4, 17], but this possibility must be considered [18]. Glomerulosclerosis is a characteristic feature of Dent disease, but definite diagnosis requires correlation of the histological lesions with the clinical picture, especially the occurrence of LMWP [19]. Initial diagnostics for Dent disease should be considered primarily in patients with a family history of kidney disease [15, 19]. Dent disease should be suspected in young boys presenting with symptoms of albuminuria and LMWP [20], even if the patient does not have hypercalciuria [21].

Treatment of Dent disease should only be implemented after establishing a definitive diagnosis. A correct diagnosis protects patients from the immunosuppressive therapy, which is recommended for the FSGS treatment but ineffective in patients with Dent disease. The case of Kanneko et al. showed that the use of glucocorticosteroids and cyclospyrin A for a period of 12 months does not produce positive therapeutic effects and leads to increased excretion of low molecular weight proteins [19]. The presented patient did not receive immunosuppressive therapy, but only ACEI renoprotective treatment. This management has also been reported to be unsuccessful, causing a reduction in the albumin-to-creatinine ratio in only 54% of patients with Dent disease [22]. Increased urinary calcium excretion accelerates the onset of renal failure [23]. Hypercalciuria in Dent disease should be primarily treated with thiazide diuretics, which have been shown to reduce calcium excretion by up to 40% in short-term follow-up [11]. The above case confirms that the rare occurrence of Dent disease causes diagnostic difficulties in patients with proteinuria, but a correct diagnostic process including low molecular weight protein assessment, calcinuria assessment and genetic testing allows the avoidance of immunosuppressive treatment, which is ineffective in this disease and is associated with debilitating side effects.

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23RD ANDROLOGY DAY – REPORT FROM THE CONFERENCE OF THE POLISH SOCIETY OF ANDROLOGY 2022

23. dzień andrologiczny – sprawozdanie z konferencji Polskiego Towarzystwa Andrologicznego 2022

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Abstract: The 2022 conference of the Polish Society of Andrology was held in the center of Poznań, Poland. It abounded with both original independent papers and heated discussions on contentious issues related to the practical aspect of the diagnosis and treatment of hypogonadism. The following paragraphs outline the most interesting reports and conclusions from each session.

Keywords: PTA, testosterone, hypogonadism.

Streszczenie: Konferencja Polskiego Towarzystwa Andrologicznego w 2022 r. odbywała się w centrum Poznania i obfitowała zarówno w oryginalne prace własne, jak i gorące dyskusje na sporne tematy związane z praktycznym aspektem diagnostyki i leczenia hipogonadyzmu. W poniższych akapitach przedstawiono najbardziej interesujące doniesienia i konkluzje z poszczególnych sesji.

Słowa kluczowe: PTA, testosteron, hipogonadyzm.

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Session 1 was participated by foreign guests from Sweden and Denmark. The opening lecture discussed the extragonadal effects of follicle-stimulating hormone (FSH) on the male tissues. The lecture ended with a conclusion that such an impact still remains ambiguous and the treatment with recombinant gonadotropins should only be carried out when absolutely indicated. Another lecture focused on the impact of the sperm DNA Fragmentation Index (DFI) on the risk of pre-eclampsia in pregnant women and on the health of the newborns. The author emphasized the highly predictive use of the above parameter in the diagnosis of conception failure in couples, especially in cases with a relatively normal seminogram result [1]. He also pointed out that the risk of complications is not only related to the first trimester of pregnancy and the increased miscarriage rate. Studies have shown that one of the main parameters that increase DFI is obesity. Next, advances in the diagnosis and treatment of testicular cancer were discussed. It was emphasized that a decision on qualification for salvage surgery should be taken prudently and that it is very important to determine eligibility for the biopsy (and result interpretation) of the other testis. The session ended with a lecture on semen testing as the most important tool for determining a male reproductive function. During the lecture, attention was drawn to the fact that even a normal spermiogram result according to WHO standards does not guarantee fertility, nor does having abnormal test results definitively indicate complete infertility.

Session 2 was one of the most interesting during the entire congress and was conducted under the “endocrinology” theme. The first lecture addressed disorders of the hypothalamic-pituitary-gonadal axis, detailing those related to genetic aspects of hypogonadism (mainly hypogonadotropic ones). Another lecture highlighted the role of body weight in fertility disorders with the conclusion that obesity negatively affects semen parameters. During the discussion, a comment was presented on the potentially negative impact of the men's metformin use in the preconception phase. A Danish study has shown that

children of such men were more likely to suffer from genitourinary defects [2]. The next lecture, with a controversial name and topic, was about considering the possible existence of a male equivalent of PCOS. It was suggested that certain metabolic (low SHBG levels, insulin resistance), clinical (androgenetic alopecia, obesity) and genetic (similarity of mutations and genetic variants found in PCOS and "male PCOS") similarities may provide a basis for identification of such a disease entity. However, it seems to be a far-reaching semantic simplification and may obscure the real clinical needs of patients with the disorders outlined above. The last lecture in the session addressed testosterone concentrations in men and women. Due to the considerable disagreement among experts about the content of the lecture, I will skip it, referring only to the testosterone treatment guidelines [3] and own article on such treatment [4].

Session 3, entitled "Andrology and related sciences", began with a lecture on the collaboration of specialists from different disciplines in the diagnostics of couples' infertility. The crucial information was that most fertility-impairing mutations do not have a defined phenotype and symptomatology, which causes great diagnostic difficulties in such cases. The next lecture (by a forensic doctor) gave rise to the greatest number of questions and provoked the longest discussion devoted to the issues of the physicians' responsibility for the treatment (the need to obtain the patient's consent for interventions), legal liability issues related to informing the services of the prohibited practice (diagnosis of pregnancy before 15 years of age or under-age intercourse must be reported; a rape does not have to be reported, as it is prosecuted only at the request of the victim(-s). Another addressed topic was vasectomy and whether it may cause permanent damage to health (Article 156 of the Penal Code). The experts' opinions were again divided. In theory, a fertility-impaired procedure meets the criteria of this article, but there is still the possibility of surgical reconstruction [5] or testicular sperm extraction (TESE) [6], both of which allow for sperm retrieval and therefore practical fertility preservation. Due to the lack of precedent in the Polish judiciary system, such procedures should be performed with great care and awareness. The subsequent lecture focused on gender dysphoria, which is a problem at the intersection of psychology and clinical medicine. The currently used International Statistical Classification of Diseases and Related Health Problems (ICD 10) clearly defines such disorders (group F64), including reimbursement guidelines (involving Rx discounts). The pending ICD 11 will completely demolish the current diagnostic procedure, introducing a diagnosis focusing more on the individual expression of the patient". However, due to the development of psychological research on gender affiliation in recent years, which may be welcomed by certain social groups, the introduction of a new classification may pose a medical problem. The patients with gender affiliation disorder, due to the need to change the Rx reimbursement indications, may go through a period of "chaos" and lose eligibility for drug reimbursement. How this will be resolved at a political level remains, as usual, a mystery. The final session lecture focused on the management of male pelvic floor myofascial disorders. It was indicated that frequent pain in the gluteal and testicular region may be associated with the myofascial structure disorders. Massage and manual therapy (including the use of rectal massagers and per rectum manual therapy of pelvic floor muscle trigger points) can be excellent ways to treat pain in this area.

Session 4 focused on the impact of the SARS-CoV2 virus. It was indicated that the virus can lead to both hypogonadotropic hypogonadism (inflammation of the hypothalamus and pituitary gland) and hypergonadotropic hypogonadism (damage to Sertole, Leydig and Spermatogonia cells). It was also shown that COVID-19 is more common in men, particularly those with low testosterone levels. Discussion concerned semen parameters in COVID-19 patients, indicating that oxidative stress and fever can lead to reduced semen volume and sperm motility. It was also suggested that the cytokine storm after SARS-CoV2 vaccination may cause fertility disorders in both men and women. The author of the lecture informed that, despite the lack of effects on fertility reported by vaccine manufacturers, he did not recommend vaccination in the first trimester of pregnancy.

The next day and session 5 addressed the diagnosis and treatment of male infertility. The first lecturer discussed the indications for gonadotropin treatment in stimulating spermatogenesis. He pointed out that such indications exist in hypogonadotropic hypogonadism, but not in non-obstructive azoospermia, and exogenous testosterone treatment is contraindicated if the patient is planning to have children, in which case if the treatment is actually used, it should be discontinued immediately. Then the discussion went on to address the influence of environmental factors on semen parameters. Based on the group of over 500 men, it was demonstrated that smoking and consumption of sweetened fizzy drinks have a significant effect on increasing the risk of teratozoospermia (both parameters increased the risk by 1.6-fold). Quitting resulted in a statistically significant decrease in the risk, thus proving the validity of quitting. It was not demonstrated that consumption of small amounts of alcohol per week had significant influence on the deterioration of semen parameters. The study did not show the influence of BMI on semen parameters, although it was noted that this may be due to the low proportion of obese patients (BMI > 30) taking part in the study. No changes in semen parameters were observed in the case of carrying a phone in the front pocket, using nutritional supplements containing whey protein or working on a laptop held on the lap. High semen quality was observed in patients performing sports (3 times higher volume and 1.5 times better progressive motility) relative to physically inactive patients. It was followed by a discussion of the WHO 2021 recommendations for semen testing highlighting standardization and unification of existing procedures [7]. The aforementioned guidelines also reinstate the description of the nature of sperm motility (rapid progressive motility, slow progressive motility, non-progressive motility, no motility). Another speaker discussed the usefulness of ultrasound in the diagnosis of male infertility, noting the need to examine the entire

scrotum and to describe not only the "regularity of the testes", but also their volume, changes in the epididymis, spermatic ducts, vascular bundle (including examination in different positions and performing the Valsalva maneuver).

The next lecture discussed the influence of the male factor on miscarriages and pointed out that miscarriage is not always associated with a female disorder. Again, the importance of the DFI as a reliable diagnostic method was highlighted. Then the discussion addressed indications for uterine insemination and the preparation for such a procedure.

The lecture on gonadotropin treatment for patients with infertility and hypergonadotropic hypogonadism was welcomed with a surprise. Attention was given to the determination of the normal upper limit of FSH (< 8 IU/l) and the potential benefit of using gonadotropins and clomiphene for oligoasthenoteratozoospermia (OAT) in a selected group of patients. The subsequent lecture discussed own study on the correlation of testicular torsion and surgical intervention on autoimmunity (no anti-sperm and anti-Leydig cell antibodies were noted) and the pituitary-testicular axis (the ability to restoring it to normal functioning was confirmed). The final discussion highlighted the need to urgently recognize the condition of testicular torsion and the fact that even a 5-hour delay in intervention may result in irreversible loss of the organ.

The concluding 6th session of the conference presented new reports on andrology, including genetic disorders, genome sequencing issues and the search for potential biomarkers of infertility. Attention was drawn to the adverse effects of immunosuppressive drugs (e.g., cyclosporine A, mycophenolate, mTOR inhibitors), the use of which may lead to infertility and mutations in the offspring.

Summary

The conference proved that andrology is becoming a rapidly developing field and highlighted its potential to address the growing problem of hypogonadism and couples' infertility in the population.

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INTERNATIONAL CONFERENCE: VIMIMED 2023 – VISEGRAD MILITARY MEDICINE CONFERENCE

Konferencja międzynarodowa VIMIMED 2023 – VISEGRAD MILITARY MEDICINE CONFERENCE

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Abstract: Colonel Prof. Paweł Krzesiński, the Deputy Director's Plenipotentiary for International Relations at the Military Institute of Medicine – National Research Institute, participated in the VIMIMED 2023 international conference, where issues related to military healthcare and challenges associated with military operations in Europe were discussed. Representatives from the healthcare services of Poland, Hungary, Slovakia, the Czech Republic, as well as NATO and EU institutions, attended the conference. Colonel Prof. Krzesiński delivered two lectures at the conference. The first lecture focused on the autonomic nervous system in soldiers and its significance in interpreting cardiac incidents. The second lecture was dedicated to telemedicine solutions that can be utilized in the care of soldiers both during peacetime and on the battlefield. During the discussions, Colonel Prof. Krzesiński advocated for preventive actions within the Visegrad Group and NATO armed forces aimed at preventing, detecting, and treating civilization--related diseases, as well as combating risk factors. The importance of healthcare for the armed forces, benefiting both individual soldiers and the effectiveness of military operations, was emphasized.

Keywords: military medicine, soldiers, telecare, preventive medicine.

Streszczenie: Płk prof. dr hab. n. med. i n. o zdr. Paweł Krzesiński, pełnomocnik Dyrektora WIM-PIB ds. kontaktów międzynarodowych, uczestniczył w konferencji międzynarodowej VIMIMED 2023, gdzie omawiano problemy wojskowej służby zdrowia i wyzwania związane z działaniami zbrojnymi w Europie. Uczestniczyli w niej przedstawiciele służby zdrowia z Polski, Węgier, Słowacji, Czech oraz instytucji NATO i UE. Płk prof. Krzesiński wygłosił dwa wykłady na konferencji. Pierwszy dotyczył autonomicznego układu nerwowego u żołnierzy i jego znaczenia dla interpretacji incydentów kardiologicznych. Drugi wykład poświęcony był rozwiązaniom telemedycznym, które mogą być wykorzystane w opiece nad żołnierzami zarówno w czasach pokoju, jak i na polu walki. Podczas dyskusji płk prof. Krzesiński propagował podejmowanie działań profilaktycznych w siłach zbrojnych Grupy Wyszehradzkiej i NATO skierowanych na zapobieganie, wykrywanie i leczenie schorzeń cywilizacyjnych oraz zwalczanie czynników ryzyka. Zwrócono uwagę na znaczenie ochrony zdrowia sił zbrojnych zarówno dla indywidualnych żołnierzy, jak i dla efektywności działań wojskowych.

Słowa kluczowe: medycyna wojskowa, żołnierze, teleopieka, medycyna prewencyjna.

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Colonel Prof. Paweł Krzesiński, the Deputy Director's Plenipotentiary for International Relations at the Military Institute of Medicine – National Research Institute, took an active part in the VIMIMED 2023 – Visegrad Military Medicine International Conference, which took place on 13–16 February 2023 in Vysoke Tatry (Slovak Republic). The conference was attended by healthcare representatives from Poland, Hungary, Slovakia, the Czech Republic and the international institutions of NATO and the European Union.

On the first day of the conference, the participants attended a plenary session devoted to the most important issues of military healthcare in the face of current challenges, especially the military operations taking place in Europe. At the very beginning, the participants watched a remote report on the challenges of the Ukrainian healthcare in the face of health problems related to the war in our neighbor's country. The subsequent presentations outlined the strategy and activities undertaken by the Multinational Medical Coordination Centre/ European Medical Command (MMCC/EMC) and the Centre of

Excellence for Military Medicine (MILMED COE), with a particular focus on organizing training sessions for armed forces personnel of the Visegrad Group countries. One presentation also dealt with the ability to identify biological threats in times of peace and war. One speaker focused on the research into the impact of coronavirus infection on soldiers' physical performance. The participants had the opportunity to learn about modern IT solutions supporting medical supervision of soldiers, which are being piloted in selected military troops. One lecture highlighted the need to implement dog rescue procedures on the battlefield, since dogs are an important resource in the tasks that cannot be performed by humans.

On the following days, working group meetings were held. Colonel Prof. Paweł Krzesiński was a member of the delegation of the Armed Forces of the Republic of Poland. During the conference, he gave two lectures and took an active part in the discussions within the Preventive Medicine working group.

In his presentation "The autonomic balance of cardiovascular system in soldiers – what is 'normal' and what is even 'better'?" Colonel Prof. Paweł Krzesiński presented the specifics of autonomic nervous system function in soldiers and how important this topic is in interpreting cardiac incidents. He pointed out that therapeutic decisions in such cases require expert knowledge. He also presented the possibilities of predicting physical performance based on resting cardiovascular and neurological indices. The presentation included, among other things, the results, and conclusions from the project "Assessment of cardiovascular and endocrine performance in military candidates exposed to particularly intensive stresses associated with military service" (MON 10/WNiI/2007). The cognitive and practical value of the Polish experience in this field gained appreciation.

The second lecture was devoted to the telemedicine solutions: Telemedicine – what can we adapt from civil cardiology? In his presentation, Colonel Prof. Pawel Krzesiński pointed out that there are several solutions that can be used in comprehensive telecare for soldiers in peacetime, and selected ones also on the battlefield. He presented the Polish experience, including:

1/ the use of the MKS-COVID19 mobile application (developed at the Military Institute of Medicine in spring 2020) in the prevention of the infection spread among military hospital staff,
2/ platforms for remote outpatient telecare ("AMULET project (STRATEGMED3/305274/8/ NCBR/20170),
3/ the objectives of the MILGEOMED project – "Intelligent integrated system for the location, initial assessment and medical assistance of the battlefield casualties using geo-information and biomedical sensors" (DOB-SZAFIR/09/A/047/01/2021).

The discussion participants acknowledged the aforementioned achievements and their coherence with the work on telemedicine solutions in the MILMED COE activities.

Colonel Prof. Paweł Krzesiński took part in numerous discussions, in particular promoting the concept of preventive interventions in the armed forces of the Visegrad Group and NATO countries, aimed at prevention, rapid detection, and effective treatment of diseases of affluence and combating their risk factors. To support his position, he presented the findings of the MIL-SCORE program "Phase II. Equalizing access to preventive and cardiovascular care for professional soldiers – MIL-SCORE" (Decision No. 15/ MON/2013).

The idea of undertaking such Force Health Protection (FHP) steps – justified not only by the soldiers' well-being, but also by the interests of the armed forces (optimal preparation for military tasks, reducing the risk of being removed from service/battlefield for health reasons related to general health) – were appreciated in discussions as an important element of FHP, which needs to be emphasized and developed within national programs and international cooperation. Colonel Prof. Paweł Krzesiński also drew attention to the research and development potential in the area of using advanced body condition assessment tools in the selection of military candidates, especially under above-average psychophysical stress.

The participation of the Polish Armed Forces representatives in international meetings and conferences becomes particularly important in times of armed conflict near our borders. It is also essential for NATO allies to build a coherent Armed Forces healthcare strategy based on both regenerative medicine and preventive medicine aimed at building the health and fitness advantage of our soldiers.

THE FACULTY OF MEDICINE AT THE UNIVERSITY OF WARSAW AND THE MILITARY INSTITUTE OF MEDICINE

Wydział Medyczny UW I WIM to spełnienie marzeń o wykorzystaniu naszego potencjału naukowego dla potrzeb medycznych

Alojzy Z. Nowak[1], Zuzanna Chodzeńska[2]

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Abstract: October 14, 2022, rector of the University of Warsaw prof. Alojzy Z. Nowak and the director of the Military Institute of Medicine, Lieutenant General prof. Grzegorz Gielerak, signed an agreement on organizational, teaching and research cooperation in creating and conducting training for doctors at the newly formed Faculty of Medicine of the University of Warsaw. The Military Institute of Medicine is the main partner of the University of Warsaw in the implementation of the program. The majority of clinical classes will also be conducted at the Military Institute of Medicine. In an interview with Prof. Alojzy Z. Nowak, talks about the innovative assumptions for educating students in the medical field of the new Faculty of Medicine of the University of Warsaw, about the planned research projects and the tradition of training civilian and military doctors at the University of Warsaw.

Keywords: Medical Faculty of the University of Warsaw, medical studies, military medicine, cooperation between the University of Warsaw and the Military Institute of Medicine – National Research Institute.

Streszczenie: 14 października 2022 r. rektor Uniwersytetu Warszawskiego prof. dr hab. Alojzy Z. Nowak oraz dyrektor Wojskowego Instytutu Medycznego gen. broni prof. dr hab. n. med. Grzegorz Gielerak, podpisali porozumienie w sprawie współpracy organizacyjnej oraz dydaktyczno-badawczej przy tworzeniu i prowadzeniu kształcenia lekarzy na nowo formowanym Wydziale Medycznym Uniwersytetu Warszawskiego. WIM jest głównym partnerem UW w realizacji programu. W WIM będzie też prowadzona większość zajęć klinicznych. W wywiadzie prof. Alojzy Z. Nowak opowiada o innowacyjnych założeniach edukacji studentów na kierunku lekarskim nowego Wydziału Medycznego UW, o planowanych projektach naukowo-badawczych oraz tradycji szkolenia cywilnych i wojskowych lekarzy na UW.

Słowa kluczowe: Wydział Medyczny Uniwersytetu Warszawskiego, studia medyczne, medycyna wojskowa, współpraca UW i WIM – PIB.

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Interview with Prof. Alojzy Z. Nowak, Rector of the University of Warsaw.

In 2023, the first medical students will be admitted to the newly established Faculty of Medicine at the University of Warsaw. What teaching facilities will the University of Warsaw offer them?

After a 70-year break, the University of Warsaw will once again educate future doctors. Although medicine was not taught at the University of Warsaw, research related to medical science has been carried out for many years in numerous divisions of our school. A special feature of the research conducted at the University of Warsaw is its great interdisciplinarity related to the fact that the University exploits skills and experience accumulated in other disciplines to explore issues lying at the intersection of these disciplines and medical science. Research groups conducting medical and peri-medical research have been established, among other things, at the faculties of: Chemistry, Biology, Physics or Mathematics, Computer Science and Mechanics, as well as in such university units as: The Centre of New Technologies, the Centre for Biological and Chemical Sciences or the Interdisciplinary Centre for Mathematical and Computational

Figure. Prof. Alojzy Z. Nowak, Rector of the University of Warsaw.

Modelling (in the latter case, research mainly concerns various aspects of mathematical and computer modelling of physiological processes and medical data analysis, which was particularly applicable to predicting the course of the COVID-19 pandemic).

Our university also conducts research in bioethics and cognitive science related to medicine, which is the field of interest of the researchers from the Faculty of Philosophy. For more than two years, the Faculty of Education has been conducting a project funded by the Medical Research Agency on the humanization of the treatment process and clinical communication between patients and medical staff before and during the COVID-19 pandemic. The project has been run by the research team headed by Prof. Zbigniew Izdebski. We should not forget about the research carried out by Prof. Jacek Jemielity, who in 2021 received the prestigious Foundation for Polish Science Award, in the Laboratory of Chemical Biology at the University of Warsaw Centre for New Technologies. He works on chemical modifications of nucleic acids, with a particular focus on mRNA. The use of modified mRNA has great prospects, as best evidenced by the COVID-19 vaccines. The mRNA modification technology may also have applications in anti-cancer therapy.

By establishing the Faculty of Medicine at the University of Warsaw we want to, on the one hand, strengthen the scientific and teaching potential in the field of medical research currently conducted at the university, and on the other – to further develop it. Thanks to this kind of symbiosis of medicine and research conducted so far at the University of Warsaw, we will be able to better carry out our social mission. We have been thinking about the return of medicine to the University for several years, maybe even decades. We have come to the conclusion that there should be a faculty that adds value to the society, resulting from the achievements of the whole University.

Why did you decide to establish this faculty together with the Military Institute of Medicine – National Research Institute?

From the very beginning, the establishment of the Faculty of Medicine at the University of Warsaw was going to be based on cooperation with the existing top medical institutions in Poland with appropriate clinical facilities. Since we need to give our students access to the best staff and medical infrastructure, it was natural for us to choose partners from Warsaw, who would collaborate with us in this regard. We must emphasize that the Military Institute of Medicine has supported our idea from the very beginning and expressed its interest in entering into the agreement and implementation of joint operations. On 14 October 2022, the agreement was signed between the University of Warsaw and the Military Institute of Medicine on cooperation in the field of organization as well as research and teaching in the establishment and delivery of medical education at the University of Warsaw. The Military Institute of Medicine is a leading partner for us in the implementation of medical education. The majority of clinical classes will also be conducted at the Military Institute of Medicine. We have created a joint Team on Clinical Education, consisting of representatives from both the Military Institute of Medicine and the University of Warsaw. The team develops joint solutions for education as well as research and teaching cooperation.

You claim that the aim is to organize an innovative medical faculty in Poland, focused on scientific and research development and the humanization of medicine. What does it mean in practice?

The Faculty of Medicine at the University of Warsaw is a 6-year, long cycle Master's Program with a general academic profile. Adopted unanimously by the University of Warsaw Senate, the study curriculum is in line with the current training standards for the medical profession as set out in the regulation of the Minister of Education and Science. At the same time, it includes specific features resulting from the potential of the University of Warsaw and the adopted teaching concept.

The innovative curriculum at the Faculty of Medicine of the University of Warsaw is largely based on teaching directed towards scientific and research development and the humanization of medicine. Therefore, an important part of the study curriculum is the methodological and research block, represented primarily by a series of classes in the following years of study: "Science Based Medicine Research Project", which prepares the students for conducting independent studies and for forming conscious and critical approach towards the results of other scientific research. It is complemented by extensive language training, primarily in English. Another important element is the humanization of medicine. Related issues include multidimensional aspects of bioethics and its practical applications, psychological and sociological conditions of medical practice, including communication with the patient and the environment, as well as organizational issues related to the functioning of the health care system. This model of education puts the patient and their needs in the center of interest of future doctors. Establishing the Faculty of Medicine at the University of Warsaw, we

understand how important contact with the patient is for future doctors. This is why the first patient care internship for medical students are going to be organized at the first year of study. The internship will be carried out in the best medical facilities in Warsaw, including, above all, the Central Teaching Hospital of Ministry of Defence, which is part of the Military Institute of Medicine, and the Warsaw Southern Hospital.

Will these studies be different from those offered by other medical universities?

A distinguishing feature of education at the University of Warsaw Faculty of Medicine will be the implementation of a new approach to educating future doctors – in line with the idea of the humanization of medicine, which focuses on strengthening aspects of communication with the patient, a comprehensive approach to the patient and their safety, and teamwork within different professional groups in the healthcare system.

The innovation of the University of Warsaw Faculty of Medicine also lies in the teaching oriented on scientific and research development. Each student will obligatorily be involved in at least one research project conducted at the University of Warsaw or at Military Institute of Medicine during their study cycle.

The University of Warsaw is also aiming for a significant internationalization of the medical studies. It will be achieved through specialized foreign language classes ensuring students' linguistic proficiency, the participation of academic staff and students in international exchanges, and the teaching of classes by academics from other countries. Particular opportunities for student development in this area arise from participation of the University of Warsaw in the 4EU+ Alliance, which is an alliance of European universities that also includes Charles University in Prague, Heidelberg University, Sorbonne University, University of Copenhagen, University of Milan, and University of Geneva. Another distinguishing feature of the Faculty of Medicine is the emphasis on using new technologies within the provided training. Therefore, education will be based on cooperation and the use of the unique and specialized laboratory, teaching and equipment of other faculties of the University of Warsaw in both basic, pre-clinical and clinical sciences.

The training process will extensively involve medical simulation methods, starting at the first year of study. Students will be offered specialized equipment, as well as rooms for developing their own research projects and self-study. Furthermore, thanks to the introduction of additional classes involving digital tools and artificial intelligence, the teaching process will be more attractive and will considerably broaden students' analytical skills and their use of the potential of Big Data, digital tools, and artificial intelligence in patient treatment processes.

What will the collaboration with Military Institute of Medicine consist of?

The agreement we have signed with the Military Institute of Medicine concerns cooperation on the establishment of the University of Warsaw Faculty of Medicine, followed by teaching and further development of the educational offer and research cooperation in medical and health sciences. The cooperation with the Military Institute of Medicine is therefore based on the one hand, on the implementation of clinical training provided by the staff and using the infrastructure of the Institute and, on the other hand, on the development of research cooperation.

In March 2023, we worked together with the representatives of the Military Institute of Medicine on the organization of the "Under the sign: Medicine" event, which was attended by researchers and authorities from both organizations. The priority theme of the meeting was joint research and development activities in the context of medical student training and using technology in the treatment process. Together with Lt. Gen. Prof. Grzegorz Gielerak, we unveiled a plate with the name of the seat of the University of Warsaw Faculty of Medicine, which is located at the University of Warsaw Biological and Chemical Research Centre.

An important part of the medical training is the internship during the summer holidays (in patient care, primary care, emergency care, internal medicine, intensive care, pediatrics, surgery). A significant part of the internship will be organized in cooperation with the Military Institute of Medicine, thanks to the possibility of involving the staff, specialized equipment, and medical facilities, including those of the Central Teaching Hospital of Ministry of Defence in Warsaw and the hospital in Legionowo near Warsaw.

Will the new Faculty of Medicine at the University of Warsaw also train military doctors? Will their training be different from that of civilian medics?

The collaboration with the Military Institute of Medicine gives us new opportunities. The training of military doctors is a promising development direction. Elements related to battlefield medicine are already included in the medical curriculum at the University of Warsaw. A significant part of the teaching will be provided by the physicians from the Military Institute of Medicine, who will share with the students their previous extensive experience also related to medical actions in emergencies. Thanks to our partner, selected aspects of military medicine (e.g., issues of medical security for the Polish army, NATO standards regulating medical security for troops, etc.) are included in the curriculum content of some subjects in the University of Warsaw Faculty of Medicine. For example, the curriculum includes the subject "Tactical and civilian emergency medicine", during which students learn the operating procedures in a combat environment, the priorities of providing medical assistance in the tactical environment and the basic methods and ways of dealing with the most common combat injuries, such as controlling massive hemorrhages, gunshot wounds and upper airway obstruction.

In the interwar period, the University of Warsaw taught military medical personnel. Is this a return to tradition?

The Faculty of Medicine was part of the University of Warsaw between 1816 and 1949. Its tradition, however, dates back as far as 1809, when the School of Medicine was founded in Warsaw alongside the School of Law. To this day, the tradition of medical education is represented on the University's emblem. Indeed, the University originally consisted of five faculties (Law, Medicine, Philosophy, Theology and Sciences

and Fine Arts), as symbolised by the five stars in the University's emblem.

The history of the University of Warsaw Faculty of Medicine is also linked to the development of Polish medicine. It is worth noting that the University was headed by nine medical rectors, the last of whom was the eminent physiologist, Prof. Franciszek Czubalski, who was against the separation of medical science from the University. Let me recall at least a few names of eminent medics who were educated at our university. Prof. Mieczysław Michałowicz, rector of the University of Warsaw in the 1930s, significantly contributed to development of pediatrics, being one of the first in Poland to conduct research into children's diseases, as well as organizing a modern pediatric clinic at Litewska street. Another outstanding pediatrician was Prof. Józef Brudziński, rector of the University of Warsaw from 1915 to 1917, who described a sign being one of the physically demonstrable symptoms of meningitis – named after him Brudziński's sign. Prof. Wiktor Szokalski, the father of Polish ophthalmology, was also connected with the University. It is also worth noting that one of the University of Warsaw lecturers was Prof. Karol Kaczkowski, who organized the world's first sanitary units operating on the battlefield. The Military Institute of Hygiene and Epidemiology is named after him.

In the interwar period, the University taught military medical personnel. When Poland regained independence, there were only three university medical faculties in operation: Cracow, Lviv and Warsaw. Staff shortages, as well as financial difficulties, prevented the establishment of further faculties of medicine. These problems also affected the army. One solution to this situation was to establish cooperation between the military authorities and the University of Warsaw. On 1 November 1922, by order of the Minister of Military Affairs, the Military Sanitary School was established in Warsaw to educate health service officers. Such education was provided to students at the University of Warsaw Faculty of Medicine or at the State Dental Institute and the cadet school. The cadets attended classes along with other students at the University of Warsaw, the difference being that they wore a uniform. The cooperation was very good.

Therefore, on the one hand, establishing the educational offer for future doctors is a return to tradition, since the Faculty of Medicine was one of the first faculties of our university, but on the other hand, it is a dream come true for many of us regarding the possibility of applying the scientific potential of the University of Warsaw to medical science.

There is a strong emphasis on preparing future medics for scientific and research work. Why is it so important?

We would like the highest possible percentage of our students to choose the research path in addition to the practical path. That is why we have included a methodology and research block in the study program, through which we want to prepare future doctors for conducting independent scientific research and for forming conscious and critical approach towards research or reports that they will come into contact with at later stages of their careers. We want our students to develop not only the competences, which are crucial for the medical profession, but also the universal competences necessary for conducting scientific research and disseminating its results. We believe that it will enable our graduates to be not only excellent researchers, but also very good practitioners, constantly improving and developing their knowledge based on the latest scientific findings.

Military Institute of Medicine – National Research Institute
Postgraduate Training Centre

The Postgraduate Training Centre organizes training for civilian and military medical staff:

- courses in emergency medicine (including MASCAL, IEM, PHTC, HTC, emergency ultrasound),
- courses in battlefield medicine,
- courses and specializations for nurses and midwives,
- training on special request.

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