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ПОРАЖЕНИЕ СЕРДЦА НА ФОНЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА: ЧТО НОВОГО?

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Acute Cerebrocardial Syndrome: What's New?

Резюме

Ишемический инсульт и сердечно-сосудистые заболевания имеют множество общих факторов риска. Соответственно, пациенты, у которых имеются общие триггеры, подвержены высокому риску развития нарушений в оси «мозг-сердце». С 2018 года в структуре церебро-кардиальных взаимоотношений выделяется синдром «инсульт-сердце» (stroke–heart syndrome), включающий любые новые нарушения со стороны сердца или ухудшение имеющихся ранее заболеваний сердца, наблюдаемые в течение первых 30 дней после острого ишемического инсульта, пик развития которых приходится на первые 72 часа после неврологической катастрофы. Патогенетические механизмы этого синдрома в настоящее время активно изучаются. Основной причиной повреждения сердца на фоне инсульта считается дисфункция автономной нервной системы, которая проявляется в снижении парасимпатической и усилении симпатической активности, что проявляется в снижении вариабельности сердечного ритма и барорецепторного рефлекса. Инсульт также сопровождается активацией гипоталамо-гипофизарно-надпочечниковой оси и симпатоадреналовой системы, развитием системной воспалительной реакции и гиперкоагуляции. Недавние данные свидетельствуют о том, что в цереброкардиальном взаимодействии играют роль микро-РНК и кишечная микробиота.

В обзоре описаны современные представления о проявлениях данного типа острого цереброкардиального синдрома, возможностях его классификации и попытках фенотипирования, а также приведены современные эпидемиологические сведения. Обсуждаются диагностические возможности рутинных лабораторно-инструментальных обследований, а также перспективные методы, требующие дополнительных исследований.

Ключевые слова: *синдром «инсульт-сердце», инсультнокардиальный синдром, ось «мозг-сердце», ишемический инсульт, сердечная недостаточность*

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Abstract

Ischemic stroke and cardiovascular diseases have many common risk factors. Accordingly, patients with common triggers have high risk of developing brain-heart axis disorders. Since 2018, the stroke-heart syndrome has been distinguished in the cerebrocardial relationships structure. It includes any new heart disorders or worsening of existing heart diseases observed during the first 30 days after acute ischemic stroke, the peak of which

occurs in the first 72 hours after the neurological catastrophe. The pathogenetic mechanisms of this syndrome are currently being actively studied. The main cause of heart damage against the background of stroke is the autonomic nervous system dysfunction, which is manifested in a decrease in parasympathetic and an increase in sympathetic activity, which is presented as a heart rate variability and baroreceptor reflex decrease. Stroke is also accompanied by the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system activation, the systemic inflammatory response and hypercoagulation development. Recent data indicate that microRNA and intestinal microbiota play a role in cerebrocardial interactions. The review describes current concepts of this type of acute cerebrocardial syndrome manifestations, the classification possibilities and attempts at phenotyping, and also provides current epidemiological data. The diagnostic capabilities of routine laboratory and instrumental examinations are discussed, as well as promising methods that require additional research.

Key words: *acute cerebrocardial syndrome, stroke-heart syndrome, brain-heart axis, ischemic stroke, heart failure*

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BNP — brain natriuretic peptide, NTproBNP — N-terminal fragment of the brain natriuretic peptide, SCD — sudden cardiac death, CAD — coronary artery disease, IS — ischemic stroke, SHS — stroke-heart syndrome, CA — cardiac arrhythmias, AMI — acute myocardial infarction, ACVA — acute cerebrovascular accident, HF — heart failure, CVD — cardiovascular diseases, TS — Takotsubo syndrome, TIA — transient ischemic attack, LVEF — left ventricular ejection fraction, AFib — atrial fibrillation, CHF — chronic heart failure, CCS — cerebrocardiac syndrome, ECG — electrocardiography

Background

831,600 people died from cardiovascular diseases in Russia in 2022. Coronary artery disease (CAD) (451,000) and cerebrovascular diseases (248,900) were predominant in the mortality structure [1]. According to the World Health Organization data, CAD was the first among leading non-infectious causes of death in 2021; however, when analyzing subgroups in higher and lower income countries, the stroke took over CAD concerning this parameter [2].

The implemented preventive measures, advances in diagnostic and treatment methods, and (on the other hand) population aging affect the composition of the population of patients with cardiovascular diseases (CVDs). This is reflected in the predicted age-standardized CVD mortality decrease by 2050 with a relatively unchanged CVD prevalence. However, due to the same causes, one can expect the increase in the total CVD mortality in the nearest decades [3]. Besides, the stroke incidence has been increasing lately among people aged younger than 55 years [4].

Heart failure (HF) is the outcome of any cardiovascular disease. The prevalence of chronic heart failure (CHF) in Russia increased by 2.1 % within the period from 2002 to 2022. Patients with CHF have more comorbidities than patients with CVDs, but without CHF [5]. In particular, the stroke risk in patients with HF is 2–5-fold higher compared to the general population [6, 7]. The association of stroke prevalence and HF severity is ambiguous: some researchers have detected the stepwise association with the NYHA functional class, while others did not observe any associations, which is probably due to the features of analyzed groups. The elderly age and atrial fibrillation (AFib) undoubtedly play an important role in the pathogenesis of strokes [8, 9].

Currently inter-organ associations in CHF, including cardiorenal [10], cardiopulmonary [11], hepatocardial [12], cerebrocardiac [13] syndromes, are extensively studied. The latter one is usually considered as brain lesions in CVDs mainly associated with acute or chronic hypoperfusion of the central nervous system [13]. On the other hand, in neurological practice the cerebrocardiac syndrome (CCS) is considered as heart lesions associated with neurological accidents. CVDs are the second most likely cause of death among patients with strokes, giving way only to direct brain tissue lesions due to cerebral hemorrhages or infarctions [14]. A recent retrospective cohort study that enrolled 365,383 patients demonstrated that cardiac complications emerged in 27.6 % patients within 1 month after a stroke (including acute coronary syndrome (ACS), 11.1 %; AFib, 8.8 %; HF, 6.4 %; severe ventricular arrhythmias, 1.2 %; Takotsubo syndrome, 0.1 %) [15].

The primary cause and consequences cannot often be clearly distinguished in real clinical practice. Complex issues may be associated with the absence of significant history, lack of knowledge about pathogenetic interactions in the brain-heart axis, and the absence of an evidence-based method that could determine the sequence of lesions. Untimely diagnosis of cardiac lesions may be associated with the absence of clinical CVD manifestations due to the neurological deficit or impaired consciousness [16]. Cardioneurology, which became a separate science in the mid-20th century, analyzes the aforementioned questions.

Definition and background

In 1947 Byer E. et al. first reported their observations that cerebrovascular diseases may lead to cardiac arrhythmias and myocardial injury [17]. In 1949 N.K. Bogolepov described CCS as an apoplexy-like syndrome in acute myocardial infarction (AMI) [18]. In 1960-1970s he continued analyzing the issues of cardioneurology, e.g. he described clinical CCS variants (cerebrovascular impairment in AIM, cardiac impairment in cerebral accidents, simultaneously developing AIM and stroke); he also noted that CCS had different manifestations depending on the stroke location [18, 19]. Subsequently, cardioneurology differentiated into two specific branches, with the first analyzing cardiac diseases developing in the setting of brain lesions, and the second analyzing diseases of the central nervous system emerging in the setting of CVDs.

In 2018 Scheitz J.F. et al. define a stroke-heart syndrome in the structure of cerebrocardiac interactions, which included all new cardiac disorders or worsening pre-existing cardiac diseases emerging within the first 30 days after an acute ischemic stroke (IS). It was reported that almost 25 % patients with IS developed early cardiovascular complications, with their incidence peaking within the first 72 hours since the initiating event onset [20].

Based on the Framingham study, heart diseases are a significant risk factor of IS, with the 2-fold risk in patients with CAD, 3-fold risk in patients with essential hypertension, 4-fold risk in patients with HF, and 5-fold risk in patients with AFib [21].

Although the stroke-heart syndrome (SHS) rate peaks during the first 3 days after the stroke, the risk of death increases with its later onset. ACS, myocardial injury, left ventricular dysfunction, and AFib are independently associated with death within 90 days after IS [22]. Besides, SHS is associated with an increased 1-year risk of dementia [23].

Stroke-heart syndrome variants

5 cardiac dysfunction types have been described in the literature in the setting of SHS [20, 24]:

1) Acute myocardial injury of ischemic or non-ischemic origin (with changing altered cardiac troponin levels; this is often asymptomatic)
2) Acute coronary syndrome (due to decreased coronary blood flow or coronary plaque destabilization)
3) Left ventricular systolic and diastolic dysfunction, including the post-stroke Takotsubo syndrome (TS)
4) Any ECG alterations, arrhythmias (including AFib) diagnosed after the stroke
5) Sudden cardiac death (SCD).

These variants may be isolated or combined in a single patient who often does not have a confirmed history of structural or functional heart changes [20].

Acute myocardial injury of ischemic or non-ischemic origin (with changing altered cardiac troponin levels; this is often asymptomatic)

Troponin levels may increase due to various coronary and non-coronary events [25]. Elevated troponin levels in neurogenic diseases have been demonstrated in many studies [26–31]. Concerning IS, the mechanisms of this marker elevation has not been fully analyzed. Main hypotheses include the sympathetic-adrenal system activation, HF, and chronic kidney disease [25].

Elevated high-sensitive troponin levels are associated with a high risk of stroke in the general populations and among patients with AFib [26], as well as with the unfavorable prognosis after the cerebral accident [27, 31].

In the study of Scheitz J.F. et al. (2021), primary endpoints (recurrent stroke, AMI, all-cause mortality) were more often among patients with elevated troponin T levels after the stroke vs. the non-elevation group (27.3 % vs. 10.2 %; adjusted odds ratio 2.0; 95 % CI 1.3-3.3) during the three-year follow-up [28].

During the retrospective comparison of troponin levels in 565 patients (including 73 with transient ischemic attacks (TIAs) and 492 with acute cerebrovascular accidents (ACVAs)), troponin levels were significantly lower in patients with TIAs, with the lowest troponin levels detected in TIA and lacunar stroke groups, while altered troponin levels (both elevated and decreased) were detected in over 30 % patients with any stroke variants (based on the TOAST pathogenetic classification), except for cryptogenic stroke. Besides, elevated troponin levels were associated with a more advanced age and higher NT-proBNP levels [32]. In the post-hoc analysis of the HEBRAS (HEart and BRain interfaces in Acute Stroke) study that analyzed the level of cardiac biomarkers and cardiac MRI parameters, elevated troponin T levels (in 21 % patients of 233) were associated with confirmed pathological alterations (focal fibrosis) during the gadolinium enhancement phase, with the decreased left ventricular ejection fraction (LVEF) and LV hypertrophy [29].

Detecting serial cardiac troponin levels is used to distinguish chronic myocardial injuries from acute ones. According to Scheitz J.F. et al. (2014), the latter ones are associated with higher short-term mortality, while the cut-off troponin level, after which the risk of unfavorable prognosis increased, was 16 ng/L [31].

However, the PRAISE-DZHK19 I DZNEB001 (Prediction of Acute Coronary Syndrome in Acute Ischemic Stroke) study demonstrated that serial alterations of highly sensitive troponin levels in patients with IS was not associated with AMI, while only highly sensitive

troponin levels 5–10-fold higher than the upper reference value were beneficial for the prediction of Type 1 MI [30].

Despite all controversy, the troponin test on admission is included into the US Stroke Treatment Guidelines [33]. However, its isolated elevation cannot confirm any specific cardiac lesion, requiring additional examinations and more thorough monitoring of such patients.

Acute coronary syndrome (due to decreased coronary blood flow or coronary plaque destabilization)

Based on a large meta-analysis including over 131,000 people, the risk of AMI after the stroke was 1.67 % per year, although recurrent IS was a more common cause of death rather than MI [34]. In another large-scale study, IS was independently associated with a higher MACE risk, especially during the first 30 days after the neurological accident (HR 25.0; 95 % CI 20.5–30.5), while subsequently decreasing within a year [35]. Coronary atherothrombosis due to the enhanced plaque instability in the setting of systemic inflammation is one of the potential post-stroke ACS mechanisms [36].

Left ventricular systolic and diastolic dysfunction, including the post-stroke Takotsubo syndrome

Animal studies (mice, rats) demonstrated that the experimental large IS was accompanied by the transient LVEF decrease for 2 weeks, as well as the short-term elevation of highly sensitive troponin levels, bradycardia, decreased myocardial mass, and signs of cardiomyocyte atrophy [37, 38]. Another analysis showed that signs of HF with a 15 % LVEF drop developed in rodents 8 weeks after the short-term occlusion of the middle cerebral artery vs. the control group, with a higher heart rate, increased end-systolic and diastolic LV volumes [39].

The prevalence of systolic and diastolic LV dysfunction in the post-stroke period in human studies significantly varies in different studies. For example, in the SIC-FAIL study the rate of HF detection in patients with the ischemic stroke was 5.4 % (HFrEF 4.35 %) [40]. The rate of HF detection with reduced LVEF ranged from 0.78 to 15 % [40, 41]. Based on various data, diastolic dysfunction is diagnosed in 23.3–59 % patients [40–42].

Currently it is unknown whether the LV dysfunction diagnosed in the post-stroke period is actually transient and whether it is gradually restored or leads to symptomatic CHF in the future [14]. For example, in the study of Sposato L.A. et al. (2020), the risk of HF 1 year after the first ACVA among patients without a history of CVDs was 3.3-fold higher than in a matched patient group without ACVAs (95 % CI 3.1–3.7) [35]. Many studies do not provide data about the presence or absence of CVDs before the stroke.

Prognostically significant risk factors for LV dysfunction development and its severity after ACVAs include the elderly age, a history of CVDs, elevated cardiac troponin [40], BNP and NT-proBNP levels [43], the focus size and its location [44]. In the study of Dieplinger B. et al. (2017), NT-proBNP levels were independently associated with the all-cause mortality within 3 months [45].

The post-stroke TS is a very rare finding, which is complex for the diagnosis and which risk is increased in Caucasians, females, and elderly persons [40, 46, 47]. According to different studies, its incidence is 0–0.42 % [15, 40, 46, 47]. This syndrome is usually considered as a transient LV dysfunction with its subsequent recovery within several months [48]. Large registry-based studies have demonstrated that acute neurological conditions form the largest group of physical TS triggers with the with the worst clinical outcomes and a slower LV function recovery [48].

The post-stroke TS is a predictor of poor prognosis, high mortality (including the in-hospital one), poor functional outcome [49, 50]; it is also associated with the risks of such complications as cardiogenic shock (OR 8.84, CI 4.07–19.17, $P < 0.001$), cardiac arrest (OR 3.17, CI 1.57–6.42, $P = 0.001$), venous thromboembolism (OR 1.68, CI 1.14–2.47, $P = 0.008$) [49].

Exact pathogenetic TS mechanisms have not been established. The most probable current hypothesis presumes the direct catecholamine-induced toxicity and associated spasm of the coronary artery microvasculature [49]. It has been established that in patients with this syndrome blood catecholamine levels are 2–3-fold higher than in patients with AMI and 20-fold higher than in the control group [50]. The post-stroke TS is often asymptomatic [51].

Any ECG alterations, arrhythmias (including atrial fibrillation) diagnosed after the stroke

ECG alterations after ACVAs emerge in 46–79 % cases based on various authors [52, 53]; however, the majority of ECG deviations are transient and disappear within 14 days [53]. The most common anomalies include QTc interval prolongation (20–65 %), altered T wave morphology (16–40 %) and altered ST segment changes (15–25 %), arrhythmias (28–36 %) [52–54]. The majority of patients have at least two pathological alterations [52]. Some data confirm that ECG anomalies correlate with outcomes. Thus, prolonged QTc interval based on the results of the regression analysis and ECG signs of ischemia ($p=0.044$) were considered independent predictors of poor prognosis during the acute stroke phase [55]. During the long-term evaluation based on the results of multifactorial analysis, the prognostic 90-day mortality factors included AFib, atrioventricular block, ST segment alterations, and T wave inversions [56].

Arrhythmias constitute approximately one third of all electrocardiographic alterations [53], with the highest probability of those detected during the first day after the stroke [57]. Some data demonstrate that the elderly age and a high National Institute of Health Stroke Scale (NIHSS) score became the predictors of arrhythmias within the first 3 days after the stroke [57]. It has been observed that arrhythmias with tachycardia occur more often than bradycardias [52, 57]. The rate of AFib after IS, based on different data, ranges from 5 to 32 % [52–54, 57, 58].

A special term AFDAS (atrial fibrillation detected after stroke and TIA) is used in English sources. This category includes AFib emerging during or after the stroke, as well as probably pre-existing AFib, but detected only after the stroke [59]. Patients with AFib detected after the stroke, based on several data, have a lower risk of recurrent stroke and have less chances of having a history of CVDs [60, 61].

It is known that 50 % of all AFib cases in patients with ACVAs and TIAs are first detected after neurological events, and in the majority of cases these arrhythmias are asymptomatic, while every second paroxysm lasts less than 30 seconds [59]. This requires prolonged ECG monitoring in the early post-stroke period.

Some data demonstrate the stroke located in the right insular lobe is associated with a higher rate of AFib than in the left one (39 vs. 4 %) [62].

AFib detected after IS may have a cardiogenic, neurogenic, or mixed origin. Cardiogenic factors include pre-existing CVDs and atrial remodeling, AFib episodes not detected earlier. Neurogenic mechanisms are associated with the left atrial changes in the setting of systemic inflammation and autonomous dysfunction as part of ACVA [63].

Despite the fact that the majority of ECG alterations are transient, AFib after the stroke may transform into persisting or permanent forms [64].

Fan X. et al. (2024) have concluded that one should define phenotypes of patients with AFib after IS with a variable risk in order to define the requirements for anticoagulant therapy and dosing in those patients. Further biomarker studies and neuroimaging patterns have to be arranged with this purpose [64]. Several prognostic models for the post-stroke AFib have been currently developed [65, 66], as well as the multimodal approach including imaging, ECG, and biomarkers (NT-proBNP, galectin 3, SR2, osteoprotegerin) [58]; however, further studies are required to clarify their prognostic significance.

Sudden cardiac death (SCD) is a non-violent death emerging instantaneously or within one hour from the moment of acute alterations in the patient's clinical status. Theoretically SCD is one of the SHS types. However, sudden cardiac and neurogenic deaths can be practically distinguished only after complete pathological examination of the brain and heart, as well as if the ECG data have been recorded. Cases with SCD after the stroke may be omitted from observations due to the study design features [24].

SHS pathogenesis

The stroke and CVDs have common risk factors [67]: hypertension, atherosclerosis, lipid metabolism disorders, diabetes mellitus, obesity, smoking, alcohol abuse, low physical activity level, stress, etc. Consequently, patients with common triggers have a higher risk of disorders in the brain-heart axis.

Pathogenetic SHS mechanisms are still being currently investigated (Fig. 1). Both true cardiomyocyte injury and reactive, potentially reversible alterations in their structure and function occur in IS.

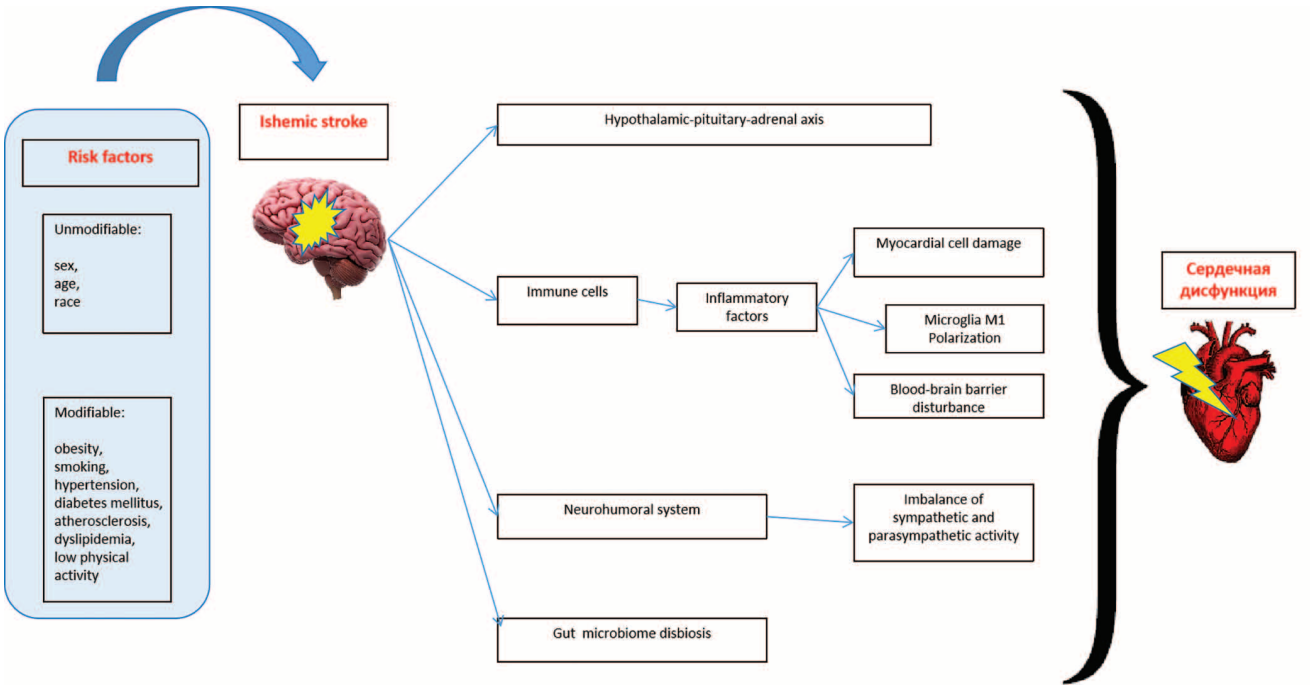
Autonomous dysfunction manifesting with the decreased parasympathetic and increased sympathetic activity is considered the main cause of cardiac lesions in the setting of a stroke. With that, parasympathetic dysfunction is more significant rather than sympathetic hyperactivity. These alterations develop in the acute stroke phase and are preserved for up to 6 months [68]. The autonomous balance shift towards sympathetic domination in the acute ischemic stroke phase manifests with the decreased cardiac rhythm variability and baroreceptor reflex [68], enhancing myocardial oxygen requirements.

Due to the enhanced sympathetic cardiac effects, catecholamines are released, which mediates electrolyte and metabolic disorders in cardiomyocytes with worsening relaxation processes [20]. In experimental animal stroke models the most significant myocardial lesions were detected in the left atrial region around pulmonary veins (area of the largest sympathetic effects) [69], which may promote AFib. Other murine stroke models demonstrated that the enhanced peripheral sympathetic activity was associated with SHS of the HFrEF type and LV dilation for 2 months [39].

ACVA is accompanied by the activation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal system, which leads to elevated levels of stress hormones, including catecholamines and cortisol [68]. It has been demonstrated that the serum cortisol level correlates to the stroke severity and prognosis (both short-term and long-term) [70].

Both enhanced sympathetic activity and the systemic inflammatory reaction may activate hypercoagulation process, enhance the activity of platelets and neutrophils, lymphocyte apoptosis, and endothelial dysfunction [71–73].

The results of articles that underscore the role of inflammatory reactions in the emergence of SHS have



Picture 1. *Heart-stroke syndrome pathogenesis.*

been published recently. Besides, the macrophagal infiltration of the myocardium significantly enhances in IS, while levels of inflammatory macrophage-associated cytokines increase, which finally leads to myocardial fibrosis and hypertrophy [74, 38].

The systemic immune inflammation index (SII, equation: [(neutrophils × platelets/lymphocytes)/1000]) which has proven itself as an independent cancer predictor is currently actively analyzed as a new marker of systemic inflammatory reaction [76]. In a recent study of Hao X. et al. (2024) this index based on the multifactorial logistic regression results demonstrated the predictive value for SHS (adjusted OR 5.089 (95 % CI 1.981–15.74, p = 0.002) [77]. Meanwhile, in the study of Weng Y. et al. (2021) the SII index in ischemic stroke was associated with the functional outcome [78]. However, a larger number of studies is required to confirm its prognostic value for SHS.

The recent data also demonstrate that micro-RNA [79] and the intestinal microbiome [80] play a role in cerebrocardiac interactions. Data have been obtained that micro-RNA-126 deficiency is closely associated to HF, AFib, IS, and (probably) post-stroke cardiac lesions [81].

The systemic inflammation increases the intestinal permeability and promotes the bacterial translocation and endotoxins into the blood flow, which worsens the systemic inflammatory reaction and the risk of myocardial disorders. Severe intestinal dysfunction in patients with IS manifests with the increased counts of opportunistic bacteria and decreased probiotic levels. Nevertheless, the exact mechanisms of intestinal microbiome effects on SHS still remain unclear [64].

SHS risk stratification

Accounting for the burden of cardiovascular diseases and neurological accidents, the issue of post-stroke cardiac lesions and changes in the progression of pre-existing CVDs remains very significant. Despite the currently accumulated knowledge concerning the interaction of the brain-heart axis, many issues remain unsolved and require a large number of original studies. Besides terms and classifications, risk stratification and prognosis, it is important to describe specific phenotypes among patients with the developed SHS.

A retrospective study using the VISTA electronic database is interesting. That included more than 12,000 patients. Using the hierarchic cluster analysis, they were divided into 5 profiles according to the pre-existing SHS risk factors and the early mortality risk after ACVA: Profile 1 (“elderly patients with AFib”); Profile 2 (“young smokers”); Profile 3 (“young patients”); Profile 4 (“patients with concomitant CVDs”); Profile 5 (“patients with essential hypertension and atherosclerosis”). Profiles 4 and 1 demonstrated the highest SHS risk (adjusted HR (95 % CI) 2.01 (1.70–2.38) and 1.26 (1.05–1.51), respectively, vs. Profile 3). Profiles 5 and 2 had a moderate risk, while Profile 3 had the lowest risk. Profile 5 had the highest risk of cardiac and respiratory arrest (adjusted HR (95 % CI) 2.99 (1.22–7.34)), while the highest 90-day mortality risk was observed in Profiles 5

and 4 [82]. Such patient division into profiles or phenotypes may help to develop diagnostic algorithms and treatment approaches, although it requires a significant evidence base, continuing works in this direction.

Conclusion

Thus, the publication data underscore that stroke is not an isolated brain lesion, but rather a multisystemic problem requiring a complex approach in each specific case.

Currently multiple issues concerning worsening cardiac function in the setting of IS remain unsolved (no unified terms, no approved classification). Besides, scales for risk stratification have to be developed, and treatment algorithms based on various SHS phenotypes have to be determined. A larger number of works with a prolonged follow-up period is required, as it's not clear in which cases SHS is time-limited and regresses, and when it progresses with severe complications, e.g. symptomatic CHF. SHS probably can be divided into acute and chronic types (just like the cardiorenal syndrome).

To remove the knowledge gaps and advance the management tactics of patients with cardiac lesions after the stroke, collaborative research initiatives guided by interdisciplinary cardiologist and neurologist teams are required.

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ФЕРМЕНТЫ ПЕЧЕНИ ПРИ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ: ОТВЕТ НА ПИРАМИДАЛЬНУЮ АЭРОБНУЮ ТРЕНИРОВКУ В СРАВНЕНИИ С НЕПРЕРЫВНОЙ АЭРОБНОЙ ТРЕНИРОВКОЙ

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Liver Enzymes in Non-Alcoholic Fatty Liver Diseases: Response to Pyramidal Versus Continuous Aerobic Training

Аннотация

Цель. Исследовалось влияние выбора типа тренировки (консервативная нефармакологическая терапия первой линии при неалкогольной жировой болезни печени (НАЖБП)) на улучшение показателей ферментов печени. Проведено сравнительное исследование, направленное на оценку ответа ферментов печени на пирамидальные упражнения с повышающейся интенсивностью (интервальные) в сравнении с непрерывными аэробными упражнениями у пациенток женского пола с НАЖБП. **Материалы и методы.** 38 участниц с НАЖБП рандомизировали в группу пирамидальных тренировок (n=19) и группу непрерывных тренировок средней интенсивности (n=19). Участницы обеих групп соблюдали рассчитанную на 12 недель диету с низким потреблением калорий и выполняли упражнения три раза в неделю. В дополнение к измерению индекса массы тела (ИМТ) и окружности талии (ОТ) у пациенток с НАЖБП определяли уровни сывороточной аланинтрансаминазы (АЛТ), щелочной фосфатазы (ЩФ), липопротеинов высокой плотности (ЛПВП), аспартатаминотрансферазы (АСТ), триглицеридов (ТГ) и гаммаглутаминтрансферазы (ГГТ) на исходном уровне и через 12 недель. **Результаты.** По завершении обеих программ тренировок наблюдались заметные улучшения. Пирамидальные аэробные упражнения привели к более существенным и заметным улучшениям показателей по сравнению со вторым типом тренировок (аэробные тренировки умеренной интенсивности). **Заключение.** Оба типа тренировок (аэробные тренировки умеренной интенсивности или пирамидальные упражнения) существенно улучшили показатели АЛТ, ИМТ, АСТ, ЛПВП, ГГТ, ЩФ, ОТ и ТГ у пациенток с НАЖБП, при этом пирамидальные тренировки оказались более эффективными по сравнению с непрерывными упражнениями умеренной интенсивности.

Ключевые слова: *Пирамидальные упражнения, аэробные упражнения, ферменты печени, липидный профиль, неалкогольная жирования болезнь печени*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Было получено согласие пациенток с НАЖБП на участие в исследовании, медицинское/клиническое исследование одобрено этическим комитетом (P.T.R.E.C/012/004669), также применялись универсальные рекомендации Хельсинской декларации. В этом исследовании НАЖБП период, рассчитанный для программы тренировок (пирамидальные и непрерывные аэробные тренировки), составил с 1 августа 2024 г. по 28 февраля 2025 г.

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Abstract

Purpose: The effect of choosing the type of exercise — the first-line conservative non-pharmacological therapy in managing non-alcoholic fatty liver disease (NAFLD) — on improving liver enzymes has not been fully investigated.: This was a comparative trial aimed to examine the response of liver enzymes to pyramidal progressive-intensity (interval) versus continuous moderate-intensity aerobic training in NAFLD women. **Materials and Methods**: Thirty-eight NAFLD women were randomized into a pyramidal training group (n=19) and a group of continuous moderate-intensity exercise (n=19). Both groups followed a reviewed 12-week low-calorie diet and received exercise training thrice weekly. Besides body mass index (BMI) and abdominal circumference (AC), NAFLD patients' serum alanine transaminase enzyme (ALTE), alkaline phosphatase enzyme (ALPE), high-density lipoprotein (HDL), aspartate transaminase enzyme (ASTE), triglycerides (TGs), and gamma-glutamyl-transpeptidase enzyme (GGTE) were assessed before and after 12 weeks. **Results**: Significant improvements in all outcomes occurred after finishing both training forms. The pyramidal aerobic form produced more significant and pronounced improvements in the tested outcomes compared to the other form of exercise, moderate-intensity aerobic exercise. **Conclusion**: Both training forms, moderate-intensity aerobic exercise or pyramidal training, significantly improved NAFLD patients' ALTE, BMI, ASTE, HDL, GGTE, AC, ALPE, and TGs, but the pyramidal form of exercise is more efficient than the continuous moderate-intensity form.

Key words: *pyramidal exercise; aerobic exercise; liver enzymes; lipid profile; non-alcoholic fatty liver disease*

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

Consenting of NAFLD women, ethical approval of conducting medical/clinical research (P.T.R.E.C/012/004669), and universal recommendations of Helsinki were applied. In this NAFLD trial, the period designed for conducting the exercise program (pyramidal versus continuous aerobic exercises) was from 1st August 2024 to 28 February 2025.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the local fat deposition/deposition in the liver's hepatocytes of more than 5 % of hepatic cells' volume/size [1-3]. The estimated incidence of NAFLD is 47 cases/patients per 1,000 subjects [4].

The pathogenesis of NAFLD may be related to genetic predisposing factors and/or clinical conditions such as insulin resistance, metabolic syndrome, obesity, and/or type 2 diabetes mellitus [5]. These conditions may accelerate the development/accumulation of macrovesicular hepatic fat which may be accompanied by local hepatic inflammation, signs of local hepatic injury, and variant hepatic fibrosis. Fibrosis disrupts normal hepatic architecture. This disruption leads to an impairment of hepatic functions. This fibrosis-induced hepatic impairment may predispose the development of hepatic cirrhosis and the risk of malignant transformation into hepatocellular carcinoma [6].

With the lack of effective/approved drugs, leaving NAFLD without management accelerates the development of cardiovascular/metabolic diseases, low work productivity, poor patients' quality of life, and rapid sensation of tiredness/exhaustion [7].

Lifestyle changes (exercise training with or without reduction of dietary calories) are considered the initial/main step of NAFLD management [8]. Exercise — as a first-line lifestyle modification treatment for NAFLD — is currently applied mainly as aerobic exercise [9]. Aerobic exercise, particularly walking, is a low-cost non-pharmacological option that is an easy exercise tool that may be handled by NAFLD patients, applied irrespective of place, and managed to improve NAFLD-associated cardiovascular complications. Despite these good characteristics/features of aerobic exercise, its usual continuous form may induce rapid fatigue/discomfort (due to depletion of glycogen stores and/or overuse of slow-twitch muscle fibers) and poor long-term compliance or adherence [10].

On the other hand, pyramidal training, a form of aerobic exercise that is applied in a nearly interrupted form with a gradual progression of the intensity from low to high intensity during the same session, is a relatively new exercise tool that could be used to improve cardiovascular risk factors. The mix between low intensity — which is directed to use local fat as a source of energy — and high intensity — which is directed to use carbohydrates as a source of energy and avoid overuse of slow-twitch muscle fibers — explain the preference of using pyramidal training compared to other forms of training (such as low or moderate intensity exercises) in treating cardiovascular risk factors such as obesity and dyslipidemia [11].

However, the most effective exercise prescription (needed frequency, type, intensity, and total time of exercise session) for the enhancement/improvement of NAFLD remains unclear/unexplained. Moreover, given the high prevalence of NAFLD-inducing cardiovascular disorders, the effect of choosing exercise type on liver enzymes has not been fully compared, especially for pyramidal training. So, this comparative trial aimed to investigate the response of liver enzymes to pyramidal versus continuous moderate-intensity aerobic training in NAFLD patients.

Materials and methods

Design

A randomized controlled pyramidal-versus-aerobic exercise trial.

Settings

Outpatient clinic of internal medicine which is affiliated to Meetghamr General Hospital.

Inclusion criteria

The diagnosis of NAFLD was thoroughly confirmed by a gastroenterologist and a radiologist. Both of them confirmed the presence of NAFLD after applying abdominal ultrasonography. Ultrasonography detected the presence of hepatic steatosis without an evidence of secondary causes such as alcohol consumption or viral hepatitis The patients (38 women) who were aged 37-51 years old and had a body mass index (BMI) > 30 kg/m^2 to < 35 Kg/m^2 were called to participate in this exercise trial.

Exclusion criteria

The presence of orthopedic surgeries, deformities, and trauma that limit the accurate performance of exercise training declined patients from participation in this exercise trial. Also, recent or current engagement in exercise trials or weight loss trials declined patients from participation. History of cardiovascular, metabolic, systemic, endocrine, autoimmune, psychic, neurological, renal, viral, or malignant disorders declined patients from participation in this exercise trial. Also, the authors prevented the engagement of pregnant or lactating females.

Randomization

Concealed sealed envelopes containing the names of NAFLD women were prepared by a physiotherapist who did not show any intention of participating as an author in this exercise trial and he did not show the passion to know the cause of randomizing the women. This

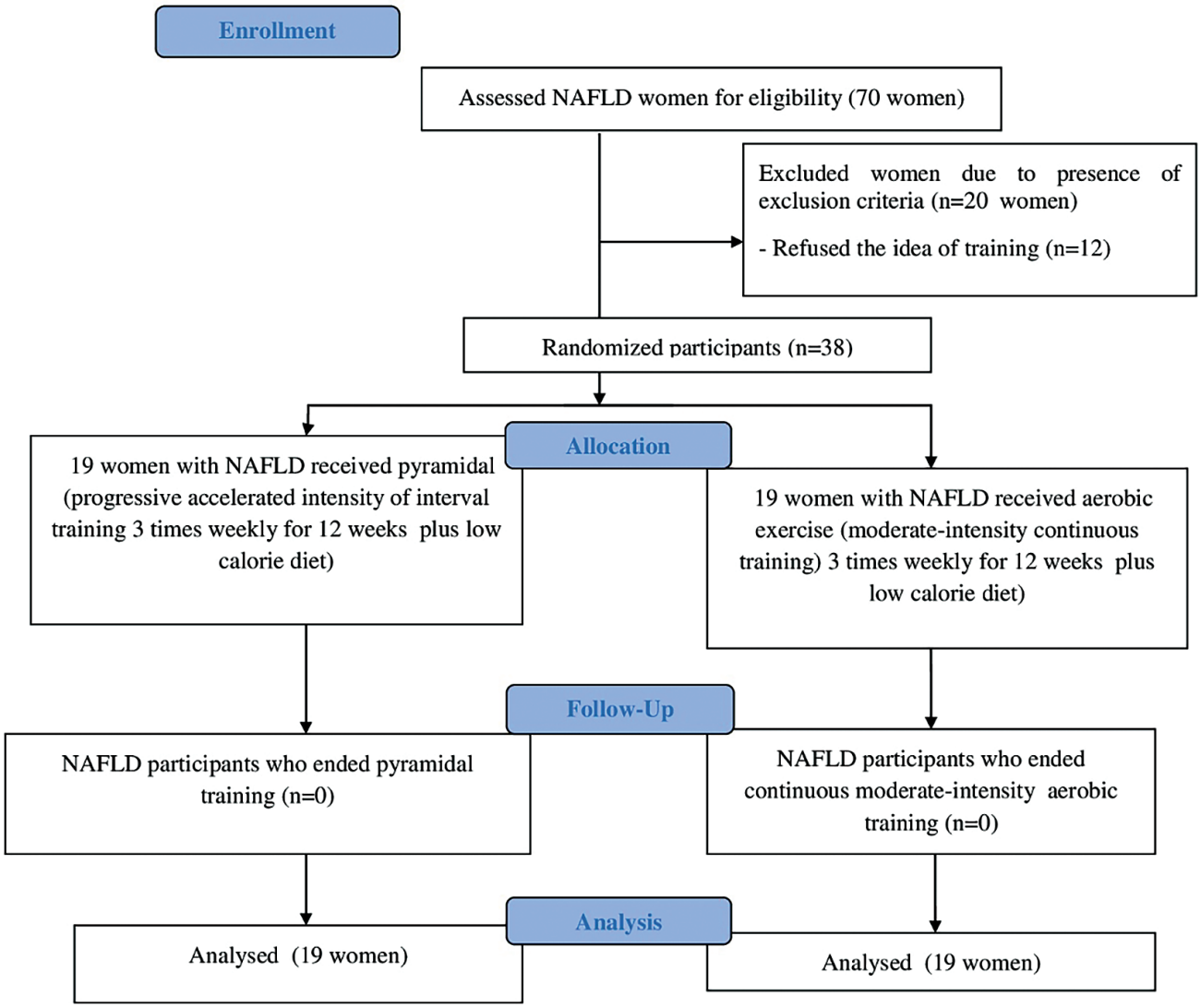

Figure 1. *Flow chart of women with NAFLD*

physiotherapist equally randomized NAFLD women into a pyramidal training group (PTG, n=19) and a group of continuous aerobic exercise (GCAE, n=19) (**Figure 1**). Exercise sessions in both groups were repeated thrice weekly for 12 weeks. Additionally, both groups followed a reviewed low-calorie diet. Before starting pyramidal training or continuous aerobic exercise, unfolding the concealed sealed envelopes was executed via an independent researcher.

Interventions

Low-calorie diet

Patients adhered to the by-last-author-reviewed low-calorie diet after subtracting 500 kilocalories from women's resting metabolic rate (RMR). The Harris-Benedict equation — the equation used to estimate RMR — was utilized as follows: RMR = 655.1 + (9.59 × NAFLD women's body mass in kg) + (1.85 × NAFLD women's height in cm) — (4.67 × NAFLD women's age in years) [12]. Besides fats (20–30 %), carbohydrates (55–65 %) and proteins (10–15 %) constituted the ration of macronutrients of NAFLD women's low-calorie diet [13].

NAFLD patients were advised to drink a large amount of fresh water or low-carbohydrate fresh drinks. Charts listing carbohydrate levels/amounts in different foods such as vegetables and dairy products were provided to all NAFLD patients. The supplied specific charts listing carbohydrate levels in appropriate food choices and meal plans were compatible with NAFLD patient's individualized preferences.

Aerobic training (moderate-intensity continuous exercise)

Walking was executed by NAFLD women on an electronic treadmill in the form of warm-up phase (the first phase of walking performed at 40-60 % of NAFLD women's maximal heart rate, MHR, for 5 minutes), middle

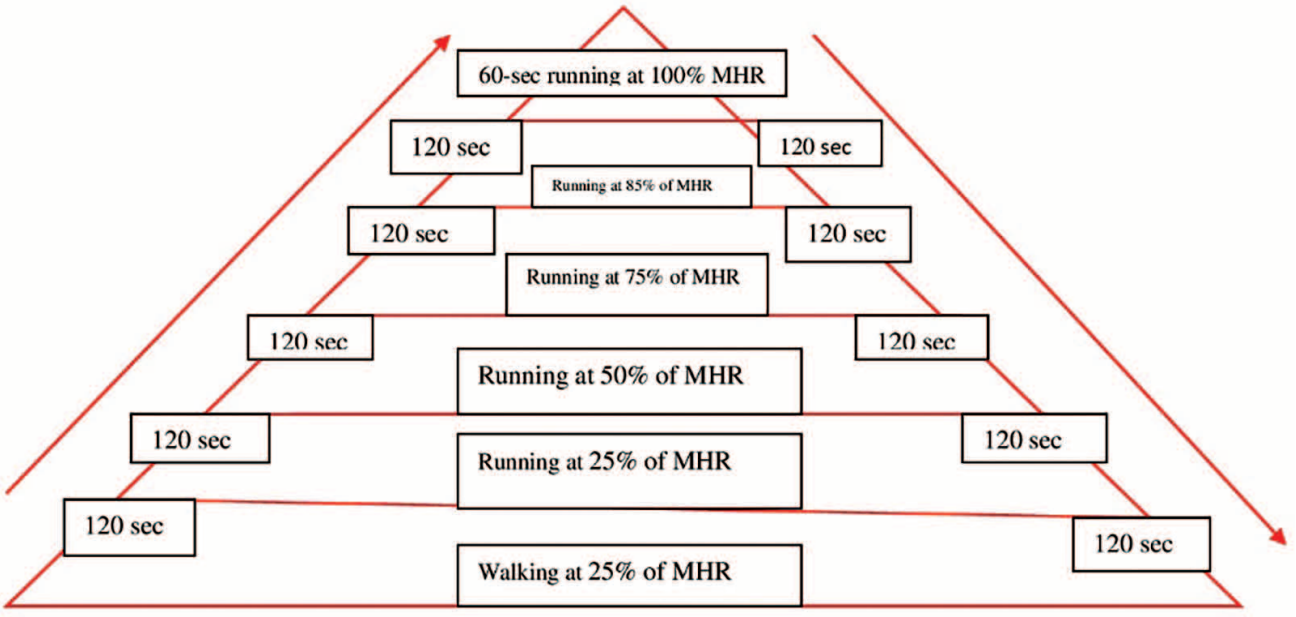

Figure 2. *The protocol of the executed pyramidal training*

phase (the second phase of walking performed at 60-75 % of NAFLD women's MHR for 50 minutes), and cooling-down phase (the third and final phase of walking which imitated the same features of warming-up phase) [14].

Pyramidal training

The 42-minute pyramidal exercise — the accelerated progressive-intensity interval training — was executed in two 21-minute cardio-training running on an electronic treadmill, with 10-minute rest between exercises and an intensity ranged from 25-100 % of MHR of NAFLD women's MHR [12] **(Figure 2)**. The training was conducted according to Karvonen's heart rate formula calculation. Ten-minute warming-up (before the pyramidal training) and 10-minute cooling-up (after the pyramidal training) were conducted in the form of light running and/or light stretching exercises [15]. To be noted, before starting the first session of the pyramidal training, a cardiopulmonary exercise test was applied to every patient who received a pyramidal training to prevent probable side effects of high-intensity exercise.

Outcomes

NAFLD patients' serum alanine transaminase enzyme (ALTE) was measured in both groups. The authors of this study designed this enzyme as the primary outcome of this clinical exercise trial. Secondary outcomes were serum levels of NAFLD patients' alkaline phosphatase enzyme (ALPE), high-density lipoprotein (HDL), aspartate transaminase enzyme (ASTE), triglycerides (TGs), and gamma-glutamyl-transpeptidase enzyme (GGTE). Also, BMI and abdominal circumference (AC) were assessed as anthropometric secondary outcomes of this clinical exercise trial.

Blinding

Details of this study were not explained to the clinical biochemistry physician or assistants who analyzed serum liver enzymes.

Sample size

Thirty NAFLD patients were needed to complete this pyramidal-vs-continuous exercise trial. The effect size of the G*power analysis was 0.94. This effect size was for NAFLD patients' serum ALT (the primary outcome of this clinical exercise trial). To manage the G*power analysis (at a power of 80 %), a pilot test was conducted on eight patients with NAFLD in every group. The authors of this pyramidal-*vs*-continuous exercise trial raised the number of NAFLD participants to 38 NAFLD patients (the ratio of the estimated increase in NAFLD patients' number was 25 % to avoid the idea of dropout).

Statistical analysis

Using SPSS 18, paired test was used to assess the significant-inducing changes of selected exercises on BMI, AC, ALPE, GGTE, ALTE, ASTE, HDL, and TGs within groups. Concerning pre-treatment or post-treatment between-group parity of data (AC, ALPE, GGTE, ALTE, ASTE, HDL, TGs, and BMI), the significant

difference was tested via unpaired test. Age, as one of demographic data, was compared before application of both exercises to assess significant difference using the unpaired test. Authors used the applied statistical tests (paired or unpaired tests) due to the normal distribution of tested data.

Results

Before starting the pyramidal training or the continuous aerobic exercise, parity of between-group pretreatment age, AC, BMI **(Table 1)**, ALPE, GGTE, ALTE, ASTE, HDL, and TGs of NAFLD patients was not significant **(Table 2)**.

Also, after ending the pyramidal training or the continuous aerobic exercise, within-group parity of AC, BMI, ALPE, GGTE, ALTE, ASTE, HDL, and TGs showed a significant improvement. The improvement level of outcomes in the PTG was higher than the improvements in GCAE **(Table 2)**.

Also, after ending the pyramidal training or the continuous aerobic exercise, between-group parity of AC, BMI, ALPE, GGTE, ALTE, ASTE, HDL, and TGs showed a significant improvement toward the PTG **(Table 2)**. The outcomes of this study revealed significant improvement after the application of both types of exercises with a superiority to the application of pyramidal training.

Discussion

This clinical exercise trial confirmed the role of pyramidal or continuous moderate-intensity aerobic exercise in improving NAFLD-associated dyslipidemia and elevation of liver enzymes with a more novel favorable effect of pyramidal aerobic training over continuous moderate-intensity intensity.

Regarding the liver enzymes' improvement after adherence to the moderate-intensity exercise program of this study, gained strength of immunity, regular release of anti-inflammatory/anti-oxidative markers, and increased fight against further inflammation or oxidative stress of new hepatocytes [14] may explain the exercise-induced improvement in GGTE, ALTE, ALPE, or ASTE.

Correction of high levels of liver enzymes means that the progressive hepatic steatosis and cirrhosis started to be limited. The limitation of hepatic steatosis/cirrhosis is associated with decline in cardiovascular risk factors in addition to the control of disturbed lipid metabolism [14].

Regarding tested lipids' improvement after adherence to the two regular exercise programs of this study, exercise-induced utilization of visceral fat as an energy supply or fuel during exercise increases general and local fat loss/lipolysis via the repeated stimulation of sympathetic activity and hormonal production (*e.g.* growth hormone). Exercise increases the production of enzymes (*e.g.* lipoprotein A and lipoprotein lipase enzymes) that not only increase catabolism of TGs but also improve their removal from the bloodstream to be utilized by exercising skeletal muscles [16-18].

Previous reports mentioned more favorable effect of high-intensity exercise over moderate-intensity exercise on lowering the risk of cardiovascular diseases by improving AC, TGs, HDL, and metabolic syndrome components [19]. The reported improvement in metabolic syndrome may improve fatty liver and its indicators (elevated liver enzymes).

Again, parallel to the presented pyramidal training results, performing this form of exercise over an eight-week training period in Egyptian women with obesity produced significantly improved HDL, TGs, BMI, and AC [12]. Again, in another recent study, regular adherence to pyramidal aerobic exercise for eight weeks fights against the development of liver disorders in patients with type 2 diabetes mellitus (via the significant lowering of ALTE and ASTE) [20].

Consistent with the above-mentioned idea of the superiority of high-intensity (interval) training over moderate-intensity training in controlling cardiovascular risk factors, a recent study confirmed this superiority after the more pronounced improvement in ALT, lipids, body composition, and percentage of body fat in obese college students [21]. Again, improvement in steatosis and fibrosis (both are considered as a progression of NAFLD) was more evident in patients with NAFLD who received high-intensity (interval) training compared to those who received the moderate-intensity continuous form of training [22].

The idea was also confirmed again in an experimental study that reported that high-intensity interval training produces more reduction in visceral fat and local fat accumulation compared to continuous low-intensity training in female rats fed a high-fat-containing diet [23]. Another experimental study reported that lipid profile and liver enzyme (ALPE, GGTE, ASTE, and ALTE) improved significantly more in diabetic rats that received high-intensity training compared with rats that received exercise training performed in continuous low-intensity form [24]. Another experimental study reported that high-intensity (interval) training was more favorable than moderate-intensity training in preventing/controlling hepatic fat accumulation in rats with diet-induced obesity (via rebuilding genetic levels of mRNA included in hepatic lipogenesis) [25]. Again, the ability of high-intensity (interval) training to control/reduce intrahepatic fat accumulation is more significant than the reduction obtained from moderate-intensity exercise in rats with NAFLD [26].

Table 1. *Demographic data before aerobic exercises*

Data	Group of pyramidal training	Group of continuous aerobic training	P value
Age (years)	45.15±4.19	47.10±4.74	0.187
Body mass index (kg/m^2)	31.95±1.43	32.91±1.54	0.054
Abdominal circumference (cm)	110.52±8.03	116.47±11.27	0.069

Note. Data (expressed as mean±SD) of this table (Table 1) are non-significant (P value >0.05)

Table 2. *Outcomes (results of training)*

Results of outcomes	Group of pyramidal training	Group of continuous aerobic training	P value (between trained groups)
Body mass index (kg/m^2)	**Mean ± SD**	**Mean ± SD**	
Before training	31.95±1.43	32.91±1.54	0.054
After training	29.74±1.36	31.74±1.51	0.001*
p-value (within trained group)	< 0.001*	< 0.001*	
Abdominal circumference (cm)	**Mean ± SD**	**Mean ± SD**	
Before training	110.52±8.03	116.47±11.27	0.069
After training	100.63±7.28	110.10±10.61	0.0028*
p-value (within trained group)	< 0.001*	< 0.001*	
Alanine transaminase (U/L)	**Mean ± SD**	**Mean ± SD**	
Before training	44.73±5.49	48.10±6.22	0.0851
After training	33.63±5.40	41.89±5.91	0.0001*
p-value (within trained group)	< 0.001*	< 0.001*	
Asparate transaminase (U/L)	**Mean ± SD**	**Mean ± SD**	
Before training	35.94±6.01	39.42±5.42	0.069
After training	28.05±5.32	34.84±5.41	0.0004*
p-value (within trained group)	< 0.001*	< 0.001*	
Alkaline phosphatase (U/L)	**Mean ± SD**	**Mean ± SD**	
Before training	168.21±17.31	178.15±15.33	0.0691
After training	150.68±15.10	168.89±15.32	0.0007*
p-value (within trained group)	< 0.001*	< 0.001*	
Gamma-glutamyl transferase (GGT) (U/L)	**Mean±SD**	**Mean±SD**	
Before training	38.68±5.74	42.31±6	0.064
After training	31.78±4.82	38.57±5.77	0.0004*
p-value (within trained group)	< 0.001*	< 0.001*	
Triglycerides (mg/dl)	**Mean ± SD**	**Mean ± SD**	
Before training	173.05±23.14	189.52±31.76	0.076
After training	150.52±22.42	175.47±32	0.0085*
p-value (within trained group)	< 0.001*	< 0.001*	
High-density lipoprotein (mg/dl)	**Mean ± SD**	**Mean ± SD**	
Before training	43.57±4.32	40.94±4.15	0.0636
After training	49.63±4.20	43.36±4.34	0.0001*
p-value (within trained group)	< 0.001*	< 0.001*	

SD: Standard deviation; *: data are significant (P value < 0.05)

Also, in obese rats involved in 12-week training, HDL improvement was greater in training performed as high-intensity (interval) exercise compared to continuous low-intensity one [27].

The idea was confirmed again in a recent study that included overweight/obese children. This study reported that exercise performed in high-intensity intervals has more positive effects than exercise performed in a continuous and moderate-intensity form because the high-intensity interval exercise produced higher improvement in overweight/obese children's serum lipids [28].

Also, in subjects aged 19.5±0.6 years, eight-week exercise performed in high-intensity interval cycling has more positive effects on AC, waist-hip ratio, and the sum of skinfolds than exercise performed in continuous and moderate-intensity cycling [29]. Again, in obese adolescent females, high-intensity interval training achieved a better improvement in lipids, AC, and percentage of body fat compared to moderate-intensity exercise [30].

Again, despite similar energy consumption, postprandial fat oxidation and TGs significantly improved with a higher percentage after one session of high-intensity exercise compared to one session of moderate-intensity exercise in healthy young subjects [31]. Again, compared to moderate-intensity training, a high-intensity (interval) form of exercise is more efficacious in local and general fat reduction in obese females, partly due to the interval-training-induced greater release/production of lipolytic hormones [32].

Opposite to us, in sedentary overweight/obese adults, no difference in the efficacy of liver fat reduction or visceral fat reduction by either 8-week aerobic exercises' dose or intensity due to the small number of trained adults [33]. Contradicting the results, although there was a significantly improved percentage of body fat, weight, BMI, and AC, 12-week aerobic exercise (running) did not improve ALTE and ASTE in inactive obese Iranian women may be due to the relatively low pre-treatment values of these enzymes [34]. Also, in disagreement with us, both forms of training, high-intensity (interval) and continuous low-intensity exercise did not show a significant change/improvement in obese adults due to the relatively short period of exercise (eight weeks) [35].

Limitations

Follow-up of results (ALTE, BMI, ASTE, HDL, GGTE, AC, ALPE, and TGs) was achieved in this clinical exercise trial, so it must be searched in future NAFLD trials. Other studies are required to advance the benefits of pyramidal training in controlling NAFLD-related evaluation of this study's outcomes via investigating molecular biomarkers, conducting longer intervention studies, or exploring broader health outcomes.

Conclusion

This study reported a more novel favorable effect of pyramidal aerobic training over continuous moderate-intensity intensity in controlling liver enzymes and lipids in NAFLD patients.

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КЛИНИКО-ЭПИДЕМИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ТУБЕРОЗНОГО СКЛЕРОЗА В РЕСПУБЛИКЕ БАШКОРТОСТАН

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Clinical and Epidemiological Characteristics of Tuberous Sclerosis in The Republic of Bashkortostan

Резюме

Актуальность. Туберозный склероз (ТС) — это наследственный опухолевый синдром с аутосомно-доминантным типом наследования, встречающийся с частотой 1:6000 — 10000 новорожденных в мире. Болезнь характеризуется тяжелыми клиническими проявлениями в виде астроцитом головного мозга, рабдомиом сердца, ангиомиолипом почек, лимфангиолеомиоматоза легких и ангиофибром кожи. Поскольку для лечения болезни разработан эффективный метод лечения ингибиторами mTOR, актуально своевременное выявление пациентов с ТС. **Цель исследования.** Определение клинико-эпидемиологических особенностей ТС в Республике Башкортостан. Материалы и методы. Проведен ретроспективный анализ данных и исследование пациентов ТС в Республике Башкортостан. **Результаты.** В Республике Башкортостан зарегистрировано 86 пациентов ТС из 82 семей, частота встречаемости составила 1:47048 человек. Средний возраст пациентов составил 18,5 лет (от 1 года до 61 лет). Характерные для ТС пятна депигментации определены у 90 % пациентов, ангиофибромы лица — у 56 %, фиброзные бляшки головы — у 33 %, шагреневые бляшки — у 36 %, субэпендимальные узлы головного мозга — у 66 %, субэпендимальная гигантоклеточная астроцитома — у 19 %, ангиомиолипомы почек — у 43 %, лимфангиомиоматоз легких — у 1,2 %. Когнитивный дефицит выявлен у 47 %, эпилепсия — у 67 %, аутизм — у 1 % пациентов ТС. **Обсуждение.** Сравнительный анализ особенностей клинических проявлений ТС у пациентов из Республики Башкортостан с мировыми данными показал значимо более редкое выявление ангиофибром лица, опухолей легких, почек и головного мозга, когнитивных нарушений и аутизма. В Республике Башкортостан 8 пациентов с идентифицированными мутациями в генах TSC1/TSC2 получают лечение ингибитором mTOR. **Заключение**. Полученные результаты свидетельствуют о низкой частоте зарегистрированных случаев ТС в республике по сравнению с мировыми данными, в связи с чем необходимо ознакомление врачей всех специальностей о необходимости направления пациентов с симптомами, характерными для ТС, на медико-генетическую консультацию. Для достоверного выявления опухолей головного мозга и внутренних органов необходимы инструментальные исследования в динамике, оценка психологических нарушений у пациентов ТС с консультацией психотерапевтов, неврологов и психологов.

Ключевые слова: *ангиомиолипомы почек, астроцитомы, ген TSC1, ген TSC2, лимфангиолеомиоматоза легких, пятна депигментации, рабдомиомы сердца, туберозный склероз, частота встречаемости.*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Relevance. Tuberous sclerosis (TS) is a hereditary tumor syndrome with autosomal dominant type of inheritance, occurring with frequency of 1:6000 — 10000 newborns worldwide. The disease is characterized by severe clinical manifestations in the form of astrocytomas of the brain, rhabdomyomas of the heart, angiomyolipomas of the kidneys, pulmonary lymphangioleomyomatosis and angiofibromas of the skin. Since effective treatment with mTOR inhibitors has been developed for TS, timely detection of patients with TS is important. **The aim of the study.** To determine the frequency and clinical features of TS in the Republic of Bashkortostan to improve organizational and therapeutic and diagnostic approaches in providing medical care to patients with TS. **Material and methods.** Determination of clinical and epidemiological features of TS in the Republic of Bashkortostan. **Results.** In the Republic of Bashkortostan, 86 patients with TS from 82 families were registered, the frequency of occurrence was 1:47048 people. The average age of patients was 18.5 years (from 1 year to 61 years). Depigmentation spots were found in 90 % of patients, facial angiofibromas in 56 %, head fibrous plaques in 33 %, shagreen plaques in 36 %, subependymal nodules of the brain in 66 %, and subependymal giant cell astrocytoma in 19 %, renal angiomyolipomas in 43 %, pulmonary lymphangioleiomyomatosis in 1.2 % of patients. Cognitive deficit was found in 47 %, epilepsy in 67 %, and autism in 1 % of patients with TS. **Discussion.** Comparative analysis of TS clinical manifestations in patients from the Republic of Bashkortostan with global data showed a significantly lower incidence of facial angiofibromas, lungs, kidneys and brain tumors, cognitive impairment and autism. 8 patients with identified mutations in the TSC1/TSC2 genes are treated with an mTOR inhibitor. **Conclusion**. The obtained results indicate a low frequency of registered cases of TS in the republic compared to world data. Therefore it is necessary to familiarize doctors of all specialties with the need to refer patients with symptoms characteristic of TS for medical genetic consultation. For reliable detection of tumors of the brain and internal organs, dynamic instrumental studies are necessary; assessment of psychological disorders in TS patients is necessary with consultation of psychotherapists, neurologists and psychologists.

Key words: *renal angiomyolipomas, astrocytomas, TSC1 gene, TSC2 gene, pulmonary lymphangioleomyomatosis, depigmentation spots, cardiac rhabdomyomas, tuberous sclerosis, frequency of occurrence*

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

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Conformity with the principles of ethics

The study was approved by the local ethics committee of UFRC RAS (protocol no. 5 dated December 7, 2009)

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RB — Republic of Bashkortostan, PLAM — pulmonary lymphangioleiomyomatosis, MGSC — Medical Genetics Scientific Center, RMGC — Republican Medical Genetics Center, SEGA — subependymal giant-cell astrocytoma, SEN — subependymal node, TS — tuberous sclerosis.

Introduction

Tuberous sclerosis (TS) is an autosomal dominant multisystemic disease [1] from the group of hereditary neoplastic syndromes, with an average global incidence within the range from 1:6,000 to 1:10,000 of newborns [2]. TS is caused by inactivating mutations in *TSC1* and *TSC2* (abbr. Tuberous SClerosis) tumor suppressor genes. Most common mutations are detected in the *TSC2* gene (in 70–90 % cases) [3]. Mutations in *TSC1* and *TSC2* genes causing TS are characterized by significant variability and absence of mutagenesis hot points. The meta-analysis of molecular-genetic test results in various countries did not demonstrate significant differences in the types of mutations and genophenotypical correlations [4]. TS is characterized by variable clinical manifestations in different organs and systems, including the emergence of hamartomas (benign neoplasms) on the skin, in the lungs, brain, heart, kidneys, and liver [3].

Depigmentation spots are detected since birth in patients with TS; their amount and sizes gradually increase [5]. Depigmentation spots are detected in 90 % patients [2, 5]. Specific facial angiofibromata start emerging from the age of 3–4 years; the number of lesions increases in adolescence, stabilizing in the adult age. Angiofibromata are determined in 83 % patients with TS. These manifest with violaceous or normally colored (depending on the blood vessel predominance) papules in zygomatic regions, the back of the nose, nasolabial fold, forehead, and chin. Periungual fibromata are detected in patients with TS over 20 years of age, most commonly — in female toes. Gingival fibromata develop in 20–50 % patients (mainly adults) [5]. “Shagreen” plaques emerge during the first 10 years of life and are detected in 50 % patients with TS, while fibrous cranial plaques (mainly on the forehead) are detected in 25 % patients [2].

Besides external manifestations, patients with TS suffer from the systemic neoplastic lesions of various organs and tissues. Brain lesions, including subependymal nodules (90 %), cortical tubers (80–90 %), subependymal giant-cell astrocytoma (5–20 %), are detected in the majority of patients with TS. Renal angiolipomata (benign neoplasms consisting of blood vessels, smooth muscles, and fatty tissue) are diagnosed in 75 % patients

with TS [6]. Cardiac rhabdomyomata (benign mesenchymal neoplasms consisting of cardiomyocytes) are detected in 90 % children with TS aged under 2 years. Cardiac rhabdomyomata usually spontaneously regress during the first year of life in patients with TS, thus this tumor incidence decreases to 20 %, starting from the second year of life [3]. Pulmonary lymphangioleiomyomatosis is detected in 40 % patients with TS [5, 6]. A specific category of renal neoplasms has been defined for TS, i.e. "TS-associated renal cell carcinoma" (eosinophilic solid cystic renal cell carcinoma) [7].

Epilepsy is detected in 63–93 % patients with TS with the onset during the first year of life; it is closely associated with the impaired neurocognitive development. Neuropsychiatric disorders develop in 90 % patients with TS [3]. Meta-analysis conducted in 2020 demonstrated that 30 % patients with TS suffered from the autistic spectrum disorder (ASD), with 90 % showing signs of intellectual deficit [8]. A significant association was detected between seizures and ASD in patients with TS — this was not affected by the genotype, number and location of neoplasms [9]. Based on the 2012 Diagnostic Criteria adopted by the International Consensus Group on the Tuberous Sclerosis Complex, 2 major or 1 major and 2 minor diagnostic criteria are required to establish the diagnosis of TS (Table 1). Major criteria include over 3 hypopigmentation spots (with the minimum diameter of 5 mm), facial angiofibromata (over 3) or fibrous plaques on the head, periungual fibromas (over 2), "shagreen" plaques, multiple renal hamartomata, cortical dysplasias, subependymal nodes, subependymal giant-cell astrocytoma, cardiac rhabdomyomas, lymphangioleiomyomatosis, angiomyolipomata (over 2). Minor criteria include polycystic renal disease, extrarenal hamartomata, achromatic retinal areas, oral cavity fibromata (over 2), foveae on the dental enamel (over 3), cutaneous "confetti"-type lesions [2]. 202 patients with TS were reported in the Russian study conducted in the N.P. Bochkov Medical Genetics Scientific Center, with mutations detected in 96.5 % patients (with 6.7 % represented by prolonged deletions) [10]. Clinical features of 71 patients with TS were described by the State Autonomous Healthcare Institution of Sverdlovsk Region "Regional Pediatric Clinical Hospital" in Ekaterinburg [11].

As mutations in *TSC1* and *TSC2* genes [3] eliminate the inhibition of mTOR (mammalian target of rapamycin), this leads to the uncontrollable proliferation of normal resting cells [1]. Thus, mTOR inhibitors are used in the TS treatment. According to the meta-analyses arranged, rapamycin (sirolimus) and its analogues decrease the sizes of cerebral astrocytomas, renal angiolipomata [6], with a significantly decreased rate of seizures [12], including in children over 1 year of age concerning astrocytomas, facial angiofibromata, optic nerve tumors [13]. Moreover, mTOR inhibitors used by females pregnant with fetuses with TS decreased the sizes of cardiac rhabdomyomata [14]. Meta-analysis conducted in 2024 confirmed the data on rapamycin efficacy in TS [1]. Various topical sirolimus levels were tested for the treatment of facial angiofibromata. Based on the meta-analysis, after the application of various topical sirolimus levels, the hazard ratio was 3.34 for the 1 % drug, 4.43 for the 0.2 % drug, 2.7 for the 0.1 % drug, 3.87 for the 0.005 % drug. The rank analysis demonstrated that the best result belonged to the 0.2 % topical sirolimus [1]. Everolimus (sirolimus derivative), which is another mTOR inhibitor, is the most efficient anticonvulsant in TS [15].

Table 1. *Diagnostic criteria for tuberous sclerosis and their frequency*

Criterion	Frequency	Author
Depigmentation spots on the skin	90 %	[5]
Faces angiofibromas	83 %	[5]
Heads fibrous plaques	25 %	[2]
Skin shagreens plaques	50 %	[2]
Pulmonary lymphangioleiomyomatosis	40 %	[5, 6]
Heart rhabdomyomas	90 % in children under 2 years of age, 20 % over 2 years of age	[3]
Subependymal giant cell astrocytoma	5–20 %	[6]
Subependymal nodes	90 %	[6]
Brain cortical dysplasia	80–90 %	[6]
Multiple renal hamartomas	75 %	[6]
Gingival fibromas	20–50 %	[5]
Multiple renal cysts	30 %	[3]

Study objective

Determining clinical & epidemiological features of tuberous sclerosis in the Republic of Bashkortostan (RB).

Materials and methods

Data were analyzed for patients with TS from RB that were followed up by the genetic specialist in SBHI "Republican Medical Genetics Center" (RMGC) with the confirmed TS diagnosis. A total of 86 patients (48 males, 37 females) aged 1 to 61 years (25 [21; 33] years) with the diagnosis of tuberous sclerosis established by genetic specialists in RMGC of RB were enrolled in the study. All patients had their history collected, they underwent the clinical examination, including the ultrasound (US) of the abdominal cavity, echocardiography, magnetic resonance imaging (MRI) or computed tomography (CT) of

the brain. *Inclusion criteria:* confirmed clinical diagnosis of tuberous sclerosis with at least 2 major or 1 major and 2 minor diagnostic criteria based on the 2012 Diagnostic Criteria adopted by the International Consensus Group on the Tuberous Sclerosis Complex [2]. The study protocol was approved at the meeting of the Local Ethics Committee (Protocol No. 5 dated December 7, 2009). Each TS patient was analyzed concerning the data about specific signs, including subependymal giant-cell astrocytoma (SEGA), subependymal nodes (SEN), pulmonary lymphangioleiomyomatosis (PLAM) according to the Russian clinical guidelines on the diagnosis and treatment of tuberous sclerosis in children [16]. The results of the US of internal organs were also accounted for when determining the presence of cardiac rhabdomyomata, renal angiolipomata; features of cognitive functions were described to detect the mental retardation and cognitive defects. See the Table 2 for baseline patient characteristics.

Features of clinical TS manifestations in patients from RB were compared to the global ones. All patients signed the informed consent. Checklists and schemes developed by international healthcare organizations (EQATOR, Enhancing the Quality and Transparency of Health Research) were used [17, 18].

Data were statistically processed and presented based on Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Ann Intern Med 1997, 126: 36–47) [19]. When preparing the Statistics section, special guidelines were used ("Quality Editorial Practice Charter", https://scardio.ru/content/publication/Buklet_150x150_v3.pdf; European Heart Journal Guidelines. Calculator link: https://medstatistic.ru/calculators/calchi.html [20]. Quality binary data were statistically processed using the 2x2 interactive contingency table calculating the link statistics (Pearson's χ^2 test) with the Yates' adjustment for continuity developed by V.P. Leonov, as well using quadrupole contingency tables. Differences were considered statistically significant with $p < 0.05$.

Table 2. *Initial characteristics of patients with tuberous sclerosis from the Republic of Bashkortostan*

Criterion	Frequency in patients from RB n (%)
Depigmentation spots	78 (90 %)
Face angiofibromas	48 (56 %)
Heads fibrous plaques	28 (33 %)
Skin shagreen plaques	36 (42 %)
Pulmonary lymphangioleiomyomatosis	1 (1,2 %)
Heart rhabdomyomas in pateints under 2 years	6 (75 %)
Heart rhabdomyomas in patients over 2 years	30 (38 %)
Subependymal giant cell astrocytoma	16 (19 %)
Subependymal nodes	57 (66 %)
Cortical dysplasia	37 (43 %)
Renal angiomyolipomas	37 (43 %)
Gingival fibromas	4 (5 %)
Multiple renal cysts	19 (22 %)

Notes: RB — Republic of Bashkortostan, TS — tuberous sclerosis

Results

86 patients (48 males, 37 females) aged 1 to 61 years (25 [21; 33] years) from 82 families were reported in RB (Fig. 1). Patients were distributed irregularly in the different Republic of Bashkortostan districts: 28 patients with TS were rural dwellers (33 %), while 58 patients lived in cities (67 %). Patient ethnicities corresponded to distribution features in the region. Accounting for the RB population in 2025 (4,046,094 people), the incidence of TS is 1:47,048 people, which is 5.9-fold lower than the global average [2]. The maternal disease inheritance was 13 cases (15 %), while the other 73 were sporadic (85 %). The analysis of clinical TS manifestations corresponding to the established diagnostic criteria of the disease [2] demonstrated that their incidence among patients from RB differed from those collected from the global TS statistics (Table 3). Cutaneous depigmentation spots were detected in 78 patients with TS (90 %), facial angiofibromata — in 48 (56 %), fibrous plaques on the forehead — in 28 (33 %), "shagreen" plaques on the skin of the torso — in 36 (42 %), pulmonary lymphangioleiomyomatosis — in 1 (1.2 %), subependymal nodes — in 57 (66 %), cortical tubers — in 37 (43 %), subependymal giant-cell astrocytoma — in 16 (19 %), renal angiolipomata — in 37 (43 %), gingival fibromata — in 4 (5 %), renal cysts — y 19 (22 %). The incidence of cardiac rhabdomyomata significantly differed depending on the age of patients with TS, accounting for the fact that many of those anomalies tended to regress spontaneously after 2 years of age [3]. The current article calculated the incidence of cardiac rhabdomyomata in various age groups: they were detected in 6 (75 %) of 8 children with TS aged under 2 year, while in patients over 2 years (n=78) this parameter reached 30 (38 %).

The analysis of data presented in Table 1 demonstrated that the incidence of polycystic kidney disease, subependymal giant-cell ependymoma, cardiac rhabdomyomata, "shagreen" plaques on the skin, fibrous plaques on the forehead, and depigmentation spots did not differ statistically from global data. At the same time, gingival fibromata, renal angiomyolipomas, cortical dysplasias, subependymal nodes, pulmonary lymphangioleiomyomatosis, and facial angiofibromata in patients with TS from RB were detected less frequently.

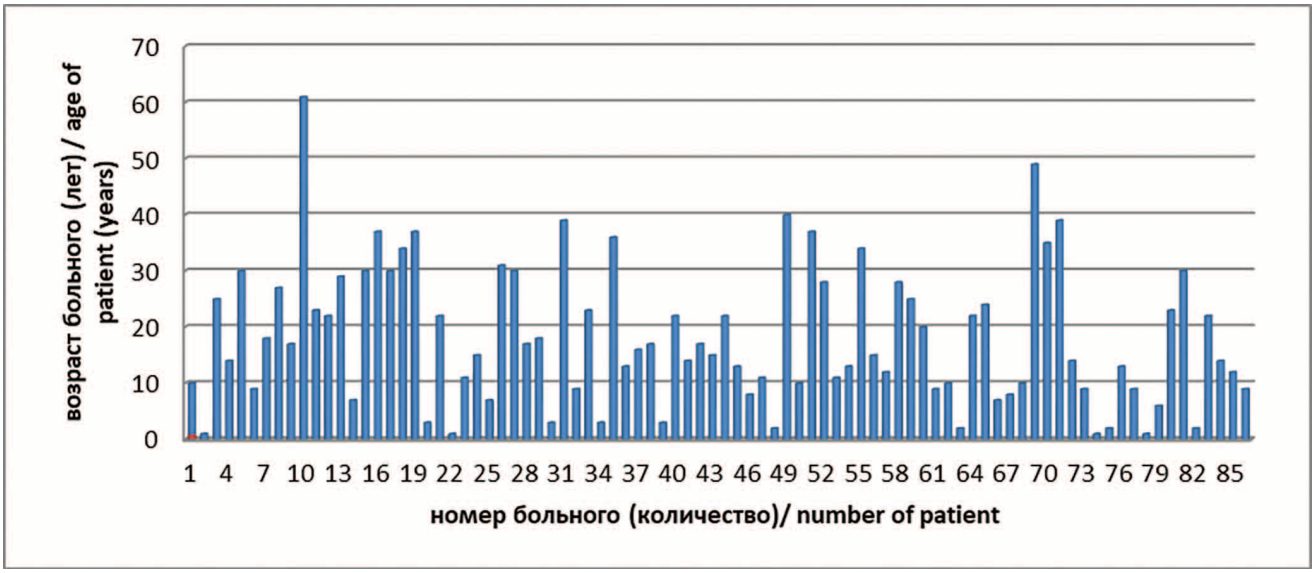

Figure 1. *Age range of patients with tuberous sclerosis in the Republic of Bashkortostan*

Table 3. *Comparative characteristics of diagnostic criteria for tuberous sclerosis in patients from RB with world data [2, 3, 5, 6]*

Criterion	Frequency in patients from RB, n (%)	World frequency in patients with TS, n (%)	χ2 test; p-value at 1 degree of freedom
Depigmentation spots	90 %	90 %	$\chi^2 = 0$; $p=1$
Face angiofibromas	56 %	83 %	$\chi^2 = 17{,}195$; $p<0{,}001$
Heads fibrous plaques	33 %	25 %	$\chi^2 = 1{,}554$; $p=0{,}213$
Skin shagreen plaques	42 %	50 %	$\chi^2 = 3{,}998$; $p=0{,}046$
Pulmonary lymphangioleiomyomatosis	1,2 %	40 %	$\chi^2 = 46{,}664$; $p<0{,}001$
Heart rhabdomyomas in pateints under 2 years	75 %	90 %	$\chi^2 = 7{,}792$; $p=0{,}006$
Heart rhabdomyomas in patients over 2 years	38 %	20 %	$\chi^2 = 7{,}868$; $p=0{,}006$
Subependymal giant cell astrocytoma	19 %	13 %	$\chi^2 = 1{,}339$; $p=0{,}248$
Subependymal nodes	66 %	90 %	$\chi^2 = 16{,}783$; $p<0{,}001$
Cortical dysplasia	43 %	85 %	$\chi^2 = 38{,}281$; $p<0{,}001$
Renal angiomyolipomas	43 %	75 %	$\chi^2 = 21{,}166$; $p<0{,}001$
Gingival fibromas	5 %	35 %	$\chi^2 = 28{,}125$; $p<0{,}001$
Multiple renal cysts	22 %	30 %	$\chi^2 = 1{,}663$; $p=0{,}198$

Notes: RB — Republic of Bashkortostan, TS — tuberous sclerosis

Table 4. *Characteristics of tuberous sclerosis clinical manifestations (not included in the criteria for diagnosis) in patients from RB compared with world data*

Criterion	Frequency in patients from RB, n (%)	World frequency in patients with TS, n (%)	χ2 test; p-value at 1 degree of freedom
Epilepsy	67 %	78 % [3]	$\chi^2 = 3{,}034$; $p=0{,}082$
Cognitive impairment	47 %	75 % [5]	$\chi^2 = 16{,}478$; $p<0{,}001$
Autism spectrum disorder	1 %	30 % [8]	$\chi^2 = 32{,}105$; $p<0{,}001$

Notes: RB — Republic of Bashkortostan, TS — tuberous sclerosis

Besides the aforementioned TS manifestations (diagnostic criteria), other clinical signs were also detected in patients from RB: epilepsy was detected in 58 (67 %), cognitive disorders — in 40 (47 %), while ASD — only in 1 (1.16 %) TS patient. Compared to global data (Table 4), the incidence of epilepsy in patients with TS from RB did not differ statistically, while cognitive disorders and ASDs occurred significantly less frequently compared to global data.

The analysis of Table 4 confirms that patients with TS need to be examined by psychiatrists and psychologists to describe the cognitive disorders and ASDs in them.

8 (9 %) people with the genetically confirmed diagnosis of TS from 86 followed up by the RMGC are administered everolimus 10 mg/day. 2 of these patients had a prolonged *TSC2* gene deletion, 1 had a binucleotide deletion in the *TSC1* gene (exon 7:c.530_531delTC (p.Leu177fs*40)), and 5 had intragene TSC2 mutations: exon 12:TSC2:c.1225G>T; exon 30:c.3610+6G>A; exon30:c.3610+1G>A; exon17:c.1840-1G>A; exon17c.1831C>T(p.R611W). All 8 patients using everolimus had neoplastic and brain lesions typical for TS: 6 (75 %) — cardiac rhabdomyomata, 5 (63 %) — renal angiolipomata, 4 (50 %) — epilepsy, 4 (50 %) — cognitive disorders in various combinations. Compared to global data, the incidence of cardiac rhabdomyomata, renal angiolipomata, cognitive disorders, and epilepsy did not differ statistically from 8 patients administered everolimus, accounting for the small sample size (using the φ test and Pearson's contingency ratio).

Discussion

The comparative analysis of TS incidence in RB (1:47,048) and global data (1:6,000 — 1:10,000) demonstrate that the incidence of reported cases is 5.9-fold lower than the expected one. This can be explained by the fact that not all patients with TS are referred for counseling to the RMGC. Thus, this issue has to be widely discussed among pediatricians, general practitioners, dermatologists, diagnostic specialists (determining typical TS manifestations on US, EchoCG, MRI); it also has to be included into educational programs for junior and postgraduate medical students, young physicians. The regional issue is also associated with the possibility of using everolimus treatment (currently in 8 patients).

The comparative analysis of clinical TS features in RB and the global statistics data demonstrates a significantly less frequent detection of facial angiofibromata. If the age effect is assumed (i.e. angiofibromata in TS emerge at the age of 3–4 years [5]), this factor cannot be used, as the mean age of examined patients was 18.5 years, while the number of patients under the age of 3 years was 7 (8 %). Subependymal nodes, cortical dysplasias, renal angiolipomata, gingival fibromata, and pulmonary lymphangioleiomyomatosis (important diagnostic criteria in TS) were also detected less frequently [2]. The results obtained may reflect the features of clinical TS manifestations in RB, however repeated imaging of internal organs and the brain is required for a more accurate evaluation. Insufficient patient examination may be the possible cause of a lower tumor diagnosis. Thus, brain neoplasms were detected in 65 (76 %) patients with TS from RB. However, only in 2 (2.3 %) patients the MRI was not abnormal, while the brain MRI was not arranged in 19 (22 %) patients.

Concerning other TS manifestations, the rate of epilepsy in patients with RB is not statistically different from the global data. However, cognitive disorders and ASDs were reported significantly less frequently, which requires counseling of neurologists, psychotherapists, psychologists to be arranged in all patients with TS with the purpose of determining the character of psychoneurological disorders and recommendations on their treatment. Although neoplastic lesions of internal organs (in various combinations) were detected in all 86 patients with TS, only 8 of those (9 %) are currently treated with everolimus. This is related to the fact that the genetic disease confirmation is required to obtain the drug via the Krug Dobra fund. This organization was created on January 5, 2021 by the Order of the President of the Russian Federation "On Creating the Fund for Supporting Children with Severe Life-Threatening and Chronic Diseases, Including Rare (Orphan) Diseases (Krug Dobra)". The procedure of obtaining drug products in the Krug Dobra Fund is presented in the Decree of the RF Government dated April 6, 2021 No. 545 according to the List of Children Categories (Krug Dobra). Criteria for everolimus administration include children with the clinical symptom complex of tuberous sclerosis; children with the symptom complex of tuberous sclerosis, but no detected TSC1 or TSC2 mutation, confirmed by the mutual statement of two Federal Medical Centers concerning the drug product administration; children with the detected TSC1 or TSC2 gene mutation; children with dysphagia under 18 years of age; children with cognitive disorders under 18 years of age [21].

To provide the drug coverage of patients with TS, mutations in *TSC1/TSC2* genes have to be identified in all patients with further referral for everolimus treatment and regular follow-up. It should be noted that when encountering pulmonary lesions in young females and children, physicians often establish the diagnosis of lymphangioleiomyomatosis without differential diagnosis with TS. It is important to accentuate the attention of general practitioners, pediatricians, and other specialists about the hereditary disease and possible lesions of other organs (mainly the heart, kidneys, and brain).

As stated in our article, in RB 24 patients (28 %) underwent the genetic testing, which differs from global data, according to which the mutation detection rate in different countries varies from 13 % in the Netherlands [22] to 72 % in the USA [23], 76 % in Taiwan [24], 78 % in Germany [25], 80 % in the UK [26], 83 % in the USA [27], 89 % in Brazil [28], and 94 % patients with TS in Mexico [29]. This situation is due to the fact that patients from RB have to apply to the N.P. Bochkov Medical Genetics Scientific Center (MGSC) for mutation testing, and this is not available to everyone due to the required trip to Moscow. One possible solution is to conduct the tests in the Republican Medical Genetics Center or to develop a scientific diagnostic program with the possibility of collecting blood in RMGC (Ufa) and sending it for free testing to N.P. Bochkov MGSC without visiting Moscow.

Only 9.3 % patients with TS from RB are administered targeted therapy, while based on global data the treatment is recommended for all patients [22–29]. This regional limitation is associated both with the incomplete genetic testing coverage of all patients from RB (as detection of mutations in *TSC1* or *TSC2* genes is required for everolimus administration) and the required informed consent of patients for treatment (not all patients consent for therapy, especially those with mild clinical disease manifestations). It should be noted that thanks to the molecular-genetic testing, 5 patients had mutations in the *TSC1* gene detected, with 3 mutations (c.530_531delTC:p.Leu177fs, c.587C>T:p.Pro196Leu, c.936C>G:p.Tyr312X) not described priorly in the scientific literature, while 2 were observed by other researchers: c.682C>T:p.Arg228X in Germany [25], c.2287C>T(p.Gln763Ter) in the Netherlands [22], the USA [23], and Brazil [27]. In our study, 19 patients had mutations in the *TSC2* gene detected, with 11 pathogenic variants (c.43delT:p.Phe15fs, c.707T>C:p.Leu236Pro, c.767G>T:p.Cys256Phe, c.931_932del:p.Ser311fs, c.973C>T:p.Gln325X, c.1225G>T:p.Glu409X, c.1840-1G>A, c.2380C>T:p.Gln794X, c.2707dupC:p.Leu902fs, c.3610+6G>A, c.4161_4162del:p.Ser1387fs) not described earlier in the scientific literature. 8 mutations detected in RMGC among patients from RB were described priorly in patients with TS in other countries: c.268C>T(p.Gln90X) in the USA [23, 27] and Taiwan [24], c.976-15G>A in Germany [30] and the USA [27], c.1831C>T(p.Arg611Trp) in India [31], the USA [23], China [32], and Mexico [29]; c.2083C>T(p.Gln695X) in the UK [26], China [33], and the USA [23]; c.3095G>C(p.Arg1032Pro) in the Netherlands [34], c.3610+1G>A in the UK [26] and the USA [27], c.4174C>T(p.Gln1392X) in China [35] and Mexico [29], c.4242dupT(p.Lys1415fs) in the USA [23].

RB has accumulated the experience of administering and using everolimus in 8 patients with mutations detected in the *TSC1* (exon 7:c.530_531delTC (p.Leu177fs*40)) and *TSC2* genes (exon 12:TSC2:c.1225G>T; exon 30:c.3610+6G>A; exon30:c.3610+1G>A; exon17:c.1840-1G>A; exon17c.1831C>T, and prolonged gene deletions in 2 patients). The treatment administered resulted in the reduction of several clinical TS manifestations, including seizures. The follow-up also confirmed the improvement of cognitive functions in patients with TS administered targeted therapy (everolimus). This confirms its efficacy and cost-effectiveness of drug administrations to a larger pool of patients with TS, which requires the molecular-genetic testing with the detection of mutations in *TSC1* and *TSC2* genes.

Conclusion

The results obtained confirm the lower (5.9-fold) rate of reported TS cases in RB compared to global data. This may be associated with the low alertness of physicians about typical TS symptoms and diagnostic criteria. When finding such signs as depigmentation spots, facial angiofibromata, fibromata on the forehead, "shagreen" plaques on the skin, renal angiolipomata, cardiac rhabdomyomata, pulmonary lymphangioleiomyomatosis, nodular cerebral lesions, clinicians should suspect TS and refer the patient to the medical genetics counseling. The detected statistically significant differences in the incidence of specific TS manifestations may be associated with the insufficient examination — thus, all patients with TS should undergo regular brain MRI, US of internal organs, EchoCG. Psychotherapist, neurologist, and psychologist counseling is required to detect and treat psychoneurological disorders. Considering the treatment of neoplastic disease manifestations, all patients in need have to be provided mTOR inhibitors, which requires the molecular-genetic confirmation of the diagnosis by detecting mutations in *TSC1* and *TSC2 genes*. Physicians in different Russian regions should know that patients with suspected TS should be referred to the genetics specialist counseling in interregional medical genetics centers or directly in Moscow MGSC (if the former ones are absent) in order to detect the disease timely and administer targeted therapy.

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ОСОБЕННОСТИ ДИАГНОСТИКИ И ВЫБОРА ТАКТИКИ ЛЕЧЕНИЯ ВПЕРВЫЕ ВЫЯВЛЕННОГО СИНДРОМА БЛАНДА–УАЙТА–ГАРЛАНДА НА ФОНЕ ТЯЖЕЛОЙ СОПУТСТВУЮЩЕЙ СОМАТИЧЕСКОЙ ПАТОЛОГИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Features Of Diagnosis and Choice of Treatment Tactics of The First-Diagnosed Bland-White-Garland Syndrome with Severe Coexisting Somatic Pathology (Clinical Case)

Резюме

Синдром Бланда-Уайта-Гарланда (БУГ-синдром) представляет собой редкую и опасную врожденную аномалию, являющуюся одной из ведущих причин ишемии и инфаркта миокарда у детей. Без своевременного лечения и коррекции заболевание может привести к крайне тяжелым последствиям: до 90 % пациентов умирают в течение первого года жизни. В случае со взрослыми, пациенты, страдающие этим синдромом, могут столкнуться с различными осложнениями, такими как дисфункция левого желудочка, митральная регургитация, бессимптомная ишемия миокарда и инфаркт, а также высоким риском внезапной сердечной смерти. Учитывая, что заболевание редко диагностируется, важно выявлять БУГ-синдром на ранней стадии для превентивного лечения и предотвращения осложнений.

В данной работе описан уникальный случай впервые выявленного БУГ-синдрома у 27-летней пациентки. Помимо порока, женщина страдала от тяжелой сопутствующей патологии — первичного склерозирующего холангита, который осложнялся циррозом печени и гиперспленизмом. Наличие данных заболеваний в значительной степени усложнило выбор лечебной тактики, требуя персонализированного подхода. В связи с высоким риском развития послеоперационных осложнений, предпочтение было отдано малоинвазивной эндоваскулярной эмболизации левой коронарной артерии. Операция показала хорошие результаты и привела к значительному улучшению состояния пациентки, в том числе к достижению компенсации сердечной недостаточности до функционального класса II (NYHA). Представленный случай демон-

стрирует важность индивидуального подхода в лечении редких врожденных пороков сердца у взрослых, особенно при наличии серьезных сопутствующих заболеваний других органов и систем.

Ключевые слова: *Синдром Бланда-Уайта-Гарланда, сосудистые мальформации, сердечная недостаточность, эндоваскулярная эмболизация*

Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики
Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «ОСОБЕННОСТИ ДИАГНОСТИКИ И ВЫБОРА ТАКТИКИ ЛЕЧЕНИЯ ВПЕРВЫЕ ВЫЯВЛЕННОГО СИНДРОМА БЛАНДА–УАЙТА–ГАРЛАНДА НА ФОНЕ ТЯЖЕЛОЙ СОПУТСТВУЮЩЕЙ СОМАТИЧЕСКОЙ ПАТОЛОГИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)» для журнала «Архивъ внутренней медицины», подписав информированное согласие

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Abstract:
ALCAPA (Anomalous Left Coronary Artery from the Pulmonary Artery) is a rare and dangerous congenital anomaly that is one of the leading causes of myocardial ischemia and infarction in pediatric patients. Without timely treatment and correction, the disease can lead to extremely severe consequences: up to 90 % of patients die within the first year of life. In adults, patients suffering from this syndrome may face various complications such as left ventricular dysfunction, mitral regurgitation, asymptomatic myocardial ischemia and infarction, and a high risk of sudden cardiac death. Given that this disease is rarely diagnosed, it is important to detect it early for preventive treatment and avoidance of serious disorders.

This paper describes a unique case of first-diagnosed ALCAPA syndrome in a 27-year-old female patient. In addition to the malformation, the woman suffered from severe concomitant pathology — primary sclerosing cholangitis, which was complicated by liver cirrhosis and hypersplenism. The presence of these diseases significantly complicated the choice of therapeutic tactics, requiring a personalized approach. Due to the high risk of postoperative complications, preference was given to minimally invasive endovascular embolization of the left coronary artery. The operation showed good results and led to significant improvement of the patient's condition, including the achievement of heart failure compensation up to functional class II (NYHA). This case highlights the importance of an individualized approach in the treatment of rare adult congenital heart disease, especially in the presence of serious concomitant diseases of other organs and systems.

Key words: *ALCAPA Syndrome, vascular malformations, heart failure, endovascular embolization*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
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BP — blood pressure, BWG-syndrome — Bland-White-Garland syndrome, LV — left ventricle, MRI — magnetic resonance imaging, FC — functional class, FN — physical activity, CHF — chronic heart failure

Introduction

Bland-White-Garland (BWG) syndrome, also known as ALCAPA (Anomalous Left Coronary Artery from the Pulmonary Artery), is a rare congenital heart disease characterized by the anomalous branching of the left main coronary artery from the pulmonary trunk. This disease incidence is 1:300,000, constituting 0.25–0.5 % of all congenital birth defects and 0.5 % of all congenital heart diseases [1].

Adequate myocardial perfusion can be maintained in the neonatal period due to the increased pressure in the left pulmonary artery, which is similar to that in the aorta,

and the disease can be quite asymptomatic. Subsequently, during the first weeks of life, the pulmonary artery pressure decreases, which leads to the inadequate myocardial perfusion. Approximately 90 % cases of the disease manifest within the first 2–3 months of life with myocardial ischemia, left ventricular dysfunction, and mitral regurgitation, with clinical signs including acrocyanosis, tachypnea, tachycardia (infantile type of the BWG syndrome). If the collateral circulation is adequate, the arterial blood retrogradely flows from the right coronary artery to the left one, which also causes the myocardial stealing phenomenon; however, this can be subclinical for a long time (adult type of the BWG syndrome). Concerning symptoms, the leading disease manifestations in this patient group include dyspnea, angina, decreased exercise tolerance, and sudden cardiac death [2–5].

Below we present a clinical case report of the newly detected Bland-White-Garland syndrome in an adult patient. This clinical case was peculiar concerning the severe concomitant pathology that affected the patient management tactics.

Clinical Case Report

The female patient V., 27 years old, visited the emergency department of the General Republican Medical Center, State Budget Healthcare Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital" (Simferopol) complaining of palpitations, dyspnea during brisk walking and when climbing to the 2nd floor, tachycardia during exertion. Physical examination demonstrated hepatomegaly, splenomegaly; the patient had a low height and was underweight (height 148 cm; body weight 43.0 kg; body mass index 19.6 kg/m^2).

Based on the patient's words, she had been followed up by the cardiologist since childhood due to minimum aortic regurgitation and minimum pulmonic stenosis. She was exempted from physical education classes in school due to low exercise tolerance. Intensive skin itching also persisted since early childhood. Since teenage years she periodically noted blood pressure (BP) elevation to 170/80 mm Hg (the patient was adapted to BP 110/70 mm Hg), occasionally taking enalapril. During the first pregnancy (in 2021), she developed BP elevation to 180–190/80 mm Hg, methyldopa was administered; thrombocytopenia (34.0x10^9/L) was also detected for the first time then. That pregnancy was complicated by eclampsia, and the delivery was arranged via the cesarean section on Week 34. One month after the delivery, the patient was hospitalized with pulmonary edema of unknown origin; she was discharged to continue diuretics, which she took for some time, but cancelled spontaneously.

Subsequently, since spring 2023, the patient noted worsening general condition and dyspnea with decreasing exercise tolerance. In September 2023 she spontaneously visited the emergency department of SBHI RC "N.A. Semashko RCH", where she was diagnosed with paroxysmal tachysystolic atrial fibrillation, and the patient was hospitalized to the Department of surgical treatment of complex arrhythmias and pacing. Chemical cardioversion was achieved with amiodarone (450.0 mg). During the hospitalization, the patient underwent echocardiography: left atrium 6.1 cm, left atrial volume 150 mL, left ventricular end-diastolic volume 87 mL, left ventricular end-systolic volume 36 mL, interventricular septum thickness 0.9 cm, left ventricular posterior wall thickness 0.9 cm, left ventricular ejection fraction 58 %, Grade 1 mitral regurgitation, bicuspid aortic valve, Grade 1 aortic regurgitation. The laboratory tests demonstrated three-lineage cytopenia, cholestatic syndrome (Table 1).

Table 1. *Results of laboratory methods of examination*

Indicator	Result	Standard
Total blood count		
Hemoglobin (g/l)	88,0	120,0-140,0
Hematocrit (%)	29,3	36,0-42,0
Red blood cells (10^12/l)	3,6	3,9-4,7
Platelets (10^9/l)	94	150-400
Leukocytes (10^9/l)	1,8	4,0-9,0
Blood biochemical examination		
Alkaline phosphatase (U/L)	128,6	<105,0
GGTP (U/L)	134,2	<32
ALT (U/L)	40,9	32
AST (U/L)	27,3	31
Bilirubin (μmol/L)	17,0	3,4-17,0

Abbreviations. GGTP — gamma-glutamyltranspeptidase, ALT — alanine aminotransferase, AST — aspartate aminotransferase

The patient underwent multispiral computed tomography of the chest and abdominal cavity with aortic contrast enhancement: Bland-White-Garland syndrome (anomalous branching of the left main coronary artery from the pulmonary artery); tortuous distal parts of the right coronary artery (3 mm in diameter) were traced. Severe left atrial dilation was noted. The spleen was significantly enlarged (68x136x177 mm; splenic index 1637); the splenic vein was dilated to 17.5 mm. Liver deformity; local area of a single hepatic vein dilation in S4b (Fig. 1).

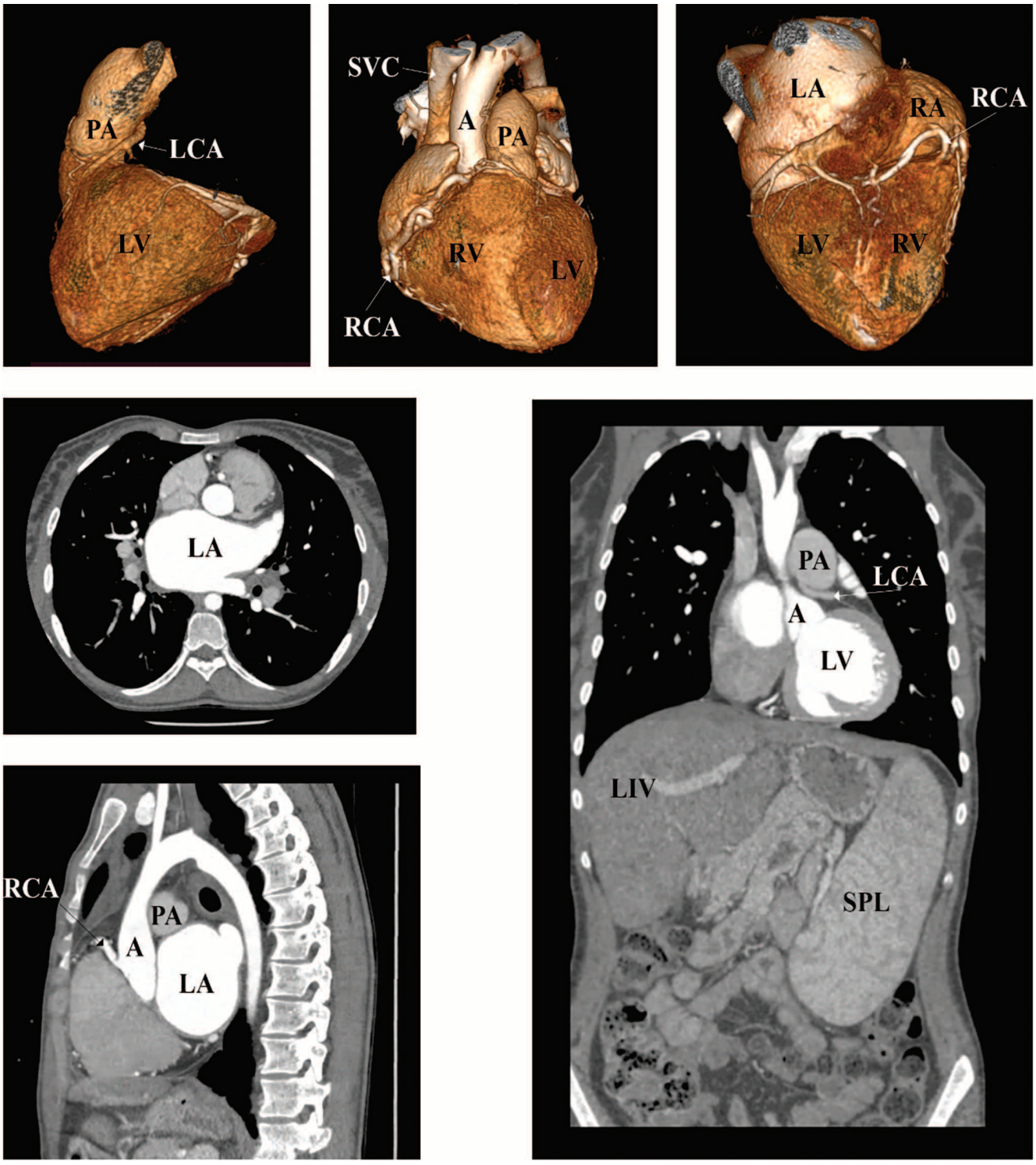

Figure 1. *Multi-slice computed tomography of the abdominal cavity and of the chest organs*
Designations: RA — right atrium, LA — left atrium, LV — left ventricle, RV — right ventricle, A — aorta, PA — pulmonary artery, RCA — right coronary artery, LCA — left coronary artery, LIV — liver, SPL — spleen

The patient was discharged with the following treatment recommendations: rivaroxaban 20 mg once daily, metoprolol succinate 50 mg once daily, allapinin 25 mg three times daily. While taking rivaroxaban, the patient developed menorrhagia and discontinued the drug herself. Later, due to significant dizziness, she spontaneously decreased the dose of allapinin to 25 mg daily. After discharge, dyspnea and substernal discomfort with moderate exertion, fatigability, weakness persisted. She was hospitalized to the V.A. Almazov National Medical Research Center (Saint-Petersburg) for examination and discussion of treatment selection.

In January 2024 she was electively admitted to the V.A. Almazov NMRC therapeutic department. Accounting for the syndrome of portal hypertension of unknown origin in the patient, magnetic resonance (MR) cholangiography and liver elastography were arranged to exclude sclerosing cholangitis. Liver elastography: F4 fibrosis based on METAVIR scale. MR-cholangiography: signs of sclerosing cholangitis. MR signs of liver cirrhosis, splenomegaly, gallstone disease, biliary dyskinesia (deformity, impaired colloidal bile properties), ectopic right kidney. The diagnosis of primary sclerosing cholangitis with the outcome of hypersplenism and liver cirrhosis was first established. Constant ursodeoxycholic acid and non selective beta-blockers were recommended for treatment.

Coronary angiography: the left anterior descending and circumflex branches of the left coronary artery were hypoperfused, diffusely altered, without significant stenosis; they filled retrogradely along intersystemic collaterals from the tortuous right coronary artery with a large diameter (~5 mm).

To evaluate the significance of myocardial ischemia, cardiac magnetic resonance imaging (MRI) was arranged: left ventricular (LV) ejection fraction 46 %; end-diastolic volume 133 mL; end-systolic volume 59 mL; dilation of left heart chambers; LV walls were not thickened; the LV contractility was moderately decreased due to diffuse hypokinesia; no signs of myocardial edema were demonstrated. No clear pathological contrast enhancement in the LV myocardium was detected on delayed post-contrast images.

During the follow-up, the patient developed short-term symptomatic, but hemodynamically insignificant paroxysmal atrial fibrillation with the maximum ventricular rate (VR) of 110 per min. Holter electrocardiography (ECG) monitoring (treatment: sotalol 120 mg/day) — paroxysmal atrial flutter with predominant conduction 2:1, 3:1, lasting max 2 sec, with the rate of 108–116 (mean 112) bpm. No other significant arrhythmias and blocks were confirmed.

The following clinical diagnosis was established in the patient:

Main disease: Congenital heart disease: Bland-White-Garland syndrome (Anomalous Left Coronary Artery from the Pulmonary Artery). Hypoplasia of the descending thoracic aorta. Bicuspid aortic valve. Grade 1 aortic regurgitation. Grade 1 mitral stenosis. Grade 3 symptomatic hypertension, partially controlled, risk of cardiovascular complications 4, target BP <130/70–79.

Complications: Paroxysmal atrial fibrillation–atrial flutter. CHA2DS2-VASc 2 points, HAS-BLED 1 point, EHRA 2 points. CHF IIA with moderately reduced left ventricular ejection fraction (46 %), FC III.

Concomitant diagnosis: Malnutrition. Hiatal hernia. Biliary dyskinesia. Gallstone disease. Small gallstones. Cholestasis. Hepatic fibrosis (METAVIR F4). Splenomegaly. Hypersplenism. Mild iron deficiency anemia. Grade 1 thrombocytopenia. Grade 1 leukopenia.

Accounting for concomitant diseases and associated postoperative risks, the mini-invasive surgery was selected. In March 2024 the patient underwent endovascular embolization of the left main coronary artery branching from the pulmonary artery. Under local anesthesia with the lidocaine solution (1 % — 20.0), the femoral vein was punctured and catheterized; the left main coronary artery was embolized with a 7x7 mm occluder. Follow-up angiography: the blood flow in the left coronary artery was collateral from the right coronary artery; no blood flow was detected to the left coronary artery from the pulmonary artery. The postoperative period was uneventful. After the surgery, the patient's condition improved, and the heart failure was compensated at the level of FC II (NYHA). The following drug therapy was recommended for the patient: ursodeoxycholic acid 500 mg daily, folic acid 15 mg daily, valsartan/sacubitril 100 mg daily, eplerenone 25 mg daily, dapagliflozin 10 mg daily, sotalol 160 mg daily, apixaban 5 mg twice daily, ademethionine 400 mg 1 tab. daily for 1 month. See the event time scale in Figure 2.

Discussion

The BWG syndrome is a disease usually manifesting clinically in childhood and (very rarely) in the adult years. Based on literature data, over 90 % patients with this pathology die during the first year of life without surgical interventions [1]. Thus, the late presentation (as in our case) is an exception. Accounting for no specific disease symptoms (most common manifestation is with the decompensated heart failure), the BWG syndrome has to be differentiated with cardiomyopathies and coronary artery disease, especially in younger patients. Apart from clinical examination, it is feasible to include modern imaging methods (i.e. echocardiography, cardiac MRI, CT angiography, coronary angiography) into

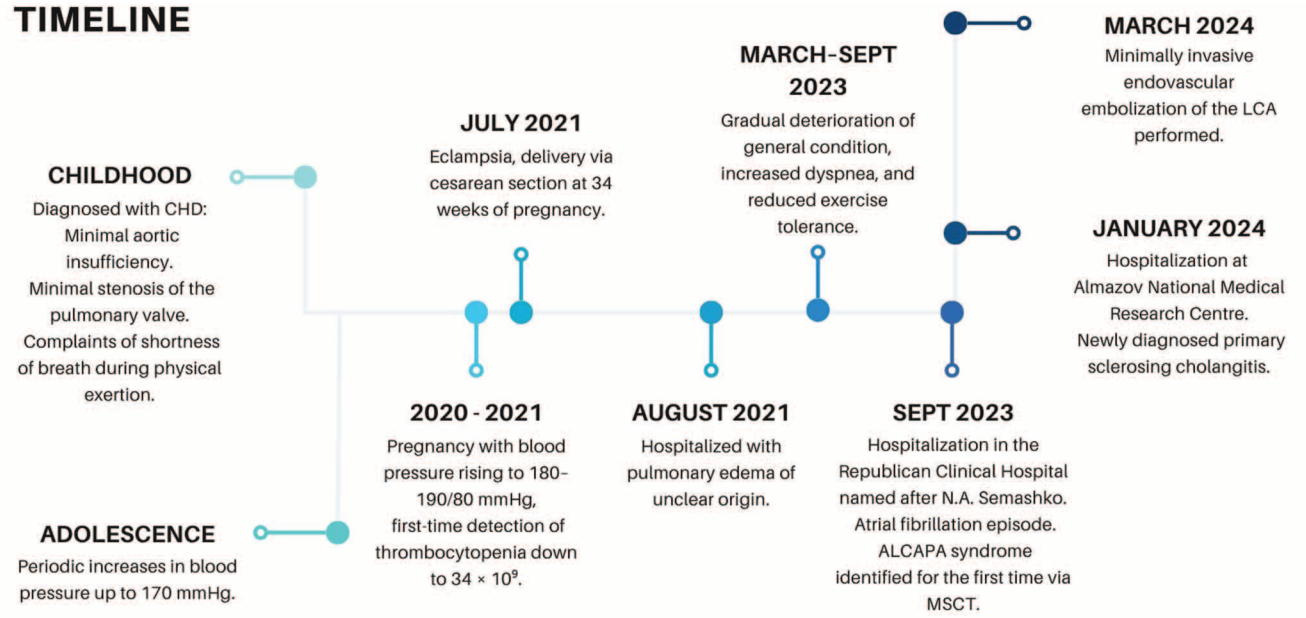

Figure 2. *Timeline*
Abbreviations: CHD — congenital heart defect; BP — blood pressure; PA — physical activity; ALCAPA — anomalous left coronary artery from the pulmonary artery; MSCT — multi-slice computer tomography; LCA — left coronary artery.

the diagnostic algorithm. These diagnostic tools are required for the accurate investigation of the coronary vessel anatomy, evaluation of myocardial perfusion, and surgery planning. In our case the prolonged relative stability was associated with the collateral circulation, promoting the retrograde blood flow from the right coronary artery to the left coronary artery territory. Nevertheless, echocardiography and cardiac MRI results demonstrated left chamber dilation and moderately decreased left ventricular contractility, which confirmed the gradual worsening of hemodynamic disorders with the emergence of diastolic and systolic dysfunction.

The clinical case above describes a rare combination of a congenital heart disease (Bland-White-Garland syndrome) and a severe hepatobiliary pathology represented by the primary sclerosing cholangitis, which manifested with liver cirrhosis and signs of portal hypertension. This combination has been described only in single literature cases, which defines its scientific significance and underlines the need for the analysis of compensation/decompensation mechanisms in similar cases. Accounting for the high risk of intraoperative and postoperative complications (massive profuse hemorrhages, acute kidney injury, infectious complications) during the open cardiac surgery, which rate usually correlates with its scope and duration of cardiopulmonary bypass, the endovascular correction of the congenital heart disease was selected in our situation due to lower operative risks [6, 7]. A mini-invasive embolization of the left main coronary artery seems justified in the setting of significant somatic diseases — that provided a partial elimination of pathological coronary blood flow, decreasing the left ventricular ischemic burden. Further patient management presumed the correction of antiarrhythmic and hepatoprotective therapy, considering persistent paroxysms of atrial fibrillation and hepatic failure. Further follow-up results will be practically significant for developing the tactics of multidisciplinary management in patients with a similar polymorbid background.

Thus, our case demonstrates the features of diagnosis and treatment in a patient with combined BWG syndrome and primary sclerosing cholangitis complicated with liver cirrhosis and portal hypertension. The clinical situation presented underlines the need for the complex approach to examination and management aimed at controlling the cardiovascular pathology and correcting severe hepatobiliary dysfunctions. This experience may be used when determining therapeutic and surgical strategies in patients with combined rare pathologies, as well as when evaluating risks and planning pregnancy in this patient category.

Conclusion

Bland-White-Garland syndrome is a rare congenital anomaly of coronary blood flow which manifests most often in infancy. The case described demonstrates the possibility of prolonged compensated course due to collateral circulation, so the patient could live to adult years without surgical correction. The patient

management was complex due to the combination of BWG syndrome with a severe concomitant pathology, including primary sclerosing cholangitis resulting in liver cirrhosis. Modern imaging methods provided the timely disease diagnosis and evaluation of the myocardial ischemia severity. Accounting for the high risk of open surgical intervention, a mini-invasive endovascular method was selected, which resulted in the condition stabilization and compensation of chronic heart failure. This case underlines the importance of early diagnosis of coronary artery anomalies, using the multidisciplinary approach and personalized treatment tactics, especially in patients with a burdened somatic background.

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НЕСВОЕВРЕМЕННОСТЬ ДИАГНОСТИКИ РАКА ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ФОНЕ ДЛИТЕЛЬНО СУЩЕСТВУЮЩЕЙ ГИПЕРКАЛЬЦИЕМИИ

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Untimeliness of Diagnosis of Parathyroid Cancer on The Background of Long-Term Hypercalcemia

Резюме

Гиперкальциемия представляет собой нарушение минерального обмена, возникающее, как правило, в результате повышения функции паращитовидных желез с развитием гиперпаратиреоза. Данное состояние могут спровоцировать различные факторы, например, развитие доброкачественной гиперплазии паращитовидных желез, облучение, употребление определенных лекарственных препаратов, снижение уровня кальция в организме, патология со стороны почек, а также нарушение функции паращитовидных желез и другие. Сложность диагностики данной патологии обусловлена как редкой встречаемостью, так и отсутствием патогномоничной симптоматики. Клинические проявления гиперкальциемии многообразны и проявляются патологией желудочно-кишечного тракта, нервной системы, а также развитием мочекаменной болезни и остеопорозом. Важность своевременного диагностирования гиперкальциемии обусловлена не только необходимостью улучшить качество жизни пациента и предотвратить развитие осложнений, но и возможностью раннего выявления наиболее грозной причины гиперпаратиреоза — рака паращитовидных желез. В статье обсуждается история болезни пациента 46 лет, отражающая позднюю диагностику гиперкальциемии и развитие рака паращитовидной железы, несмотря на длительно существующие клинические проявления гиперкальциемии и стойкие отклонения лабораторных показателей с повышением уровня щелочной фосфатазы; свободного и ионизированного кальция. Сделан акцент на проявлениях гиперкальциемии, которые должны были насторожить врачей и направить диагностический поиск в правильное русло. Подчеркивается важность тщательного сбора анамнеза и интерпретации каждого клинического проявления.

Ключевые слова: *гиперкальциемия злокачественных новообразований, паратиреоидный гормон, паращитовидные железы, кальций*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «НЕСВОЕВРЕМЕННОСТЬ ДИАГНОСТИКИ РАКА ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ФОНЕ ДЛИТЕЛЬНО СУЩЕСТВУЮЩЕЙ ГИПЕРКАЛЬЦИЕМИИ» для журнала «Архивъ внутренней медицины», подписав информированное согласие

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Abstract

Hypercalcemia is a disorder of mineral metabolism that typically arises due to increased parathyroid gland function, leading to hyperparathyroidism. This condition can be triggered by various factors, such as the development of benign parathyroid hyperplasia, radiation exposure, the use of certain medications, decreased calcium levels in the body, renal pathology, impaired parathyroid gland function, and others. The complexity of diagnosing this condition is attributed to its rare occurrence and the absence of pathognomonic symptoms. The clinical manifestations of hypercalcemia are diverse and include gastrointestinal and nervous system disorders, as well as the development of urolithiasis and osteoporosis. The importance of timely diagnosis of hypercalcemia lies not only in the need to improve the patient's quality of life and prevent complications but also in the early detection of the most severe cause of hyperparathyroidism—parathyroid cancer. This article discusses the case history of a 46-year-old patient, illustrating the delayed diagnosis of hypercalcemia and the development of parathyroid cancer despite long-standing clinical manifestations of hypercalcemia and persistent laboratory abnormalities, including elevated levels of alkaline phosphatase, free and ionized calcium. The clinical case analysis emphasizes the manifestations of hypercalcemia that should have alerted clinicians and guided the diagnostic process in the right direction. The importance of thorough history-taking and the interpretation of each clinical manifestation is underscored.

Key words: *hypercalcemia of malignant neoplasms, parathyroid hormone, parathyroid glands, calcium*

Conflict of interests

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Conformity with the principles of ethics

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IL — Interleukin, PTHrP — parathyroid hormone-related protein, HCM — hypercalcemia of malignancy, M — malignancy, PTH — parathyroid hormone, PTG — parathyroid gland, US — ultrasound diagnosis, ALP — alkaline phosphatase

Introduction

Parathyroid gland (PTG) cancer is a rare sporadic or hereditary endocrine malignancy (M) encountered in <1 % of primary hyperparathyroidism cases, characterized by the impaired calcium-phosphorus metabolism, affecting other organs and systems [1, 2].

Hypercalcemia is detected in approximately 1 % of the global population, and in 90 % cases it is associated with Ms [3, 4].

Hypercalcemia of malignancy (HCM) is a condition accompanied by enhanced mortality, which is the most common metabolic complication of malignancies [5].

In tumors hypercalcemia is most likely associated with the increased bone resorption and calcium release with subsequent hypercalcemia-induced renal injury [6].

Hypercalcemia is confirmed with calcium levels over 10.5 mg/dL and is a relatively common issue, which always reflects the underlying disease [3, 6].

Mechanisms of hypercalcemia

Four main hypercalcemia mechanisms have been described:

1. Excessive synthesis of extrarenal 1,25[OH]2D.
2. Humoral HCM.
3. Local osteolytic hypercalcemia with the secretion of other humoral factors associated with increased calcium levels in blood.
4. Ectopic PTH production.

Primary hyperparathyroidism.

In 80 % cases, primary hyperparathyroidism emerges due to the benign hyperplasia (adenoma) of a single parathyroid gland, in 20 % — due to that of two-three glands, while four glands are affected in rare situations. This leads to excessive PTH secretion. This condition in <1 % cases is associated with the PTG cancer both in males and females.

Secondary hyperparathyroidism.

This condition develops if such pathologies as hypocalcemia or chronic kidney disease provoke the increased PTH secretion by parathyroid glands.

Tertiary hyperparathyroidism.

The function of parathyroid glands transforms to the autonomous PTH production which is independent of exogenous stimulation is called tertiary hyperparathyroidism.

Clinical manifestations

HCM symptoms emerge with the total calcium levels over 3.0 mmol/L and are non-specific; however, their manifestations directly depend on the disease severity, calcium levels, presence or absence of bony metastases [5].

Depending on calcium levels, hypercalcemia is divided into:

- mild, with serum calcium levels <10.5-12 mg/dL [3 mmol/L];
- moderate, with Ca levels 12.1–14 mg/dL [3–3.5 mmol/L];
- severe, with Ca levels >14 mg/dL [>3.5 mmol/L] [4, 5, 7].

Cardiovascular clinical manifestations of hypercalcemia depend not just on calcium levels in blood, but also on concomitant diseases. If calcium levels increase to 3.2–3.4 mmol/L, automatism may decrease, while ventricular systole may shorten.

With calcium levels over 3.3 mmol/L, QT interval shortens; atrioventricular block may develop at levels of 3.3–4.0 mmol/L; the risk of sudden cardiac death increases with levels over 4.0 mmol/L. Ventricular fibrillation, bradyarrhythmia, hypertension may develop in patients.

Psychoneurological disorders include fatigue, malaise, apathy, hyporeflexia, muscle weakness with paresis and paralysis, headache, seizures, perception and behavior disorders, signs of subcortical edema, sopor, coma. As neurological disorders progress, polyuria and polydipsia lead to dehydration, renal failure, progressive urolithiasis with nephrocalcinosis and nephrolithiasis.

Such dyspeptic signs as nausea, vomiting, constipation, may lead to anorexia, peptic ulcer disease, or bowel obstruction. Non-specific manifestations also include skin itching and ossalgia [2, 6].

Diagnosis

During the primary examination, the serum calcium level (total physiologically inactive transporter-bound calcium and active ionized calcium) is determined. However, increased calcium levels require repeated confirmation, clarifying the total and ionized calcium levels. In this case one has to account factors that affect the interpretation of results, including serum albumin and blood pH. If the albumin level is abnormal, the serum calcium level should be adjusted using the following equation:

$$\text{Corrected calcium} = \text{total calcium} + [0.8 \times (4.0 - \text{albumin})].$$

PTH and PTHrP are measured subsequently — their levels do not increase simultaneously, except if more than one cause can be detected. Hypophosphatemia, hyperchloremia, and mild metabolic alkalosis are possible with high PTH levels against the background of hypercalcemia. If PTHrP levels decrease, 1.25-dihydroxyvitamin D levels are measured. Hypercalcemia with the detected low PTH, PTHrP, and 1.25[OH]2D levels along with bony metastases may be considered a cause of HCM.

Imaging methods are not mandatory in primary hyperthyroidism, however they provide information about the location of gland lesions for further surgical interventions. Densitometry is also used to assess the mineral bone density.

Parathyroid cancer

The incidence of PTG cancer does not depend on the gender, unlike primary hyperthyroidism, where the female-to-male ratio of the disease incidence is 3–4:1; no ethnic predisposition has also been described. The disease onset is approximately at the age of 50 (as of the diagnosis) [8–10].

Clinical manifestations

PTG cancer in the majority of cases is represented by the functioning tumor with typical hypercalcemia signs. In PTGMs, the most common symptoms include bony and renal ones: polyuria, polydipsia, urolithiasis manifestations (renal colics), ossalgia, pathological fractures [8, 11].

In very rare situations PTG cancer may manifest with the non-functioning tumor, normocalcemia, and a palpable neck lesion, which is often detected late due to diagnostic difficulties. This tumor type tends to metastasize to various locations, including cervical lymph nodes, bones, liver, and lungs [8].

Diagnosis

Due to dehydration and nephrolithiasis and/or nephrocalcinosis against the background of hypercalcemia and increased serum PTH levels, the glomerular filtration rate decreases.

In outpatient practice, the biochemistry panel is feasible to detect increased alkaline phosphatase levels (determining the severity of skeletal lesions) and human chorionic gonadotropin levels, especially its hyperglycosylated isoform [9, 11].

The ultrasound (US) is primarily arranged to diagnose PTG cancer — this can reveal large-sized lesions (>3.0 cm), irregular homogeneity with decreased echogenicity, signs of degeneration (cystic cavities, calcifications, irregular borders). US is also used to exclude the lymph node lesions (with subsequent biopsy if necessary).

Contrast-enhanced computed tomography is arranged to clarify the location of lesions.

Magnetic resonance imaging helps to assess the condition of soft tissues in the neck for the possible diagnosis of ectopic glands and to determine the relations to the surrounding structures.

The enhanced glucose metabolism is typical in malignant cells due to a large amount of transporter proteins. Thus, positron emission tomography with fluorodeoxyglucose is used as a highly informative method that can easily evaluate primary tumors; however, micrometastatic lesions sized <6 mm may be missed. The PTG tumor aggression is associated with the standardized uptake values [8, 11].

[99mTc]-technetium scan is arranged to determine the primary location of the malignancy and to detect metastatic lesions. However, such scans are not very informative in the differential diagnosis of benign and malignant neoplasms [11, 12].

Signs of PTGMs with atypical cytological and architectural features include cellular nests in the fibrous septum, significant tissue fibrosis, tumor cells detected in the tumor capsule or suspected invasion, cytological atypia manifesting with mitotic activity >5/10 mm^2 or Ki-67 proliferation index >5 % [8, 9, 11, 12].

The molecular-genetic testing (along with immunohistochemistry) is recommended in patients with the verified PTG cancer to exclude germinal mutations in the CDC73 gene [13].

Despite the sufficient diagnostic investigations for PTGMs, one should note that primary care physicians do not often provide adequate cancer alertness due to such factors as overwork, shortage of staff, limited visit time.

The clinical case described below presents a 46-year-old patient followed up by the general practitioner since 2014; it specifically demonstrates the importance of checking and thoroughly analyzing all clinical and laboratory manifestations of a specific disease, which is especially important in the diagnosis of diseases rarely occurring in the regular practice of the general practitioner.

In January 2017, the patient attended the general practitioner complaining of epigastric pain, abdominal bloating, heartburn, dark stools for 2 months during the administration of bismuth tripotassium dicitrate. Gastroscopy was arranged: superficial gastritis with moderate bulbitis was detected. Based on the patient's words, the duodenal ulcer was diagnosed; however, no documents confirming the diagnosis were provided. Colonoscopy confirmed the hypertonic dyskinesia, while no organic diseases were detected. Hepatobiliary US: hepatomegaly, signs of fatty liver. Blood tests demonstrated moderately elevated transaminases (ALT 79 U/L, AST 81 U/L (N <40 U/L)), hypercholesterolemia (total cholesterol 7.1 mmol/L; N 3.4–6 mmol/L), elevated ESR (77 mm/h; N 1–30 mm/h). The patient was counseled by the gastroenterologist. Diagnosis: chronic superficial gastritis, chronic duodenitis (exacerbation), steatohepatitis, irritable bowel syndrome without diarrhea. Diet, proton pump inhibitors, enzyme preparations, and probiotics were recommended.

While collecting history, the gastroenterologist noted urolithiasis, which was diagnosed earlier, but not clarified in the general practitioner examination.

In 2018 the patient was hospitalized three times (in January, April, and May) due to recurrent renal colics.

The medical chart contained the renal US investigation dated May 2021: no pathology detected.

In December 2018, a routine fracture (due to fist-fighting) was confirmed, followed by a 3-week immobilization.

On May 30, 2019, the patient visited the general practitioner complaining of tremor in the left leg, stiffness, and worsening vision, progressing within six months. The neurologist counseling was recommended.

On June 6, 2019, the patient was counseled by the neurologist. While collecting history, the patient noted that tremor started at the age of 20 and developed during excitation, although it worsened within the preceding years. Weakness, memory lapse also emerged and progressed. After examination, the following preliminary diagnosis was established: "Unspecified extrapyramid and motor disorder. Episyndrome". A 2-month cycle of gopantenic acid and ethylmethylhydroxypyridine succinate treatment was administered. The patient was referred to the Center of Extrapyramidal Diseases of S.P. Botkin CCH; however, the counseling was not arranged due to personal patient circumstances.

When the patient returned to the general practitioner, the following abnormalities were detected in the biochemistry panel (total and ionized Ca — 3.2/1.43 mmol/L (N 2.2–2,65/0.9–1.38 mmol/L); phosphorus — 0,72 mmol/L (N 0.87–1.45 mmol/L); alkaline phosphatase (ALP) — 405 U/L (N 30–120 U/L); glucose — 8 mmol/L). The patient was referred to the endocrinologist.

Visiting the endocrinologist on September 6, the patient complained of a glomus sensation in the throat, frequent urination, burning sensation in feet. The preliminary diagnosis of impaired glucose tolerance was established, however upon subsequent follow-up the glucose level was not elevated, and HbA1c level was

within normal limits (5.3 %). The diagnosis of impaired glucose tolerance was not confirmed, no additional investigations were arranged.

The patient was also counseled again by the neurologist with extra examinations. Electroencephalography demonstrated altered bioelectrical brain activity of irritative origin. The patient was again referred to the Center of Extrapyramidal Diseases of S.P. Botkin CCH.

Subsequently the patient was followed up personally by a private neurologist, and based on word, Parkinson's disease was diagnosed, however no documental confirmations were presented.

In 2020 the patient did not visit the polyclinics.

He visited the general practitioner on April 29, 2021 complaining of dizziness, frequent headaches. The examination revealed persistent hypertension, and essential hypertension was diagnosed; amlodipine 5 mg was administered as hypotensive treatment. The patient was subjected to regular monitoring.

During such monitoring, biochemistry panels revealed persistent elevation of ALP levels, moderate (no negative changes) elevation of transaminase levels, mild elevation of gamma-glutamyl transferase levels, gradually increasing creatinine levels.

In August 2023, the patient visited the general practitioner complaining of neck and leg pain, myalgias worsening after physical exertion, numbness in arms, weakness, morning stiffness, hand tremor. Laboratory tests revealed decreased vitamin D (6.44 ng/mL; N 30–70 ng/mL) and inorganic phosphorus levels (0.81 mmol/L; N 0.87–1.45 mmol/L), increased creatinine (127 μmol/L; N 61–120 μmol/L, glomerular filtration rate 57 mL/min/1.73 m^2), ionized Ca (1,49 mmol/L), total Ca (3.24 mmol/L), PTH levels (58.21 mmol/L; N 1.48–7.63 mmol/L). The patient was referred to TG and PTG US followed by the endocrinologist counseling with suspected hyperparathyroidism. TG and PTG US demonstrated focal lesions: almost the whole left lobe was represented by an hypoechoic nodule sized 52x30 mm with a non-uniform structure and a fluid component (14 mm), with a significant blood flow of mixed type; regional lymph nodes were normal. Conclusion: right lobe — TI-RADS1; left lobe — TI-RADS4 (node over 1 cm in size). Based on the data obtained, the endocrinologist established the diagnosis: "Hyperparathyroidism (not otherwise specified). Grade 2 multinodular goiter". With the preliminary diagnosis "Thyroid neoplasm of undetermined or unknown origin. Cytology signs suspicious of Ms", the patient was referred to the oncologist.

To determine the mineral bone density, X-ray densitometry was conducted: T-test = -2.7 standard deviations at the level of L1-L4 vertebrae (i.e. osteoporosis); T-test = -1.7 standard deviations at the level of right and left femoral necks (i.e. osteopenia).

It should be noted that body weight (92 kg) and height (178 cm) did not change during the whole follow-up period. No gait disorders were observed as well.

In September 2023, the patient underwent an outpatient fine-needle aspiration biopsy (FNAB), with the result of nuclear atypia (Grade III. The Bethesda System for Reporting Thyroid Cytopathology). In October, after the repeated FNAB of the nodule in the left thyroid gland lobe, the oncologist established the diagnosis "Thyroid neoplasm of undetermined or unknown origin", which was followed by the videoassisted minimally invasive thyroidectomy, nerve-sparing cervical lymph node dissection (Level VI). The following main diagnosis was established: "Thyroid gland M. Papillary thyroid cancer, Grade 1a, Stage 1. Neoplastic process stage 1, clinical group IIa". The histology of the surgical material confirmed the focus of the malignant clear-cell malignancy with focal doubtful vascular invasion and invasion into structures of displaced PTG lobules.

After receiving the histology results of both lobes of the excised thyroid gland (Left lobe sized 5.3x4x3 cm. Its section demonstrated total substitution with a dense-elastic grayish nodule, containing a cystic cavity 1.5 cm in diameter), the following main diagnosis was established: "Clear-cell carcinoma of the left parathyroid gland. Condition after surgery on October 10, 2023". During the postoperative period, the patient's general condition significantly improved (weakness and tremor decreased; paresthesia and dyspeptic signs disappeared). The calcium level normalized soon after the surgery. Normocalcemia has been preserved for a year after the surgery.

The patient history steps from the emergence of first symptoms until the diagnosis and surgery are presented in the Figure 1.

Currently the patient is monitored by the oncologist and endocrinologist. Diagnosis: postoperative hypothyroidism, hypoparathyroidism. Accounting for no metastatic tumor spread and its complete surgical removal, the favorable clinical outcome is highly possible in our patient; however, untimely hypercalcemia detection could lead to a partially irreversible pathology (mainly neurological), which could significantly worsen the quality of life. The patient is subject to lifelong follow-up with regular medical examinations to prevent complications, detect recurrencies and disease progression, and to correct the treatment timely.

Discussion

Hypercalcemia is a rather rare pathology in the outpatient physician practice, which leads to its late detection due to low physician awareness. The complexity of diagnosing this mineral disorder is associated with the absence of pathognomonic signs and variable clinical

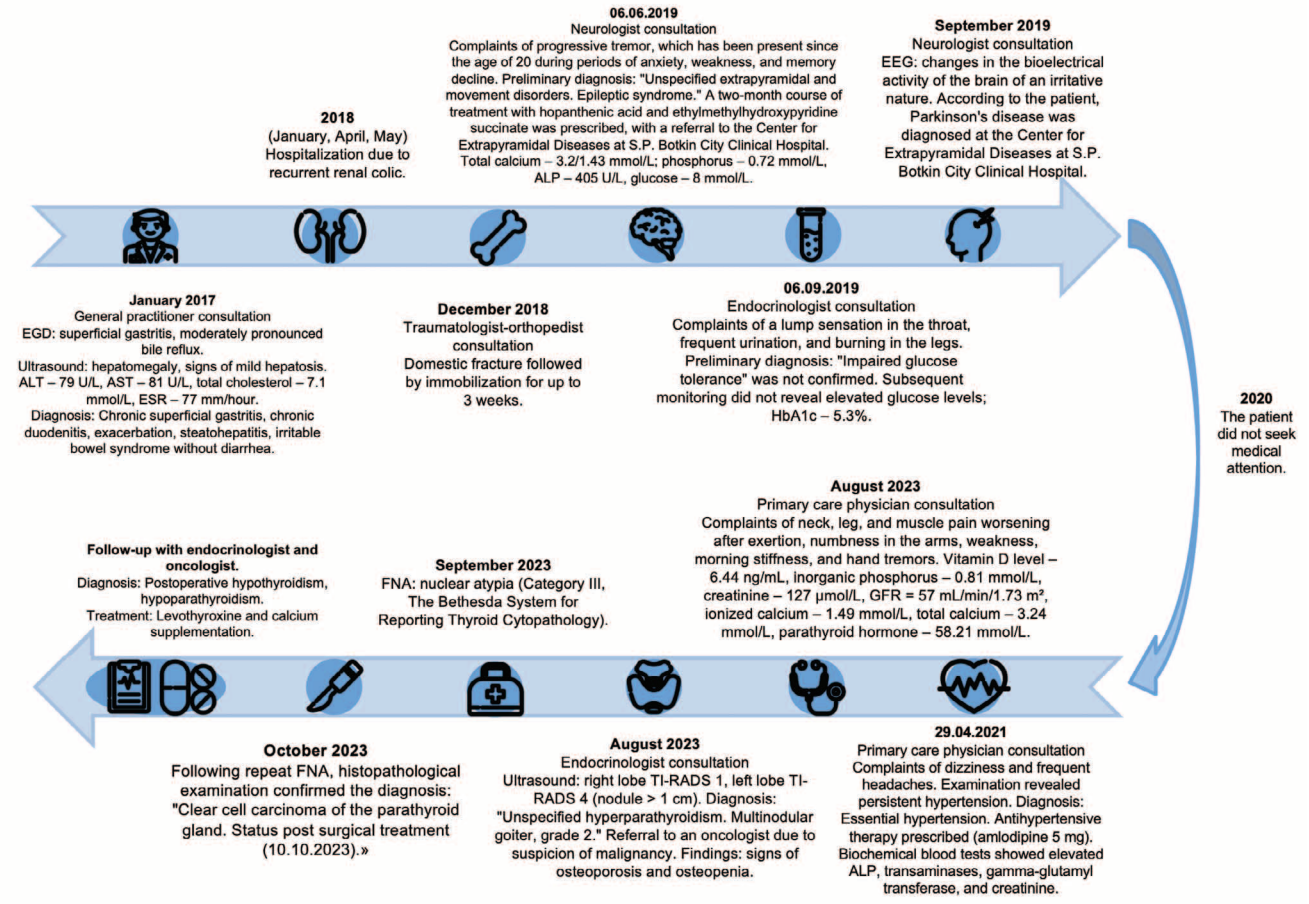

Figure 1. *Timeline of clinical follow-up in a patient with parathyroid carcinoma.*

manifestations, with each potentially representing a separate disease. Such patients may be followed by various physicians with such diagnoses as "Urolithiasis", "Chronic gastritis/Peptic ulcer disease", "Essential tremor", which was demonstrated in the clinical case above.

Parathyroid malignancies are the most rare cause of hypercalcemia; thus, the description of such cases is very interesting for practicing physicians. Although this disease is slowly progressive, the diagnosis in the majority of patients is not established for a long time, which leads to metastases (25 % cases) and severe hyperparathyroidism. Case histories of 15 patients that underwent surgeries due to PTGMs were analyzed by specialists of the National Medical Research Center of Radiology, Ministry of Health of Russia. Metastases were detected at the time of surgery in 3 patients, severe osseous form of hyperparathyroidism — in 6 patients, nephrolithiasis — in 9 patients, thus demonstrating late diagnosis of this disease [14].

PTG tumors may develop as part of various syndromes. Multiple endocrine neoplasia (MEN) syndrome is an example — this emerges due to genetic mutations. PTG hyperplasia or adenomas are reported most frequently. PTG malignancies in this syndrome are very rare, which explains their late detection. Due to this, a description of 2 clinical cases of PTG carcinomas in patients with the MEN syndrome is of a significant interest [15].

The diagnosis of PTG tumors developing against the background of a pre-existing secondary hyperparathyroidism may be challenging. Cases of PTGMs have been reported in patients with secondary hyperparathyroidism against the background of a long-standing CKD C4 [16, 17].

Intrathyroid PTG lesions form another serious diagnostic issue, requiring thorough assessment of calcium and PTH levels [18].

Our patient had a combination of several pathologies, with each of those potentially caused by the calcium metabolism disorders. Prolonged dyspeptic disorders not eliminated by treatment, frequently relapsing renal colics, low-energy fractures, tremor may be manifestations of specific diseases themselves; however, their combination should alert the physician, forming the basis for targeted examination with the purpose of detecting hypercalcemia.

Progressive elevation of ALP levels over several years is significant — this was interpreted as a manifestation of steatohepatitis by physicians. However, one should remember that elevated ALP levels may be a sign of not just cholestasis, but osteoporosis as well, which requires additional examinations. Persistently elevated ALP levels against the background of GGT levels in the reference range more likely suggests osteoporosis rather than cholestasis [9, 11].

In 2019 the following laboratory deviations were detected in a patient: Ca (total) — 3.2 mmol/L, Ca (ionized) — 1.43 mmol/L, P — 0.72 mmol/L, ALP — 405 U/L (with tremor worsening). However, these laboratory alterations were left unnoticed by physicians: the calcium level was not monitored, PTG examinations were not arranged. Meanwhile, neither the general practitioner nor the endocrinologist stressed out hypercalcemia, with the latter one assessing the patient due to the detected hyperglycemia.

Thus, the diagnosis of hypercalcemia could be established quite early, as the alerting combination of clinical manifestations emerged already in 2018, while increased total and ionized calcium levels were reported in 2019. At that moment, the following tests were necessary: serum PTH levels, PTG examination (US and technetium [99mTc]/sestamibi scan), densitometry for bone density evaluation [14].

While analyzing this clinical case, one should pay attention of primary care physicians to the importance of correct interpretation and formulation of clinical diagnoses. In 2021, the patient was diagnosed with essential hypertension. However, he already had long-standing urolithiasis. Thus, hypertension should have been evaluated as a secondary (symptomatic) one. The patient with urolithiasis should also have his chronic kidney disease noted with the stage, especially when in 2023 the glomerular filtration rate decreased to 57 mL/min/1.73 m^2 (corresponding to CKD C3) — that required the mandatory administration of nephroprotective agents (renin-angiotensin-aldosterone system blockers). Thus, the patient should have his hypotensive treatment corrected with the addition of an angiotensin-converting enzyme inhibitor to amlodipine.

Using the clinical case above as an example, one can define several important points for the algorithm of diagnosing the disease without clear pathognomonic symptoms.

1. Each clinical manifestation should be assessed not just as a sign of a specific disease, but also as a part of a common pathological process.
2. Every laboratory deviation should be analyzed, with clarifying investigations and further follow-up arranged.
3. The patient should be counseled by specialists (even with consilium) with the atypical disease course, if the treatment administered has no effect. An independent literature search and continuous medical self-education form an inseparable part of a smart patient management.

Conclusion

This clinical case represents an example of a complex and long path to the diagnosis “Parathyroid gland cancer. Secondary parathyroidism”, while its uniqueness lies in the prolonged course of an undiagnosed hypercalcemia along with a slowly developing PTGM. The discussed case demonstrates the necessary comprehensive evaluation of all patient pathologies, analysis of associations of various diseases (not related at first glance), and thorough attention to all deviations detected during the physical, laboratory, and instrumental patient examinations.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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КАК НЕ ПРОПУСТИТЬ БОТУЛИЗМ? КЛИНИЧЕСКИЙ СЛУЧАЙ, АНАЛИЗ ОШИБОК И РЕКОМЕНДАЦИИ ДЛЯ ПРАКТИКУЮЩИХ ВРАЧЕЙ

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How Not to Miss Botulism? Clinical Case, Error Analysis, And Recommendations for Practitioners

Резюме

Ботулизм — острое инфекционно-токсическое заболевание, возникающее вследствие блокирования нервно-мышечной передачи из-за действия экзотоксина, продуцируемого вегетативными формами анаэробных грамположительных бактерий *Clostridium botulinum,* характеризующееся развитием парезов и параличей гладких и поперечнополосатых мышц. Актуальность ботулизма обусловлена тяжестью течения, длительными сроками госпитализации, риском летального исхода и трудностями клинической диагностики на начальном этапе заболевания, когда при появлении у пациентов первых признаков болезни они обращаются к врачам различных специальностей — неврологам, офтальмологам, что приводит к диагностическим ошибкам, несвоевременному назначению специфической терапии и ухудшению прогноза заболевания. В статье представлен клинический случай лабораторно подтвержденного ботулизма у пациента, который дважды был доставлен в стационар с подозрением на острое нарушение мозгового кровообращения, и только при повторной госпитализации был заподозрен ботулизм. Относительная редкость патологии и недостаточная информированность врачей в отношении начальных симптомов ботулизма являются причинами трудностей диагностики. Цель публикации и разбора клинического случая — актуализация знаний практикующих врачей по вопросам диагностики и дифференциальной диагностики ботулизма.

Ключевые слова: *ботулизм, Clostridium botulinum, ботулотоксин, дифференциальная диагностика, диагностические ошибки, клинический случай*

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Abstract

Botulism is still an urgent medical problem, leading to fatal outcomes. The article presents a typical clinical case of severe botulinum toxin poisoning, characterized by the maximum severity of all symptoms of the disease with signs of decompensated acute respiratory failure, dysphagia,

ophthalmoplegic and bulbar syndromes. The difficulties and errors of clinical diagnosis that have arisen due to the similarity of botulism with other pathologies are analyzed.

Key words: *botulism, Clostridium botulinum, botulinum toxin, differential diagnosis, diagnostic errors, clinical case*

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Introduction

Botulism is an acute infectious & toxic disease from the saprozoonosis group emerging due to the neuromuscular transmission block caused by the effects of the exotoxin produced by vegetative forms of anaerobic Gram-positive bacteria *Clostridium botulinum*; it manifests with paresis and paralysis of smooth and striated muscles [1, 2].

Botulism is not a common disease, although its severity, prolonged hospitalization, high mortality, and misleading early disease symptoms make it a challenging healthcare issue. Botulism is usually reported as sporadic cases or group (most often family) outbreaks. Massive outbreaks of food-borne botulism are rare, but they are considered public health emergencies that require quick detection of the infection source, determination of the disease outbreak type (wound botulism; infantile botulism; intestinal botulism of adults — food-borne, iatrogenic, or inhalational [3]) to prevent new cases. Botulotoxin does not change the organoleptic features of the food product, while the poisoning can be suspected only when the first symptoms emerge [4, 5].

Thus, in June 2024 the first Russian massive outbreak of food-borne botulism in 30 years was reported simultaneously in Moscow and four regions (Novgorod, Yaroslavl, Kostroma, Tambov Regions; Republic of Tatarstan). Within some days several hundred people got sick, while all of them ate the same product — a salad from the dark kitchen service[1],[2],[3] [6]. The causative agent was detected almost immediately in the canned red beans (main salad ingredients) kept in vacuum packaging[4]. According to the investigation, significant violations of the raw material storage, production technology, periods and temperatures of the finished preservative storage led to the accumulation of botulotoxin in the canned beans[5] [7]. 417 people with the diagnosis of botulism were reported during the 2024 outbreak. Two cases were lethal. For reference: 112 people suffered from botulism in Russia in 2020 (with 7 deaths), 148 people were reported in 2021 (with 22 deaths) [8].

Advanced botulism has signs that enable the differential diagnosis. Several (especially initial) botulism manifestations are similar to those of other diseases, thus patients with the emerging botulism symptoms do not often seek the attention of infectious disease specialists, but rather other physicians. With that, the majority of physicians lacking the experience of clinical botulism diagnosis do not match the clinical signs with this disease, which becomes the source of diagnostic errors [9–11].

The following botulism forms have been described: food-borne botulism, wound botulism, infantile botulism, botulism of uncertain origin [1]. Food-borne botulism occurs in over 90 % of all cases; it is caused by the toxin contained in food products. In the setting of wound botulism the toxin is produced by Clostridia in the infected tissues. Infantile botulism usually occurs in infants under 6 months of age infected by *Cl. botulinum*

[1] "Kukhnya na Rayone" Director Detained: New Details about the Botulism Case // REN TV. 2024. June 18. [Electronic source]. URL: https://ren.tv/longread/1231693-zaderzhan-direktor-kukhni-na-raione-novye-detali-v-dele-o-botulizme (Date accessed: January 14, 2025)

[2] Botulism Outbreak Reported in Four Russian Regions // First Channel. 2024. June 23. [Electronic source]. URL: https://www.1tv.ru/news/2024-06-23/479293-vspyshka_botulizma_zafiksirovana_srazu_v_chetyreh_rossiyskih_regionah (Date accessed: February 8, 2025)

[3] Botulism Cases Detected in Three More Russian Regions // Izvestiya. 2024. June 24. [Electronic source]. URL: https://iz.ru/1717203/2024-06-24/sluchai-zabolevaniia-botulizmom-vyiavleny-eshche-v-trekh-regionakh-rossii (Date accessed: February 8, 2025)

[4] Rospotrebnadzor Named Kidney Beans as the Cause of Massive Botulism Infection in Regions // Interfax. 2024. June 18. [Electronic source]. URL: https://www.interfax.ru/russia/967068 (Date accessed: March 12, 2025)

[5] Rospotrebnadzor Has Detected Suppliers and Manufacturers of Food Products that Caused Botulism in Several Regions // Business Newspaper. 2024. June 18. [Electronic source]. URL: https://www.business-gazeta.ru/news/637449 (Date accessed: February 8, 2025)

that produce the toxin in the gastrointestinal tract. The diagnosis of botulism of uncertain origin is established if it is impossible to associate the disease with the food product [5].

Clinical manifestations of various botulism forms are characterized by several syndromes:

- gastrointestinal (nausea, vomiting, liquid stool, abdominal bloating);
- intoxication (short-term subfebrile fever);
- paralytic (myasthenia, respiratory failure, tachypnea, shortness of breath (with patients forcing an inspiration after saying 3–5 words));
- ophthalmoplegic ("mist" in the eyes, blurry object contours, diplopia, limited eyeball motions, pupil dilation, absence of all pupil reactions, nystagmus, diminished corneal and conjunctival reflexes, ophthalmoplegia, ptosis, strabismus (in cases of unequal paresis bilaterally), anisocoria);
- bulbar (voice hoarseness, nasal speech tone, aphonia, dysarthria, flattened nasolabial folds, inability to bare teeth or frown the forehead, dysphagia, dry mouth, glomus sensation in the throat, thirst) [5, 12].

The paralytic syndrome is the leading one in the differential diagnosis. The aforementioned syndromes might not emerge together, and some of those are not specific — thus, patients may refer to different physicians based on the predominant syndrome.

The standard laboratory diagnosis of botulism includes the toxin isolation and identification in biological fluids and food products uding the neutralization test in mice — this requires significant time efforts and special laboratory conditions, thus in the first days the diagnosis is based solely on clinical and epidemiological data [5, 13]. Due to this, the physician should know the main manifestations of this disease and features of the botulism course that will help in the differential diagnosis with several diseases having similar symptoms [14].

Patients with neurological symptoms are referred to the neurologist in order to exclude encephalitis, myasthenia, Guillain-Barre syndrome, acute cerebrovascular accidents (as demonstrated in the clinical case report below).

The clinical case report is aimed at analyzing the typical clinical situation in order to revise the knowledge of practical physicians concerning the clinical diagnosis and differential diagnosis of botulism.

Clinical Case Report

The female patient Sh., 50 years old, was admitted to the emergency department of the infectious hospital on Day 2 of the diseases complaining of diplopia, weakness in extremities, difficulty swallowing and breathing, dry mouth and a sensation of "porridge in the mouth".

History: diplopia, dizziness, blurred vision, weakness in extremities emerged on Day 1 of the disease. The patient was transported by the ambulance to the emergency department of the city hospital due to the suspected acute cerebrovascular accident. She was examined by the general practitioner and neurologist there. The computed tomography and the magnetic resonance imaging of the brain were arranged, and the acute cerebrovascular accident was excluded. The diagnosis of dyscirculatory encephalopathy was established. The patient refused the hospitalization and went home. During the day, diplopia, dizziness, blurred vision persisted, while the weakness in extremities worsened. The body temperature was not elevated, while the patient did not take any medications. During the second day of the disease, while diplopia and weakness in extremities persisted, the patient developed difficulty swallowing and breathing, dry mouth and a sensation of "porridge in the mouth", nausea, with a single liquid stool episode. The patient was transported urgently by the ambulance again to the emergency department of the city hospital due to the suspected acute cerebrovascular accident. The computed tomography of the brain was repeated, and no pathological alterations were detected. The patient was examined by the neurologist. Accounting for neurological signs (diplopia, dizziness, blurred vision, worsening weakness in extremities, difficulty swallowing and breathing, dry mouth and a sensation of "porridge in the mouth"), the neurologist suspected botulism and referred the patient to the infectious hospital.

During the repeated examination, the neurologist clarified the epidemiological history. The patient reported that 3 days before the disease she had eaten home-made canned vegetables (carrots and onions).

Upon the hospitalization to the infectious department, the patient's condition was considered severe based on neurological signs. She was conscious, lying passively in mild stupor; the verbal contact was preserved. She scored 13 points in the Glasgow Coma Scale (opening eyes upon request; confused speech; directed motor response upon request). RASS (Richmond Agitation and Sedation Scale) score was 1 point (drowsy; loss of attention, but the patient did not close eyes for over 10 seconds during the verbal contact). The pupil sizes were normal, symmetric. The photoreaction persisted. The corneal reflex was normal. Bilateral hemiptosis, convergent strabismus, dysphagia, dysphonia. Motions in extremities were preserved. No alterations were detected in other organs and systems. The skin had a normal color and turgor; visible mucous membranes were normal. Respiratory rate: 18 per minute. Oxygen saturation (on room air) 98 %. No dyspnea was reported. Blood pressure 132/94 mm Hg. Pulse 86 beats per minute, with satisfactory filling. Cardiac tones were clear and regular. The tongue was dry and coated with white plaque. The abdomen was soft and non-tender.

The liver and spleen were not enlarged. According to the patient, the urination was not painful (last urination in the morning). Meningeal signs were negative.

Accounting for the epidemiological history (consumption of home-made canned vegetables), clinical signs suggestive of the gastrointestinal (nausea, one-time liquid stool), paralytic (difficulty breathing, weakness in extremities), ophthalmoplegic (diplopia, blurred vision, bilateral hemiptosis, convergent strabismus), bulbar syndromes (difficulty swallowing, dysphonia, confused speech), as well as the dry mouth sensation, the preliminary diagnosis of botulism was established. The patient was hospitalized into the intensive care unit of the infectious hospital. She was administered the polyvalent antitoxic anti-botulism serum (10,000 IU — types A & E; 5,000 IU — type B) intravenously once based on the Instructions for Medical Use.

The following pathogenetic therapy was administered: tube feeding during Days 4–12 of the hospitalization, enterosorbents (activated charcoal for 3 days), infusion therapy (crystalloid solutions with the purpose of detoxification and correction of the water-electrolyte balance), administration of Group B vitamins, oxygen therapy (humidified oxygen, 5 L/min), as well as antibiotics (cephalosporins) for 10 days to suppress *Cl. botulinum* in the gastrointestinal tract and to prevent secondary bacterial infections.

Respiratory disorders, including difficulty breathing, accessory muscles activated for breathing, emerged on Day 2 of the hospitalization, while bulbar disorders (significant dysphagia) worsened — the patient was intubated and connected to the mechanical ventilation device.

See Tables 1–4 for examination results.

Table 1. *Blood analysis*

Parameter	Result	Reference Value	Units of measurement
Complete Blood Count			
Erythrocytes	4.64	3.90 — 4.70	cells x10^{12}/L
Hemoglobin	142.00	120.00 — 140.00	g/L
Leukocytes	5.90	4.00 — 10.00	cells x10^{9}/L
Thrombocytes	91.00	180.00 — 320.00	cells x10^{9}/L
Biochemical blood analysis			
Aspartate aminotransferase	18.50	0.00 — 31.00	U/L
Alanine aminotransferase	8.90	0.00 — 31.00	U/L
Total bilirubin	6.10	5.00 — 20.50	μmol/L
Creatinine	65.00	53.00 — 106.00	μmol/L
Total creatine kinase	113.00	0.00 — 145.00	U/L
Creatine kinase-MB	19.10	0.00 — 25.00	U/L
Total protein	63.10	65.00 — 85.00	g/L
Albumin	37.20	38.00 — 51.00	g/L
α-Amylase	39.00	0.00 — 100.00	U/L
Procalcitonin	<0.50	0.00 — 0.50	ng/mL
C-reactive protein	1.60	0.00 — 5.00	mg/L
Lactate dehydrogenase	363.00	195.00 — 450.00	U/L
Troponin T	negative	negative	ng/L
Gas-electrolyte blood test			
cK+	3.70	3.40 — 4.50	mmol/L
cNa+	139.00	135.00 — 146.00	mmol/L
cCa2+	0.97	1.15 — 1.29	mmol/L
cCL-	110.00	98.00 — 106.00	mmol/L
cGlu	5.40	3.89 — 5.83	mmol/L
cLac	1.10	0.50 — 1.60	mmol/L
pH(t)	7.30	7.350 — 7.450	-
cBase(Ecf), c	-4.40	-3...+3	mmol/L
cHCO3-(P, st), c	20.20	21.00 — 28.00	mmol/L

Table 2. Analysis of cerebrospinal fluid

Parameter	Result	Reference Value	Units of measurement
Protein	0.57	0.15 — 0.45	g/L
Glucose	3.60	2.20 — 3.90	mmol/L
Cell count	0.67	0.00 — 10.00	cells/μL
Lactate	1.50	1.10 — 2.40	mmol/L
Color: colorless, transparent			
Cerebrospinal fluid culture: No microflora growth was detected			

Table 3. Examination of cerebrospinal fluid for the presence of nucleic acids of neuroinfection pathogens by polymerase chain reaction (PCR)

Parameter	Result
Non-polio enteroviruses (*non-polio enteroviruses*)	Negative
Pneumococcus (*Streptococcus pneumoniae*)	Negative
Listeria (*Listeria monocytogenes*)	Negative
Streptococcus (*Streptococcus agalactiae*)	Negative
Meningococcus (*Neisseria meningitidis*)	Negative
Human herpesvirus 6 (*Human herpesvirus 6*)	Negative
Haemophilus influenzae type b (*Haemophilus influenzae b*)	Negative
Herpes simplex virus 1 and 2 (*Human alphaherpesvirus 1, 2*)	Negative
Epstein–Barr virus (*Epstein-Barr virus*)	Negative
Cytomegalovirus (*Human cytomegalovirus*)	Negative
Varicella zoster virus (*Varicella-zoster virus*)	Negative
Borrelia (*Borrelia burgdorferi*)	Negative

Table 4. Other investigations

Investigation	Result
Stool tests	No nucleic acids of viruses or pathogenic bacteria were found in the stool samples
Urine analysis	Without pathological changes
Electrocardiography	Sinus rhythm with a heart rate of 80 beats per 1 min

To confirm the diagnosis of botulism, the patient's blood serum collected before the administration of the polyvalent antitoxic anti-botulism serum was sent to the laboratory of natural focal & hazardous infections and parasitic invasions of FBHI "Center of Hygiene and Epidemiology in the Arkhangelsk Region". The biological test was arranged in mice, as well as the serum was tested for *Cl. botulinum* botulotoxin using the neutralization test. The diagnosis of botulism caused by the A toxin was confirmed on Day 8 of the hospitalization (Day 9 of the disease). On Day 8 of the hospitalization, extubation was attempted with the transfer to mask oxygenation; however, on Day 9 the respiratory failure worsened, with significant confusion (severe stupor), and the patient was again transferred to mechanical ventilation, until spontaneous breathing emerged on Day 12. Paresis regressed by Day 8, although weakness in extremities remained during the whole inpatient period. Dysarthria and dysphagia persisted until Day 15, while dysphonia — until Day 18. Diplopia persisted until Day 9 of the hospitalization. Bilateral ptosis gradually improved and completely resolved by Day 12. Bulbar disorders (convergent strabismus, ophthalmoplegia, difficulty swallowing) gradually improved and regressed by Day 8–9. Salivation completely recovered on Day 10 of the hospitalization.

The follow-up magnetic resonance imaging of the brain was arranged on Day 15 of the hospitalization — no focal brain lesions were detected. On Day 17 of the hospitalization, the patient Sh. was transferred from the intensive care department to the infectious department in the satisfactory condition for further observation and treatment. On Day 18 of the hospitalization, she was examined by the physical therapist, with the rehabilitation cycle recommended.

The patient was discharged on Day 21 of the hospitalization, with severe asthenia and decreased muscle strength in extremities preserved. During the muscle strength examination, the patient could partially overcome the physician's resistance. She completed the finger-nose and heel-knee tests satisfactorily, although she mildly missed during the left-sided heel-knee test. The patient was not stable during the Romberg test, with unsteady gait (the patient required assistance, seeking support with the furniture, walls while walking). Her rehabilitation routing score was 4 points (significantly impaired functions and daily activities). She was discharged in the satisfactory condition, being transferred to Step 2 of the inpatient rehabilitation.

Discussion

A clinical case of severe food-borne botulism (A05.1) (toxin type A) has been presented; this was characterized by the maximum severity of all disease symptoms

with the signs of decompensated acute respiratory failure, dysphagia, ophthalmoplegic and bulbar syndromes. The diagnosis was delayed for 2 days. Due to diplopia, dizziness, blurred vision, weakness in extremities emerging on Day 1 of the disease, the patient was transported by the ambulance to the therapeutic inpatient department with the suspected acute cerebrovascular accident (ACVA). One should account for the fact that neurological signs in ACVA are determined by the locations of brain lesions [15, 16]. The specific feature of the paralytic syndrome in botulism is its symmetry and bilateral signs, which was observed in the case described. Diplopia, blurred vision, weakness in the upper and lower extremities were confirmed bilaterally. Neurological signs in ACVA is more often asymmetric and depends on the blood supply area or the location of the affected vessel, as well as the duration of the disease course. During the first visit, the diagnosis of ACVA was excluded due to no history of cardiovascular diseases typical for ACVA, no unilateral central hemi- and monoparesis, unilateral soft palate, vocal cord and tongue lesions; no alterations were also detected in the brain CT or MRI. With that, after instrumental examinations, despite no data confirming ACVA, botulism was not suspected, although the first complaints in the majority of patients with botulism include visual disorders, i.e. mist in the eyes, unclear object contours, diplopia worsening with the lateral gaze (all observed in the clinical case described). Besides visual disorders, weakness complaints were also underestimated. Weakness is the mandatory complaint in patients even with mild botulism forms. It can be explained both by the intoxication and paralytic toxin effects on the skeletal muscles. These effects mainly manifest in proximal muscle groups, however in general lesions are generalized, which can be explicitly confirmed by the decreased hand strength easily detected during the physical examination [17].

Less than a day from the disease onset passed during the first examination, and clinical signs of botulism were not completely represented. The epidemiological history (consumption of home-made canned vegetables) was not confirmed by the neurologist and the general practitioner during the examination.

Changes in botulism symptoms and the disease severity can be evaluated only following up the patient; in our case the patient refused the hospitalization and went home, despite neurological signs. It is possible that the exclusion of the acute cerebrovascular accident that could require urgent surgical or conservative inpatient treatment and the established diagnosis of dyscirculatory encephalopathy affected the decision to refuse the hospitalization.

Specific botulism signs (mild difficulty breathing, worsened weakness in extremities, diplopia, blurred vision, bilateral hemiptosis, convergent strabismus, dry mouth, sensation of "porridge in the mouth", difficulty swallowing, dysphonia, confused speech) emerged on Day 2 of the disease. Botulism was suspected during the second visit to the general department after the neurologist examination and clarification of the epidemiological history.

Dysphagia and dry mouth caused by the atropine-like effects of botulotoxin on the autonomous nervous system are significant for the diagnosis, being early signs of botulism, which has to be accounted for during the differential diagnosis [17].

Regarding the diagnosis, it is very important to record the time of the emergence of clinical signs from consuming the food "suspicious" of possible botulism. In our case, this period was 3 days, which is typical for the average duration of the incubation period in botulism [1].

Late botulism diagnosis is also associated with its signs being similar to the poisoning with other toxins (i.e., food-borne toxin infections). Nausea and a single liquid stool were observed on Day 2 of the disease in our patient. With the gastrointestinal syndrome, such mistake is possible, as botulism and the food-borne toxin infection are associated with the alimentary factor. Both diseases are characterized by the short incubation period and similar initial symptoms (nausea, vomiting, abdominal pain, stool disorders). However, botulism lacks fever, while food-borne toxin infections are not characterized by the paralysis, visual, speech, and swallowing disorders, which are the main botulism symptoms that determine the severity in this disease [18].

If botulism is suspected, specific laboratory diagnosis is required in all patients to confirm the diagnosis [1]. In this case, detection of the botulotoxin in blood becomes the absolute laboratory confirmation of botulism. The blood serum was collected from the patient before the administration of the botulism antitoxin. The botulotoxin was detected using the biological test and the biological toxin neutralization test in white mice using the diagnostic anti-botulism polyvalent sera [19].

The microbiological culture to detect and identify the causative agent of botulism (*Clostridium botulinum*) and/or determination of its (*Clostridium botulinum*) toxins in vomitus/gastric lavage discharge was not arranged, as the patient was admitted three days after the consumption of canned foot, vomiting was absent, while the products suspicious of botulism were disposed of.

During the first day of hospitalization to the infectious department, the botulism antitoxin (types A, B, E) was administered based on clinical & epidemiological indications, while the result of the biological test confirming the diagnosis of type A botulism was obtained on Day 8 of the hospitalization (Day 9 of the disease). Systemic antibiotics are administered to patients with botulism with the purpose of prevention of complications

emerging due to paresis and paralysis [1], which was also applied in our clinical case, despite no foci of bacterial infections upon the hospital admission. Within 72 hours from the disease onset, patients with botulism undergo gastric lavage and siphon enema to eliminate the toxin [1]. In our case this recommendation was not followed as the patient was hospitalized on the third day from eating the canned food, and botulotoxin already absorbed through the oral and intestinal mucosa [14]. Patients with botulism may remain on nasotracheal intubation for 80 days without any significant adverse effects, allowing to avoid tracheostomy [1]. In our clinical case the patient underwent elective tracheal intubation, which remained for 11 days. It should be noted that the final extubation of patients with botulism is possibly only with the complete recovery of respiration and fluid swallowing [1]. Early extubation with the incompletely restored respiration in our clinical case led to the worsening condition, emergence of the respiratory failure symptoms, depressed consciousness (severe stupor), which required repeated intubation and switching to the mechanical ventilation.

Conclusion

The presented typical clinical case of food-borne metabolism confirmed by the laboratory biological test demonstrated difficulties in the clinical diagnosis of the disease; these were caused, on the one hand, by the relative rarity of the pathology, and on the other hand — by neurological signs during the disease onset (diplopia, dizziness, blurred vision, weakness in extremities) that formed the basis to refer the patient to the inpatient department with the suspected acute cerebrovascular accident.

Thorough collection of the epidemiological history is significant during the botulism diagnosis. Insufficient awareness of physicians of various specialties (general practitioners, neurologists, ophthalmologists) due to the relative rarity of botulism, superficial history collection (including epidemiological history) leads to the fact that even with the timely visit symptoms of typical botulism are underestimated and considered as manifestations of another disease — this requires updating the physician knowledge concerning the issues of clinical botulism diagnosis.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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ЛЕГОЧНЫЙ ГИСТИОЦИТОЗ ИЗ КЛЕТОК ЛАНГЕРГАНСА: РЕДКАЯ ПАТОЛОГИЯ В ПРАКТИКЕ ПУЛЬМОНОЛОГА

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Pulmonary Langerhans Cell Hysiocytosis: A Rare Pathology in The Practice of a Pulmonologist

Резюме

Легочный гистиоцитоз из клеток Лангерганса — редкое заболевание с коварным началом и неспецифическими проявлениями. В статье рассматриваются два клинических случая пациентов с редкой патологией — легочным гистиоцитозом из клеток Лангерганса. Описаны молодые пациенты, курильщики. У обоих пациентов были типичные рентгенологические признаки: кистозные и узловые образования. Диагноз был верифицирован морфологически. В первом случае на фоне прекращения курения отмечается положительная рентгенологическая динамика, во втором — пациентка не прекратила курить, в связи с выраженностью одышки, изменений при компьютерной томографии легких, был назначен преднизолон. На этом фоне значимой положительной динамики получено не было.

Ключевые слова: *гистиоцитоз Х, редкие болезни, диагностика*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

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Abstract

Pulmonary Langerhans cell histiocytosis is a rare disease with insidious onset and nonspecific manifestations. The article discusses two clinical cases of patients with a rare pathology — pulmonary histiocytosis from Langerhans cells. Young patients and smokers are described. The diagnosis was verified morphologically. In the first case, positive X–ray dynamics was noted against the background of smoking cessation, in the second case, the patient did not stop smoking, due to the severity of shortness of breath, changes in computed tomography of the lungs, prednisone was prescribed. Against this background, there was no significant positive trend.

Key words: *Pulmonary Langerhans' cell histiocytosis, rare diseases, diagnosis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The patients consented to the publication of laboratory and instrumental research data in the article « Pulmonary Langerhans Cell Hysiocytosis: A Rare Pathology in The Practice of a Pul-monologist» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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CS — corticosteroids, CT — computed tomography, LCH — Langerhans cell histiocytosis, FEV_1 — forced expiratory volume during the first second, CRP — C-reactive protein, FVC — forced vital capacity, EchoCG — echocardiography

Langerhans cell histiocytosis (LCH) is a rare disease causing the clonal proliferation of dendritic cells and macrophages that belong to the mononuclear phagocytic system and affecting multiple organs and systems. The concept of histiocytosis was first proposed by Farber in 1941, and this disease got several names, including eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian disease, while Liechtenstein renamed it to histiocytosis X in 1952. As lungs are often involved first, the disease was also called pulmonary Langerhans cell histiocytosis. Pulmonary Langerhans cell histiocytosis is a smoking-associated interstitial lung disease characterized by Langerhans cell proliferation and their infiltration in the lung parenchyma [1]. The clinical LCH course in adults is unpredictable, varying from spontaneous regression to progressive respiratory failure even after smoking cessation [2–5]. LCH usually starts insidiously, without specific manifestations (25 %), or with non-specific findings (pneumothorax as the first symptom was detected in approximately 10–15 % patients).

This article demonstrates two cases of pulmonary Langerhans cell histiocytosis with a variable disease course.

Clinical Case Report No. 1. Male patient S., 33 years old.

Patient S., 33 years old, visited the pulmonologist in the polyclinics in September 2023. The patient had no complaints at the time of examination. History: on July 28, 2023, during the routine chest X-ray, first pulmonary lesions were detected (with a relatively satisfactory health and no complaints); the patient was referred to the pulmonologist. Before 2023, he did not undergo chest X-ray for several years. History: the patient had been smoking 1.5–2 packs daily since the age of 13. He had also been involved in welding works for several years, often contacting with the welding aerosol. The family and allergy histories were negative. The patient denied other concomitant diseases and chronic treatment. His household conditions were satisfactory.

No significant alterations of organs and systems were detected during the physical examination. SpO_2 (on room air) 98 %.

On August 2, 2023, the patient underwent computed tomography (CT) of the chest (Figure 1): multiple, predominantly centrilobular nodules sized 0.3–0.7 cm are detected in all pulmonary fields of both lungs. Conclusion: signs of structural pulmonary lesions (differential diagnosis of tuberculosis, sarcoidosis, Pneumocystis pneumonia). Left-sided pleural adhesions. Lymphadenopathy. The TB specialist counseling was recommended.

The patient S. was counseled by the TB specialist, and a PPD test was arranged. The diagnosis of tuberculosis was excluded. Laboratory tests did not reveal any abnormalities; pulmonary function tests (including spirometry, body pletysmography, DLCO) were normal as well.

On September 2, 2023, the patient underwent videothoracoscopy with the left lung biopsy to clarify the diagnosis in the thoracic surgery department of SHI Regional Clinical Hospital (Saratov). Histology: a fibrotic stellate focus with peribronchial cellular infiltration consisting of histiocytes, plasma cells, lymphocytes with an admixture of eosinophils and pigmented macrophages was detected in the pulmonary tissues (with local irregular cysts). Conclusion: interstitial fibrotic focus based on the described histological signs. No signs suggesting active tuberculosis. Accounting for the cellular infiltrate composition, Langerhans cell histiocytosis X cannot be excluded.

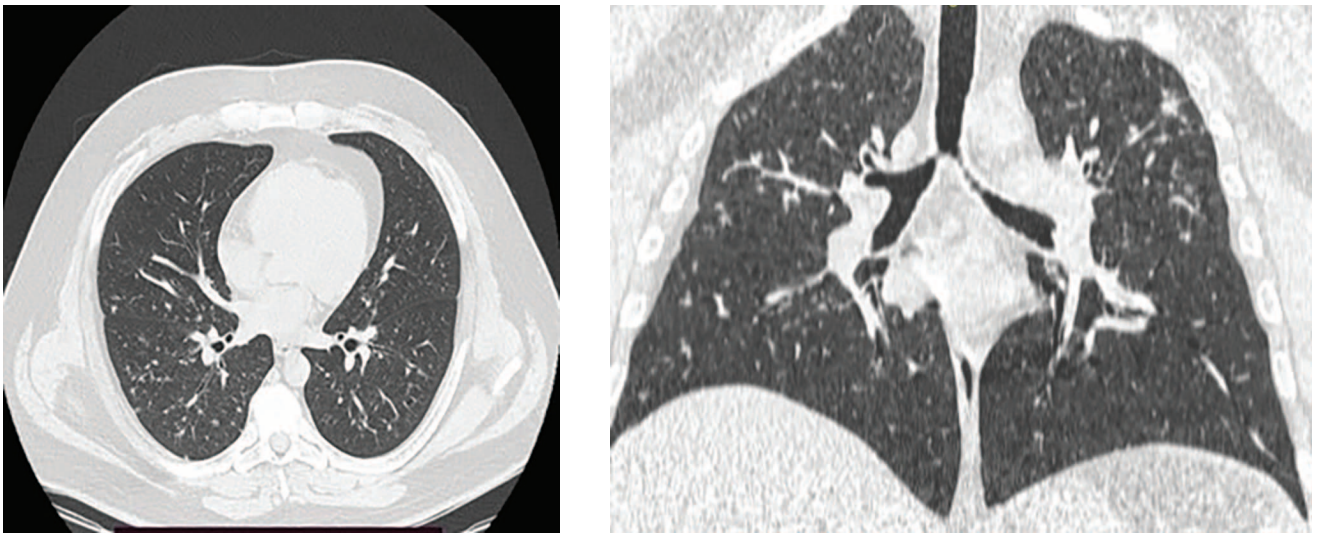
Accounting for the fact that the described CT signs did not correspond to histiocytosis well, it was decided to review the radiological and morphological conclusions. Second radiologist conclusion (acknowledgments to Ya.L. Manakova, SHI Novosibirsk Regional Clinical Hospital): lesions were distributed axially (diffusely, with relatively preserved subpleural areas); craniocaudally (with predominant lesions in upper areas); pulmonary dissemination syndrome: combination of cystic and focal patterns, multiple centrilobular polymorphic foci 0.15–0.65 cm in diameter. Multiple small spherical air-filled cavities with irregularly thick walls. Some cavities were irregularly shaped (clover leaf-shaped, branching).

CT demonstrated signs of pulmonary Langerhans cell histiocytosis.

Pathology blocks were reviewed in the Federal State Budget Institution "Scientific Research Institute of Pulmonology", Federal Medical-Biological Agency of Russia (acknowledgements to M.V. Samsonova, A.L. Chernyaev): pulmonary tissue with thickened interalveolar septa due to lymphoid infiltration, terminal bronchioles with narrowed lumen and significant peribronchiolar infiltration represented by lymphocytes, histiocytes, pigmented brown macrophages, with scarce eosinophils, clear-nucleated cells (Langerhans cells with langerin and CD1a expression); lymphoid aggregates were also observed. Conclusion: histological signs and immunophenotype of Langerhans cell histiocytosis.

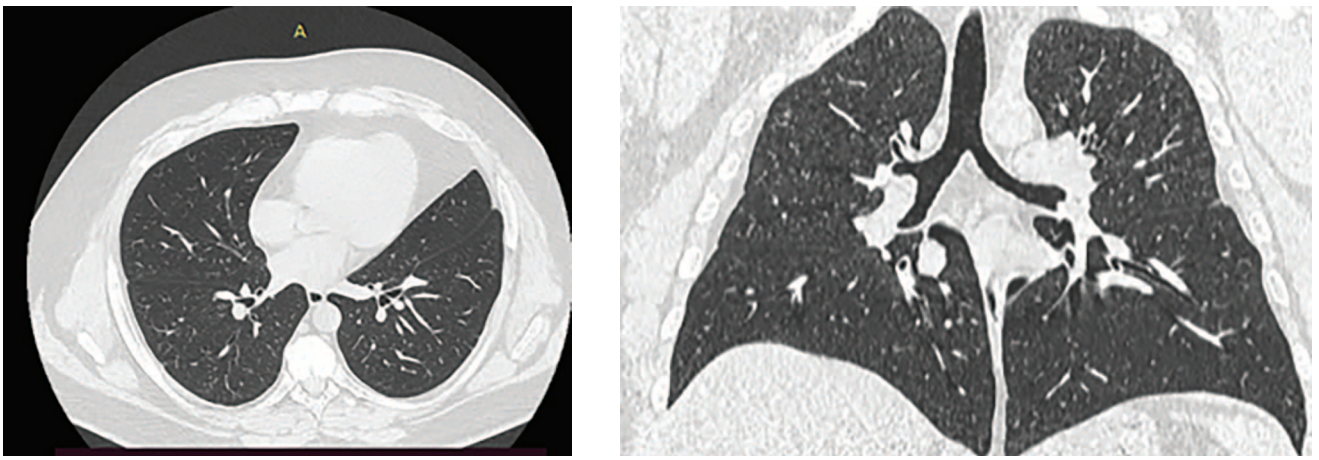
Additional studies (skull X-ray, endocrinologist counseling, EchoCG) did not demonstrate systemic signs of histiocytosis. Thus, the diagnosis of Langerhans cell histiocytosis with pulmonary lesions was established. Regular follow-up and smoking cessation were recommended for the patient. Accounting for the absence of clinical disease manifestations, respiratory dysfunction, no medications were administered.

Follow-up counseling in one year (November 2024): the patient stopped smoking, had no complaints; pulmonary function tests, body pletysmography, DLCO results did not demonstrate negative changes. Follow-up CT of lungs: clearly positive changes — significantly decreased sizes and numbers of focal-cystic pulmonary lesions (Fig. 2).



a) b)

Figure 1. *Computed tomography of the chest (a, b)*



a) b)

Figure 2. *Computed tomography of the chest (a, b)*

Clinical Case Report No. 2. Female patient M., 38 years old.

The patient M. was first admitted to the Pulmonology Department of SHI "Regional Clinical Hospital" (Saratov) on September 2, 2021 complaining of dyspnea of mixed origin with moderate physical exertion, periodic dry cough.

History: she started having the abovementioned complaints since March 2021. She visited the polyclinics at place of residence, and chest X-ray was arranged (pneumofibrosis) (Fig. 3), after which she was referred to the CT of lungs.

Computed tomography demonstrated CT signs of diffuse interstitial changes with ground-glass opacities and multiple air-filled cavities in the pulmonary tissue (Fig. 4).

The patient was referred to the morphological diagnosis verification, i.e. videothoracoscopy with the left lung biopsy. Histology: pulmonary tissue with peribronchial fibrosis, focal emphysema; lumina of several bronchi and their walls contained infiltrates made of large histiocytes and eosinophils; the mediastinal lymph node had a normal histological structure. Conclusion: Pulmonary histiocytosis.

Life history: bad habits: the patients had been smoking 1 pack daily for 13 years; she worked at the household chemical warehouse for 3 years. Prior annual chest X-rays were normal (based on the patient's words).

No significant alterations of organs and systems were detected during the physical examination. SpO_2 (on room air) 97 %. Height 165 cm, body weight 116 kg.

Pulmonary function tests + bronchodilator test (September 3, 2021): restrictive changes cannot be excluded (FEV_1 2.02 L, (66 % of reference values), FVC 2.43 L (69 % of reference values); FEV_1/FVC 83 %). The bronchodilator test was negative. 6-minute test (September 3, 2021): the patient walked 900 m, baseline SpO_2 98 %, after the test — 94 %. Laboratory tests demonstrated elevated CRP levels to 26.8 mg/L (N 0–5 mg/L), elevated glucose levels to 6.9 mmol/L (N 3.9–6.1 mmol/L). Other tests did not reveal any significant alterations. Additional studies (skull X-ray, endocrinologist counseling, EchoCG) did not demonstrate systemic signs of histiocytosis.

Thus, based on CT signs and morphological data, the diagnosis of Langerhans cell histiocytosis with pulmonary lesions was established.

Pathology blocks were reviewed in the Federal State Budget Institution "Scientific Research Institute of Pulmonology", Federal Medical-Biological Agency of Russia (acknowledgements to M.V. Samsonova, A.L. Chernyaev): histological signs and immunophenotype of Langerhans cell histiocytosis.

The patient was consulted online in the GSBSI "Central Scientific Research Institute of Tuberculosis" (Moscow); lung transplantation was to be considered, and systemic corticosteroids (methylprednisolone 8–12 mg daily) were recommended.

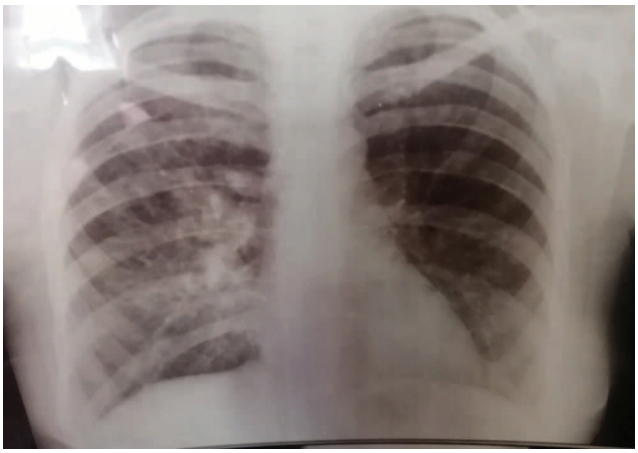
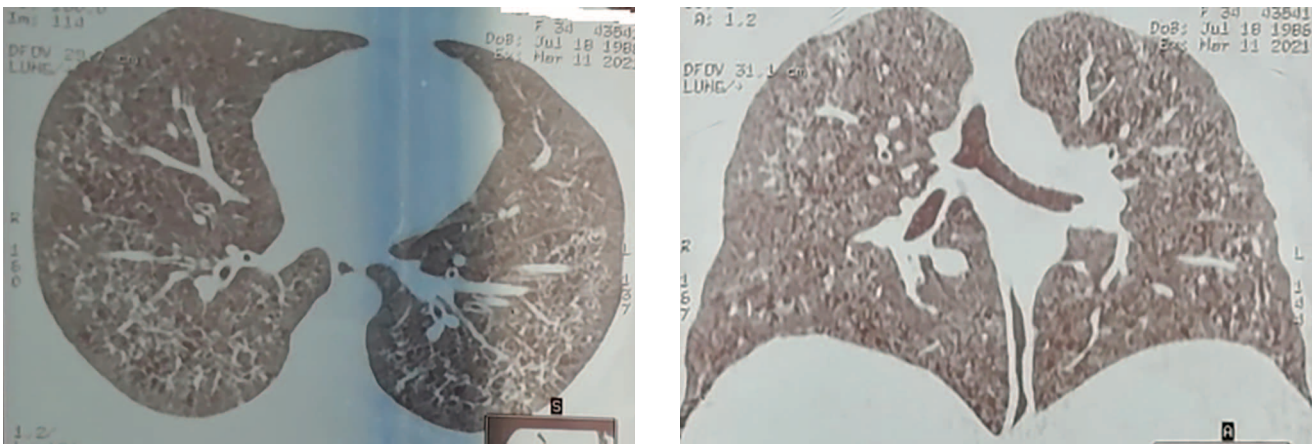
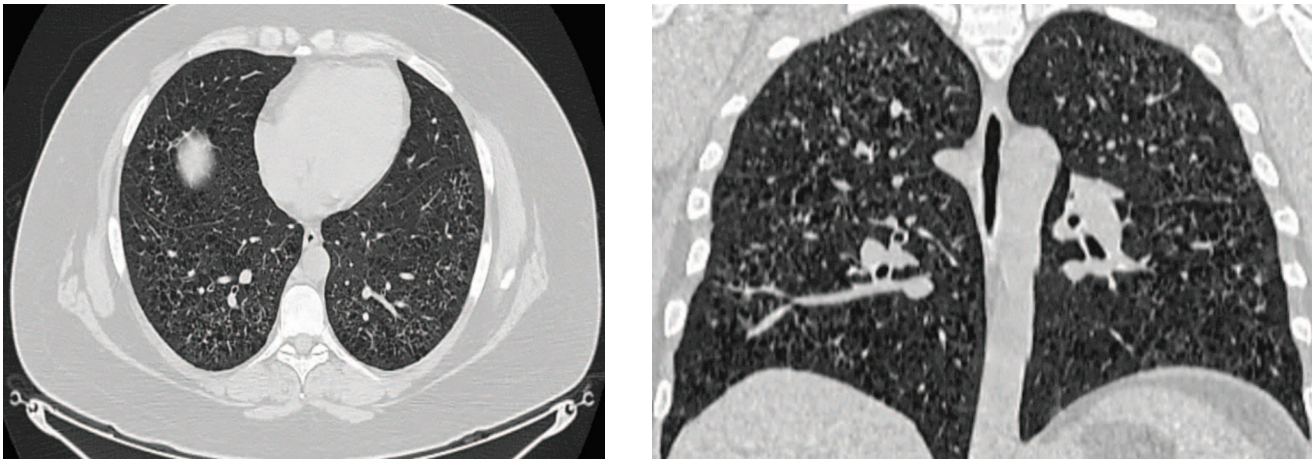


Figure 3. *Chest X-ray*



a) b)

Figure 4. *Computed tomography of the chest (a, b)*



a) b)

Figure 5. *Computed tomography of the chest (a, b)*

Long-term methylprednisolone therapy (8 mg/day) was recommended. The next follow-up was scheduled in 6 months. The patient did not come to the scheduled hospitalization, continuing to take prednisolone 10 mg/day.

In July 2023 she was again hospitalized to the pulmonology department of SHI Regional Clinical Hospital of Saratov. No significant changes concerning the disease severity or signs were reported. Steroid-induced diabetes, Cushing syndrome developed due to long-term prednisolone treatment. CT of lungs (June 19, 2023): significant bilateral emphysema, diffuse reticular lesions, linear streaking without definitive changes (Fig. 5). A consolidated fracture and an osteodestruction focus was detected in the right 8th rib.

Pulmonary function tests: FEV_1 2.16 L, (73 % of reference values), FVC 3.14 L (92 % of reference values); FEV_1/FVC 69 %. The bronchodilator test was negative.

Echocardiography did not demonstrate signs of pulmonary hypertension; no structural or functional alterations were detected.

Laboratory tests: CRP 11.7 mg/L, glucose 6.8 mmol/L, HbA1c 6.01 %.

The patient was recommended to continue prednisolone in the same dose, with the follow-up visit in 6 months. After that, the patient did not come to the follow-up visits.

Discussion

Langerhans cell histiocytoses with isolated pulmonary lesions form a specific group of histiocytoses. LCH occur at any age, mainly in adults (aged 20–40 years), especially in cigarette smokers [5–6]. Currently LCH is considered a smoking-associated excessive immune response in the pulmonary tissue complicated with chronic inflammation, which finally leads to the deposition of Langerhans cells in the interstitial zones of small airways. LCH have been described developing after marijuana smoking, prolonged contact with aroma grass and constant household contacts with fumes [6]. Both active and passive smoking is hazardous — it can also worsen the LCH course [6]. Experimental and clinical studies detected the overexpression of antiapoptotic proteins in dendritic Langerhans cells affected by the tobacco smoke [6], which is possibly one of the main LCH triggers. Both clinical cases presented demonstrate the disease developing in young active smokers.

Priorly LCH was considered a reactive process; however, based on articles from recent years, the clonal disease nature could be proven at least for some patients. Thus, H. Liu et al. detected BRAF V600E expression in LCH cells [6]. A. Roden et al. found the BRAF V600E mutation in 7 (28 %) of 25 examined patients with LCH [7]. Besides, LCH relapses were reported in patients after the lung transplant [6]. Thus, currently LCH is more often considered a myeloid neoplasm with an inflammatory component. On the other hand, in many cases LCH evolution differs from that typical for tumors: the number of Langerhans cells in proliferates gradually decreases, the number of fibroblasts increases, and sclerotic deforming foci develop in lungs.

The incidence of LCH is very small — it constitutes only 4–5 % of all diffuse pulmonary diseases diagnosed using the open lung biopsy [6]. Consequently, LCH can be easily misdiagnosed. It is important that practical physicians are aware of clinical & radiological LCH features.

Patients with LCH usually complain of dyspnea or dry cough (approximately in two-thirds of all such cases) [4]. Constitutional manifestations (asthenia, fever, night sweats, weight loss) may be observed in 10–20 % of these patients. Spontaneous pneumothorax is another common clinical manifestation of the disease (15–20 % cases). It may emerge at any time during the disease and

may be bilateral and/or relapsing; it should be suspected in any patient complaining of worsening dyspnea or chest pain. Hemoptysis is rare and requires the exclusion of other etiologies. Extrapulmonary LCH manifestations usually affect bones (lytic lesions), the pituitary gland (diabetes insipidus), and (less frequently) the skin. Physical examination is usually normal, besides cases of pneumothorax, late-stage LCH, or patients with extrapulmonary lesions. Wheezing is rare, while finger clubbing is very rare [4].

Cystic and nodular shadows in middle or upper lung segments are considered typical radiological signs of LCH: the diagnostic accuracy based on their detection may reach 84 % [4–6], while 10–25 % patients might not have clinical disease manifestations. As the disease progresses, pneumofibrosis worsens, and the cystic remodeling starts affecting all lung segments [4-6].

Pulmonary function disorders are variable and depend on both predominant anatomical lesions and the severity of cystic lesions on computed tomography [4]. Obstructive, restrictive, and mixed patterns have been described. During early stages, pulmonary function tests may be normal in approximately 10 % patients [4]. Decreased DLCO is the most common anomaly, which is observed in 80–90 % cases and primarily reflects the pulmonary vasculature dysfunction. The obstructive pattern of pulmonary disorders is observed in many patients, especially in those with severe cystic lesions. Isolated restrictive lesions are less frequent.

Resting levels of blood gases remain normal for a long time, however physical exertion may caused increased oxygen gradient to alveolar arteries and hypoxemia [4].

Histology and immunohistochemistry of the biopsy specimen is the main diagnostic method of LCH and other histiocytoses [4]. Various methods are used to collect biopsy specimens. The pulmonary tissue for LCH diagnosis can be collected transbronchially, however this method has a low sensitivity. I. Housini et al. demonstrated that the diagnosis was established only 2 (16.6 %) of 12 patients after the transbronchial biopsy [6]. Besides, this method bears the hazard of pneumothorax, which often complicates LCH itself [6]. Bronchoalveolar lavage testing may be helpful, as excessive CD1a-positive cells (>5 %) are often detected in the lavage, although smoking also leads to the increased number of these cells. Due to low sensitivity, bronchoalveolar lavage testing is used only as an auxiliary method [6, 8]. Videothoracoscopy-assisted lung biopsy is the "golden standard" of LCH diagnosis — it can help to obtain sufficient material for the analysis, minimizing the risk of complications [6, 8]. Both patients in our cases underwent the lung biopsy, and the diagnosis of LCH was confirmed morphologically.

The general prognosis for LCH is usually favorable, especially if patients stop smoking early during the disease. Unfavorable prognostic factors include multisystemic lesions, large cysts, significantly decreased DLCO, low FEV_1/FVC ratio, high residual volume to total lung capacity ratio. The first clinical case demonstrates the benign disease course, early diagnosis of pulmonary histiocytosis with positive changes after smoking cessation. The second clinical case represents a less favorable LCH variant: large volume of pulmonary lesions, impaired respiratory function, adverse treatment effects with the preserved risk factor (smoking). This defines a rather unfavorable prognosis for this patient.

Various methods are used in LCH treatment. However, the first recommendation is to stop smoking [4–6, 9]. For example, the study of A. Delobbe et al. demonstrated that the risk of severe respiratory failure in smokers increased more than 10-fold [10]. Just stopping the tobacco smoke inhalation without the drug exposure may lead to improved pulmonary patterns based on computed tomography and ventilation parameters [5]. Stopping contacts with the smoke, smoking (including smoking mixtures and inhalation drugs) is a mandatory prerequisite for efficient LCH treatment.

Besides cigarette smoking cessation, corticosteroids (CSs) are also considered possible treatment methods, especially in patients with significant symptoms and severely impaired respiratory function [5]. However, no standard criteria and approaches exist for CS administration. Cytostatic agents (including chlorodeoxyadenosine, cyclophosphamide, methotrexate) may be considered a possible treatment option for patients with no corticosteroid therapy effects, especially with the involvement of several organs. In our second clinical case systemic CSs were used due to a significant volume of pulmonary lesions, PFT disorders, and respiratory failure (desaturation during physical exertion). One should note adverse effect of prolonged CS treatment (diabetes mellitus, Cushing syndrome) in this patient.

Unilateral pneumothorax is the most common complication of LCH [5]. Based on various data, its rate may range from 16 to 32 % [6]. It was reported that pneumothorax emerged in 16 of 100 patients with LCH, with 10 of those having at least 1 episode of pneumothorax; patients with a complication of pneumothorax usually started LCH in a young age, while the rate of pneumothorax recurrence was approximately 58 % [6]. The rate of pneumothorax recurrences was significantly higher in cigarette smokers than in those who stopped smoking. Pleurodesis is efficient in the setting of recurrent pneumothorax [6]. Lung transplant may be considered for patients with the late-stage disease [4–6]. In this prognostically unfavorable group transplant enhances survival and improves the patient's quality of life. A retrospective study enrolling 39 patients demonstrated the 1- and 10-year survival rates of 76 % and 54 % after the lung transplant, respectively, although recurrences

were especially common in those with other organs affected. In our cases none of the patients developed pneumothorax.

Conclusion

The clinical cases presented demonstrate specific features of this disease: young patient age, smoking as a risk factor, minimum clinical signs (or their absence) with rather significant pulmonary lesions. Chest CT most often demonstrates cystic and focal patterns, multiple centrilobular polymorphic foci of variable diameter. Despite typical radiological symptoms, both cases incorporated the morphological verification of the diagnosis. Pulmonary lesions regressed in the first case with smoking cessation, while the second patient demonstrated progressive pulmonary lesions despite corticosteroid treatment while she continued smoking.

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Рванина Е.С.: сбор, анализ данных, интерпретация результатов.

Кароли Н.А.: концепция статьи, анализ, интерпретация данных, написание рукописи, проверка интеллектуального содержания, утверждение рукописи для публикации.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Rvanina E.S.: data collection, analysis, interpretation of results.

Karoli N.A.: article concept, analysis, data interpretation, manuscript writing, intellectual content verification, manuscript approval for publication.

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ОСТРОЕ ПОВРЕЖДЕНИЕ ПОЧЕК У ПАЦИЕНТКИ С ТРОМБОЭМБОЛИЕЙ ЛЕГОЧНОЙ АРТЕРИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Acute Kidney Injury in A Female Patient with Pulmonary Embolism (Clinical Case)

Резюме

Представлен клинический случай, посвященный тромбоэмболии легочной артерии (ТЭЛА) высокого риска у 74-летней пациентки, осложнённой развитием острого повреждения почек (ОПП). В статье рассматриваются манифестация, клинические, диагностические и терапевтические аспекты ведения пациентов с ТЭЛА, включая применение тромболизиса и антикоагулянтной терапии. Описаны клинические проявления заболевания, включая выраженную одышку, слабость, отёки нижних конечностей. Течение ТЭЛА осложнилось развитием ОПП, установленного по олигурии и высокому уровню сывороточного креатинина. Представлены данные лабораторных и инструментальных исследований, демонстрирующие динамику восстановления функции почек после проведенного лечения. Оговаривается возможная роль врождённой аномалии развития (агенезии) левой почки у пациентки, как условия предрасположенности к ОПП. Приводятся основные сведения о патофизиологических механизмах ОПП при ТЭЛА. Обсуждается влияние острой правожелудочковой недостаточности, которая приводит к повышению центрального венозного давления, пассивной почечной гиперемии, увеличению интерстициального давления и отёку интерстиция почек. В развитии ОПП выделяют также снижение сердечного выброса с последующей гипоперфузией почечной паренхимы. Полагают, что сопутствующие заболевания, такие как сахарный диабет, артериальная гипертензия, хроническая болезнь почек, являются как факторами риска развития ОПП, предрасполагающими к повреждению почек в условиях тяжелого гемодинамического стресса, так и факторами, усугубляющими почечную дисфункцию при гипоперфузии и застойной нефропатии. Особое внимание уделено влиянию ОПП на прогноз ТЭЛА. Авторы делают вывод о необходимости комплексного подхода к оценке состояния больных с ТЭЛА, мониторингу почечной функции и разработке индивидуальных терапевтических стратегий для минимизации рисков повреждения почек. Статья подчеркивает значимость своевременного вмешательства и дифференцированной тактики лечения пациентов с ТЭЛА и сопутствующим ОПП.

Ключевые слова: *венозные тромбоэмболические осложнения, тромбоэмболия легочной артерии, диагностика, лечение, клиническая картина, острое повреждение почек, осложнения*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «ОСТРОЕ ПОВРЕЖДЕНИЕ ПОЧЕК У ПАЦИЕНТКИ С ТРОМБОЭМБОЛИЕЙ ЛЕГОЧНОЙ АРТЕРИИ (клинический случай)» для журнала «Архивъ внутренней медицины», подписав информированное согласие

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Abstract:
The article presents a clinical case of high-risk pulmonary embolism (PE) in a 74-year-old patient complicated by the development of acute kidney injury (AKI). The article discusses the manifestations, clinical, diagnostic, and therapeutic aspects of managing patients with PE, including the use of thrombolysis and anticoagulant therapy. Clinical manifestations of the disease are described, including severe shortness of breath, weakness, and swelling of the lower extremities. The course of PE was complicated by the development of AKI, established by oliguria and high serum creatinine levels. The data from laboratory and instrumental studies are presented, demonstrating the dynamics of recovery of kidney function after treatment. The possible role of congenital malformation (agenesis) of left kidney in the patient as a condition of predisposition to AKI is mentioned. The basic information about the pathophysiological mechanisms of AKI in PE is presented. The effect of acute right ventricular failure, which leads to increased central venous pressure, passive renal hyperemia, increased interstitial pressure, and renal interstitial edema, is discussed. In the development of AKI, a decrease in cardiac output is also distinguished, followed by hypoperfusion of the renal parenchyma. It is believed that concomitant diseases such as diabetes mellitus, arterial hypertension, and chronic kidney disease are both risk factors for the development of AKI, predispose to kidney damage under severe hemodynamic stress, and factors that exacerbate renal dysfunction with hypoperfusion and congestive nephropathy. Special attention is paid to the effect of AKI on the prognosis of PE. The authors conclude that an integrated approach is needed to assess the condition of patients with PE, monitor renal function, and develop individual therapeutic strategies to minimize the risks of kidney damage. The article highlights the importance of timely intervention and differentiated treatment tactics for patients with PE and concomitant AKI.

Key words: *venous thromboembolism, pulmonary embolism, diagnostics, treatment, clinical picture, acute kidney injury, complications*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
The patient consented to the publication of laboratory and instrumental research data in the article «Acute Kidney Injury in A Female Patient with Pulmonary Embolism (Clinical Case)» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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BP — blood pressure, VTE — venous thromboembolism, EH — essential hypertension, CAD — coronary artery disease, LV — left ventricle, LA — left atrium, CBC — complete blood count, AKI — acute kidney injury, PT — prothrombin time, RV — right ventricle, HF — heart failure, Amb — ambulance, PE — pulmonary embolism, AFib — atrial fibrillation, CKD — chronic kidney disease, CVP — central venous pressure, RR — respiratory rate, HR — heart rate, ECG — electrocardiogram, EchoCG — echocardiography

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE), are the third globally prevalent acute cardiovascular syndrome (after myocardial infarctions and strokes) [1–3]. It is very hard to define an accurate number of VTE cases, accounting for the fact that the major proportion of events remains undiagnosed [4]. 375,000–425,000 VTE cases are reported annually in the USA, not including undiagnosed and untreated cases [1, 3, 5, 6]. According to the US National Registry, PE incidence increased from almost 60,000 (23 per 100,000 people) in 1993 to 202,000 (65 to 100,000 people) in 2012 [7]. Empiric estimates of annual PE incidence in European countries range from 15 to 16 per 100,000 population [8]. According to the Ministry of Health of the Russian Federation, approximately 80,000 new VTE cases are reported annually in Russia, while the PE incidence is 35–40 per 100,000 people, i.e. 51,000–58,000 cases per year [1, 9].

Despite the fact that hospital mortality in acute PE reaches 9–15 %, 30-day all-cause mortality among patients with a high-risk PE ranges from 40 to 65 % [1, 3, 10]. The pulmonary artery obstruction significantly impairs the pulmonary blood flow and gas exchange. Depending on PE severity, right ventricular (RV) postload increases, right heart chambers dilate with the development of tricuspid regurgitation, increased tension of right heart chamber walls, and increased central venous pressure (CVP) [2, 11].

Due to high CVP and macro- and/or microcirculatory renal hypoperfusion, PE is often complicated by the acute kidney injury (AKI), which is accompanied

by the unfavorable prognosis even with mild and reversible renal dysfunction [12, 13]. Despite a relatively high PE incidence, the issue of acute renal dysfunction is not sufficiently analyzed, and we have considered it interesting to demonstrate a case of reversible AKI in the setting of PE.

Clinical Case Report

Patient Information

The female patient V., 74 years old, was hospitalized into the cardiological department of the Central City Clinical Hospital No. 1 (Donetsk) on January 14, 2025. Upon admission the patient complained of severe dyspnea at rest worsening with minimum physical exertion, significant general weakness, edema of thighs, legs, and feet. The patient also noted the decreased urine output within the preceding several days ("about a glass daily").

Medical history. Within 15 years she periodically suffered from pressure-like pain in the precordial region during physical exertion and blood pressure (BP) elevation to 200/100 mm Hg. She was followed up in the outpatient setting concerning the coronary artery disease (CAD), essential hypertension (EH); she did not take the recommended therapy regularly, although she used enalapril during BP elevation episodes. The patient reported that her usual BP values were 160–170/90–95 mm Hg.

Her latest exacerbation emerged on January 9, 2025, when significant dyspnea, general weakness, hypotension (100–80/70–50 mm Hg) emerged; the patient called the ambulance several times, but refused to hospitalize. On January 14, 2025 her dyspnea worsened, she again called the ambulance and was hospitalized into the cardiological department at 12:55 p.m.

History: in 1986, during the elective ultrasound examination of the abdominal cavity, the patient was diagnosed with a single right kidney, and the diagnosis of congenital unilateral agenesia of the left kidney was established.

Physical examination: severe condition. The patient was alert and oriented in herself, time and place. Normal constitution, overweight. Peripheral lymph nodes and the thyroid gland were not enlarged. Pupils: D=S. Skin and visible mucous membranes were clean. Moderate cyanosis of lips. SpO_2 95 % on room air. Respiratory rate (RR) 22–24/min. Chest percussion demonstrated the pulmonary sound over the whole lung surface; during lung auscultation, vesicular breathing with no rales was detected. Relative cardiac dullness borders: left — shifted 1.5 cm outwards from the left midclavicular line; right — 0.5 cm outwards from the right sternal border; upper — 3rd rib. Regular heart rhythm was auscultated with muffled heart sounds. Heart rate (HR) 65/min, BP 120/70 mm Hg. During palpation, the abdomen was soft and non-tender, but enlarged, with the dull percussion sound in the flanks. The bowel palpation was difficult due to a significant amount of subcutaneous fat. The liver protruded 2 cm from under the costal arch. Kidneys and the spleen were not palpable. Symmetric soft edema of thighs, legs, and feet.

Electrocardiogram (ECG) (January 14, 2025): regular sinus rhythm, heart rate 60 min^{-1}. Right axis deviation (α angle: +106°). $S_IQ_{III}T_{III}$ sign, negative T waves in II, III, aVF, V_1–V_6 (Fig. 1).

Common blood count (CBC): Hb 73 g/L, RBC 4.08×10^{12}/L, Ht 25.2 % (36–45 %), mean corpuscular volume 61.8 fL (80.0–96.1 fL), mean corpuscular hemoglobin 17.9 pg (27.5–33.2 pg), mean corpuscular hemoglobin concentration 29 % (33.4–35.5 %), RBC distribution width 21 % (11.5–14.5 %), platelet crit 0.213 % (1.0–10.3 %), CI 0.56 (0.85–1.0). Other CBC parameters were within reference ranges.

Biochemistry panel: total protein 58 g/L (65–85 g/L), urea 20.5 mmol/L (2.5–8.3 mmol/L), glucose 7.1 mmol/L (3.38–5.55 mmol/L).

Coagulation panel: prothrombin time (PT) 17 seconds (13–17"), prothrombin index 80 % (80–100 %), international normalized ratio 1.31. Semi-quantitative D-dimer test: positive.

Cardiac markers: troponin I (cTnI) (January 14, 2025; 1:10 p.m.) 12 ng/mL (<0.2 ng/mL).

Amino-terminal fragment of brain natriuretic peptide (NT-proBNP) 1056 pg/mL (<600 pg/mL).

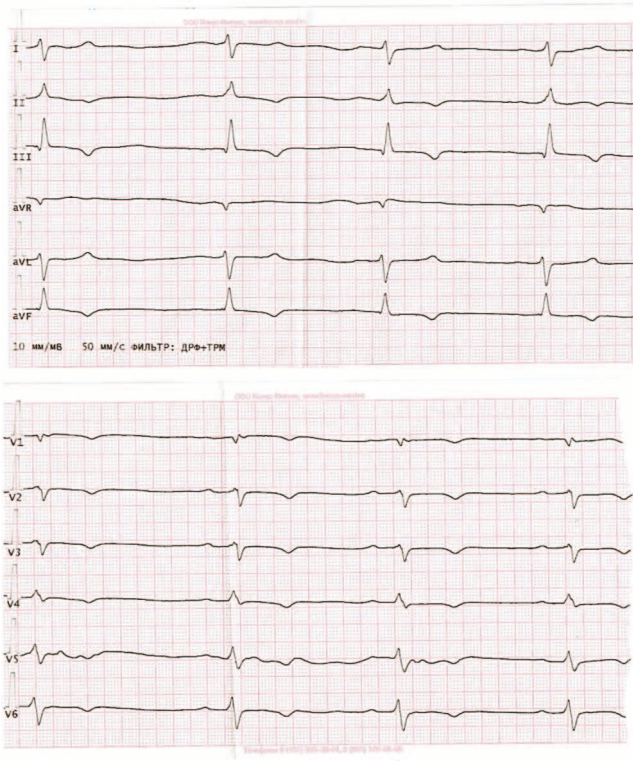

Figure 1. *Electrocardiogram on the day of admission (14.01.2025). Description in text*

Based on the aforementioned complaints, history, physical examination, laboratory tests, and ECG changes, the following preliminary diagnosis was established: 1) CAD: Acute non-ST elevation acute coronary syndrome (January 9, 2025; based on the history). Heart failure (HF), Stage I, with the undetermined left ventricular (LV) ejection fraction, functional class IV. Stage II, Grade 3 essential hypertension, risk of cardiovascular complications 4 (very high). 2) PE (January 9, 2025).

Concomitant diseases: Congenital unilateral agenesia of the left kidney.

The following treatment was administered upon admission: enoxaparin 60 mg subcutaneously twice daily; furosemide 40 mg intravenously once (since January 15, 2025 — furosemide 20 mg in the morning and afternoon); dexamethasone 8 mg intramuscularly once; spironolactone 25 mg in the afternoon; atorvastatin 40 mg in the evening; acetylsalicylic acid 100 mg in the evening; clopidogrel 75 mg in the morning; omeprazole 40 mg in the morning, 30 minutes before meals.

Next day (January 15, 2025), by 6:00 a.m. no diuresis was reported since the previous evening (for 10 h), and the patient's condition worsened (dyspnea worsened, the saturation and BP decreased). Physical examination: very severe general condition. The patient was alert and oriented in herself, time and place. Significant diffuse cyanosis. RR 34/min; the patient lies supine with no orthopnea; body temperature 36.5 °C, SpO_2 85 % (on room air), 95–96 % (with O_2 inhalations). Regular heart rhythm with muffled heart sounds. HR 60/min, BP 80/50 mm Hg. The abdomen was soft and non-tender on palpation; due to the severe patient's condition, the detailed palpation of abdominal organs was impossible. Symmetric edema of legs and feet; leg palpation was non-tender, with preserved pulses bilaterally. ECG (January 15, 2025; 6:15 a.m.): sinus regular rhythm, rate 64/min. Right axis deviation (α angle: +112°). $S_IQ_{III}T_{III}$ sign, negative T waves in leads III, V_1–V_6. Signs of right heart strain. Compared to ECG on January 14, 2025, the right axis deviation worsened (α angle increased from +106° to +112°), the Q_{III} wave became deeper (from 1.5 mm to 2.5 mm), and the depth of the negative $T_{V1–V6}$ increased as well, which were considered signs of RV strain worsening (Fig. 2).

Transthoracic echocardiography (EchoCG) (January 15, 2025; 8:30 a.m.): pulmonary artery pressure 50–54 mm Hg. Inferior vena cava dilation 3.29 cm, collapsing <50 % on inspiration. Right atrial volume index 85.83 mL/m² (<27 mL/m²), RV wall thickness 0.38 cm, proximal RV diameter 4.5 cm (<3.5 cm), EDV index 70.63 mL/m² (29–61 mL/m²). Dilated right heart chambers and LV. Paradoxical interventricular septum motion (sign of RV strain). Left atrial (LA) diameter 4.36 cm, LA volume index 27.92 mL/m², LV ejection fraction 55 %.

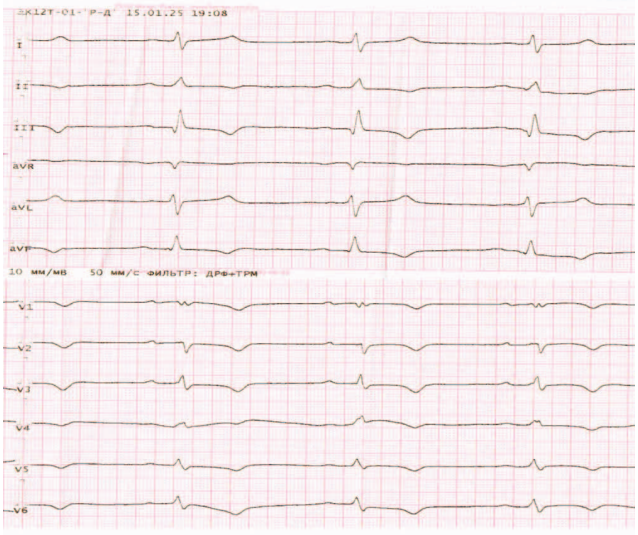

Figure 2. *Electrocardiogram at the time of impairment of the condition (01/15/2025, 06:15). Description in the text*

Ultrasound duplex scanning of veins in lower extremities was not arranged due to technical limitations.

Common blood count and biochemistry panel (January 15, 2025; 9:00 a.m.): WBC 15.14×10^9/L, 12 % lymphocytes, RBC 4.08×10^{12}/L, Hb 73 g/L, total protein 58 g/L, urea 23.1 mmol/L, alanine aminotransferase 304.8 mmol/L, aspartate aminotransferase 244.2 mmol/L, PT 24.4 sec. Urinalysis could not be arranged due to the absence of urine.

Based on the patient complaints of worsening dyspnea, significant weakness, physical findings (edema of lower extremities, hypotension, tachypnea), decreased SpO_2, ECG results (worsening right axis deviation, increased depth of pathological Q wave in lead III and T waves in chest leads), and EchoCG (pulmonary hypertension, inferior vena cava dilation, absence of its adequate inspiratory collapse, dilated right heart chambers), high-risk PE (PESI mortality risk 10–24.5 %) with the circulatory collapse (January 9, 2025) was diagnosed in the patient. Pulmonary hypertension (mean pulmonary artery pressure 54 mm Hg).

No urination for 10 hours with the significant drop in diuresis within the prior days, prolonged hypotension emerging in the setting of PE helped to establish the diagnosis of prerenal AKI, RIFLE class/AKIN Stage 3, in the setting of CKD: congenital unilateral agenesia of the left kidney.

Due to the very high-risk PE, the patient was administered thrombolysis with recombinant prourokinase in the total dose of 8 million U (2 million U as a bolus, 6 million U as an IV drip). The enoxaparin dose was increased to 80 mg subcutaneously twice daily (before the creatinine results turned in), while aspirin and clopidogrel were discontinued. After thrombolysis, the

patient's condition remained stably severe, with BP of 115/70 mm Hg, while dyspnea did not get worse.

The result of the creatinine test was received on January 15, 2025 on 12:30 p.m. — 540 μmol/L (N 30–110 μmol/L). The treatment administered was corrected: enoxaparin, spironolactone, and atorvastatin were discontinued, and a combined phospholipid + glycyrrhizinic acid drug was started (2.5 g twice daily, IV drip).

Coagulation panel (January 15, 2025): PT 24.4 sec, PTI 61%, fibrinogen 1.9 g/L, D-dimer 2,420 ng/mL (0–500 ng/mL).

On January 17, 2025 (Day 3 of inpatient hospitalization), the patient started to excrete urine (350 mL/day). Urinalysis: proteinuria (1.31 g/L), leukocyturia, casturia (see the Table for urinalysis changes).

During the period of January 17 to 21, 2025, the patient continued complaining of significant dyspnea at rest worsening with minimum activity, severe general weakness. Her condition was stably severe. Symmetric, soft edema of lower extremities spanned up to the middle of thighs; it was more prominent by the evening. The patient was on constant oxygen therapy, with SpO_2 95–97% (during O_2 inhalations), HR 70–84 bpm,

Table. *Dynamics of the patient's general urine analysis during her hospital stay*

Parameter	Date (day in hospital)				
	17.01.2025 (4)	20.01.2025 (7)	28.01.2025 (15)	31.01.2025 (18)	04.02.2025 (22)
Urine volume, ml/day	350	1200	2700	2400	1700
Relative density	l/u	l/u	1026	1018	1013
Protein, g/L	1,31	0,246	0,749	1,3	0,104
White blood cells, single in f/v	7-12	–	10-15	8-0	30-40
Red blood cells, single in f/v	–	–	10-12	1-2	–
Cylinders, single in f/v	6-9	–	–	–	–

Notes: l/u — little urine, f/v — field of view.

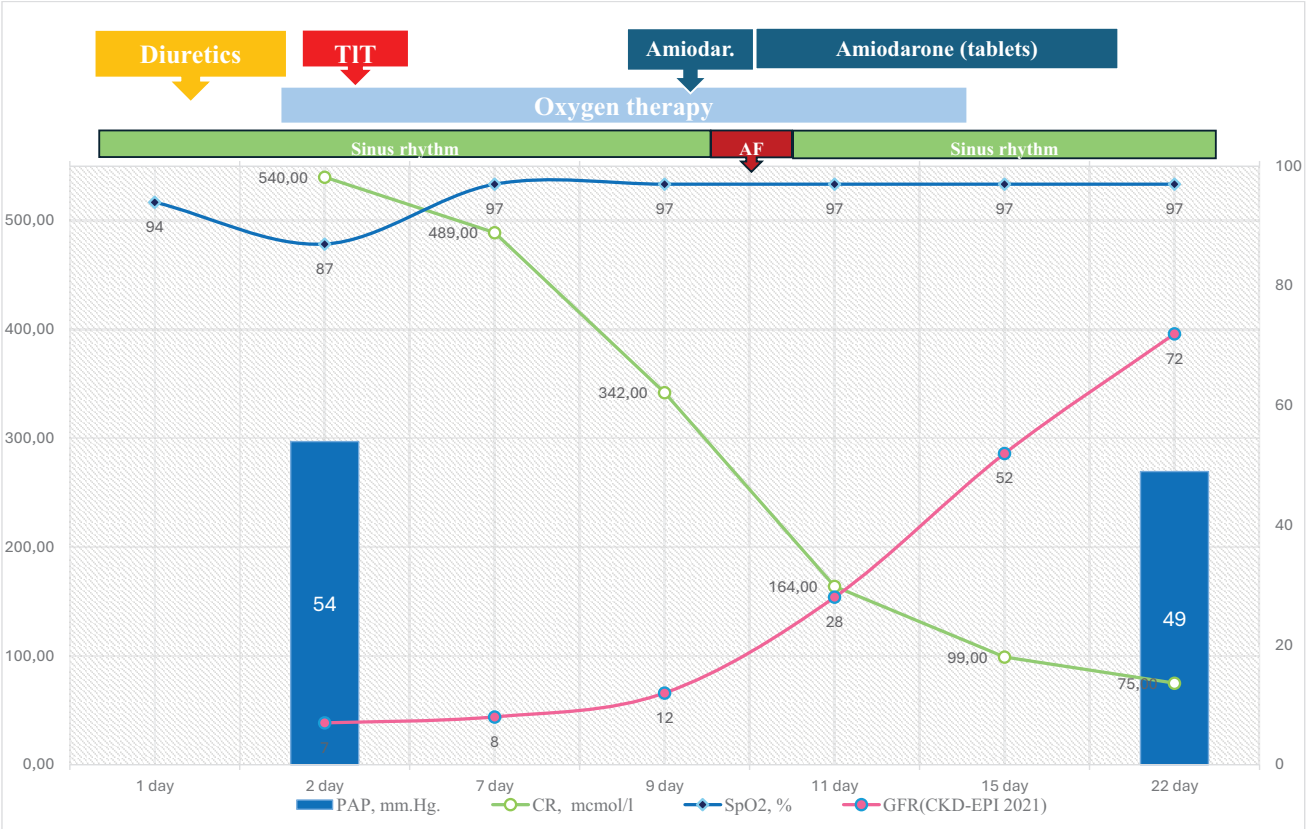

Figure 3. *Dynamics of laboratory and instrumental parameters of the patient during her hospital stay*

Notes: TIT — thrombolytic therapy, AF — atrial fibrillation, PAP — pulmonary artery pressure, SpO_2 — blood oxygen saturation level, %, GFR — glomerular filtration rate, CKD-EPI 2021 — formula for calculating GFR according to Chronic Kidney Disease Epidemiology Collaboration 2021, CR — creatinine, mcmol/

RR 20–22/min, BP 130–120/80–70 mm Hg. The diuresis restored since January 20 (800–1200 mL daily). See Figure 3 for changes in hemodynamic parameters, heart rhythm, blood saturation, common blood count and biochemistry panel results during the whole treatment period in the inpatient setting.

On Day 9 of inpatient treatment (January 22, 2025), the patient noted the improved well-being, while the dyspnea intensity decreased. Her condition was still stably severe. Physical examination revealed moderate cyanosis of lips. Vesicular breathing was auscultated in lungs. SpO_2 97 % (during O_2 inhalations), RR 20/min. Regular heart rhythm, with muffled heart sound. HR 85 bpm, $BP_D = BP_S$ = 120/70 mm Hg. Due to creatinine level decrease to 305 μmol/L and GFR of 17 mL/min, enoxaparin was again added to treatment (60 mg/day, one-time).

ECG (January 22, 2025): regular sinus rhythm, rate 85/min. Right axis deviation (α angle +109°). S_IQ_{III} sign, isoelectric T wave in leads II, III, aVF, weakly positive T wave in leads V_2–V_6. Compared to prior ECGs, negative T waves became flattened and weakly positive.

On January 23, 2025, at 8:05 a.m. (Day 10 of hospital stay), the patient noted decreased dyspnea intensity and improved well-being in the setting of general weakness, however she started complaining of palpitations. During the examination, irregular heart rhythm with the rate of 100/min was detected; RR 23/min. ECG (January 23, 2025; 8:25 a.m.): tachysystolic atrial fibrillation (AFib) (Fig. 4).

Amiodarone 300 mg (diluted in 0.9 % saline, 400 mL), IV drip infusion was started on 8:40 a.m. The paroxysm was stopped at 12:10 p.m., the patient noted that her condition improved, while the dyspnea intensity decreased; RR 19/min. ECG (January 23, 2025; 12:00 p.m.): irregular sinus rhythm due to atrial extrasystoles (bigeminy) with the rate of 120/min. Right axis deviation (α angle +102°). S_IQ_{III} sign, positive T waves in leads V_1–V_2 (Fig. 5).

During the treatment (amiodarone 300 mg IV drip one, followed by 200 mg orally three times daily; oxygen therapy; combined phospholipid + glycyrrhizinic acid drug 2.5 g/day; furosemide 20 mg twice daily; pantoprazole 40 mg; iron [III] hydroxide dextrane solution 2.0 mL twice daily), the patient's condition improved. The patient noted the disappearance of palpitations, while her dyspnea and general weakness improved;

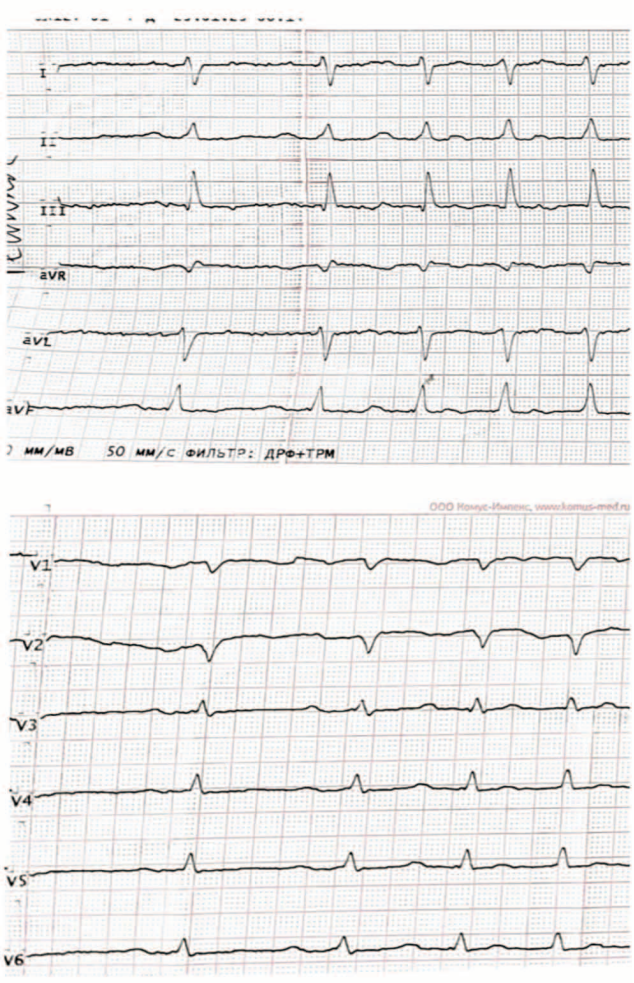

Figure 4. *ECG of the patient during arrhythmia (01.23.2025, at 08:25)*

Description: atrial fibrillation with ventricular rate (VR) of 140 min^{-1}. Right axis deviation (α angle +109°). S_IQ_{III} sign, weakly negative T wave in leads V_1–V_2.

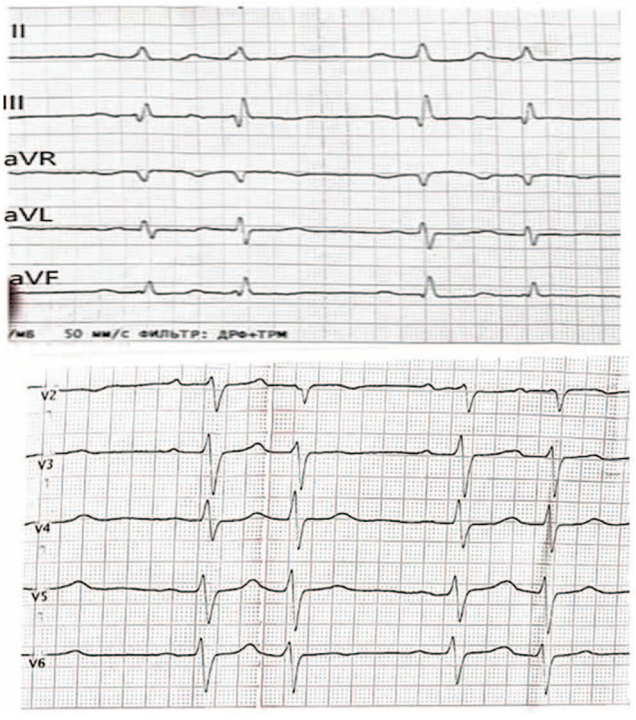

Figure 5. *ECG after abortion of an atrial fibrillation attack (01/23/2025, 12:00).*

Description: irregular sinus rhythm due to atrial bigeminy with heart rate of 120 min. The electric axe is deviated to the right (angle α +102°). S_IQ_{III}, positive T in V_1-V_2

the motor activity enhanced. Edema of thighs, legs, and feet improved. The patient preserved a sinus rhythm with HR 60–80/min, BP in the range of 120–130/76–80 mm Hg. SpO_2 98 % on room air, RR 18/min. Cardiac tones were regular, muffled. Vesicular breathing with no rales or crepitation was auscultated in lungs.

Laboratory tests before discharge: CBC (February 4, 2025): RBC 3.95×10^{12}/L, Hb 82 g/L, Ht 28.1 %, mean corpuscular volume 71 fL, mean corpuscular hemoglobin 20.7 pg, mean corpuscular hemoglobin concentration 29.2 %, RBC distribution width 15.4 %, platelets 148 g/L (150–450 g/L), platelet crit 0.141 %; all other parameters were within reference ranges.

Biochemistry panel: total protein 50 g/L, creatinine 75 μmol/L, serum iron 8 μmol/L (9–30 μmol/L), ferritin 8 μg/L (15–150 μg/L), transferrin 3.5 g/L (2.0–4.0 g/L), vitamin B_{12} 250 pg/mL (190–900 pg/mL); all other parameters were within reference ranges, including aminotransferase levels.

EchoCG (February 4, 2025): pulmonary artery pressure decreased from 54 to 49 mm Hg, LA volume index increased from 27.92 mL/m^2 to 52.75 mL/m^2, right atrial volume index decreased from 85.83 mL/m^2 to 64.75 mL/m^2.

On February 5, 2025 the patient was discharged under the monitoring of physicians at place of residence with the following diagnosis:

Main disease: High-risk PE (in-hospital mortality risk >15 %) with the circulatory collapse on January 9, 2025 (based on history), recurrent course. Condition after thrombolysis (prourokinase) on January 15, 2025. Pulmonary hypertension (mean pulmonary artery pressure 49 mm Hg based on EchoCG dated February 4, 2025) (ICD code I26).

Complications of the main disease: prerenal AKI (RIFLE Stage 3) dated January 14, 2025, with the renal function restored on February 4, 2025, in the setting of CKD Stage 2: agenesia of the left kidney combined with the hypertensive nephropathy of a single right kidney. Hypoxic hepatitis.

CAD: first-detected tachysystolic AFib paroxysm (January 23, 2025), drug-induced cardioversion (amiodarone) on January 23, 2025, CHA_2DS_2-VASc 4 points, HAS-BLED 5 points, HF 1 with preserved LV ejection fraction (61.99 % based on EchoCG dated February 4, 2025), functional class II. Essential hypertension, Stage II, Grade 3, Risk 4 (very high).

Moderately severe iron deficiency anemia.

She was recommended to continue regular follow-up at the general practitioner and the cardiologist. Outpatient diagnosis to determine the cause of anemia. EchoCG, Holter ECG monitoring to be arranged annually. Monitoring serum creatinine, iron, potassium levels; common blood count and urinalysis in 1 month. Salt-restricted (<5 g daily) and fluid-restricted (1–1.5 L daily) diet. Medications recommended: bisoprolol 2.5 mg in the morning, long-term treatment with HR and BP monitoring; lisinopril 2.5 mg daily; amiodarone 100 mg in the afternoon after 1 month with HR and ECG monitoring; rivaroxaban 20 mg daily during meals for 3 months with the following cardiologist counseling; iron [II] sulphate in combination with ascorbic acid 2 tablets daily with hemoglobin and serum iron level monitoring.

Discussion

PE is a variant of VTE, which comes third among the most common causes of cardiovascular mortality, giving way just to myocardial infarction and stroke [14]. Timely detection of acute PE and immediate initiation of anticoagulants, thrombolytics in combination with mechanical thrombectomy provides a significant decrease in mortality risks [15, 16]. PE manifestations may simulate a wide range of other conditions; thus, the most common cause of death in PE is the inability to confirm a correct diagnosis [14]. PE is often called a "great pretender", as this condition may be very complex for detection and final diagnosis. Patients with PE often demonstrate symptoms simulating acute myocardial infarction, HF, syncope caused by arrhythmias, pneumonia, influenza, asthma, panic attack, depression, or other diseases. The diagnosis of PE primarily requires that the physician includes it into the differential diagnosis; however, unfortunately, it is not uncommon that this life-threatening condition is not even considered a potential cause of symptoms in a patient [14, 17, 18].

Typical clinical PE manifestations usually included the sudden-onset complaints of variable dyspnea, chest pain, dizziness, presyncope and syncope, pain and edema of extremities, hemoptysis, cough, malaise, diaphoresis, and other symptoms [9, 19–23]. Based on T. Holder et al. [21] who analyzed the features of acute PE among 829 patients, the rate of presenting symptoms was as follows: dyspnea, 55.2 %; chest pain, 28 %; cough, 12.2 %; pain and edema of lower extremities, 8.8 % and 11.3 %, respectively; weakness, 8.9 %; presyncope and syncope, 8.3 %; hemoptysis, 2.3 %. One should not that dyspnea (38 %) and chest pain (20 %) were relatively rare in the high-risk patient subgroup (n=50), while hemoptysis and cough were absent completely. Based on the analysis of several reports by Doralisa and Vincenzo Morrone [20], clinical manifestations of acute PE were characterized by dyspnea (in 32–88 % cases), tachypnea (60–66 %), tachycardia (30–40 %), chest pain (40–70 %), syncope (6–39 %), cough (9–37 %), hemoptysis (2–13 %), and fever (7–10 %).

In our case the patient complained of dyspnea at rest, significant general weakness, edema of lower extremities. At the very onset of the disease (January 9, 2025), hypotension (80/60 mm Hg) was noted along with severe

dyspnea and general weakness, confirming the hemodynamic collapse. Despite multiple requests from the ambulance physicians, the patient refused the hospitalization. Unfortunately, the medical charts have not been presented, but it is very likely that the physicians considered the patient's condition worsened due to the exacerbation of the main disease, accounting for the history of CAD and EH. Even upon admission to the cardiology department on January 14, 2025, the diagnosis of PE was put second after the proposed ACS. The ambiguity concerning PE was associated with the complex exclusion of ACS in the setting of CAD and the absence of EchoCG results during the first day of hospital stay, although ECG already demonstrated right axis deviation, the $S_IQ_{III}T_{III}$ sign, negative T waves in chest leads. Only on January 15, 2025, when the patient's condition significantly worsened in the morning (due to increasing dyspnea, weakness), PE was diagnosed after obtaining the EchoCG results.

It should be noted that clinical PE manifestations are not always characterized by the combination of all complaints, i.e. dyspnea, chest pain, hemoptysis, palpitations. As presented above, such typical PE sign as dyspnea is not detected in all patients. Accounting for the PE severity and its potentially lethal prognosis, cases with the non-"classic" PE presentation (with the "classic" meaning the simultaneous combination of all hazardous signs) should be assessed very attentively [17, 23].

Despite the fact that PE is one of the leading causes of cardiovascular morbidity and mortality, insufficient attention is usually paid to the renal function assessment in this complication [24, 25]. Renal dysfunction is observed rather frequently in patients with PE, with the rate ranging from 5 % to 60 % [25, 26]. Based on the ICOPER registry covering 2,454 patients with acute PE, renal dysfunction (creatinine levels >176.8 μmol/L) was observed in 5.1 % cases, being an independent mortality predictor (HR 2.0; 95 % CI 1.4–3.0) [27]. When analyzing the association of various biomarkers and prognosis in 100 patients with acute PE, M. Kostrubiec et al. [28] detected renal failure (serum creatinine levels >135 μmol/L) in 13 patients (13 %); the hazard ratio (HR) for the renal failure-associated mortality was 6.4 (95 % CI 2.22–18.61). Based on the results of the meta-analysis (13 studies enrolling 35,662 patients), signs of renal failure were observed in each third patient (32.8 %) [29].

According to the large Russian SIRENA registry enrolling 604 patients with PE, renal dysfunction (assessed as glomerular filtration rate <60 mL/min/1.73 m^2) was detected in 320 (53 %) patients, with severe dysfunction in 63 (10 %) examined subjects [30]. AKI was diagnosed in 59.6 % PE patients in the study of P.F. Klimkin et al. [31]. Besides, AKI in patients with PE was associated with the severity of respiratory failure, systolic pulmonary hypertension, and RV dysfunction parameters.

In our cases PE course was complicated with AKI, defined as a sudden-onset renal function loss evaluated based on serum creatinine level increase and decreased diuresis (oliguria) lasting up to 7 days [32–34].

Several mechanisms are considered in the pathogenesis of AKI in the setting of PE. Acute right heart strain leads to tricuspid regurgitation and increased CVP, which leads to passive renal hyperemia, increased interstitial pressure, and renal interstitium edema [12, 25, 35]. To describe the renal disorder due to decreased renal venous blood flow and increased renal interstitial pressure, the term "congestive nephropathy" is used — it can be reversible if the venous circulation parameters are restored [25, 36]. The renal venous congestion activates the hormonal activation with enhanced sodium resorption, which leads to worsening volume overload, increased intraabdominal pressure, and (consequently) increased RV wall tension. Thus, decreased renal perfusion along with the worsening vascular congestion and, thus, increased CVP leads to renal function worsening in acute HF [35]. E.M. Boorsma et al. [37] proposed the "renal tamponade" hypothesis to explain the renal function worsening with increased CVP in HF. Increased CVP leads to the increased interstitial pressure in kidneys with the compression of renal structures (tubules, intrarenal vessels, glomeruli) in the encapsulated kidney, which is rather rigid for expansion.

Besides, acute PE with the drop in the stroke volume leads to renal hypoperfusion and hypoxia, neurohumoral activation enabling vasoconstriction and additional sodium resorption [12, 35]. Such concomitant diseases as diabetes mellitus, hypertension, CKD, congenital anomalies, are both risk factors for AKI, predisposing to renal injury in the setting of severe hemodynamic stress and factors worsening renal injury in the setting of hypoperfusion and congestive nephropathy [12, 25, 26, 38]. Thus, when analyzing AKI features in 36 patients with PE, V.V. Filimonova et al. [24] detected CKD in 24 (67 %), *de novo* AKI — in 12 (33 %) examined patients. Our patient was earlier diagnosed with a single kidney and a congenital agenesia of the left kidney, which, being a variant of CKD, predisposes to AKI [39].

AKI course in the case presented was characterized by the period of oliguria, azotemia (maximum creatinine level 540 μmol/L) in the setting of PE. The management of patients with PE and AKI presumes quick blood flow restoration in the pulmonary circulation, RV strain and CVP improvement, diuresis restoration. In our case, all nephrotoxic medications and drugs increasing the risk of adverse effects were discontinued after establishing the final diagnosis.

Besides severe renal dysfunction, acute HF and respiratory failure in the setting of PE in our case led to hypoxic hepatitis, manifesting with more than 10-fold elevated aminotransferase levels. According to the up-to-date information, hypoxic hepatitis is associated with complex disorders of hemodynamics and neurohumoral regulation; hepatocyte hypoxia is the initial cause of their injury [40]. The analysis of multiple studies helped to define the following mechanisms of hepatocyte hypoxia: ischemia and venous congestion (17–78 % cases of acute HF); hypoxemia (12 % cases of respiratory failure, anemia) [40]. Our patient had several mechanisms combined, including ischemia, venous congestion, and hypoxemia. Aminotransferase levels in hypoxic hepatitis typically normalize in 10–15 days, which was the case for our patient.

AKI in PE is associated with an unfavorable prognosis. In the study cited above, the analysis of PE features depending on the presence (n=36) or the absence (n=75) of AKI detected that 16 (44 %) patients with kidney injury and 26 (23 %) patients without AKI eventually died [24]. The in-hospital mortality risk was increased among patients with AKI: OR 5.2 (95 % CI 2.02–13.39; p <0.001). Besides, authors demonstrated that the risk of 30-day mortality based on the PESI scale in patients with AKI was higher than in patients with AKI (120.0 (87.5–158) and 90 (87.5–158.0), respectively; p=0.004) [24]. Based on the detected clear association between the decreased glomerular filtration rate and increased in-hospital mortality, the Russian SIRENA registry experts [30] propose to add the renal dysfunction (glomerular filtration rate <60 mL/min/1.73 m^2) to the simplified PE Severity Index (sPESI) in order to improve the risk stratification and identify patients with the high risk of in-hospital mortality.

Conclusion

The case presented illustrates the emergence of AKI in high-risk PE in a patient with a pre-existing congenital renal anomaly. The AKI course was characterized by oliguria and increased serum creatinine levels. AKI in PE is associated with several mechanisms, in particular with congestive nephropathy and severe hypoperfusion caused by the decreased stroke volume and hypotension. AKI in PE is associated with unfavorable prognosis evaluated based on the in-hospital mortality level. Knowing the renal dysfunction features provides the complex approach to the evaluation of the clinical status of PE patients, helps to monitor diuresis and serum creatinine levels, as well as to develop the differentiated algorithms of patient management.

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