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СОДЕРЖАНИЕ

Лекции

Обзорные статьи

Оригинальные статьи

Разбор клинических случаев

С 2021 ГОДА СТАТЬИ В ЖУРНАЛ ПРИНИМАЮТСЯ
ТОЛЬКО ЧЕРЕЗ РЕДАКЦИОННУЮ ПЛАТФОРМУ:

http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

НОВЫЕ ПРАВИЛА ПУБЛИКАЦИИ АВТОРСКИХ МАТЕРИАЛОВ (2021):

http://www.medarhive.ru/jour/about/submissions#authorGuidelines

CONTENT

SINCE 2021, ARTICLES IN THE JOURNAL HAVE BEEN ACCEPTED ONLY THROUGH THE EDITORIAL PLATFORM:

http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

NEW GUIDELINES OF PUBLICATION FOR AUTHORS OF ARTICLES (2021):

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ИНГИБИТОРЫ ПРОТОННОЙ ПОМПЫ В ПЕРИОД ПАНДЕМИИ COVID-19

T.E. Kugler *, I.S. Malovichko, V.B. Gnilitskaya, A.L. Khristulenko, N.F. Yarovaya

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Proton Pump Inhibitors in the COVID-19 Pandemic

Резюме

Безопасность применения ингибиторов протонной помпы (ИПП) при коронавирусной инфекции (COVID-19) является недостаточно изученной. ИПП являются мощными супрессорами желудочной секреции и входят в десятку наиболее широко используемых препаратов в мире. Предполагается, что препараты влияют на восприимчивость к вирусу, тяжесть течения и исходы у пациентов с диагнозом COVID-19. Это беспокойство основано на механизме действия ИПП — подавлении кислотности желудочного сока, который считается первой линией защиты от инфекций. В совокупности результаты большинства исследований и метаанализов подтверждают возможность того, что использование ИПП может способствовать развитию более тяжелой формы COVID-19. Однако учесть все потенциальные факторы риска тяжести COVID-19 в реальной клинической практике представляется затруднительным, поэтому следует с большой осторожностью относиться к выводам о причинно-следственных связях применения ИПП. Дополнительная интересная точка зрения на использование ИПП во время пандемии заключается в том, что их прием может привести к снижению всасывания некоторых витаминов. С другой стороны, в литературе появилось несколько исследований в отношении защитных терапевтических эффектов ИПП. Все больше доказательств иммуномодулирующей и антифиброзной роли ИПП, что может быть использовано в лечении COVID-19. Кроме того, способность препаратов подщелачивать содержимое эндосом и лизосом служит препятствием для проникновения вируса в клетки. В представленном обзоре проанализированы возможные эффекты приема ИПП у пациентов с COVID-19.-

Ключевые слова: *ингибиторы протонной помпы, COVID-19, SARS-CoV-2, пневмония, смертность, тяжесть течения, факторы риска, лечение, витамины*

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Abstract

The safety of proton pump inhibitors (PPIs) use in coronavirus infection (COVID-19) is not well understood. PPIs are potent suppressors of gastric secretion and become one of the ten most widely used drugs in the world. They are expected to influence virus susceptibility, severity, and

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outcomes in patients diagnosed with COVID-19. This concern is based on their mechanism of action — suppression of gastric acidity, which is considered the first line of defense against infections. Taken together, the results of most studies and meta-analyses support that PPIs use has been associated with increased risk of COVID-19 and severe outcomes. However, taking into account all potential risk factors for disease severity seems impossible in the real world in the context of COVID-19, so conclusions about causal relationships between PPI use and COVID-19 should be treated with great caution. An additional interesting point about the use of PPIs in the pandemic is that it reduced absorption of certain vitamins. On the other hand, several studies have appeared in the literature regarding the protective therapeutic effects of PPIs. There is growing evidence of an immunomodulatory and antifibrotic role of PPIs that could be used in the treatment of COVID-19. In addition, their ability to alkalize the contents of endosomes and lysosomes serves as an obstacle to the penetration of the virus into host cells. This review analyzes the possible effects of PPIs in patients with COVID-19.

Key words: *proton pump inhibitors, COVID-19, SARS-CoV-2, pneumonia, mortality, severe outcomes, risk factors, treatment, vitamins*

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ACE — angiotensin-converting enzyme, ATPase — adenosine triphosphatase, BMI — body mass index, CI — confidence interval, GERD — gastroesophageal reflux disease, GIT — gastrointestinal tract, HR — hazard ratio, NSAIDs — nonsteroidal anti-inflammatory drugs, OR — odds ratio, PPI — proton pump inhibitors, RCT — randomized controlled trial

Introduction

The coronavirus disease (COVID-19) pandemic, which was first reported in December 2019 [1], was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 infection had led to more than 5.9 million deaths from COVID-19 by early 2022 worldwide, as well as a global health crisis [2]. Although common post-COVID complications caused by this virus include damage to the respiratory system, SARS-CoV-2 was found to affect almost all organs, including the gastrointestinal tract (GIT) [3]. Tian Y. et al. (2020) [4] described gastrointestinal symptoms in patients infected with SARS-CoV-2, with a frequency of 3 % to 79 %.

There are several confirmed risk factors for severe COVID-19: elderly age, smoking, obesity, diabetes mellitus, malignant neoplasms, HIV infection, chronic diseases of the lungs, kidneys, or cardiovascular system [1]. There were also concerns over the use of different medications in cases of COVID-19. Evidence emerged that angiotensin-converting enzyme (ACE) inhibitors have a possible modulating effect on disease severity [5]. However, no further evidence was obtained of a positive or negative association with the use of ACE inhibitors in cases of COVID-19 [6–8].

Currently, there is uncertainty regarding the safety of using proton pump inhibitors (PPIs) in patients with SARS-CoV-2, as available data demonstrate both protective and adverse effects. PPIs are expected to have an effect on viral susceptibility, disease severity, and outcomes in patients with COVID-19. This concern is due to the mechanism of action of these agents, i.e., suppression of gastric acid secretion [9]. SARS-CoV-2 is similar to two other previously identified coronaviruses, namely severe acute (SARS-CoV) and Middle East (MERS-CoV) respiratory syndromes [10]. SARS-CoV was reportedly inactivated under acidic conditions (pH 1.0–3.0), while higher gastric pH, which can be achieved with the help of PPIs, does not inactivate this virus [11]. This seems crucial since SARS-CoV-2 can enter the body not only through the respiratory but also through the digestive system [3]. The virus uses the ACE2 receptor, which is extensively expressed in the gastrointestinal tract, for rapid entry and replication in enterocytes [12]. In addition, since the gut is the largest immune organ and can host colonies of rapidly replicating SARS-CoV-2, there is concern that the virus could spread outside the gastrointestinal tract, specifically in the respiratory tract via the gut-lung axis [3, 13]. Therefore, gastric fluid is considered the first line of defense, so the risk of viral infection increases with hypoacidity [14].

This review analyzes the safety of using PPIs during the COVID-19 pandemic. Studies on the link between the use of PPIs and coronavirus infection were searched between January 2020 and March 2022 in three electronic databases, including MEDLINE/PubMed, the Cochrane Library, and Google Scholar.

PPIs as a risk factor for severe COVID-19

PPIs are potent suppressors of gastric secretion and are among the ten most widely used agents in the world. The U.S. Food and Drug Administration (FDA) has approved these drugs for the long-term management of

a range of gastrointestinal conditions, including peptic ulcer, Barrett's esophagus, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, as well as for the prevention of gastrointestinal bleedings during the administration of non-steroidal anti-inflammatory drugs (NSAIDs) [9]. However, in less than 30 years, PPI use has turned into an epidemic — prescription with no clear indications in up to 70 % of cases. According to studies, PPIs are prescribed for 2/3 of hospitalized patients with no corresponding indications [15]. It is generally accepted that PPIs are relatively well tolerated, with most patients reporting adverse reactions such as headache, rash, dizziness, and gastrointestinal symptoms including nausea, abdominal pain, flatulence, constipation, and diarrhea. Physicians are generally not concerned about the serious side effects of PPIs at approved dosages for a short treatment period of about two weeks. However, prolonged and often unjustified use significantly increases the number of adverse events [16, 17]. Although a large randomized controlled trial (RCT) by Moayyedi P. et al. (2019) that included 17,598 patients did not confirm most of the supposed side effects, it was found that daily use of PPIs for three years increased the possibility of intestinal infection by 33 % (odds ratio (OR) = 1.33; 95 % confidence interval (CI) 1.01–1.75) [18]. This effect was probably related to hypochlorhydria and developed due to the long-term use of PPIs, which reduced microbial diversity in the gut, contributing to the colonization of certain pathogenic gut bacteria [19]. However, the authors found no increased risk for the most dangerous associations reported previously, such as cardiovascular diseases (OR = 1.04; CI 0.93–1.15), kidney diseases (OR = 1.17; CI 0.94–1.45), dementia (OR=1.20; CI 0.81–1.78), pneumonia (OR = 1.02; CI 0.87–1.19), fractures (OR = 0.96; CI 0.79–1.17), malignant neoplasms (OR = 1.04; CI 0.77–1.40) [18, 20]. However, not all researchers agreed with the correctness of the method and the duration of this work, considering that the evidence for the long-term safe use of PPIs was insufficient [21, 22].

In July 2020, Almario C.V. et al. [23] conducted an online survey among the American population (n = 53,130) and identified 6.4 % of participants who tested positive for COVID-19. Regression analysis revealed that individuals who took PPIs once a day (OR = 2.15; 95 % CI 1.90–2.44) or twice a day (OR = 3.67; 95 % CI 2.93–4.60) were significantly more likely to test positive for COVID-19 than those who did not take PPIs (Table 1). However, this study had a number of significant shortcomings: the PPI-treated group was younger than the overall population; the number of participants tested for COVID-19 was not reported for either the cohort or separate groups; it is not clear if the control group participants were tested for COVID-19 and the results were negative, or if there were both tested and untested participants [24]. Tarlow B. et al. (2020) [25] also pointed out the disadvantages of the unusual distribution of demographic data in the study conducted by Almario C.V.

In contrast, Lee S.W. et al. (2021) [1] published the results of a nationwide cohort study and reported that short-term ongoing use of PPIs may be a risk factor for severe COVID-19, but not for infection. Similarly, Zhou J. et al. (2021) [26] reported a link between PPIs and severe COVID-19 outcomes, including intensive care unit hospitalization, intubation, or death. A retrospective observational study of 152 hospitalized patients with confirmed COVID-19 performed by Luxenburger H. et al. (2021) [27] revealed an increased risk of secondary infections (statistical significance $p = 0.032$) and acute respiratory distress syndrome when taking PPIs after considering other predisposing comorbidities. Moreover, GERD became an important independent prognostic factor ($p = 0.034$), which indicates the important role of microaspiration in the pathogenesis of secondary infection in this category of patients.

A meta-analysis conducted by Kim H.B. et al. (2021) demonstrated a significant association between PPIs and severe COVID-19 outcomes (including the development of acute respiratory distress syndrome), albeit with a high degree of heterogeneity (hazard ratio (HR) = 1.53; 95 % CI 1.20–1.95, I^2 =74.6 %) [28]. In regard to the subgroup analysis of patients taking PPIs, an increase in severe COVID-19 outcomes was observed in individuals younger than 60, in the Asian population, and during hospitalization. However, a separate analysis with adjustment for body mass index (BMI) or smoking status revealed no significant association. All studies included in the meta-analysis were observational. Several important factors associated with the use of PPIs in cases of COVID-19 were not considered in several studies. This includes, for example, using concomitant medications such as ACE inhibitors, angiotensin II receptor blockers, or statins. While other studies with adjustment for these factors demonstrated no significant association between PPIs and COVID-19 severity (HR = 1.24, 95 % CI: 0.76–2.00, I^2 =68.7 %).

According to Israelsen S.B. et al. (2021) (n = 83,224) [29], current use of PPIs was associated with an increased risk of SARS-CoV-2 infection and was not associated with an increased risk of severe disease outcomes, including intensive care unit hospitalization or death, as reported in previous meta-analyses [30–33]. In addition, a multicenter study in North America and a nationwide study in the United Kingdom, which were not included in any meta-analysis, also revealed no association between PPIs and severe COVID-19 outcomes [34, 35].

In a meta-analysis conducted by Italian researchers led by Zippi M. (2021) [9], no difference in severity or mortality due to COVID-19 was found between patients taking and not taking PPIs.

Another point of view on PPIs during the COVID-19 pandemic is that their administration may lead to the decreased absorption of some vitamins [36].

Table 1. Large studies and meta-analyses examining the association between PPI use and COVID-19

№	Author	Study design	Number of patients	Risk of COVID-19	Severe outcomes and mortality risk of COVID-19
1.	Almario C.V. et al. [23]	Online survey	53 130 (14 855 PPI use once daily)	OR=2,15 (95 % CI 1,90-2,44)	no data
2.	Lee S.W. et al. [1]	Nationwide cohort study	132 216 (14 163 PPI users)	*OR=0,90 (95 % CI 0,78-1,01)	OR=1,90 (95 % CI 1,46-2,77)
3.	Zhou J. et al. [26]	Territory-wide study	4 445 (524 PPI users)	*OR=1,18 (95 % CI 1,13-1,23)	HR=2,73 (95 % CI 2,05-3,64)
4.	Kim H.B. et al. [28]	Meta-analysis	18 109 (no data about PPI users)	*OR=1,26 (95 % CI 0,89-1,79)	OP=1,53 (95 % ДИ 1,20-1,95)/ HR=1,53 (95 % CI 1,20-1,95)
5.	Israelsen S.B. et al. [29]	Nationwide study and meta-analysis	83 224 (4 473 PPI users)	OR=1,08 (95 % CI 1,03-1,13)	*OR=1,0 (95 % CI 0,75-1,32)
6.	Kow C.S. et al. [30]	Meta-analysis	37 372 (14 452 PPI users)	no data	OR=1,46 (95 % CI 1,34-1,60)
7.	Li G.F. et al. [31]	Meta-analysis	318 261 (87 074 PPI users)	*OR=1,33 (95 % CI 0,86-2,07)	OR=1,67 (95 % CI 1,19-2,33)
8.	Kamal F. et al. [32]	Meta-analysis	21 285 (no data about PPI users)	no data	OR=1,79 (95 % CI 1,25-2,57) — severe outcomes OR=2,12 (95 % CI 1,29-3,51) — mortality
9.	Toubasi A.A. et al. [33]	Meta-analysis	195 230 (no data about PPI users)	*OR=1,19 (95 % CI 0,62-2,28)	OR=1,67 (95 % CI 1,41-1,97)
10.	Zippi M. et al. [9]	Meta-analysis	42 086 (no data about PPI users)	no data	*OR=1,65 (95 % CI 0,62-4,35, p=0,314) — severe outcomes *OR=1,77 (95 % CI 0,62-5,03, p=0,286) — mortality

Notes: *study results are not statistically significant; CI — confidence interval, PPI — proton pump inhibitors; HR — hazard ratio; OR — odds ratio

PPIs reduce the bioavailability of vitamin C, which leads to its decreased concentration [37]. This observation is important in the context of COVID-19, considering the data obtained by Feyaerts A.F. et al. (2020) [38] that low doses (0.5–2 g/day) of vitamin C can be used for prevention, and high doses lower the level of inflammatory mediators (interleukin-6 and endothelin-1) in the development of a severe disease. The benefits of vitamin C in high doses for the management of COVID-19 were also shown by Hoang B.X. et al. (2020) [39]. Regarding the role of magnesium and vitamin D in the pathogenesis of coronavirus infection, hypomagnesemia should be considered one of the side effects of PPIs. Magnesium is absorbed in the intestines with the help of two proteins located on the apical membrane of enterocytes — TRPM6 (Transient Receptor Potential Cation Channel Subfamily M Member 6) and TRMP7 (Transient Receptor Potential Cation Channel Subfamily M Member 7) [40–42]. PPIs reduce the activity of TRPM6, which leads to decreased magnesium absorption and hypomagnesemia [43]. Fat-soluble vitamin D requires magnesium to turn into its active form (1,25[OH]2D) [44]. Moreover, more and more studies are demonstrating the link between low vitamin D levels and increased susceptibility to SARS-CoV-2 infection, as well as the severity of the clinical course of this disease [45, 46].

It should be noted that study results can be interpreted in different ways. For example, the information obtained on the decreased anti-inflammatory activity of neutrophils when taking PPIs is regarded by some authors as a factor of aggression, considering the decrease in protection against infectious agents [28]. Other researchers suggest that this phenomenon is a protective factor, since the ability of PPIs to inhibit the production of pro-inflammatory cytokines indicates their ability to suppress the cytokine storm associated with COVID-19 and prevent the development of acute respiratory distress syndrome [30].

Taken together, most of the above studies support the possibility that using PPIs may be a risk factor for a more severe course of COVID-19. However, study results should be interpreted with caution, as some studies provide limited information on the type, dose of studied drug, duration of its administration, concomitant therapy, and indications for PPIs [47]. Most studies are retrospective observational cohorts or case-control studies that are prone to bias even after the necessary adjustments. For example, there is a significant risk of protopathic bias, as in the case of the increased risk of developing pneumonia with PPIs [48]. Protopathic bias, or reverse causality, is a source of bias when exposure conditions change in response to a demonstration of potential consequences. Smoking, NSAIDs, and obesity increase the risk of gastroesophageal reflux and the severity of GERD. GERD patients taking PPIs are at increased risk of developing pneumonia, so an increase in severe COVID-19 outcomes may be due to obesity, smoking, or NSAIDs rather than to the use of PPIs.

It is noteworthy that all studies reporting the effect of PPIs on the severity of COVID-19 differed significantly in their design. First, the study populations were heterogeneous, including different ethnicities and ages (from young to elderly with several comorbidities), as well as hospitalized and non-hospitalized patients. Second, several studies had obvious shortcomings in design. For example, many scientists [49–52] have highlighted the questionable reliability of the sampling method in the online survey of the American population [23]. Based on this work, the American College of Gastroenterology has issued an information letter for gastroenterologists and patients. However, Tarlow B. et al. (2020) [25], having studied the relationship between the use of PPIs and COVID-19 using STARR Stanford Research Repository databases, found no confirmation of the results obtained by Almario C.V. [23]; they concluded that before making changes in practical instructions, a more thorough study of the issue and independent verification of data in reliable medical databases that are not based on surveys is required.

In most studies, the observed associations were relatively weak and were in the zone of "potential bias" (OR < 3, according to observational studies, indicates a weak relationship between two events, which is multifactorial but not causal in such cases). Many factors are known to have an effect on COVID-19 outcomes, including the male sex, age, geographic region, and comorbidities [53], so results should be interpreted in relation to a specific population. For example, Gao M. et al. (2021) [54] reported that patients with BMI >23 kg/m^2 have a linear increase in the risk of severe COVID-19, leading to death. Perez-Araluce R. et al. (2021) [55] found that adherence to a Mediterranean diet was associated with a lower risk of COVID-19. Therefore, BMI and the effect of a diet on risk and disease severity should not be ignored, as has been observed in some studies.

The strongest link between PPIs and severe COVID-19 outcomes was found in Asia. The first possible mechanism is that the use of PPIs may suppress gastric acid secretion to a greater extent in Asians due to lower parietal cell mass. Secondly, the frequency of cytochrome P450 2C19 genetic polymorphism is higher in Asians compared to the representatives of other regions, which facilitates the slowing down of PPI metabolism, and, therefore, inhibition of gastric acidity may be stronger [56]. Finally, the prevalence of *Helicobacter pylori* infection in Asia is higher than in Europe or North America [57]. Therefore, PPIs may inhibit gastric acid secretion more strongly. The study by Mena G.E. et al. (2021) [58], which was published in Science (Journal of the American Association for the Advancement of Science), demonstrated that socioeconomic status has an effect on COVID-19-related mortality; this fact was also not considered in most of the studies mentioned.

According to Burchill E. et al. (2021) [59], COVID-19 has a direct or indirect effect on the gut microbiota, suggesting a difference in immune response to the pathogen. Wearing masks, hygiene practices, and social distancing also affect COVID-19 outcomes. Consideration of all potential risk factors, such as BMI, diet, geographic area, socioeconomic status, gut microbiota status, degree of reducing social interaction, and other yet unidentified causes, seems impossible in real clinical practice; therefore, conclusions about causal relationships between the use of PPIs and COVID-19 should be taken with caution.

PPIs do not worsen the course of COVID-19

Several studies based on experimental data were performed that have confirmed the benefits of using PPIs in COVID-19 [24]. Tastemur S. et al. (2020) [60] suggested that PPIs may play a role in the prevention and management of COVID-19 due to their anti-inflammatory, immunomodulatory, and antifibrotic properties.

Ray A. et al. (2020) [61], based on available research papers, proposed using PPIs for therapeutic purposes in the management of COVID-19 (Fig. 1). An *in vitro* study demonstrated that these drugs can inhibit the production of pro-inflammatory cytokines such as interleukin-6, interleukin-8 and tumor necrosis factor-α [62]. In addition, there is evidence that supports the protective role of omeprazole and lansoprazole in reducing oxidative stress in gastric epithelial and endothelial cells. Lansoprazole has been shown to reduce the number of monocytes expressing ICAM-1 (Inter-Cellular Adhesion Molecule 1) in peripheral blood. According to the *in vivo* study, omeprazole reduced the production of cytokines by duodenal epithelial cells [61].

PPIs can also regulate fibrogenesis, exhibiting antifibrotic properties by inhibiting molecules such as fibronectin, collagen, and matrix metalloproteinase enzymes [63]. Many studies associate the use of PPIs with clinical improvement in patients with idiopathic pulmonary fibrosis. These results are important as they involve the use of antifibrotic agents in the management of COVID-19 [61].

Vacuolar adenosine triphosphatase (V-ATPase), which is located on the plasma membrane and on the surface of acidic organelles such as lysosomes and endosomes, is one of the key factors controlling vesicular pH [64]. Endosomal acidification mediated by V-ATPase is an essential step for the entry of viruses, including coronaviruses. The use of PPIs leads to the acidification of the cytosol and alkalinization of endolysosomes [65]. *In vitro* screening of 60 FDA-approved drugs revealed the antiviral activity of omeprazole, which justifies its use in COVID-19 [66]. It was proved that taking omeprazole, along with vonoprazan, is associated with increased pH within the endosomes and the Golgi apparatus. This is thought to occur either by blocking V-ATPase pumps or by acting as a pH buffer.

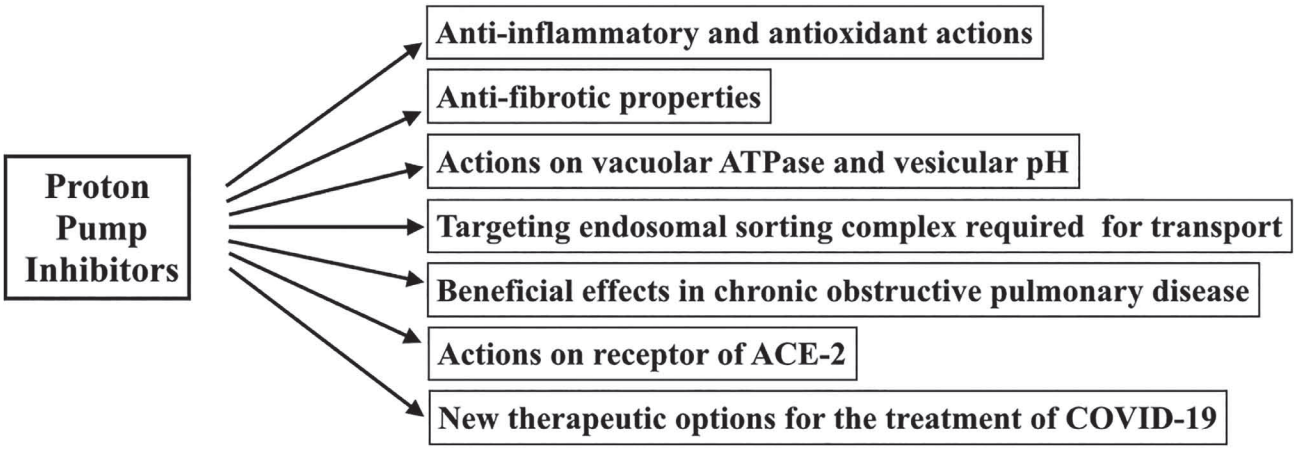

Figure 1. *Potential beneficial effects of proton pump inhibitors. (adapt. from Ray A., et al. [61])*
Notes: ACE-2 — angiotensin-converting enzyme 2, ATPase — adenosine triphosphatases

Such changes in pH will interfere with the processing of the spike protein (S1) by endosomal proteases and limit the spread of SARS-CoV-2 infection [61].

As mentioned earlier, SARS-CoV-2 uses ACE2 as a receptor to enter the human body [12], while the activity of ACE2 depends on pH level. A pH in the range of 7–7.5 is considered optimal for its functioning [67]. It is known that PPIs tend to alkalize the intraluminal environment by inhibiting V-ATPase. Since a significant decrease in the activity of ACE2 receptors occurs at pH above 7.5, using PPIs that increase pH level may prevent the penetration of SARS-CoV-2 into cells [61].

In addition to the direct antiviral activity, PPIs can also be used together with other therapeutic agents. In an *in silico* study, omeprazole increased the efficacy of aprotinin — a serine protease inhibitor, and remdesivir by 2.7 and 10 times, respectively [68]. Therefore, the combination of aprotinin and remdesivir with omeprazole may be a potential candidate for the management of COVID-19. The combination of PPIs with NSAIDs with antiviral properties, such as indomethacin, was also proposed as a new therapeutic option for COVID-19 [69].

Therefore, the antiviral mechanism of PPIs needs further exploration in clinical studies in order to confirm whether PPIs can be used in the management of COVID-19.

Conclusion

Currently, there is uncertainty regarding the safety of using PPIs during the COVID-19 pandemic, as available data demonstrate both protective and adverse effects. Taken together, most of the above studies and meta-analyses support the possibility that the use of PPIs may be a risk factor for a more severe course of COVID-19. However, these results should be interpreted with caution and with consideration of different study designs, limited information on concomitant treatment, and other risk factors for disease severity, indications for the use of PPIs, and the risk of protopathic bias. There is evidence that PPIs may play a positive role in the prevention and management of COVID-19 due to their antiviral, immunomodulatory, and antifibrotic properties. To provide more convincing evidence, further randomized controlled trials and prospective studies are required, considering that the effects of PPIs are likely to influence clinical decision-making in COVID-19 cases.

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ОСТРЫЙ ОСТЕОПОРЕТИЧЕСКИЙ ПЕРЕЛОМ ПОЗВОНОЧНИКА. ЧАСТЬ 1. ОПРЕДЕЛЕНИЯ, КЛИНИЧЕСКАЯ КАРТИНА, ОЦЕНКА БОЛЕВОГО СИНДРОМА, ДИАГНОСТИЧЕСКАЯ ВИЗУАЛИЗАЦИЯ, ВВЕДЕНИЕ В ДИФФЕРЕНЦИАЛЬНЫЙ ДИАГНОЗ

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Acute Osteoporotic Vertebral Fracture. Part 1. Definitions, Clinical Presentation, Pain Assessment, Diagnostic Imaging, Introduction to Differential Diagnosis

Резюме

Остеопороз — широко распространенное метаболическое заболевание скелета среди лиц 50 лет и старше. Значимым проявлением заболевания являются остеопоретические переломы, которые могут оказывать существенное влияние на качество жизни. Целью данной публикации является рассмотрение подходов к ведению пациентов с острым остеопоретическим переломом. Данная работа разделена на две части. В первой части рассматриваются общие сведения об остеопорозе, варианты течения остеопоретического перелома, дифференциальный

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диагноз болевого синдрома, методы визуализации переломов, дифференциальная диагностика остеопороза. Во второй части работы рассматриваются особенности дифференциальной диагностики остеопоретического перелома по данным визуализирующих методов, немедикаментозные, медикаментозные и хирургические методы лечения.

Ключевые слова: *остеопоретический перелом, остеопороз, перелом позвоночника*

Конфликт интересов

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

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Abstract

Osteoporosis is a widespread metabolic disease of the skeleton among the elderly. Osteoporotic fractures are significant manifestation of the disease, which can substantially affect the quality of life. The purpose of this article is to review approaches to the management of patients with acute osteoporotic fracture. This article consists of two parts. The first part reviews general information about osteoporosis, clinical course of osteoporotic fracture, differential diagnosis of pain syndrome, methods of visualization of fractures, differential diagnosis of osteoporosis. In the second part, we discuss differential diagnosis of osteoporotic fracture according to the data of imaging methods, non-pharmacologic, pharmacologic and surgical methods of treatment.

Key words: *osteoporotic fracture, osteoporosis, vertebral fracture*

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25(OH)D — 25-hydroxycalciferol, CT — computed tomography, DXA — dual energy X-ray absorptiometry, ESR — erythrocyte sedimentation rate, GIT — gastrointestinal tract, MPS — myofascial pain syndrome, MRI — magnetic resonance imaging, OP fracture — osteoporotic fracture, STIR — Short Tau Inversion Recovery (inversion recovery spin echo sequence, fat suppression mode)

Introduction

Osteoporosis is a metabolic disease of the skeleton characterized by decreasing bone mass, impaired micro-architectonics of bone tissue and, as a result, minimal trauma fractures [1].

Two opposite processes constantly take place in bone tissue: bone formation by osteoblasts, and bone resorption determined by osteoclasts. Osteoblasts are derived from immature progenitor cells in periosteum and bone marrow; they produce and mineralize bone matrix composed primarily of type I collagen. Insulin-like growth factor II and transforming growth factor-beta stimulate the formation of bone tissue by mature osteoblasts. Osteoblasts surrounded by matrix transform into osteocytes that stop participating in the processes of mineralization and matrix synthesis, however, participate in the paracrine regulation of active osteoblasts, and also, according to some data, inhibit the formation of osteoclasts. Osteoclasts are derived from cells of monocyte-macrophage series. Osteoclast activity is regulated by: parathyroid hormone, calcitonin and interleukin-6; soluble factors such as macrophage colony stimulating factor (deficiency of this factor causes osteopetrosis); transcription factors. Maximum bone mass in humans is observed at the age of about 30 years; then there is a gradual decrease in bone mass [1, 2].

Dysregulated bone formation processes can result in severe skeletal disorders characterized by decreased (e.g., osteoporosis) or increased (e.g., osteopetrosis) bone mass. Bone tissue remodeling depends on the level of estrogens, the state of phosphorus and calcium metabolism, the level of parathyroid hormone, vitamin D, growth hormone, calcitonin, thyroid hormones, glucocorticoids, senescence and senescence-associated secretory phenotype, etc. [1, 3].

Senescence and decreased gonadal function are the most important factors in the development of osteoporosis. Estrogen deficiency leads to bone loss not only in postmenopausal women, but also in men. Results of studies conducted revealed that the rate of bone loss increases significantly in the first few years after menopause onset. Estrogen deficiency leads to increased number of osteoclasts and decreased number of osteoblasts what, in general, results in bone mass loss. The risk of fractures in post-menopausal period is inversely related to estrogen levels. Osteoblasts, osteocytes and osteoclasts express estrogen receptors. In addition, estrogen has indirect effect on bones through cytokines and paracrine factors [3].

Senile osteoporosis is associated with both excessive activity of osteoclasts and progressively decreasing number of osteoblasts. At the age of 30+, bone resorption exceeds bone formation; it results in osteopenia and, in severe cases, in osteoporosis. Cortical bone loss in women amounts to 30–40 %, and cancellous bone loss — to 50 %; these values for men are 15–20 % and 25–30 %, respectively. Senescence leads to thinning of cortical layer, increased porosity of cortical tissue, and thinning of trabeculae. [3]

Calcium, vitamin D and parathyroid hormone are involved in the regulation of bone formation. Calcium deficiency in the diet or its malabsorption in the intestine can lead to secondary hyperparathyroidism. Parathyroid hormone is secreted in response to low serum calcium level. It increases bone resorption (what, in its turn, increases plasma calcium levels), reduces calcium excretion by kidneys, and increases renal production of 1.25-dihydroxyvitamin D (active hormonal form of vitamin D) that increases calcium and phosphorus absorption, and inhibits synthesis of parathyroid hormone. Vitamin D deficiency is common among the elderly and can result in secondary hyperparathyroidism due to reduced intestinal absorption of calcium [3].

Generally, all effects on bone tissue metabolism are realized via main regulation systems of osteoblastogenesis (canonical Wnt signaling pathway) and osteoclastogenesis (RANKL/RANK/OPG pathway). Changes in the expression of molecules that regulate osteoblastogenesis and osteoclastogenesis due to aging and the negative influence of other factors lead to decreased bone strength that can have presentation as impaired internal microarchitectonics, decreased bone mass and, as a result, minimal trauma fractures [1].

In Russia, 34 % of women and 27 % of men 50+ are diagnosed with osteoporosis, and the incidence of osteopenia is 43 and 44 %, respectively. The incidence of osteoporosis increases with age [4].

Osteoporosis may be primary or secondary. Primary osteoporosis develops as a separate disease that is not associated with other causes of reduced skeletal bone strength. 95 % of osteoporosis in postmenopausal women (postmenopausal osteoporosis) and 80 % of osteoporosis in men 50+ are cases of primary osteoporosis [5]. Primary osteoporosis also includes idiopathic osteoporosis that develops in women before menopause, in men under the age of 50, and juvenile osteoporosis (in children under the age of 18). Idiopathic and juvenile types of primary osteoporosis are extremely rare.

Secondary osteoporosis is caused by various diseases or conditions, as well as medications. The list of possible causes of secondary osteoporosis includes more than 70 diseases and pathological conditions and at least 20 drug categories and separate medications. 5 % of osteoporosis in women and 20 % in men correspond to secondary osteoporosis [5].

Osteoporosis of mixed genesis is also possible. For example, women with primary postmenopausal osteoporosis may develop secondary glucocorticoid-induced osteoporosis associated with administration of glucocorticoids.

The most significant clinical sign of osteoporosis is an osteoporotic fracture (OP fracture). Fractures with underlying osteoporosis occur due to a minimal trauma (for example, falls from standing height, weight lifting, or even coughing, sneezing, awkward turn/flexion of trunk, bumpy ride in a car, etc.), therefore, such fractures are also called low energy, or low trauma, or pathological. The term “pathological fracture” refers to the fractures that result from a disease, not from a traumatic effect, for example, a fracture in patients with metastatic skeletal disease, Paget’s disease, etc., thus, a fracture in osteoporosis is also a pathological one [1].

OP fractures occur most often in certain areas of the skeleton, therefore, they are called “marker fractures” [6]. The typical fractures in osteoporosis are those of the proximal femur (“femoral neck”), distal radial metaphysis, proximal humerus, and vertebral bodies. Fractures of ribs, pelvic bones, and tibia are also possible. The vertebral compression fractures are the most common type of OP fracture. [7]. They tend to happen in the mid-thoracic and thoracolumbar spine (Th7 — L2) [8]. Vertebral fractures due to osteoporosis are diagnosed in 7–12 % of men and 7–16 % of women 50+. According to several reports, the incidence of such fractures reaches 30 % in women 75+ [9]. A history of OP fracture is a risk factor for subsequent fractures. Approximately 19 % of patients with vertebral compression fractures will have another fracture next year [10].

Clinical presentation of OP vertebral fracture

There are two types of vertebral damage in osteoporosis: acute compression fracture of vertebral body, and chronic compression deformity.

Chronic compression deformity

Slow gradual compression of vertebrae ("delayed fracture") is asymptomatic or low symptomatic for a long time. Patients complain of aching pain or a sensation of heaviness in the lumbar and/or lower thoracic regions of moderate or slight intensity, rapid back fatigue in a standing position [11]. As a rule, two or three vertebrae are involved in deformation, and in this case, there is no significant deformation of a whole spinal column. Such fractures often become incidental findings during imaging studies (radiography, computed tomography (CT), magnetic resonance imaging (MRI)).

Multiple compression or complete compression of single vertebrae results in a gradual decrease in patient's height, development of thoracic kyphosis and other deformities of trunk. Most patients develop more or less significant pain syndrome and have restrictions in daily motor performance.

Back pain in chronic compression deformity is primarily represented by myotonic and vertebral pain syndromes. Vertebral deformity is also accompanied by structural changes in intervertebral discs, facet joints, ligaments; involvement of spinal cord roots, narrowing of spinal canal, and other disorders are also possible. In this regard, discogenic, radicular, facet and other pain syndromes may develop.

Acute compression vertebral fracture

Acute compression vertebral fracture is diagnosed mainly in women 15–20 years after menopause [11]. An acute fracture of vertebral body, like other OP fractures, is a result of a low energy impact. Unlike OP fractures of other localizations, most vertebral fractures are caused not by a fall, but by a compression that occurs during lifting weights, or changing body position, or during routine daily activities; there is often no indication of a traumatic moment [11].

Clinical presentation of an acute fracture

This fracture is accompanied by sharp pain in the area of damaged vertebra [6]. Vertebrae with maximum axial load (T10-12 and L1-2) are typically involved [11]. If thoracic vertebrae are damaged, girdle pain is possible; if lumbar vertebrae are involved, pain may irradiate to the anterior part of abdomen or to the posterior superior iliac spine; it is especially typical for L1 fracture [6, 11]. Pain irradiation to the limb caused by an OP fracture is rare, unlike pain caused by intervertebral hernias, however, it is possible if a nerve root is compressed by bone fragments or a simultaneous protrusion of an intervertebral disc.

Pain in acute fracture, as in the case of chronic compression deformity, usually includes vertebral and myotonic components. This pain is caused by periosteal hemorrhage, a large number of simultaneously occurring microfractures of trabeculae, and spasm of paravertebral muscles [12]. Other types of pain are also possible depending on the degree of damage and the nature of the impact of damaged vertebra on the surrounding structures.

Pain severity can be different: from moderate and tolerable that resolves spontaneously to pronounced that requires hospitalization and potent pain medications. Acute pain lasts, as a rule, for 1–2 weeks, then it gradually decreases during 2–3 months [11]. Longer duration of pain may indicate a non-healing fracture and/or progressive compression.

Pain after a fracture occurred can be either acute and paroxysmal with certain movements, or monotonous and dull. Spinal extension, sitting position, attempts to lie on one side from a sitting position, turning in bed, and the Valsalva maneuver often aggravate pain and may be accompanied by muscle spasms [8].

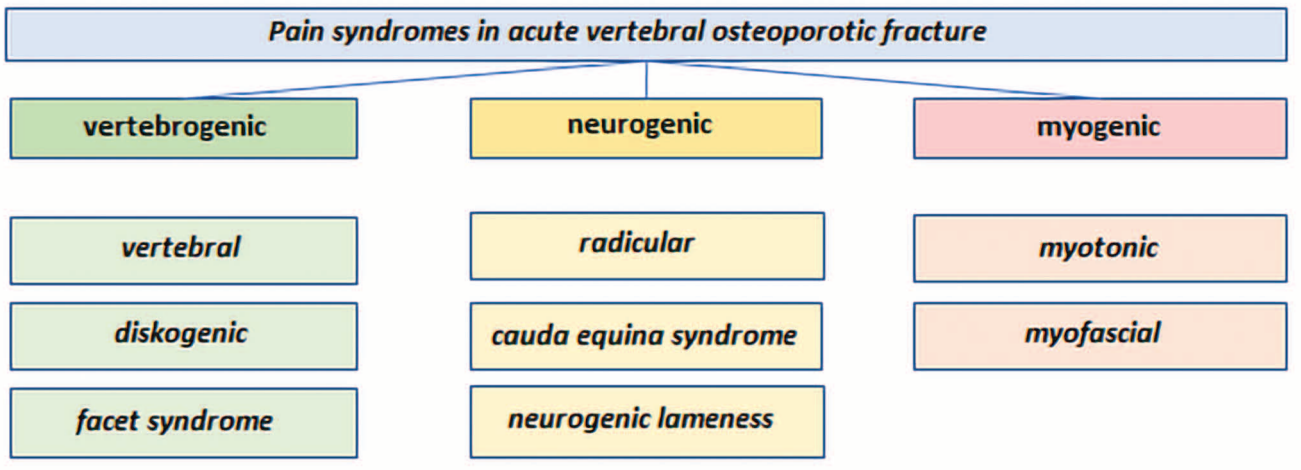
Palpation and/or percussion of spinous processes and paravertebral structures may be painful [8]. Palpation is carried out with a patient standing, with moderate pressure along the midvertebral line. Percussion is also performed with a patient standing. For percussion, a physician positions the palm of one hand over the patient's spine, and taps on it with the closed fist of the other hand. Tenderness on palpation/percussion indicates possible vertebral injury and is a highly specific clinical sign.

A patient also requires neurological examination to exclude possible compression of roots or spinal cord. Sensory deficits and weakness in limbs may indicate root compression or the presence of bone fragments in spinal canal; in such cases urgent surgical treatment may be required.

Differential diagnosis of pain syndrome in acute OP vertebral fracture

Vertebral and myotonic syndromes usually predominate in the clinical presentation of an acute OP fracture [13], however, there can be other pain syndromes that may require different treatment approaches. Pain status of each patient should be detailed as much as possible in order to select proper disease management.

Three groups of pain syndromes are routinely distinguished when it comes to spine diseases: vertebrogenic, neurological and myologic (scheme 1) [14].



Scheme 1. *Pain syndromes in acute vertebral osteoporotic fracture*

The term "vertebrogenic pain" describes pain associated with any pathology of the spine itself. Pronounced structural changes in spine, in turn, can lead to neurological disorders (radicular syndrome, cauda syndrome, neurogenic lameness, myelopathy) that are characterized by neurological pain syndromes. It is also reasonable to identify myogenic pain syndromes associated with the reaction of soft skeleton to structural changes in spine.

Vertebral pain develops with the direct damage to vertebrae. In addition to an OP-fracture, such pain can be caused by an infectious lesion of vertebra (osteomyelitis, tuberculosis) or metastasis. By nature, it is pain with a mechanical rhythm that is accompanied by tenderness of one or two spinous processes during palpation/percussion [8].

Discogenic pain originates from damaged intervertebral disc. This pain is described as extradermatomal (i.e., with no definite localization in a dermatome). Discogenic pain is most often observed in lumbar region; its typical sign is the bilateral pain in lumbar region that extends to buttocks [14, 15]. The pain is aggravated during spine flexion (forward lean), rotation, prolonged sitting or standing, as well as coughing/sneezing/straining, and is relieved in lying position. Typical signs are pain provocation during vibration load (tuning fork test) and the so-called "centralization" (onset/intensification of midline back pain that is provoked by flexion) [14].

Arthrogenic (facet) pain indicates arthrosis and/or overload of facet (zygapophyseal) joints. Its sign is a dull monotonous diffuse pain that aggravates after long standing, with extension and rotation of spine (during these movements, there occurs a strong tension of joint capsules and decrease in the volume of joint with close contact of articular surfaces), and relieves at sitting, walking, slight bending. Facet pain that originates from lumbar region often irradiates to the proximal thigh mimicking radicular pain syndrome, however, unlike it, facet pain never extends below the popliteal fossa. This pain may also irradiate to buttocks, groin, lower abdomen, and sometimes even to perineum [16]. Diagnostic block of facet joints is often used for the differential diagnosis of arthrogenic pain.

Radicular (neuropathic) pain is unilateral, with irradiation to leg often below the knee. This pain spreads along the dermatome (Figure 1), is asymmetrical (unilateral), is accompanied by sensory (numbness, paresthesia) and motor (paresis) disorders in the area of innervation by the corresponding root. Pain in limb is often the single sign of radiculopathy [15]. Table 1 presents the clinical features of radicular pain.

Cauda syndrome is a cauda equina syndrome. It is characterized by severe back pain spreading to both legs (symmetrically or asymmetrically), with the development of weakness and impaired sensitivity in legs and S-dermatomes (intergluteal fold), as well as impaired pelvic functions [19].

Neurogenic lameness develops with spinal stenosis (narrowing of spinal canal) that leads to the compression of nerve structures before their exit the intervertebral foramina. This causes lumbar pain; heaviness and weakness in legs; numbness, paresthesia and weakness in lower part of legs. Painful sensations usually appear when walking or standing for a long time and disappear after a short rest and when leaning forward [14].

Myofascial and myotonic pain syndromes. Changes in muscles can both be a separate cause of back pain, and accompany pain syndromes of other types what is a very common situation. Myofascial pain syndrome (MPS) is characterized by the formation of painful tight areas in muscles that are a result of acute or chronic overload of separate muscles. These areas are called

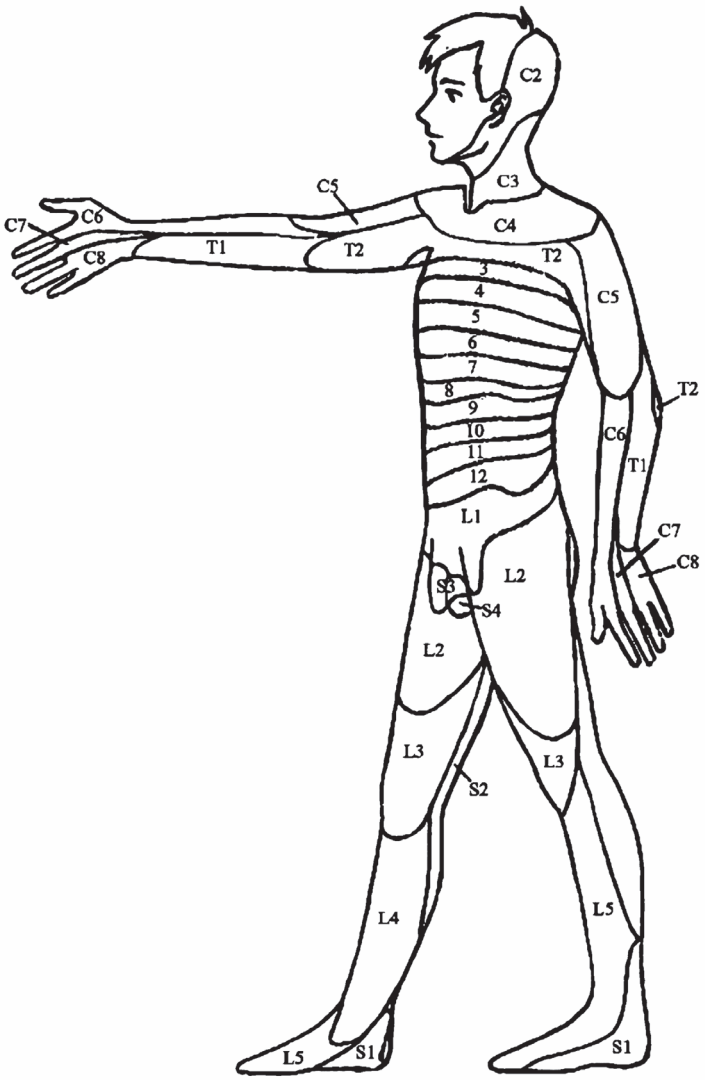


Figure 1. *Human dermatomes. According to Hawkes H.C., et al. (2019) [17]. Illustrator A.K. Rudykh*

Table 1. *Characteristics of radicular pain (adapted from Wolf J.K. (1981) [18], with additions).*

Radix	Site of pain	Irradiation	Sensory Disorders	Muscle weakness	Reflex alterations
Th	Girdle pain and dysesthesia in the area of the corresponding dermatomes				
L1	Below the groin fold	Groin area	Groin area	Hip flexion	Cremasteric
L2	Middle third of the anterior thigh	Groin area, Anterior thigh	Anterior thigh	Hip flexion, hip adduction	Adductor
L3	Anterior thigh and knee	Anterior thigh, knee	Distal anteromedial thigh, knee area	Lower leg extension, thigh flexion and adduction	Knee, Adductor
L4	Middle part of the lower leg and ankle	Anterior thigh, knee	Medial thigh	Lower leg extension, thigh flexion and adduction	Adductor
L5	Buttocks, posterolateral thigh, lower leg and foot	Posterolateral surface of the thigh, lateral surface of the lower leg, medial edge of the foot up to I — II fingers	Lateral surface of the lower leg, dorsum of the foot, I — II toes	Dorsiflexion of the foot (flap foot) and big toe, hip extension	No
S1	Posterior surface of the leg and buttocks	The back of the thigh and lower leg, lateral edge of the foot	Posterolateral surface of the leg, the lateral edge of the foot	Plantar flexion of the foot and toes, flexion of the lower leg and thigh	Achilles

trigger points, or myofascial nodules; the outdated name of "myogelosis" is also often observed. MPS is characterized by local "spot" and/or regional pain while its area often does not coincide with the topographic boundaries of the trigger muscle and can extend far beyond its limits. MPS results in asymmetric restriction of movements. When the affected muscle is stretched, the pain decreases. Main diagnostic method is palpation when sharply painful trigger points can be found in certain areas of muscle. When trigger points are stimulated, patient's habitual pain restarts or increases [20]. Myofascial pain can be debilitating, persisting for many years, and has a significant impact on motor activity and, in general, on patient's quality of life. MPS associated with the large square muscle of lower back and with piriformis muscle is more often detected with underlying structural damage of lower thoracic and lumbar regions [21, 22].

Myotonic pain, on the contrary, is more extensive, dull, aching, and dragging. It is triggered by movements and increases significantly in positions when the muscles surrounding the spinal column are stretched. Pain can also increase with prolonged staying in one posture (during driving a car, a long flight, etc.). Paravertebral muscles are tight, tense, and painful on palpation [21]. Secondary muscle pain can become chronic and persist independently, even after the initial cause disappears.

Diagnosis

Diagnostic search in a patient with an acute OP fracture involves the verification and classification of a fracture itself, as well as the differential diagnosis of its causes.

Fracture verification

Visualization methods.

To verify an acute OP fracture, radiography, computed tomography (CT) and magnetic resonance imaging (MRI) are used. Use of these methods is presented in Figures 2 and 3.

A patient with a suspected acute vertebral body compression fracture should first have an X-ray of the thoracic and/or lumbar spine.

X-ray is a fast, affordable, and low-cost method [23]. It allows identifying the deformity of vertebral body, however, not the age of the fracture what is especially important in cases when healing should be evaluated over time, as well as in situations when the fracture occurred with already existing multiple deformities of other vertebrae. In addition, X-ray demonstrates only bone structures of the spine; it does not allow assessing the state of other structures (discs, ligaments, spinal canal), roots and spinal cord.

CT is also a fast and fairly affordable method [23]. Unlike X-ray, CT provides more detailed information about the state of the bone structures of spine, allowing not only to assess the anatomical integrity, but also to find compression deformities of a separate part of vertebra. In addition, CT evaluates the condition of spinal canal and its contents. Therefore, CT may be the method of choice if a fracture is suspected. Disadvantages of CT include high cost and predominant visualization of bone structures.

MRI demonstrates in detail all the structures of spine, spinal cord and roots, and also allows assessing the stage and changes in fracture healing over time based on the parameters of bone edema (Figures 2c and 2d) [23]. From this point of view, MRI is preferable to radiography and CT, however, the use of MRI is limited by cost, inequal availability, and contraindications. Moreover, one should keep in mind that spinal MRI is a long examination that requires about 30 minutes when a patient should be motionless in the tomograph. For a patient in acute fracture stage and with severe pain, this may be

Thus, X-ray and/or CT help to quickly diagnose a vertebral fracture and to obtain approximate information about the state of surrounding structures. If the results of these examinations and/or clinical presentation give the reason to suspect significant damage to intervertebral discs, nerve roots, spinal cord, etc., associated with a fracture, then MRI is mandatory. In addition, indications for MRI include the ineffectiveness of conservative treatment, progression of symptoms, and the need to assess the fracture over time.

Classification of OP fractures

Both acute and chronic OP fractures are classified according to their shape and grade.

According to the shape, biconcave ("medium deformation"), wedge-shaped ("anterior deformation"), and compression ("posterior deformation", "compression deformation") fractures are distinguished (Figure 4). [18] Anterior wedge-shaped deformity is the most common [8].

Depending on the decrease of vertebral height, 3 grades of fractures are distinguished: Grade 1 — decrease in vertebral height by 20–25 %, Grade 2 — by 25–40 %, Grade 3 — >40 % [18]. This classification is convenient and illustrative, however, it gives no idea of the changes in the spatial geometry of vertebra after fracture, thus, creating a misleading impression of "damage in one plane". Besides, keep in mind the possibility of combined compression and comminuted injuries in acute OP fracture that can cause neurological complications.

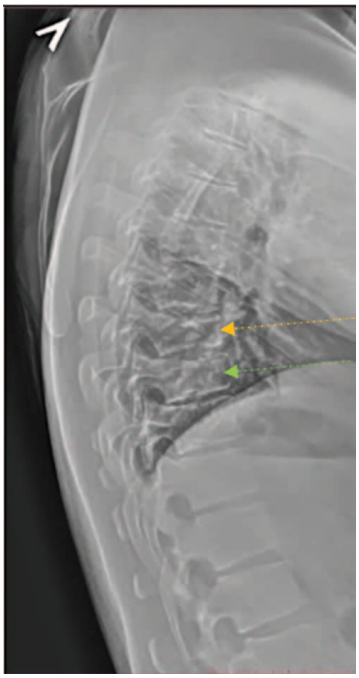


Figure 2а. *Digital radiography of the thoracic spine: acute compression fracture of the T8 (yellow arrow), T9 (green arrow) vertebrae: decrease in the height of the ventral part of the body, wedge-shaped vertebral body*

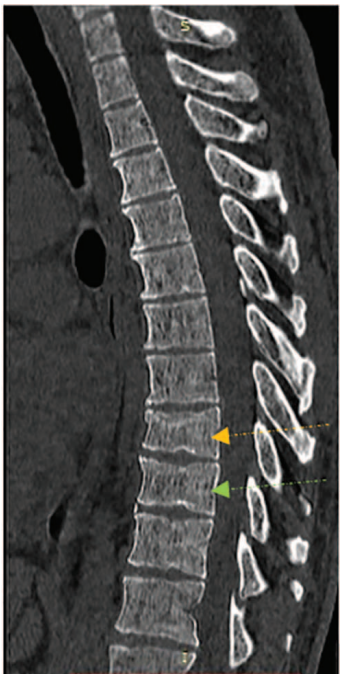


Figure 2б. *CT of the thoracic spine, sagittal reconstruction. Acute compression fracture of the Th8 (yellow arrow) and Th9 (green arrow) vertebrae: decrease in the height of the ventral part of the bodies, wedge-shaped shape of the vertebral bodies, fracture line can be traced in the compression zone as well as compaction of the spongy part of the bodies, a bony «notch» along the ventral surface as a sign of acute compression in the Th8 vertebra*

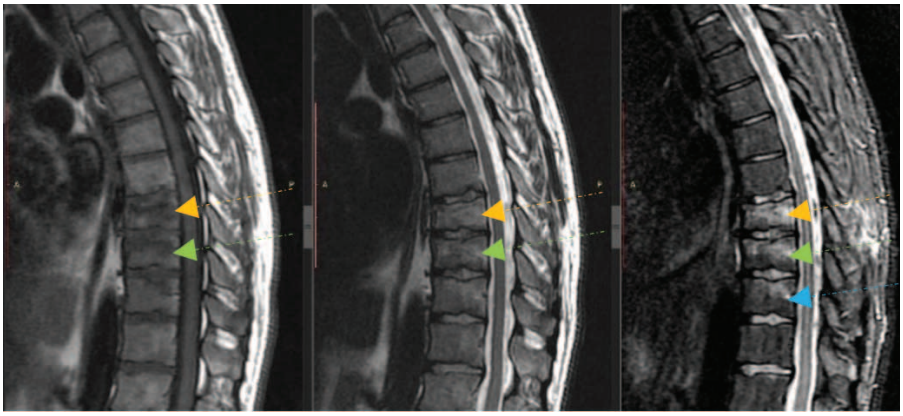


Figure 2в. *MRI of the thoracic spine: acute compression fracture of the T8 (yellow arrow), T9 (green arrow) vertebrae: decrease in the height of the ventral part of the bodies, wedge-shaped shape of the vertebral bodies, decreased signal intensity in T1 WI, an increased intensity in T2 WI, significantly increased signal intensity in STIR mode from the body as a manifestation of an acute bone edema on the background of a "fresh" fracture. Similar changes in the body of the Th10 vertebra (blue arrow), as a reflection of bone contusion or incipient compression fracture.*

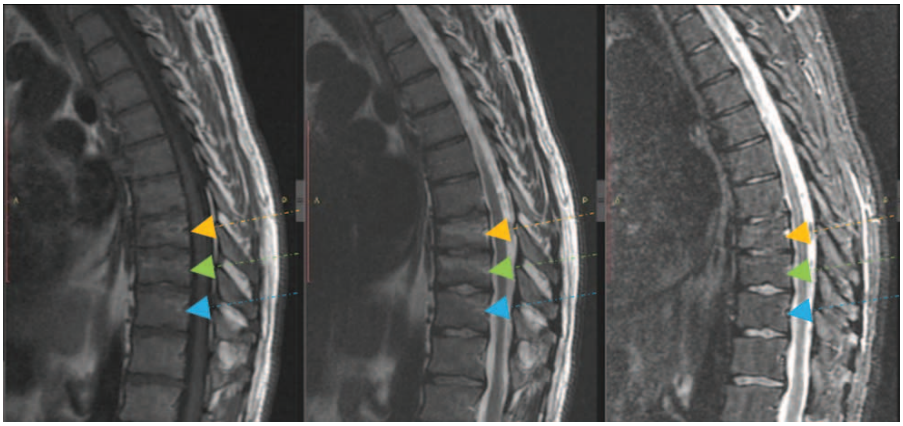
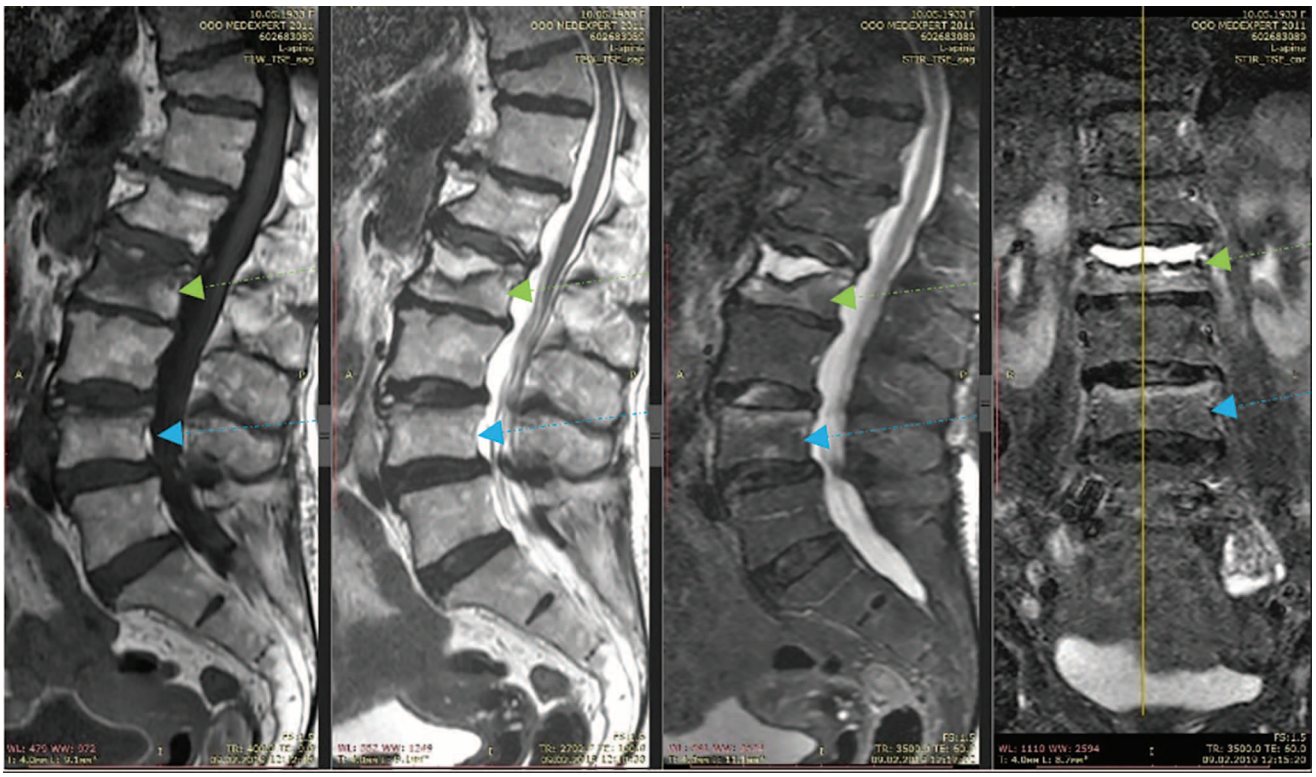


Figure 2г. *MRI of the thoracic spine 3.5 months after the fracture. Signs of fracture consolidation and disappearance of bone edema: increased signal intensity from the body in T1 WI, iso-intensive or slightly hyperintense signal from the body in T2 WI, iso-intensive signal from the vertebral bodies in STIR mode as a reflection of the of edema resolution and replacement of this area with adipose tissue of the bone marrow. Regression of bone edema of the Th10 vertebra (blue arrow), the fracture did not develop, the vertebral body is not deformed*

Picture 2. *Acute compression fracture of the Th8, Th9, Th10 vertebrae*
Note: CT — computed tomography, MRI — magnetic resonance imaging, WI — weighted image, STIR — short tau inversion recovery)



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Picture 3 a, b, c, d. *MRI of the lumbar spine. Acute compression fracture of the L2 vertebral body (green arrow)*

Picture 3a. *Significantly decreased intensity of the signal from the vertebral body (green arrow) in the area of bone edema in T1 WI. Signal intensity in the line of bone compression and compaction of bone tissue is even lower*

Picture 3b. *zone of increased signal intensity from the preserved part of the vertebral body (green arrow) as a manifestation of bone edema, significantly increased signal intensity from the fracture zone, as a manifestation of hemorrhage in the fracture zone in T2-WI (sagittal)*

Pictures 3c and 3d. *Significantly increased signal intensity from the zone of fracture (green arrow), hemorrhage and bone edema (sagittal and frontal sections) in STIR mode*

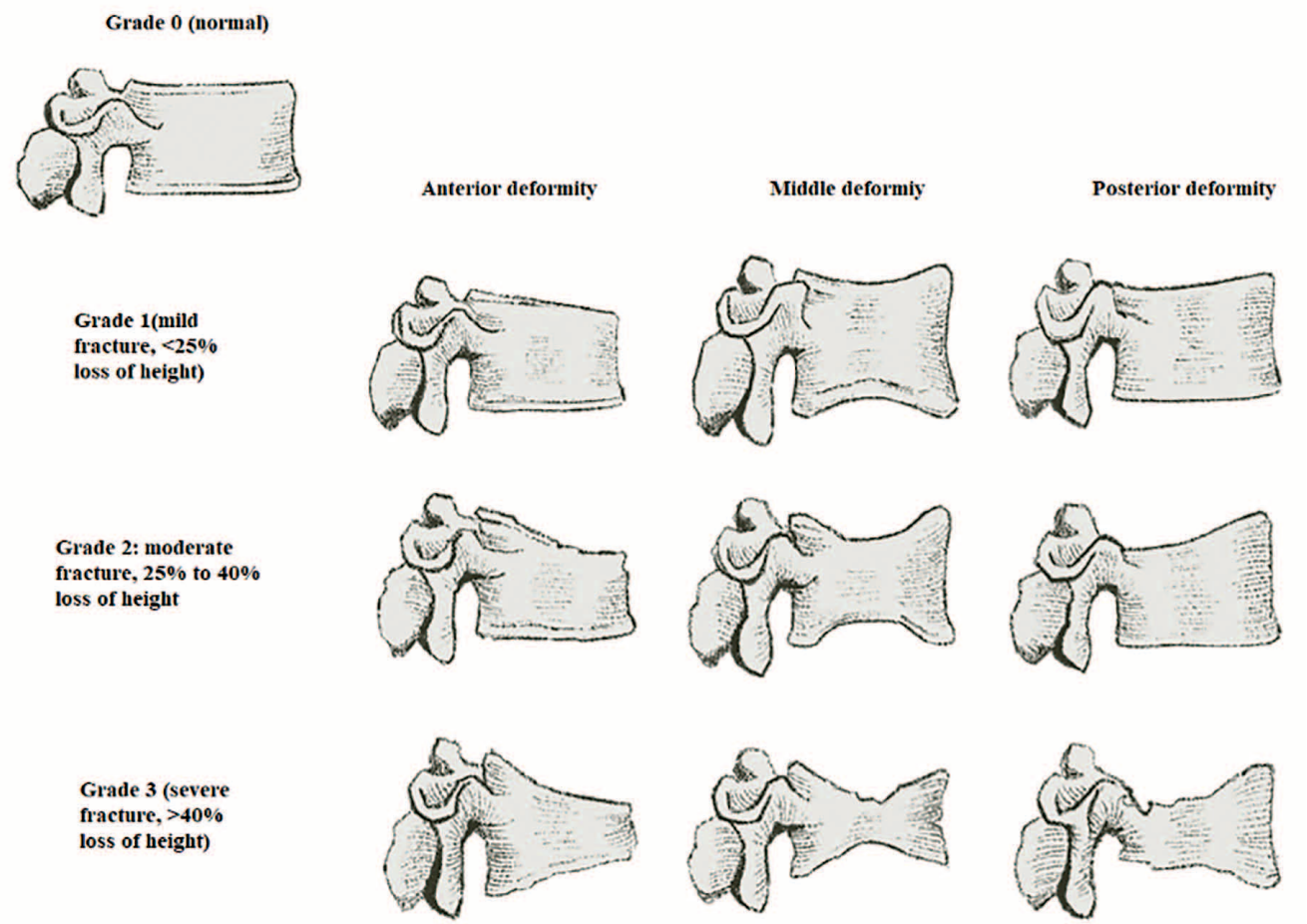
Minimal compression fracture of the superior part of the body of the L4 vertebra (blue arrow): decreased signal intensity from the subcortical parts of the body in T1 WI, T2 WI and an increased signal intensity in STIR mode from this area

Picture 3. *Acute compression fracture of the L2 vertebral body*
Note: MRI — magnetic resonance imaging, WI — weighted image, STIR — short tau inversion recovery)

Differential diagnosis of osteoporosis

A routine method for diagnosing osteoporosis is X-ray densitometry (dual energy X-ray absorptiometry, DXA). The measurement of bone density in the region of lumbar vertebrae, as well as in proximal femur is considered to be the most informative method. Several parameters are calculated including the absolute bone density value (grams per square centimeter), as well as the T-score (difference between patient's bone density and the data in the reference base for the corresponding sex, race and age, expressed as standard deviations). The diagnosis of osteoporosis in individuals 50+ is based on the T-score that indicates how much patient's bone density differs from the normal value. Osteoporosis is diagnosed if this value in L1–L4 region and proximal femur is –2.5 standard deviations and lower [1].

In the case of compression deformities, especially multiple and accompanied by spinal curvature progressing over many years, the diagnosis of osteoporosis is not a challenge: results of spinal X-ray, examination findings and history are sufficient. However, one should understand that in patients with severe compression deformities, DXA in lumbar region is often false negative, i.e. bone density values are within normal or even elevated. First of all, this is due to the fact that the sagging vertebra becomes more compact



Picture 4. *Classification of vertebral deformities. According to H.K. Genant (1993) [24]. Illustrator A.K. Rudykh*

and is represented as an area of increased density. Moreover, aortic calcification, endplate sclerosis, ligament calcification, osteophyte proliferation, and other morphological changes that develop with age can contribute to the misrepresentation of results [23]. In such cases, one is recommended to focus on the parameters in the area of proximal femur or to make additional measurements in the distal third of forearm. [6].

If the fracture occurred for the first time in a patient with no known history of osteoporosis and normal shape of other vertebrae, then the cause should be established very thoroughly. It can be the following diseases, except osteoporosis: hyperparathyroidism, multiple myeloma, metastatic, infectious lesions and primary vertebral neoplasias [8]. Thus, DXA plays an important, however, not decisive role in the diagnostic search, since even positive results confirming osteoporosis do not allow us to assert the absence of other possible causes of fracture. On the other hand, negative results of densitometry (normal or slightly reduced bone density) does not mean the absence of osteoporosis, as it is a highly specific but low-sensitive test, and its result can be affected by many factors [6]. In some cases, the diagnosis of osteoporosis can be established even with a negative DXA result, if it is a minimal trauma fracture with all other causes that have been excluded [6].

The following approximate examination plan is recommended (Table 2):

The most difficult task from this list is the exclusion of a single metastatic and myeloma lesion of vertebra, as well as hemangioma; final diagnosis in some cases can only be established based on biopsy results. If there are strong suspicions of the secondary nature of vertebral damage and a single lesion of this vertebra is observed, then it is reasonable to first perform a needle biopsy [25]. If the patient has indications for surgical treatment of a fracture (vertebroplasty or kyphoplasty), then these interventions are recommended to be performed only after receiving the results of a histological test. This is required because the primary biopsy may not be informative enough; then a repeated sampling from vertebra will be required that is impossible with cement placed into vertebral body.

Table 2. Differential diagnosis of osteoporosis

Examinations	Assumed diseases
Parathyroid hormone, alkaline phosphatase, total calcium (serum)	Hyperparathyreosis
ESR, total protein, plasma protein fraction(serum)	Multiple myeloma
Phosphorus, 25(OH)D	Oncogenic osteomalacia
Skeletal scintigraphy, Comprehensive oncological examination	Metastatic bone lesion
DXA	Osteoporosis
Exclusion of secondary causes of osteoporosis	Endocrinological, rheumatological, gastrointestinal, renal diseases, blood disorders, drugs (steroids, aluminum in antacids, antiepileptic drugs, barbiturates, aromatase inhibitors), alcohol
Vertebral biopsy (If surgery (kyphoplasty or vertebroplasty) is planned, vertebral biopsy is mandatory)	Haemangioma, multiple myeloma, metastatic lesion, primary spine tumor

Note: ESR — erythrocyte sedimentation rate, 25(OH)D– 25-hydroxycalciferol, DXA — Dual-energy X-ray absorptiometry

Conclusion

Back pain is a complex clinical issue; it requires extensive differential diagnostic search. Osteoporotic fracture is one of the most common causes of back pain in elderly patients. Diagnosis of an osteoporotic fracture is based on a thorough analysis of clinical findings and laboratory test results, and also requires the targeted use of advanced imaging methods.

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ПЕРСПЕКТИВЫ ЛЕЧЕНИЯ ИДИОПАТИЧЕСКОГО ЛЕГОЧНОГО ФИБРОЗА

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Prospects for Treatment of Idiopathic Pulmonary Fibrosis

Резюме

Идиопатический легочный фиброз (ИЛФ) является тяжелым прогрессирующим заболеванием легких неизвестной этиологии со средней распространенностью 15 на 100000 населения в мире. Различают спорадические, синдромальные и семейные случаи болезни. Спорадические случаи относятся к многофакторным заболеваниям и ассоциированы с возрастом, вирусными инфекциями, курением и вдыханием пыли, контактом с химическими реагентами и лекарствами, гастроэзофагальной рефлюксной болезнью. Выявлена ассоциация спорадического ИЛФ с аллельными вариантами генов *AKAP13, ATP11A, DPP9, DSP, IVD, IL1RN, FAM13A, MUC5B, SFTPC, SPPL2C, TERC, TERT, TOLLIP*. Синдромальный ИЛФ описан при синдроме Германского-Пудлака. Семейные случаи болезни обусловлены мутациями в генах, кодирующих белки сурфактанта (*SFTPC*), муцина (*MUC5B*), нуклеазу деаденилирования (*PARN*), участвующие в функционировании теломер (*RTEL1, TERC, TERT*). В 2000 году Американское торакальное сообщество рекомендовало глюкокортикоиды и цитостатики для лечения ИЛФ с целью воздействия на воспалительный процесс при активации фибробластов и их аккумулировании во внеклеточном матриксе легких. Эти рекомендации до сих пор используются практике, несмотря на публикации достоверных данных о повышенной смертности и случаев госпитализации пациентов с ИЛФ, принимающих преднизолон и азатиоприн. Согласно данным недавних метаанализов, наиболее эффективными в лечении ИЛФ являются пирфенидон (ингибитор синтеза факторов роста проколлагенов I и II) и нинтенадиб (ингибитор тирозинкиназы). Поскольку важную роль в этиопатогенезе болезни играют генетические факторы, перспективен поиск методов таргетной терапии с использованием в качестве мишеней специфических некодирующих РНК, изменения экспрессии которых не характерны для других бронхолегочных заболеваний. К ним относятся miR-9-5p, miR-27b, miR-153, miR-184, miR-326, miR-374, miR-489, miR-630, miR-1343 (уровень их снижается при болезни); miR-340, miR-424, miR-487b, miR-493, lncRNA AP003419.16, lncRNA AP003419.16 (повышенная экспрессия при ИЛФ).

Ключевые слова: *диагностика, идиопатический легочный фиброз, лечение, механизм развития, микроРНК, наследственность*

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

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a severe, progressive lung disease of unknown etiology with an average worldwide prevalence of 15 per 100,000. According to the etiology, IPF is classified into sporadic, syndromic, and familial cases. Sporadic cases refer to multifactorial diseases and are associated with age, viral infections, smoking and inhalation of dust, contact with chemicals and drugs, gastroesophageal reflux disease.

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There were revealed an association of sporadic IPF with allelic variants of the genes *AKAP13, ATP11A, DPP9, DSP, IVD, IL1RN, FAM13A, MUC5B, SFTPC, SPPL2C, TERC, TERT, TOLLIP*. Syndromal IPF develops in German-Pudlak syndrome. Familial cases of the disease are caused by mutations in the genes encoding surfactant (*SFTPC*), mucin (*MUC5B*), deadenylation nuclease (PARN), components of telomere functioning (*RTEL1, TERC, TERT*). In 2000, the American Thoracic Society recommended glucocorticoids and cytostatics for the treatment of ELISA in order to influence the inflammatory process due to the activation of fibroblasts and their accumulation in the extracellular matrix of the lungs. These recommendations are still used by many doctors, despite the publication of reliable data on the increased mortality and hospitalizations of IPF patients taking prednisolone and azathioprine. According to recent meta-analyzes, pirfenidone (an inhibitor of the synthesis of procollagen I and II growth factors) and nintenadib (a tyrosine kinase inhibitor) are the most effective treatments for IPF. Since genetic factors play an important role in the etiopathogenesis of the disease, it is promising to search for methods of targeted therapy for IPF using specific noncoding RNAs as targets, changes in the expression of which are not specific of other bronchopulmonary diseases. These RNAs include miR-9-5p, miR-27b, miR-153, miR-184, miR-326, miR-374, miR-489, miR-630, miR-1343 (decreased expression in IPF); miR-340, miR-424, miR-487b, miR-493, lncRNA AP003419.16, lncRNA AP003419.16 (increased expression in IPF).

Key words: *diagnosis, idiopathic pulmonary fibrosis, treatment, developmental mechanism, microRNA, heredity*

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ATS — American Thoracic Society, CT — computed tomography, EGCG — epigallocatechin gallate, ERS — European Respiratory Society, GWAS — genome-wide association study, IPF — idiopathic pulmonary fibrosis, ncRNA — non-coding RNA, PRM — pulmonary rehabilitation mixture, TGF-β — transforming growth factor beta, ThO — thoracic organs, VC — vital capacity

List of genes with decoding:

AKAP13 — A-kinase anchor protein 13

AP3B1 — adaptor related protein complex 3 subunit beta 1; gene of the protein of AP-3 heterodimer complex that interacts with the scaffold protein clathrin

ATP11A — sodium/potassium/transporting ATPase subunit alpha-1; gene of the alpha-1 ATPase subunit that transports sodium and potassium

DPP9 — dipeptidyl peptidase 9; gene encoding a serine protease of the S9B family

DSP — desmoplakin gene

IVD — isovaleryl-CoA dehydrogenase

IL1RN — interleukin 1 receptor antagonist

FAM13A — family with sequence similarity 13 member A; small GTPase-mediated signal transduction regulation gene

KANSL1 — KAT8 regulatory NSL complex subunit 1; subunit gene of two protein complexes (MLL1 and NSL1) involved in histone acetylation

MUC5B — mucin 5B

PARN — poly(A)-specific ribonuclease; deadenylation nuclease gene

RTEL1 — regulator of telomere elongation helicase 1; gene encoding telomere elongation helicase

SFTPC — surfactant protein C; gene encoding surfactant proteins

SPPL2C — signal peptidase like 2C; gene encoding a protein involved in the proteolysis of membrane proteins

TERC — telomerase RNA component; gene involved in the functioning of telomeres

TERT — telomerase reverse transcriptase; gene encoding telomere reverse transcriptase

TOLLIP — toll interacting protein; gene for a ubiquitin-binding protein that interacts with Toll-like receptors

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe progressive interstitial lung disease with average prevalence of 15:100,000 individuals worldwide [1]. Based on etiology, this disease can be classified into familial, syndromic and sporadic types. About 10–15 % of all IPF cases are familial [2]. They are caused by mutations in genes *SFTPC* [3], *TERC* [4], *TERT* [5], *MUC5B* [6], *RTEL1, PARN* [7]. Syndromic IPF can develop in Hermansky — Pudlak syndrome (mutation in gene *AP3B1*) [8]. Age-associated sporadic cases of IPF are prevailing. Average age of patients with these types is 66, and the risk of disease development in people 75+ increases 50-fold compared with the age group 18–34 [9]. Further, IPF is associated with viral infections (Epstein–Barr virus, cytomegalovirus, herpesviruses [10], Kaposi's sarcoma, and hepatitis C), as well as with smoking and inhalation of metal [11], silicon, beryllium and coal dust; exposure to asbestos, radiation, drugs such as antibiotics (nitrofurantoin, ethambutol), cytostatics (bleomycin, methotrexate), non-steroidal anti-inflammatory drugs [2]; gastroesophageal reflux disease [12]. The aforementioned environmental factors cause chronic damage to alveolar epithelium that contributes to the development

of immune response with the release of transforming growth factor β (TGF-β) that is a profibrotic cytokine activating angiogenesis and the production of extracellular matrix components (collagen and fibronectin) [2]. Fig. 1 is a schematic presentation of mechanisms of the development of different IPF types.

To diagnose IPF, a clinician should consider the specific features of the clinical presentation of disease, the results of X-ray examinations, and physiological parameters of patients. Surgical lung biopsy (open thoracotomy or videothoracoscopy) is recommended for most patients with IPF. The main objective of subsequent histological examination is to confirm the diagnosis of IPF [13]. Basic clinical signs of IPF include dyspnea (in 88 % of patients), dry cough (70 %), and chest pain (24 %) [5]. In 2000, the American Thoracic Society established major and minor criteria for IPF. Major criteria include the following: 1) absence of other known causes of idiopathic lung diseases, such as exposure to toxic drugs and environmental factors, connective tissue diseases; 2) decreased vital capacity (VC), often along with increased forced expiratory volume/VC ratio, signs of impaired gas exchange; 3) bibasilar reticular anomalies with minimal ground-glass opacities found during the computed tomography (CT) of thoracic organs (ThO); 4) absence of the signs of an alternative diagnosis based on the results of transbronchial lung biopsy or bronchoalveolar lavage. Minor criteria are listed below: 1) age 50+; 2) latent onset of unexplained dyspnea during physical exertion; 3) disease duration more than 3 months; 4) bibasilar rales on suspended deep inspiration (dry or velcro-type) [13]. ThO CT results with subpleural honeycombing and traction bronchiectasis (Fig. 2) or specific combinations of X-ray and histological signs in patients after surgical lung biopsy are essential for the diagnosis [11].

Since an important mechanism for IPF development is inflammation that leads to the activation of fibroblasts and their accumulation in extracellular matrix, in 2000, American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommended administration of glucocorticoids (prednisolone at a dose of 0.5 mg per kg body weight per day), azathioprine (2–3 mg/kg body weight) or cyclophosphamide (2 mg/kg body weight) for the management of this disease [13]. Unfortunately, these recommendations are still used by practitioners, although in 2012 there was evidence of the ineffectiveness of this treatment. Moreover, patients with IPF receiving the combination of prednisolone, azathioprine, and N-acetylcysteine

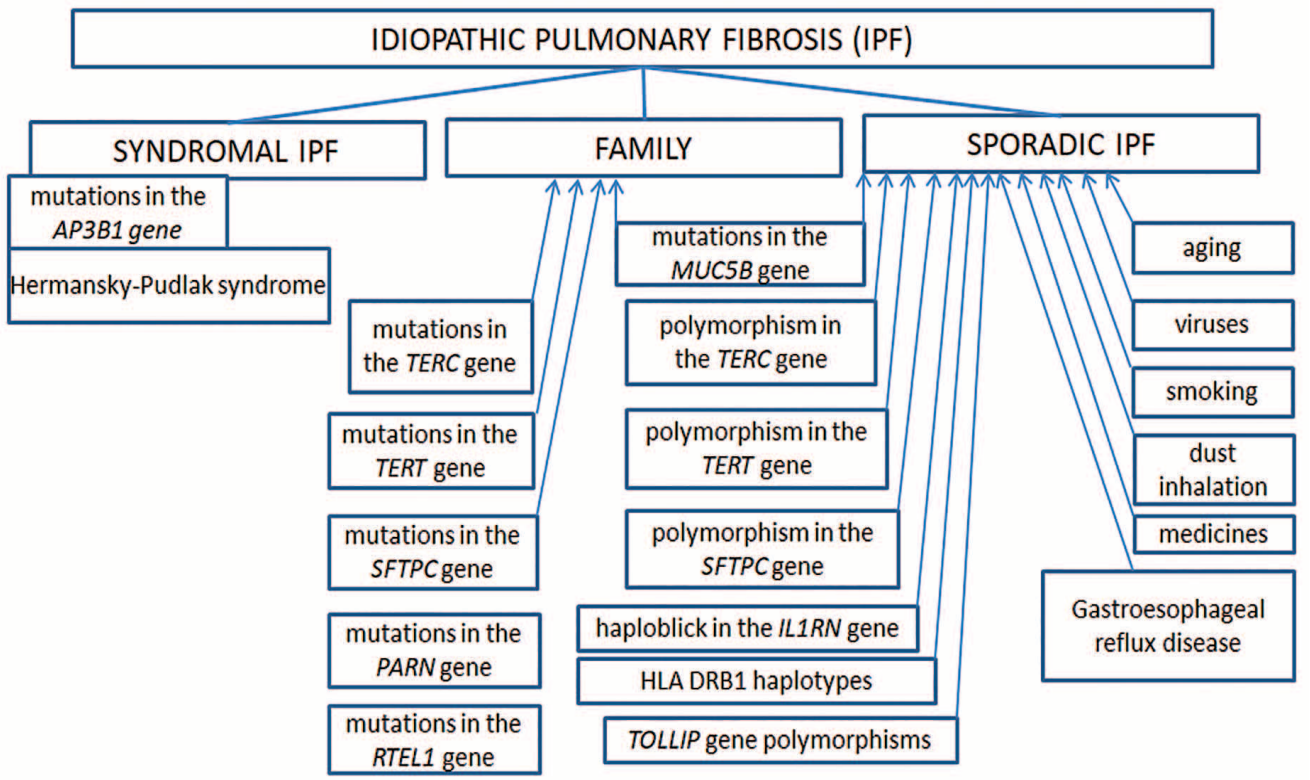

Figure 1. *Scheme of pathogenetically significant mechanisms of IPF* [1]

[1] AP3B1 gene — Adaptor Related Protein Complex 3 Subunit Beta 1; TERC gene — Telomerase RNA Component; TERT gene — Telomerase Reverse Transcriptase; SFPC gene — Surfactant Protein C; PARN gene — Poly(A)-Specific Ribonuclease; RTEL gene — Regulator of Telomere Elongation Helicase 1; MUC5B gene — Mucin 5B; IL1RN gene — Interleukin 1 Receptor Antagonist; HLA DRB1 — Human Leukocyte Antigens DR beta chain; TOLLIP gene — Toll Interacting Protein

had an increased risk of mortality and hospitalization [14]. Despite ongoing treatment, survival rate in cases of IPF is about 3 years [15]. Therefore, analysis of the molecular mechanisms of IPF development can become the basis for new effective treatment methods. Thus, one of the approaches is to activate the expression of sirtuin (histone acetylase) SIRT7 that reduces collagen production by lung fibroblasts. SIRT7 levels are reduced in lung tissues of IPF patients and experimental mice with bleomycin-induced IPF [15]. Since up to 15 % of all cases of this disease are monogenic [2], that is, they are caused by mutations in a specific gene, consideration of the mechanisms of their development can become the basis for the development of a pathogenetic therapy for patients with IPF.

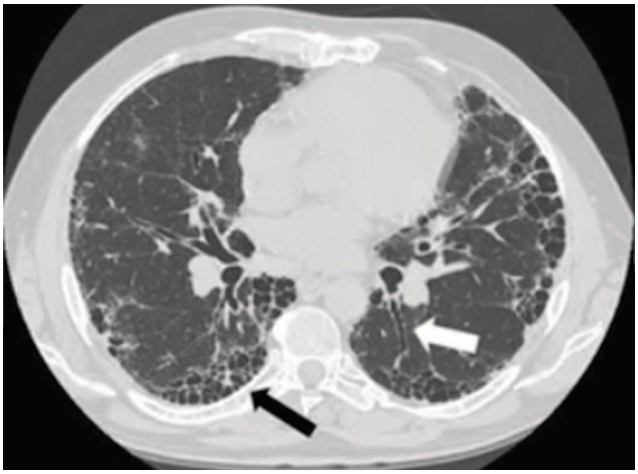

Figure 2. *Typical manifestations of IPF on CT sections of the chest (the black arrow shows the «honeycomb lung», the white arrow shows traction bronchiectasis) [11]*

According to ThO CT, differential diagnosis of IPF should be carried out with pulmonary signs of systemic scleroderma and rheumatoid arthritis, asbestosis and sarcoidosis. These diseases have signs that are generally similar to those of IPF on CT. However, asbestosis is characterized by the presence of parenchymal strands of fibrosis and pleural plaques. Laboratory blood test is required to exclude systemic connective tissue diseases. Similar to IPF ThO CT with reticular opacities and honeycombing is observed in subacute and chronic hypersensitivity pneumonitis, however, there is no typical for IPF bibasilar predominance [13]. It should be mentioned that risk factors for IPF development are the causes of the development of lung diseases (Fig. 3) that were listed in differential diagnosis [2, 11].

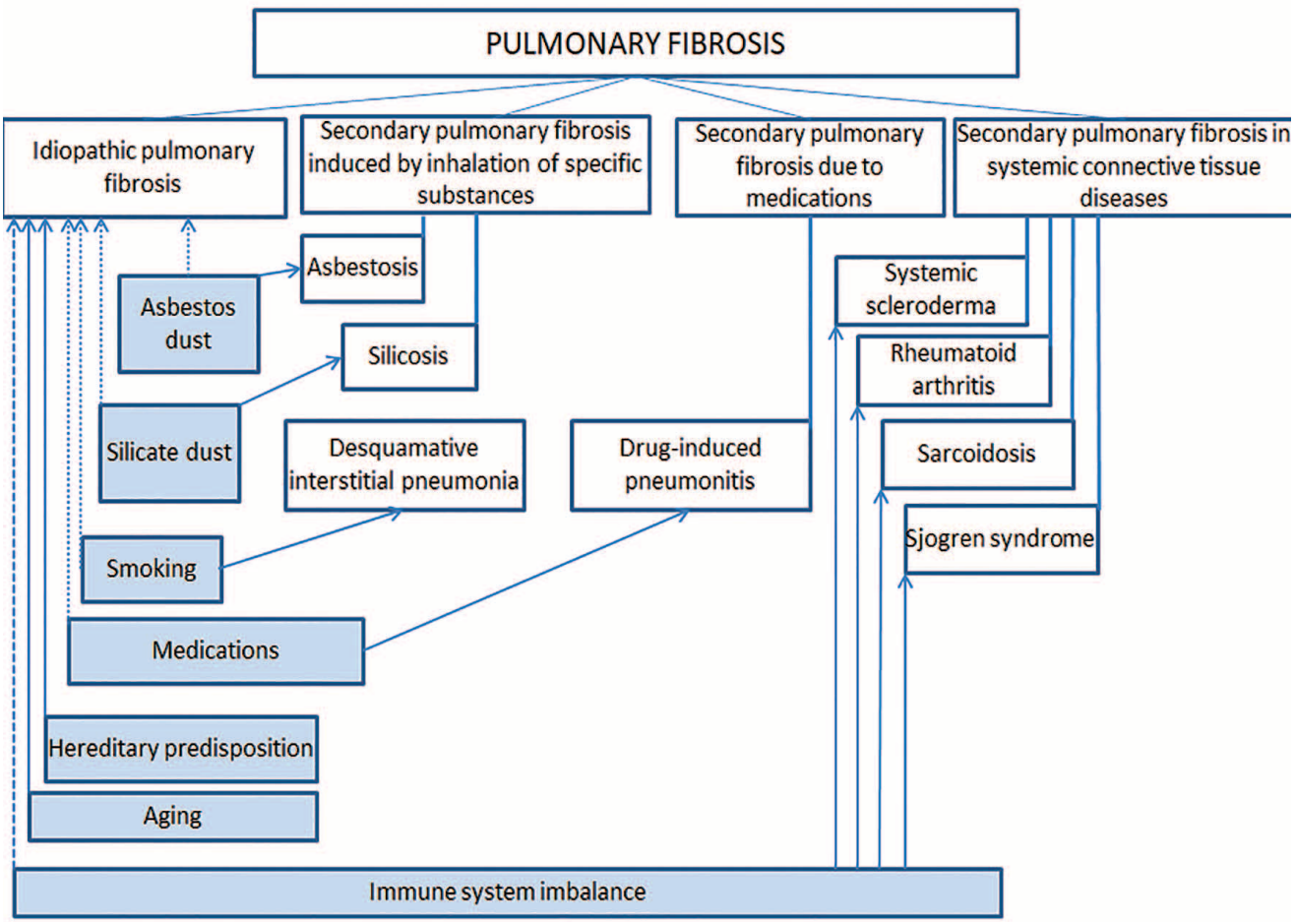

Figure 3. *Scheme of differential diagnosis of IPF with the definition of common causes of disease development*

Familial types of idiopathic pulmonary fibrosis

Clinical signs of monogenic cases of IPF caused by mutations in specific genes are characterized by earlier manifestation [16], autosomal dominant inheritance, and varying penetrance. These types of IPF were described as early as 1958 [17]. Mutations are most often (18 % of all family cases) detected in the genes encoding telomerase complex: *TERT* (c.97C>T, c.430G>A, c.1456C>T, c.2240delT, c.2593C>T, c.2594G>A, c.3346_3522del [4]; c.1892G>A, c. 2594G>A, c.2648T>G [5]) and *TERC* (r.37a>g) [4]. Major missense mutation 128T>A in exon 5 of the gene *SFTPC* (encodes surfactant) is typical [3]. Rarer mutations are c.602delG, c.1451C>T, c.1940C>T, c.2005C>T, c.3371A>C in the gene *RTEL1* that encodes a helicase that regulates telomere elongation, as well as IVS4-2a>g, c.529C>T, c563_564insT, c.751delA, IVS16+1g>a, c.1262A>G mutations in the gene *PARN* that encodes deadenylation nuclease [7].

It should be mentioned that sporadic cases of IPF may be associated with allelic variants of genes with mutations that cause familial IPF. Thus, there's a description of association rs12696304 in the gene *TERC,* rs7725218 in the gene *TERT* [18], polymorphisms G4702C, C4859G, G4877A, G5089A, C5210A, G5236A, G5574A, A5786C, T6108C, C6699T in the surfactant gene *SFTPC* [16] with the development of sporadic IPF. Allelic variant rs35705950 (nucleotide substitution in the promoter region) in the gene *MUC5B* (encodes mucin) was reported as a cause of both familial [6] and sporadic cases of IPF [18–20]. The significance of mutations in genes *TERT* [4, 5], *TERC* [4], *RTEL1* [7] in the development of monogenic IPF forms, as well as the association of sporadic forms of the disease with allelic variants of genes *TERT* and *TERC* [18], whose expression products are necessary for the functioning of telomeres, explains the association of IPF with aging. Genomic instability, mitochondrial dysfunction, cellular aging, and loss of proteostasis are actually mentioned in the pathogenesis of this disease [21].

According to the results of meta-analyzes, allelic variants of many other IPF-associated genes were found that are not monogenic types of this disease. Many of the products of these genes may be involved in IPF pathogenesis. For example, VNTR*2 haploblock in the interleukin receptor gene *IL1RN* was significantly associated in 5 different clinical trials indicating pathological inflammatory reactions [22]. Information on the association of haplotypes *DRB1*15:01* and *DQB1*06:02* of major histocompatibility complex genes *HLA* is illustrative of the role of autoimmune processes [23]. The association of allelic variants of the gene *TOLLIP* was also identified; this gene encodes a Toll-interacting protein involved in the innate immune system function (variants rs111521887, rs5743894, rs5743890) [19]. According to the results of the genome-wide association study (GWAS), IPF was associated with allelic variants of genes, the role of protein products of which was not yet determined. These include the gene of serine protease *DPP9* (rs12610495), lymphoblastic oncogene *AKAP13* (rs62023891), desmoplakin for intercellular contacts *DSP* (rs2076295), component of histone acetylation complex *KANSL1*, membrane ATPase that regulates the transport of calcium ions *ATP11A* (rs9577395), isovaleryl-CoA dehydrogenase *IVD* (rs59424629), hypoxia-induced gene associated with lung cancer *FAM13A* (rs2013701) [18], lysosomal membrane protein with a conserved transmembrane domain *SPPL2C* (rs17690703) [19]. Analysis of the role of specific genes in IPF development can become the basis for the development of both criteria for accurate diagnosis and management of this disease.

Present-day methods of management of idiopathic pulmonary fibrosis

Considering the key role of fibroblasts in the pathogenesis of IPF [15], use of antifibrotic agents for the management of this disease seems to be the most promising way. A 2016 meta-analysis of the results of treatment of 2,254 patients with IPF demonstrated significant effectiveness of pirfenidone (an inhibitor of the synthesis of procollagen growth factors I and II) and nintenadib (a tyrosine kinase inhibitor) in improving reduced FVC (forced vital capacity) during 12 months. The inefficiency of N-acetylcysteine and the development of several adverse drug reactions during its administration were found [24]. Similar results were obtained in a 2021 meta-analysis that revealed greater efficacy of pamrevlumab (a human monoclonal antibody that inhibits the activity of connective tissue growth factor). However, only pirfenidone was able to reduce overall mortality [25]. It should be mentioned that nintedanib that is also effective in the management of lung cancer affects the same pathways, including MAPK, PI3K/AKT, JAK/STAT, TGF-β, VEGF, Wnt [26] that involve miRNA (ribonucleic acid) associated with IPF [27]. In addition to antifibrotic agents, present-day treatment for IPF includes proton pump inhibitors, oxygen therapy, and lung transplantation. In some cases, the effectiveness of antibacterial and antiviral agents was demonstrated due to the role of bacteria and viruses in the development of IPF. It was found, for example, that macrolides have immunomodulatory and anti-inflammatory effect in IPF preventing the production of mediators of the immune system [2].

In addition to medications, the possibility of using traditional medicine for IPF management is also being considered. A Chinese herbal pulmonary rehabilitation mixture (PRM) that has been used for decades was proposed as a potential multipurpose oral agent for IPF management. Pharmacodynamic studies have shown that PRM affects the state of the epithelium, endothelium, fibroblasts, platelet growth factor, toll-like receptor-4, and fibroblast growth factor. PRM contains 8 herbs: roots of astragalus, codonopsis, ophiopogon, pseudoginseng, anemarrhena, licorice, bulbs of Fritillaria thunbergii, fruits of Schisandra chinensis [1]. Components of *Hypericum longistylum* demonstrated effect on TGF-β1/Smad3 signaling pathways which indicates their potential use for IPF management [28]. Epigallocatechin-3-gallate (EGCG) that is found in green tea inhibits the aggregation of pathological structures of SP-A2 by increasing the instability of this protein and activating its proteasomal degradation. Therefore, EGCG can be an agent in the management of IPF [29].

Since genetic factors are central to the development of this disease, finding ways to impact these IPF development mechanisms is an important task. Investigation of the role of epigenetic factors is the most promising trend of studies, since these factors are reversible and can be corrected using non-coding RNAs (ncRNAs) that are the potential targets as well. One example is microRNA miR-506 that specifically binds to the RNA of the p65 NF-κB subunit gene (nuclear transcription factor for apoptosis, cell cycle, and immune response genes) and suppresses its expression. In IPF, level of this miRNA is significantly reduced; therefore, miR-506 can be used to inhibit excessive cell proliferation and inflammation in lung tissues [30]. Back in 2010, the efficacy of antisense miR-21 in mice with bleomycin-induced lung fibrosis was described. The effect of these molecules could also be due to the suppression of proliferation, since increased expression of miR-21 is typical for malignant neoplasms, and in IPF it contributes to the pathological activation of fibroblasts that synthesize this miRNA. MiR-21 regulates the expression of Smad7 by influencing TGF-β1 that contributes to the hyperproduction of extracellular matrix [31].

An inverse correlation of miR-708-3p expression with the development of pulmonary fibrosis was found what indicates the potential use of this miRNA in the management of IPF. Direct targets for miR-708 include transcripts of the genes of disintegrin and metalloproteinase 17 (*ADAM17*). In an animal experiment, the therapeutic efficacy of this microRNA in pulmonary fibrosis was demonstrated [32]. MiR-184 also has an antifibrotic effect that suppresses TGFβ-induced fibrotic processes in lungs and can be considered for the targeted therapy of IPF [33]. In addition to miRNAs, long ncRNAs can be used in the management of IPF. Although the results of clinical trials have revealed decreased expression of 1,376 and increased expression of 440 different long ncRNAs in the blood plasma of IPF patients compared with healthy individuals, changes in the levels of certain ones is more specific. These include lncRNA AP003419.16 that is expressed at the highest level and activates TGF-β1 signaling pathways [34]. An interfering sequence for profibrotic lncITPF (involved in TGFβ pathways) has already been used in clinical practice in patients with IPF. This agent called sh-lncITPF actually reduced lung fibrosis score [35]. Antifibrotic lncRNA PCAT29 (prostate cancer-associated transcript 29) suppresses TGF-β and can be used to influence the TGF-β pathway in IPF [36]. Thus, studies of ncRNAs in the development of IPF can become the basis for both diagnosis and the development of more effective methods of treatment (Fig. 4).

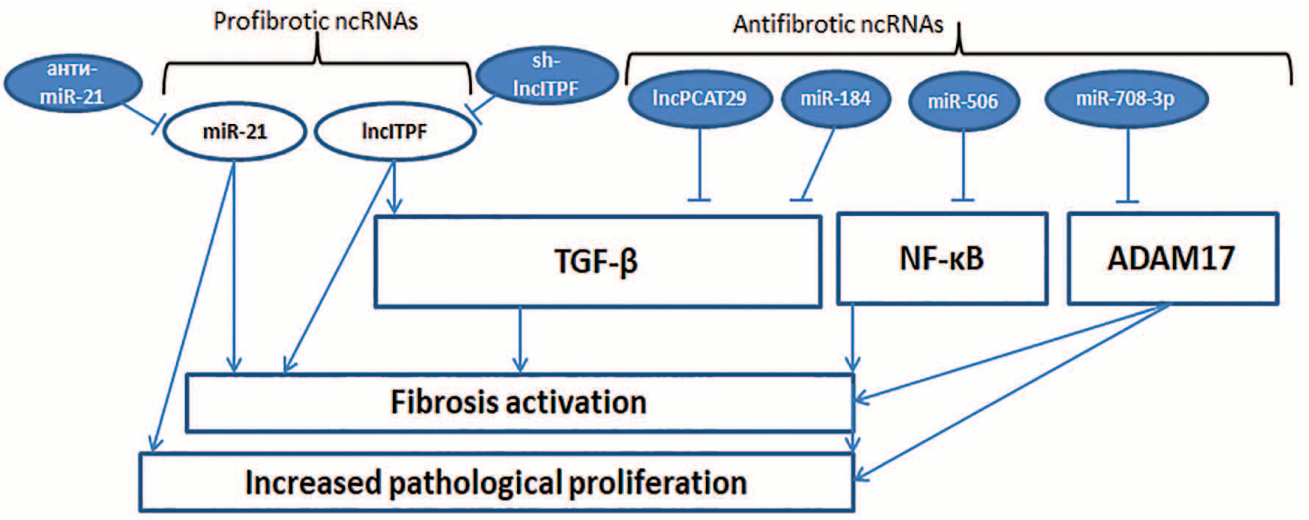

Figure 4. *Scheme for the use of specific non-coding RNAs (ncRNAs) in the treatment of idiopathic pulmonary fibrosis*

Table 1. *IPF-specific miRNAs*

miRNAs (gene localization)	Expression changes specificity in IPF/ mechanism of influence	Reference
miR-9-5p (5q14.3)	decreases / prevents fibrosis	[38]
miR-27b (9q22.32)		
miR-153 (2q35)	decreases / suppresses TGF-β	
miR-184 (15q25.1)	decreases / suppresses TGF-β and p53	[33]
miR-326 (11q13.4)	decreases / prevents fibrosis	[38]
miR-340 (5q35.3)	increases / affects MAPK signaling	[41]
miR-374 (Xq13.2)	decreases / suppresses mTOR signaling, expression of MID1 ubiquitin ligase	[27, 42]
miR-424 (Xq26.3)	increases / stimulates fibrosis	[38]
miR-487b (14q32.31)	increases / suppresses IL-33 expression	[36, 43]
miR-489 (7q21.3)	decreases / prevents fibrosis	[38]
miR-493 (14q32.2)	increases / inhibits Wnt/B-catenin, Wnt/PCP, MEK/ERK, PI3K/AKT pathways	[43, 44]
miR-630 (15q24.1)	decreases / regulates *CDH2, VIM, EZH2, SOCS2, TFG, TLR4, Smad9, EP300* gene expression	[45]
miR-1343 (11p13)	decreases / inhibits TGF-β receptors	[40]

miRNAs as potential diagnostic markers of idiopathic pulmonary fibrosis

In addition to the miRNAs described above that can be considered as targets for targeted therapy, a significant change in the expression of miR-29, miR-21-5p, miR-92a-3p, miR-26a-5p, and let-7d-5p was found in patients with IPF [37]. Patients with IPF demonstrate changes in the levels of miRNAs that activate TGF-β (miR-424) and suppress its transcription (miR-9-5p, miR-18a-5p, miR-26a, miR-27b, miR-101, miR-153, miR- 326, miR-489, miR-1343) [38]. MiR-323a inhibits both TGF-β and TGF-α signaling pathways. Expression of this miRNA is significantly reduced in the lung tissue of patients with IPF [39]. Fibroblasts in the lung tissue of patients with IPF express lower levels of miR-101 [40]. In patients with IPF have altered levels of many specific microRNAs that may be involved in the pathogenesis of this disease compared with healthy ~~control~~ individuals. 47 microRNAs were identified that are involved in the regulation of actin cytoskeleton, in signaling pathways TGF-β, Wnt, PI3K-Akt, Notch, HIF-1, and mitogen-activated protein kinase [27]. Analysis of literature sources presented in PubMed, Scopus, Web of Science databases revealed that changes in the expression of many IPF-associated microRNAs are also found in patients with other diseases of bronchopulmonary system, such as asthma and chronic obstructive pulmonary disease. However, the expression of several microRNAs is detected only in IPF (Table 1). These miRNAs can be used as diagnostic markers of this disease, as well as for the development of effective targeted therapy.

Conclusion

Average incidence of IPF is 1:6,500. From 10 to 15 % of cases of this disease are autosomal dominant monogenic diseases caused by mutations in the genes of telomerase complex (*TERC, TERT, RTEL*), surfactant (*SFTPC*), deadenylating nucleases (*PARN*) and mucin (*MUC5B*). Sporadic cases of IPF are associated with allelic variants of different genes, the products of which may be involved in the pathogenesis of this disease. The ineffectiveness of IPF management with glucocorticoids and cytostatics has been proven; these agents can aggravate disease course and increase the risk of mortality. Present-day effective methods of treatment implemented in clinical practice are the use of pirfenidone (an inhibitor of the synthesis of procollagen growth factor), nintenadib (a tyrosine kinase inhibitor) and pamrevlumab (an anti-connective tissue growth factor monoclonal antibody). Promising method of laboratory tests for IPF is determining the levels of miRNAs, changes in the expression of which is specific only for this disease. These include miR-9-5p, miR-27b, miR-153, miR-184, miR-326, miR-374, miR-489, miR-630, miR-1343 (decreasing levels); miR-340, miR-424, miR-487b, miR-493 (increasing level). MicroRNAs and long non-coding RNAs can also be used in the development of targeted therapy for IPF.

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ДИАГНОСТИКА И ТЕРАПИЯ ПСИХОСОМАТИЧЕСКИХ РАССТРОЙСТВ ГЕНЕРАТИВНОГО ЦИКЛА ЖЕНЩИН В ОБЩЕЙ МЕДИЦИНСКОЙ ПРАКТИКЕ (ОБЗОР ЛИТЕРАТУРЫ)

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Diagnosis and Therapy of Psychosomatic Disorders in Reproductive Cycle of Women in General Medical Practice (Review)

Резюме

Своевременное выявление врачами общей медицинской практики психических и психосоматических расстройств у пациенток при планировании, а также во время ведения беременности и в послеродовый период, остается значимой медицинской задачей. Частота встречаемости гетерогенных психосоматических расстройств (аффективные, тревожные, дисморфические, соматовегетативные, психотические) на фоне менструаций, беременности и в послеродовом периоде достигает 80 %. В свою очередь, психосоматические расстройства являются факторами риска для отсроченного наступления и сокращения продолжительности менструаций, развития предменструального синдрома, неадекватных эмоциональных реакций при менструациях, перебоев в цикле, снижения регулярности и удовлетворенности половой жизнью, фертильности, невынашивания беременности, сокращения лактационного периода, раннего наступления менопаузы с большой длительностью и клинической тяжестью пременопаузы и др. При индивидуальном подходе к назначению схемы лечения требуется учитывать факторы риска (наследственность, коморбидные расстройства, пол, возраст и др.) развития нежелательных явлений (НЯ), баланс эффективности и безопасности лекарственных средств.

Ключевые слова: *психические расстройства, депрессия, тревога, дисморфическое расстройство, психозы, предменструальный синдром, беременность, лактация, послеродовый период*

Конфликт интересов

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

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Abstract

The incidence of different psychiatric disorders (affective, anxious, dysmorphic, psychotic) during menstruation, pregnancy and the postpartum period reaches 80 %. Mental disorders are risk factors for the delayed onset and shortening of menstruations, manifestation of the premenstrual syndrome (PMS), inadequate emotional reactions during menstruations, disruptions in the menstrual cycle, decreased regularity and satisfaction of sexual activity, fertility, pregnancy failure, reduction of the lactation period, early onset of menopause with long duration and clinical severity of premenopause, etc. An individual approach to treatment should take into account risk factors (heredity, comorbid disorders, sex, age, etc.) of adverse events (AD), the balance of efficacy and safety of drugs.

Key words: *mental disorders, depression, anxiety, dysmorphic disorder, psychoses, premenstrual syndrome, pregnancy, lactation, postpartum period*

Conflict of interests

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ACTH — adrenocorticotropic hormone, AE — adverse events, BDD — body dysmorphic disorder (dysmorphia, dysmorphophobia), BPAD — bipolar affective disorder, DACH-syndrome (D — depression; A — anxiety; C — craving; H — hyperhydration), DSM — Diagnostic and Statistical Manual of mental disorders, GABA — gamma-aminobutyric acid, ICD-11 — International Classification of Diseases, OCD — obsessive-compulsive disorder, PMDD — premenstrual dysphoric disorder, PMS — premenstrual syndrome, PTSD — post-traumatic stress disorder, RID — relative infant dose, SNRIs — selective serotonin and norepinephrine reuptake inhibitors, SSRIs — selective serotonin reuptake inhibitors, TCAs — tricyclic antidepressants, TSH — thyroid stimulating hormone

Timely detection by general practitioners of mental and psychosomatic disorders in female patients during pregnancy planning, as well as during pregnancy and postpartum period, remains a significant medical issue.

The objective of this review was to analyze the results of basic research studies on the pathogenetic and clinical and dynamic characteristics of the generative cycle of a woman (menstrual cycle and pregnancy). Search by keywords “mental disorders”, “depression”, “anxiety”, “dysmorphic disorder”, “psychosis”, “premenstrual syndrome”, “pregnancy”, “lactation”, “postpartum”, “treatment” was conducted in the databases of articles published by domestic and foreign authors over last 25 years (PubMed, eLibrary, Scopus, and ResearchGate).

According to the scientific ideas predominating at late 20th — early 21st century, psychosomatic disorders associated with menstruation, pregnancy and postpartum period are caused by sharp and cyclic fluctuations in the level of blood estrogen, changes in the prevalence of estrogen receptors in brain structures associated with affect regulation (including amygdala, hippocampus, and hypothalamus), as well as suppression of the activity of GABAergic neurons (GABA, gamma-aminobutyric acid) by progesterone [1–2]. The other possible causes include decreased secretion of gonadoliberin, melatonin, stimulating effect of thyreoliberin on the secretion of thyroid-stimulating hormone (TSH), of corticoliberin on adrenocorticotropic hormone (ACTH), and of vasopressin on cortisol [1-2].

On the other hand, the mental/psychosomatic disorders in female patients are a risk factor for delayed onset and shortening of menstruation period, development of premenstrual syndrome (PMS), inadequate emotional reactions (fear, exaltation) during menstruation, irregularities in the menstrual cycle, decreased regularity (50.4 %) and satisfaction (62.2 %) with sexual life, decreased fertility (decreased number of ovulations, pregnancies, deliveries), miscarriage, reduced lactation period, early onset of menopause with a long duration and clinical severity of premenopause, etc. [3].

The first classifications of psychiatric disorders associated with the reproductive cycle in women included pregnancy-related disorders; postpartum disorders (first 6 weeks (4 weeks — 12 months) after childbirth), and lactation disorders (starting from the week 7 after childbirth) [4]. DSM-II (Diagnostic and Statistical Manual of mental disorders) (1968) also included “postpartum psychosis” as a diagnosis of exclusion. ICD-11 (International Classification of Diseases) has a separate section “Mental or behavioral disorders associated with the reproductive cycle”, with codes 6E20-6E21.

Mental disorders that are most often associated with the reproductive cycle of women and detected during general examination, include depressive, anxiety, dysmorphic, and psychotic complexes of symptoms.

Depressive symptoms are observed in premenstrual syndrome in 27 % of women; premenstrual dysphoric disorder (PMDD) with clear clinical signs — in 7 %. Depression is diagnosed in 5–41 % of pregnant women and in 12–22 % of women in postpartum period [5–7].

Clinical presentation of depression associated with female generative cycle is characterized by a predominance of asthenic, or asthenic and apathetic symptoms in combination with anxiety, phobias, dysphoria, lethargy, tearfulness, ideas of guilt, sleep disorders (hypersomnia), hyperphagia, somatic symptom disorders (hysteralgia). Dissociated (mixed) disorders are rather common: euphoric mood with total inactivity and motor retardation, as well as mood lability with causeless changes from depression to mania with euphoria and anger [8–9].

Anxiety disorders, including panic, generalized, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and tocophobia (pathological fear of childbirth), are most common in pregnant women (13 %) and in women in postpartum period (up to 43 %) [10–11].

Anxiety disorders with tropism to suspicious personalities, stress factors, interpersonal conflicts, complications of pregnancy (preeclampsia, etc.), are characterized by irritability, tension, moderate autonomic disorders (dizziness, drowsiness, lethargy) [12].

According to our observations, clinical presentation of a body dysmorphic disorder (dysmorphia, dysmorphophobia, BDD) associated with the generative cycle in 15–47 % of women is heterogeneous [13–15]. The most common symptoms include an unreasonable idea of a defect in appearance that is objectively minimal or even non-existent, excessive detailing of the nature of an imagined flaw or defect, detailed presentation or, at the contrary, inability to effectively describe a flaw in appearance. Sometimes female patients feel fear that other people will see an imagined deformation of their appearance; this can result in social isolation.

Along with general medical examinations, patients with BDD often visit aesthetic medicine specialists with bizarre requests (for example, to perform a facial tuck-up surgery at the age of 20–30, to achieve "perfect symmetry" (Goldilocks syndrome), etc.) [13–15].

Other signs of BDD are either excessive mirror gazing ("mirror symptom") in order to find the best view when the supposed "defect" is not visible, or to determine what kind of correction is required, or, on the contrary, "negative mirror symptom" when female patients remove all mirrors and other reflective objects from their place. Another particular sign of BDD is "negative photo symptom" (patients categorically refuse to get their picture taken) and "defect camouflage" with clothes, hair, make-up, and body position [15–17].

In 83 % of cases, aggression delegated to physicians (desire for surgeries and other medical procedures) in accompanied by a tendency to auto-aggressive behavior [18]. In addition to numerous and persistent visits to physicians and cosmetologists, patients constantly demand their family members to confirm (or refute) defects in their appearance, search for information (read special literature, popular publications) related to "defect" correction.

The incidence of psychotic states in the postpartum period is 1–2 per 1 thousand (3–5 % of women after childbirth) [11, 19]. Among the latter, about 43.5 % of cases are "isolated postpartum psychoses" [20]; 72–88 % belong to the structure of bipolar affective disorder (BPAD) type I or schizoaffective disorder [21, 22]; 12 % are within the dynamics of schizophrenia [22].

Prevalence of **premenstrual syndrome** (PMS/PMDD, N94.3 in ICD-10; "Pain and other conditions associated with female genital organs and menstrual cycle", N94.8; "Other specified mood [affective] disorder", F38.8; premenstrual tension syndrome, "cyclic disease", ovarian cyclic syndrome, premenstrual disease, premenstrual dysphoric disorder , DACH-syndrome (D — depression; A — anxiety; C — craving; H — hyperhydration [23]) is 25–95 % among all women [24]; 62.6–80 % in different regions of Russia; 70–100 % among women with mental disorders [23].

PMS is registered in 20 % of women under the age of 30; in 47 % of women at the age 30–39; in 55 % of women 40+ [26].

Upon that, PMS is clinically significant in 30–40 % of female patients of reproductive age, and in 4–5 % of them it leads to temporary disability [25].

The complex of symptoms in PMS includes more than 200 different psycho-emotional, somatic and autonomous, as well as metabolic and endocrine disorders with underlying hypothalamus dysfunction (Table 1) [1, 23].

Based on the most common symptoms, several types of PMS can be defined (Table 2), with only one of them (edematous) that does not include psychopathological signs [1, 25].

Specific dynamic characteristics of PMS allow identifying several types of alternating premenstrual disorders. Symptom(s) in *premenstrual tension* do not significantly affect the functioning of female patients; *PMS* during two menstrual cycles is characterized by at least 3 days of worsened state of health (mental and/or physical symptoms) that reduces functioning; *PMDD* is described by growing psychoemotional anxiety and depressive symptoms that affect functioning and have recurring course during several menstrual cycles; and *premenstrual enhancement* is an exacerbation of existing somatic diseases and mental disorders [2]. In the latter case, we are talking about a high comorbidity of PMS with unipolar depressive disorders and BPAD (60 %), dysthymia (53 %), anxiety disorders (80 %), and personality disorders [27–29].

Pregnancy is an important factor in the natural psychological development of a woman (status of maturity, establishing social identity, fulfilling the gender role, strengthening a marriage) [28].

General practitioners should keep in mind that some of the chronobiological characteristics of pregnancy are

Table 1. *Psychopathological symptoms of premenstrual disphoryc disorders*

«Negative»	«Positive»
Anxiety, fear or anxiety	Excess energy
Sadness	Widening of interests
Tearfulness	Increased capacity for work
Difficulty concentrating	Frequent changes in activities
Physical weakness	Increased social activity
Disorders of appetite and thirst	Self-confidence
Decreased libido	Increased libido
Headaches	Higher than in other days satisfaction with own appearance
Breast pain and tension	

Table 2. *Clinical variants of premenstrual disphoryc disorders*

Name	Leading symptoms
Emotional-affective	Subdepressive mood Dysphoria Tearfulness
Cephalgic	Migrainous or tension headaches
Crisis	Sympathoadrenal crises like panic attacks
Oedematous	Swelling and soreness of the mammary glands Facial swelling Bloating
Combined	

associated with a risk of not only somatic and/or intrapartum, but also mental complications. According to several studies, mother's age under 20 or 30–34+, three or more pregnancies, childbirth in winter or in demi-season (winter-spring) period in the northern hemisphere are comorbid with the "maternal prenatal stress", and with pathocharacterological or psychopathological (anxiety, panic, depressive, dysmorphic, psychotic) disorders in mothers [29–33]. At the same time, most female patients with severe prenatal stress (3.5–5 % of 6 %) have to take selective serotonin reuptake inhibitors (SSRIs) [34].

Development of prenatal stress during pregnancy is facilitated by hyperactivation of hypothalamic-pituitary-adrenal system [35], high levels of cortisol and penetration of 10–20 % of its amount through the placental barrier [35, 36], increased level of catecholamines (adrenaline, norepinephrine) in sympathoadrenal system [11], vasospasm of placenta, decreased uteroplacental blood flow and development of hypoxia in fetus [37], impaired neuronal proliferation and migration in fetus [34].

The prevalence of severe (high) prenatal stress reaches 6 % among all pregnant women [38]; 11.8 % in women at the 18th week of pregnancy, and 13.5 % in those at the 32nd week [39].

The established negative consequences of prenatal stress include increased risk of miscarriage, premature birth, obstetric problems, low birth weight of the child, impaired maternal interaction with child, development of somatic diseases (asthma, hyperlipidemia, diabetes mellitus, obesity, hypertension) in adolescence and adulthood [32, 40–43]. Several girls born in the setting of prenatal maternal stress have impaired ovulatory cycle, ability to conceive and carry a pregnancy, labor, lactation, development of postpartum depression; several boys have feminization and impaired spermatogenesis [43].

One of the complications of prenatal stress in 40 % of women is the persistent mental disorders after childbirth [10, 11], as well as the development of mental diseases in a child (delayed speech development, attention deficit hyperactivity disorder, behavioral, affective, cognitive disorders, autism, and schizophrenia) [42–43].

Psychosomatic disorders in postpartum period have been studies for quite along period[1]. Despite this, there is still no single idea about the duration of postpartum period: it is estimated as 3 weeks, or 4 weeks, or 12 months [20–22].

The most common mental disorders in postpartum period are anxiety (15–80 %) [11, 22], affective (10–33 %

[1] Hippocrates (400 BC) described a case of "puerperal delirium" with severe insomnia and restlessness that developed in a woman during a week after the delivery of twins. T. Ruggier (11th century) reported of "involuntary crying" in women after childbirth; he associated it with "the excessive moisture of the uterus". F. Plater (16th century) described delirium and anger in postpartum period. In the 18th century, F. Osiander, obstetrician, observed postpartum mania with rapid onset and increasing symptoms in the form of intense excitement, agitation, disorganized speech, as well as abnormal thoughts about motherhood ("the baby is still in the womb", "the baby is Jesus Christ", "the baby can fly"). L. Berger explained such symptoms as headache or stupor in postpartum period by "the irritating effect of breast milk on the brain." J. Esquirol, on the contrary, argued that the development of mental disorders is due to the suppression or impossibility of lactation [97–99].

of depressive, up to 20 % of hypomanic), and dysmorphic disorders [13–17, 44]. At the same time, symptoms of depression develop in 40 % of female patients during pregnancy [10, 11]. Postpartum depression increases the risk of depression in future, therefore, it is regarded as a marker of general susceptibility to affective disorders [18].

Management of psychosomatic disorders during menstrual cycle, pregnancy and lactation at general medical level

Analysis of literature sources revealed that the issue of pharmacological management of PMS and premenstrual enhancement remains debatable. To eliminate the physiological decrease in serotonin level in the luteal phase of cycle that is associated with decreased concentration of sex steroids, hormone replacement therapy (combined oral contraceptives, long-acting gonadotropin-releasing hormone agonists) are considered in combination with "general tonic" agents, vitamins, dietary supplements, physiotherapy [45, 46]. As an alternative option, decreased level of serotonin may be effectively compensated by short-term administration of its agonists, antidepressants of SSRI group [45].

Data on the psychopharmacotherapy of mental disorders in pregnant women are based not on the results of evidence-based clinical trials (that are difficult to conduct due to ethical issues and legal restrictions), but on the accumulated information on cases of self- or medical prescription of drugs due to the severe mental state of a woman.

The main principle for deciding whether to use drug treatment is the evaluation of benefit/risk ratio for mother and fetus in case of increased severity or recurrence of a mental disorder in the absence of proper pharmacotherapy. Psychotropic agents are used only in cases when the risk of persisting and developing mental disorder is clearly and significantly higher than the risk of adverse events (AEs). In particular, the choice of any medication should be based on the fact that all agents, in various amounts, penetrate the placental barrier. Effect of a drug product on fetus depends primarily on gestational age. In particular, in early pregnancy (up to 12 weeks), there is a possibility of developing severe structural anomalies, i.e. embryopathies [46].

We present data on the results of the administration of different groups of psychotropic agents by pregnant women.

8.7 % of women in the United States of America receive **antidepressants** during pregnancy [47]. In the world, the use of treatment with antidepressants during pregnancy increased 3-fold in the period from 1995 to 2005 [47]. At the same time, 57 % of women who stopped taking antidepressants due to pregnancy have to restart treatment for worsening mental state [47].

Pregnant women most often take thymoleptics of SSRI group. Experiments on mice/rats revealed that SSRIs reduce fetal body weight, slow down the development of motor reflexes, physical growth, impair learning ability, increase head circumference, cause anxiety, depression and mortality rate [10, 48].

Comparison of the range of neonatal AEs conducted by M.P. Marachev (2018) in children who were exposed to antidepressants during their mothers' pregnancy is presented in Table 3 [49].

Literature data demonstrated that the assertions about the teratogenic potential of **antipsychotic agents** have no evidence [49, 50]. However, the incidence of other neonatal AEs during administration of antipsychotics during pregnancy ranges from 15.6 to 34 % (Table 4).

It should be noted that in these studies, no evaluation of the presence of other potential factors for the development of these AEs was performed (hereditary background, ethnicity, smoking, substance abuse, obesity, diabetes mellitus, socioeconomic status, additional drug treatment) that were associated with them in the studies on other patient populations.

Normotimics have a negative impact on the development of fetus and children of mothers who used these agents in 2–8.6 % of cases (Table 5) [49].

Table 3. *Neonatal Adverse Events of Antidepressants*

Drugs	Adverse Event
TCA: Clomipramine	Increased risk of cardiovascular defects
SSRI: Paroxetine	Cardiovascular malformations Persistent pulmonary hypertension, respiratory distress Tremor Hypoglycemia (19 %)
SNRI: Venlafaxine	Relatively safe
Duloxtine	Insufficient data
OTHER: Mirtazapine Trazodone	Insufficient data

Note: TCA — tricyclic antidepressants, SSRIs — selective serotonin and noradrenaline reuptake inhibitors, SSRIs — selective serotonin and noradrenaline reuptake inhibitors

To assess the effect of medications on a child in postpartum period (period of breastfeeding), the parameter of "relative infant dose" (RDI) is used, i.e. dose received by the child with breast milk in relation to the maternal dose and expressed as a percentage. For example, SSRI antidepressants (citalopram, escitalopram, fluoxetine) pass well through the placental barrier and into breast milk [49–51].

The dose is considered "relatively safe" for the child with RDI <10 % (Table 6) [49–51].

Psychotherapy of psychosomatic disorders of the reproductive cycle in female patients is aimed at building constructive psychological defense (in particular, self-control and responsibility) and adaptive coping strategies (reattribution with a decrease in the threatening meaning of somatized symptoms, development of conviction in the absence of a life-threatening physical disease, adequate assessment of a real-life situation, and refusal to manipulate) [51].

Table 4. *Neonatal Adverse Events of Antipsychotics*

Adverse Events (frequency)	Group /Drugs	
	Traditional	**Atypical**
	Haloperidol Flufenazine	Aripiprazole Quetiapine Clozapine Olanzapine Risperidone
Obstetrical (34 %)	Preterm birth	
Neonatal (15,6-21,6 %)	Prematurity Neurodevelopmental delay Central neurology system abnormalities Respiratory Cardiology (heart defects) Gastrointestinal pathology Low body weight Diabetes mellitus	

Table 5. *Neonatal Adverse Events of Mood Stabilizers*

Drugs	Neonatal Adverse Events, frequency (%)
Lithium	4,1-8 % Cardiovascular abnormalities, Epstein's abnormality, arrhythmia, hypoglycemia, non-sugar diabetes, thyroid dysfunction, goiter, dullness, lethargy, liver abnormalities, and respiratory disorders
Valproates	4,5-8,6 % Congenital defects (interventricular septal defect, roto-facial defects, hypospodias, abnormal upper limb bone structure, hypoplasia of finger phalanges, neural tube defects) The neuro-psychic development disorders Behavioral
Carbamazepine	4-5 % Congenital malformations (spina bifida, single ventricle and atrioventricular septal defect, atrial septal defect, cleft palate, hypospadias, poplidactyly, craniosynostosis)
Lamotrigine	2-5,6 % Isolated cleft palate or cheiloschisis

Table 6. *Relative Infant Dose (RID) of Psychotropic Drugs*

Drugs	RID <10 % «relatively safe», %	RID>10 %
Antidepressants SSRI	Sertraline Paroxetine Fluvoxamine	Citalopram Excitalopram Fluoxetine
Antidepressants TCA	Amitriptyline (1,5 %) Clomipramine (2,8 %) Imipramine (0,15 %)	
Mood Stabilizer	Valproates Carbamazepine	Lamotrigine (9,2–18,3 %) Lithium (12–30,1 %)

Note: RID — relative infant dose, TCA — tricyclic antidepressants, SSRIs — selective serotonin and noradrenaline reuptake inhibitors, SSRIs — selective serotonin and noradrenaline reuptake inhibitors

Conclusion

Thus, psychosomatic disorders associated with abnormal menstrual cycle, pregnancy and lactation period, have a significant negative impact on the social functioning of a woman and the mental and somatic health of a fetus and child. Diagnosis, management and prevention of these disorders is a complex multidisciplinary challenge that requires the involvement of both general practitioners and specialists (i.e., gynecologist, psychiatrist, neurologist).

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НОВЫЕ ДИАГНОСТИЧЕСКИЕ ВОЗМОЖНОСТИ ОПРЕДЕЛЕНИЯ АКТИВНОСТИ ЯЗВЕННОГО КОЛИТА: РОЛЬ НЕЙТРОФИЛОВ

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New Diagnostic Possibilities for Determining the Activity of Ulcerative Colitis: The Role of Neutrophils

Резюме

Заболеваемость язвенным колитом в последние годы растет, и его развитие в молодом возрасте стало тенденцией, которая прогностически неблагоприятна. Клиническая картина язвенного колита часто расплывчата, что приводит к изначально ошибочному диагнозу. Оценка эффективности лечения и риска рецидива язвенного колита, требующая инвазивного вмешательства — одна из основных диагностических проблем. Целью исследования был анализ данных современной научной литературы о неинвазивных биомаркерах язвенного колита. Проанализированы данные зарубежных и отечественных статей по теме исследования, опубликованных в Pubmed и eLibrary за последние 5-10 лет. Биомаркеры нейтрофильного происхождения являются перспективным направлением в первичной диагностике и оценке активности язвенного колита.

Ключевые слова: *язвенный колит, воспалительные заболевания кишечника, нейтрофилы, неинвазивные биомаркеры*

Конфликт интересов

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

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Abstract

The incidence of ulcerative colitis has been increasing in recent years, and its manifestation at a young age has become a trend that is prognostically unfavorable. The clinical picture of ulcerative colitis is often vague, which leads to an initially erroneous diagnosis. One of the main problems is to assess the effectiveness of treatment and the risk of recurrence of ulcerative colitis, which requires invasive intervention. The aim of the study was to analyze the data of modern scientific literature on noninvasive biomarkers of ulcerative colitis. The data of foreign and domestic articles on the research topic published in Pubmed and eLibrary over the past 5-10 years are analyzed. Biomarkers of neutrophil origin are a promising direction in the primary diagnosis and assessment of ulcerative colitis activity.

Key words: *ulcerative colitis, inflammatory bowel diseases, neutrophils, noninvasive biomarkers*

Conflict of interests

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ANCA — anti-neutrophil cytoplasmic antibodies, CD — Crohn's disease, CRP — C-reactive protein, FC — faecal calprotectin, HNE — human neutrophil elastase, IBD — inflammatory bowel disease, IBS — irritable bowel syndrome, IL-6 — interleukin 6, LF — lactoferrin, MMP — matrix metalloproteinases, NGAL — neutrophil gelatinase-associated lipocalin, TIMPS 1–4 — tissue inhibitor of metalloproteinase 1–4, UC — ulcerative colitis

Introduction

Ulcerative colitis (UC) is one of the two primary subtypes of inflammatory bowel disease (IBD). The average prevalence of UC is 50–230 cases per 100,000 individuals, and its annual increase amounts to 5–20 per 100,000, with an upward tendency in all age groups [1]. The pathogenesis of UC is not completely studies; new studies on the development of new diagnostic techniques are performed which is especially important in view of the chronic and unpredictable course of UC. Spontaneous healing and persistent remission of UC with no drug treatment is rare; repeated ulceration and constant renewal of the epithelium increase the risk of colorectal neoplasia and cancer [2]. The healing of mucosa is a key therapeutic target in cases of inflammatory bowel disease (IBD), including UC, with endoscopy being the gold standard for diagnosis and treatment. [3]. However, this examination is invasive and stressful for patients, with monitoring of the mucous membrane condition required at different stages of the disease. In view of this fact, the search and implementation of new effective and minimally invasive UC activity markers remain relevant. Therefore, the objective of our review was to analyze the current literature data on potential biomarkers and their possible prognostic significance associated with UC.

Risk factors for the development and progression of UC

The etiology of this disease is currently not completely investigated. UC has historically been a disease of the population of European countries, however, in recent years there has been an increased incidence among non-European population groups, including African American and Asian, so, it was the reason for investigating the genetic determinants of IBD development [1, 4]. Results of studies have revealed about 200 susceptibility loci for IBD in the European population and at least 35 loci in the Asian population; some of the latter were identified as Asian-specific ones [4]. Many genetic tests resulted in the identification of IBD gene polymorphisms, including *NOD2/CARD15, IL-10, IL23R* [4]. Impaired intestinal homeostasis is currently considered as the main factor contributing to the pathogenesis and progression of intestinal inflammation associated with IBD [5]. Recent studies demonstrated that special genetic features contribute to the impairment of intestinal microbiome. So, prostaglandin EP4 receptor encoded by *PTGER4* gene is necessary to maintain the integrity of epithelial barrier, and its impaired structure is associated with the development of IBD [5].

Interaction of genetic and environmental risk factors is certainly important for the development of IBD. Thus, Min Zhao et al. in their review (2022) analyzed 255 studies and defined 25 risk factors of IBD development; seven of these factors were relevant to both eastern and western populations: family history of CD or UC, history of smoking, appendectomy, tonsillectomy, diet that includes meat and meat products, vitamin D deficiency [6]. Other factors, that is, living in an urban area, current smoking, use of antibiotics and oral contraceptives, caesarean section, use of isotretinoin, obesity, diet that includes fat, eggs, and non-alcoholic products, were associated with an increased risk of IBD in only one of these populations. Risk factors for IBD development in the eastern population were the following: diet that includes eggs, increased

consumption of fat and fatty acids (both monounsaturated and polyunsaturated) [6]. At the same time, the authors identified more than 20 protective factors in relation to IBD; eight of them became common for the eastern and western populations: contact with domestic and farm animals, many births, physical activity, history of breastfeeding, H. pylori infection, current smoking status, and coffee consumption [6]. It should be mentioned that the protective role of H. pylori was also previously demonstrated in a meta-analysis by Y. Zhong (2021): negative correlations were obtained between H. pylori and the prevalence of IBD, H. pylori had a protective effect against IBD, and according to the results of meta-analysis, eradication of H. pylori contributed IBD relapse [7].

A recent meta-analysis of 19 studies demonstrated the important role of nutrition in the development of IBD [8]. The objective of this paper was to summarize data on the daily diet of adults with IBD compared with healthy individuals of the same age and sex. It was discovered that adults with IBD do not get enough energy, fiber, fat-soluble vitamins, as well as important nutrients such as folic acid, vitamins B1, B2, B3, B6, potassium, magnesium and phosphorus. The adults with UC have been found to consume significantly more fat and copper, and CD patients consume significantly less protein, iron, and fiber compared to healthy controls. Another important result of this review was that the consumption of basic products that are considered to form the basis of a healthy diet, such as cereals, legumes, fruits, vegetables and dairy products, was found to be insufficient for people with IBD [8]. Based on the above, it is possible to define the groups of individuals with high risk of UC in order to provide earlier diagnosis of this disease, including non-invasive methods.

Instrumental examinations in UC

The preferred method for UC confirmation is endoscopic examination that allows to directly observe its macroscopic signs, as well as to obtain material for histological examination [9]. Endoscopic findings in UC include mucosal edema, loss/decrease of vascular pattern, pseudopolyps, loss of haustration, diffuse hyperemia, and mucosal granularity [2]. It should be mentioned that the aforementioned endoscopic signs can be observed in other colitis; therefore, differential diagnosis essentially depends on the type of endoscopic findings and the nature of their generalization in the intestine rather than on their range [3]. The histological findings typical for this disease include basal plasmacytosis and the altered structure of mucosa and/or crypts. The altered structure of mucosa and crypts includes several signs: crypt branching, changed size of crypts, atrophy and irregularity of mucous membrane. The abovementioned signs indicate the chronicity of the inflammatory process in colon mucosa; they appear when the underlying inflammation lasts more than 4 weeks and remain during remissions [3, 10]. The other signs of inflammation in the patients with UC exacerbation are: the groups of neutrophils are found in the lamina propria of the mucosa; neutrophils invade the superficial epithelium and the crypt epithelium with the development of “crypt abscesses”; erosions and granulation tissue are visualized. These signs indicate the active process; they are observed in the exacerbation phase with underlying signs of chronicity and resolve in inactive UC [11].

The ongoing clinical trials routinely include endoscopic evaluation of healing as an endpoint, and expert consensus recommends it as an important treatment goal in clinical practice. [11]. Despite progress in the drug treatment of UC, a significant part of patients have disease relapse [3, 11]. This is due to the fact that patients who have achieved mucosal healing according to endoscopy usually have active microscopic inflammation of colonic mucosa [12]. Many studies demonstrated persistent microscopic inflammation in most patients with the endoscopic diagnosis of remission what allows suggesting that the level of inflammation with underlying UC can not be fully characterized using just endoscopic evaluation [13, 14]. Thus, it is reasonable to assume that histological remission is associated with improved clinical outcome, and it is the parameter that may be the ultimate therapeutic goal in the management of UC.

The role of neutrophils in the pathogenesis of UC

Patients with UC have massive neutrophil infiltration of the intestinal wall followed by the production of reactive oxygen species and release of serine proteases, matrix metalloproteinases, and myeloperoxidase [15]. It has been established that neutrophils express more than 1,200 cellular proteins; 400 of these proteins are located in secretory vesicles, and almost 300 — in granules [16]. Disease activity corresponds to progressive neutrophil infiltration, crypt involvement, and neutrophil exudation, ranging from minimal inflammatory activity to severe ulceration [15, 16]. Thus, neutrophil infiltration is a special histopathologic feature of UC that indicates the central role of neutrophils as effector cells in mucosal damage [17]. Neutrophil infiltration into epithelium and lamina propria is the essential component in assessing the severity of UC, in particular, in its histological assessment using Riley and Geboes scores, as well as in the recently proposed Nancy histological index [17]. Neutrophil infiltration of mucosa correlates with the endoscopic severity of UC and such systemic indicators of inflammation as C-reactive protein (CRP) level in blood serum [16, 17]. Patients with UC also have altered neutrophil apoptosis that may be associated with the release of

anti-apoptotic cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) that prolongs the life span of granulocytes during mucosal inflammation [14]. Uncontrolled accumulation of neutrophils and their persistence in the intestinal mucosa in cases of active UC may delay timely improvement of intestinal inflammation [14–17]. Therefore, neutrophils are important in the pathogenesis of UC; they are also a valuable marker in defining disease activity/severity, as well as a potentially attractive drug target for therapeutic intervention.

Non-invasive biomarkers of neutrophilic origin in cases of UC

At present, the following faecal markers of neutrophilic origin are the most widely studied as potential non-invasive markers of UC activity: faecal calprotectin (FC) and lactoferrin (LF) [18].

Faecal calprotectin (FC) is a 36 kDa zinc- and calcium-binding protein. It is located mainly in neutrophils and, to a lesser extent, in monocytes and macrophages. Calprotectin makes up 60 % of the soluble cytosolic proteins of neutrophils and is used as a marker of neutrophil turnover. It can be found in different biological fluids, such as blood serum, saliva and urine, feces [18]. FC concentration in feces is proportional to the neutrophil migration into gastrointestinal tract; thus, calprotectin is the most widely used faecal marker [18, 19]. FC measurement is used in clinical practice for the differentiation between functional bowel disorders, mainly, irritable bowel syndrome and inflammatory bowel diseases [18]. It is used as a valuable non-invasive method for monitoring disease activity in patients with IBD [20].

Lactoferrin is an 80 kDa iron-binding protein that was first found in milk and is present in many other secretions of human body. Lactoferrin is released from secondary granules in neutrophils upon activation and has many functions. In addition to its antibacterial properties, it is involved in immune response, cell growth, and cell differentiation [14].

Several clinical trials were conducted concerning the usefulness of FC and LF in the differential diagnosis of IBD and irritable bowel syndrome (IBS), as well as for predicting relapse, and as a biomarker of disease activity in patients with UC [21, 22]. The recent ACERTIVE multicentre cross-sectional study that included 371 patients demonstrated that FC levels were statistically higher in patients with endoscopic and histological activity, and cut-off level of 150–250 μg/g was proposed [23]. The results of a large study conducted in 2013–2017 that involved 185 patients revealed that FC levels ≥170 μg/g were a predictive factors of endoscopic activity, and FC levels ≥135 μg/g predicted histological activity [24]. Therefore, lower threshold FC values may be chosen to optimize the identification of patients with persistent endoscopic and histological disease activity in clinical practice. A systematic review of FC and LF as surrogate markers for endoscopic monitoring in patients with UC performed by M.N. Mosli et al. (2017) demonstrated their high sensitivity and specificity (0.88 and 0.73 for FC and 0.82 and 0.79 for LF, respectively) [16]. In other publications, FC and LF sensitivity and specificity vary from 70 % to 90 % [25].

FC value in the patients with UC correlated with endoscopic disease activity with higher accuracy, reaching 89 %, in comparison to clinical activity index, increased CRP, and leukocytosis (overall accuracy: 73 %, 62 % и 60 %, respectively) [26]. Moreover, FC is used to differentiate the severity of colitis (sensitivity: 84 %, specificity: 88 %, AUC: 0.92) [27]. FC is a prognostic factor for assessing the management and the progress of disease (relapse and postsurgical relapse), remission (sensitivity: 92.3 %, specificity: 82.4 %, AUC=0.924) and exacerbation of UC (sensitivity 76 %, specificity 85 %) [28]. Decreased FC level in patients with UC treated with infliximab was a prognostic factor for disease remission [29, 30]. FC is used for the comprehensive evaluation of patients in clinical trials conducted to test new drugs [23–26].

LF was also used to predict UC relapse. LF cut-off value of 140 μg/g of feces predicted relapse with a sensitivity of 67 % and a specificity of 68 % [29, 30]. W.A. Faubion et al. (2018) performed a comparative assessment of biomarkers in patients with UC and CD compared with endoscopic parameters [31]. The markers that feature with the closet association with the endoscopic pattern included FC, LF, and lipocalin [31]. A systematic review conducted by Y. Wang et al. (2015) demonstrated that LF in feces is a sensitive and specific marker that can help to differentiate IBD from IBS, at least, at the cohort level [32]. The highest levels of LF were observed in patients with UC. At the same time, the informative value of LF as a biomarker of UC was questioned by D. Turner et al. (2010) due to the fact that LF has demonstrated limited value in predicting sensitivity to corticosteroids in severe pediatric UC [30].

Considering the strong association with IBD, FC is currently a common secondary endpoint in clinical interventional trials. M.T. Ostermann et al. (2014) found that increased doses of mesalazine resulted in a consistent decrease in FC levels what correlated with a lower relapse rate [33]. Several studies by R. Molander et al. (2013) demonstrated that normalization of FC levels after infliximab induction therapy predicts sustained clinical remission [34].

It is important to realize that both LF and FC are derived from activated neutrophils (as well as macrophages), and their levels correlate well with the amount of neutrophils in the intestine [35]. Both markers have antimicrobial properties including iron binding that is essential for bacterial replication and binding

of lipopolysaccharides [19, 21]. These proteins can be used as biomarkers is due to their resistance to proteolytic cleavage and stability in feces [23].

Other biomarkers of neutrophilic origin in the diagnosis of UC

Neutrophils are multifunctional cells that coordinate and initiate host immune response to an infectious agent or tissue damage. During the degranulation of activated neutrophils, leukocyte proteases are released on the cell surface and into extracellular space; they regulate the interaction of innate and adaptive immune systems by modulating the expression and activity of cell receptors produced by different cytokines [35]. Sensors for leukocyte and bacterial proteinases are proteolytically activated receptors expressed on the surface of platelets, blood leukocytes and macrophages, as well as of epithelial, endothelial, mast, dendritic and other cells involved in the development of inflammation and immune response [36]. Evaluation of the intensity of neutrophil degranulation can be important with regard to the pathogenesis of many diseases, as well as the assessment of the properties of immunostimulating agents.

The family of matrix metalloproteinases (MMPs) includes 24 zinc-dependent endopeptidases that are involved in the destruction of extracellular matrix in normal physiological processes [37]. Their activity is regulated by a tissue inhibitor of MMPs (TIMPS1-4) [38]. One of the most well-studied MMP enzymes is MMP-9 (matrix metalloproteinase-9, gelatinase B, or 92-kDa gelatinase) that is increased in serum and intestinal mucosa in patients with active UC [38]. In a study that involved 85 patients with UC, 64 patients with CD, and 27 control individuals, serum MMP-9 levels were positively correlated with disease activity and were significantly higher in patients with active IBD compared with inactive IBD, as well as in patients with active UC compared with those with active CD [39]. MMP-9 level demonstrated positive correlation with serum IL-6 level, platelet and WBC count in cases of UC. It was found that MMP-9 levels in feces significantly correlate with total Mayo score and serum levels of CRP and FCP [39]. Reported results of a phase I clinical trial concerning GS-574 (anti-MMP-9 antibody) demonstrated a clinical response rate of 43 % for patients with UC vs 13 % in placebo group [40].

In patients with active UC and CD, serum levels of neutrophil gelatinase-associated lipocalin (NGAL) are increased compared with controls what indicates its potential as a biomarker of UC activity [38]. M. de Bruin et al. in their two recent trials investigated MMP-9/NGAL complex as a surrogate marker of mucosal healing in both UC and CD [41]. They measured serum MMP9/NGAL levels in two independent infliximab-treated UC cohorts and observed that the decrease in MMP-9/NGAL levels found in the subjects could predict mucosal healing with specificity as high as 91 % [41].

Elafin (a peptidase-3 inhibitor, or antileukoprotease) is a neutrophil elastase inhibitor with broad spectrum antimicrobial activity. J. Wang et al. demonstrated that elafin levels in colon bioptates were increased in the presence of strictures in patients with IBD; this fact, according to the authors, demonstrated the altered balance of proteases and antiproteases [42]. However, W. Zhang et al. in a recently published paper demonstrated a statistically significant decrease in elafin mRNA in active UC and its increase during remission [43]. The relative expression of elafin mRNA in peripheral blood leukocytes in UC negatively correlated with erythrocyte sedimentation rate, C-reactive protein level, and modified Mayo score, and in patients with CD it negatively correlated with clinical activity index [43].

Human neutrophil elastase (HNE) of serine proteases family, stored in azurophilic granules of neutrophils has broad substrate specificity and can degrade structural proteins, including elastin, collagens, and proteoglycans [44]. Alongside with elafin, HNE extracellular activity is controlled by many other endogenous protease inhibitors, such as α1-antitrypsin (α1-AT), secretory leukoprotease inhibitor (SLPI), and α2-macroglobulin [45]. According to some authors, human neutrophil elastase level is increased in the mucosa of patients with UC, so it can be used as the disease activity biomarker [46].

The presence of autoantibodies against neutrophil cell proteins is a specific feature of many autoimmune diseases. A number of published papers include the description of different anti-neutrophil cytoplasmic antibodies (ANCA) that are biomarkers for the diagnosis and prognosis of UC [47, 48]. In particular, anti-proteinase-3 ANCA is significantly more common in UC than in CD patients [48]. This allows suggesting a possible role of anti-proteinase-3 ANCA as a serological biomarker not only for diagnosis but also for differentiating UC and CD.

Cat-G is another serine protease associated with UC. Cat-G expression was found to be higher in colon and stool samples of UC patients compared to healthy individuals in control group [48]. In these samples, PAR4 expression is not only higher but is also localized mainly in crypts. On the contrary, in samples of healthy volunteers, PAR4 expression is observed in the cytoplasm of non-epithelial cells [48].

Neutrophil surface markers CD16, CD177, CD64

The outer surface of neutrophils expresses molecules that can be biomarkers or drug targets. Thus, the potential significance of these molecules as biomarkers is extremely important [35, 36]. These molecules

are not just markers on the surface of neutrophils, they are also involved in the regulation of cellular functions. For example, CD16, or Fc gamma receptor IIIb that was found on the surface of neutrophils, as well as on the natural killer cells and monocytes/macrophages, is a Fc receptor with low affinity to IgG [36, 49]. *In vitro* studies demonstrated that CD16 was involved in the activation of neutrophils by immune complexes, however, takes no part in other neutrophil functions such as phagocytosis or bacterial killing. This makes CD16 a particularly attractive potential therapeutic target in inflammatory diseases, since its inhibition would not compromise host defense against infection [50]. Neutrophilic CD16 is also involved in therapeutic response in IBD [36, 49]. There is information in literature sources on infliximab-induced neutrophil-specific CD16-related autoantibodies [50].

CD177 is another surface marker that is selectively expressed by a distinct subset of neutrophils. It is interesting that CD177 expression on neutrophils was associated with clinical response to treatment with corticosteroids in severe UC [50]. CD177 transcript doubled in patients with UC with no response to systemic corticosteroid therapy; it became one of the top 10 indicators of steroid resistance in these patients during the test for prognostic value [50]. CD64 expression is relevant for the management of UC, as CD64 upregulation correlates with loss of infliximab efficacy, and CD64 mRNA expression in colon is increased in infliximab non-responders.

Conclusion

Neutrophil infiltration is central in the pathogenesis of UC. Currently available information on the role of biomarkers of neutrophilic origin in the diagnosis of UC is extremely vast and is of potential research and practical interest. The main challenges for their use at present are the variety of cut-off values, methods and timing of feces sampling, high cost of diagnostic tests. Further improvement in the understanding of pathophysiology and increased validation of biomarkers of neutrophilic origin are likely to help in the development of an optimal procedure that includes a number of clinical and laboratory markers and will help to reduce the need for invasive diagnostic procedures in routine practice.

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РЕГЕНЕРАТИВНАЯ ТЕРАПИЯ ПРИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ: ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ КЛЕТОЧНЫХ И БЕСКЛЕТОЧНЫХ ТЕХНОЛОГИЙ

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Regenerative Therapy for Chronic Heart Failure: Prospects for the Use of Cellular and Acellular Technologies

Резюме

Хроническая сердечная недостаточность (ХСН) является одной из наиболее распространенных и тяжелых форм ишемической болезни сердца (ИБС), на фоне которой существенно снижается продолжительность и качество жизни пациентов. Применяемые в настоящее время фармакологические и немедикаментозные методы ~~ее~~ лечения недостаточно эффективны, а трансплантация сердца ограничена организационными и техническими сложностями, возникающими при выполнении этого оперативного вмешательства, а также недостаточной доступностью донорских органов. Известно, что потенциал клеток миокарда к репарации невелик, поэтому регенеративная терапия может быть востребована, как новое перспективное направление лечения ХСН.

Существует несколько направлений клеточной терапии, способствующей улучшению процессов репарации миокарда. Одним из них является трансплантация соматических стволовых клеток, которая считается безопасной и несколько улучшает сократимость миокарда, преимущественно за счет паракринных механизмов регуляции клеточного цикла. В качестве альтернативы этой методики, для трансплантации непосредственно в поврежденные участки миокарда могут быть использованы кардиомиоциты, полученные из индуцированных плюрипотентных стволовых клеток (iPSC). Однако до начала применения таких клеток у лиц, страдающих ХСН, предстоит решить проблемы их потенциальной онкогенности и недостаточно хорошей выживаемости в условиях редукции кровотока на фоне тяжелого коронарного атеросклероза. В ряде исследований рассматривались и другие направления клеточной терапии, в частности бесклеточный подход к прямому перепрограммированию, заключавшийся в преобразовании эндогенных сердечных фибробластов в индуцированные кардиомиоцитоподобные клетки. В обзоре рассматривается текущая ситуация и перспективы использования регенеративных клеточных и бесклеточных технологий при ХСН, которые могут быть введены в клиническую практику в ближайшем будущем.

Ключевые слова: *хроническая сердечная недостаточность, регенеративная клеточная терапия, клеточные и бесклеточные технологии, кардиомиоциты, фибробласты*

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Abstract

Cardiovascular diseases are the second leading cause of death and disability worldwide after malignancies. Heart failure (HF) has a large impact not only on the economics of healthcare but also on the quality of life, functionality and life expectancy of patients. Pharmacological and non-pharmacological therapies have been developed, but these medical therapies have limited effects to cure patients with severe CH. Heart transplantation is limited due to the low number of donor organs. Human cardiac potential for spontaneous repair is insignificant, so regenerative therapy is in great demand as a new treatment strategy. Currently, there are several strategies for heart regeneration. Transplantation of somatic stem cells was safe and modestly improved cardiac function after myocardial infarction and in patients with CF mainly through paracrine mechanisms. Alternatively, new cardiomyocytes could be generated from induced pluripotent stem cells (iPSCs) to transplant into injured hearts. However, several issues remain to be resolved prior to using iPSC-derived cardiomyocytes, such as a potential risk of tumorigenesis and poor survival of transplanted cells in the injured heart. Recently, direct cardiac cell-free reprogramming has emerged as a novel technology to regenerate damaged myocardium by directly converting endogenous cardiac fibroblasts into induced cardiomyocyte-like cells to restore cardiac function.

Many researchers have reported direct reprogramming of the heart in vivo in animal and human cells. In this review, we review the current status of cardiac cell-based and cell-free regenerative technology, a great hope to treat cardiovascular diseases in clinical practice.

Key words: *chronic heart failure, regenerative cell therapy, cell and cell-free technologies, cardiomyocytes, fibroblasts*

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CHF — chronic heart failure, CMPCs — cardiomyocyte progenitor cells, DCM — dilated cardiomyopathy, EF — ejection fraction, ESCs — embryonic stem cells, IHD — ishemic heart disease, iPSCs — induced pluripotent stem cells, LV — left ventricle, MNCs — mononuclear cells

Introduction

Ischemic heart disease (IHD) is reasonably considered the leading cause of disability and death in most countries of the world. IHD leads to the development of chronic heart failure (CHF) that is a global problem of present-day society, dramatically reduces the duration and quality of life of the population, and increases medical care economic burden. More than 40 million adults worldwide suffer from CHF. By 2030, its prevalence is supposed to increase by no less than 45-50 %. The incidence of detection of circulatory failure increases with population aging and is approaching a critical value of 10 per 1,000 individuals in the age group 65+.

The pathogenetic basis of CHF is primarily impaired systolic function of the myocardium of left and right ventricles. As a result, the volume of intercellular fluid increases, congestion develops in pulmonary and systemic circulation, perfusion of organs and tissues worsens, and multiple organ failure gradually develops. Classifications of circulatory failure that are currently widely used in clinical practice define the need for mechanical support of blood circulation and heart transplantation as the basic criteria for assessing disease severity, along with the degree of limitation of patient's functional activity, severity of congestive changes and their resistance to ongoing therapy. This need is due to a sharp decrease in the left ventricle (LV) ejection fraction (EF) in the vast majority of patients hospitalized for decompensated CHF. Moreover, the analysis of the prevalence of decreased LV contractile function reveals a number of significant racial and gender differences. Thus, the highest incidence of CHF is observed in African American male patients; it is accompanied by significantly decreased EF in approximately 70 % of cases. On the contrary, in Caucasian female patients, EF in 60 % of cases is slightly reduced or within normal [1, 2].

Management of CHF mainly includes pathogenesis-targeted combined drug therapy. The optimal

treatment, first of all, contributes to maintaining LV myocardium contractile function, reducing pulmonary hypertension, eliminating congestive changes, suppressing excessive activity of humoral regulatory systems, in particular, renin-angiotensin-aldosterone system that causes generalized disorders in electrolyte balance. However, the options of drug treatment, especially after the development of severe congestive circulatory failure, are often limited what results in high mortality rate in such patients. One of the most important reasons for the low efficiency of conservative treatment is the constant degradation and death of cardiomyocytes, their gradual replacement with fibroblasts that are not able to ensure the proper functional activity of ventricles. Surgical treatment can be considered as an alternative to the drug therapy of terminal CHF, the options are coronary artery bypass grafting, atrioventricular annuloplasty, valve replacement, aneurysmectomy, etc. However, their practicability and effectiveness are ambiguously assessed by different authors. Heart transplantation is considered to be the most effective procedure, however, it is limited by severe shortage of donors, stringent criteria for selecting patients, and high risk of surgical intervention. Thus, currently available pharmacological and surgical methods of CHF treatment are in some cases not effective enough and require further improvement.

One of the promising areas for the treatment of CHF patients can be considered regenerative cell-based and cell-free therapy that allows potentiating the processes of myocardial repair and thereby increasing the duration and quality of life of patients. It is generally assumed that mammalian cardiomyocytes are terminally-differentiated cells. As a result, mammals are not able to spontaneously restore the myocardium damaged by one or another pathological factor, unlike, for example, amphibians or fish that demonstrate stable regenerative reactions of myocardial after traumatic injury. However, neonatal mice demonstrated their ability to regenerate significant parts of heart muscle after its partial surgical resection [3]. Results of studies conducted by a group of researchers from Karolinska Institute revealed that the pool of cardiomyocytes is renewed during life, in humans at a rate of 0.5–1 % of the entire population per year [4]. However, the regenerative capacity of human cardiomyocytes is not sufficient enough and is not able to ensure the restoration of a more or less significant area of myocardium. At the initial stage, there were attempts of heart muscle regeneration using bone marrow mononuclear cells (MNCs). Although early clinical trials have demonstrated improvement in myocardial contractility, results of subsequent studies were less encouraging [5]. With the development of cellular technologies and the ability to obtain *in vitro* cardiomyocyte progenitor cells (CMPCs) that are able to proliferate and differentiate into mature specialized myocardial cells, there was a start of new stage of regenerative cell therapy [6]. Use of autologous CPC culture resulted in some improvement in myocardial contractile function and appeared to be safe. However, the survival rate of transplanted cells remains low, and their ability to differentiate into mature cardiomyocytes is very limited. Positive effects observed with the use of MNC and CPC cell therapy are most likely associated with paracrine effects on functioning cardiomyocytes than with their regeneration [7]. Use of cardiomyocytes derived from allogeneic pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), has also demonstrated its effectiveness. However, the use of these cell sources is limited due to the low rate of engraftment, as well as their potential oncogenicity, risk of graft rejection, and ethical reasons. Currently, cell-free regenerative methods are also developed. Stem cell therapy and reprogramming of resident fibroblasts into cardiomyocyte-like cells performed directly *in vivo* by transduction of certain cardiac-specific factors is one of the newest technologies aimed at the regeneration of cardiomyocytes and the restoration of myocardial functional performance [8, 9].

This review summarized achievements of present-day medical science and practice in investigating the options for regeneration of highly specific heart cells, as well as possibilities and issues of the use of cell-based and cell-free technologies in the clinical practice of CHF management in the near future.

Regenerative cell therapy for myocardial damage

Use of adult somatic stem cells and embryonic cells

At the early stages of regenerative medical trials, bone marrow MNCs generated considerable interest, as they demonstrated cardiogenic potential *in vitro*, as well as effectiveness in rodent models of myocardial infarction [5, 10]. Results of small clinical trials of various routes of administration of MNCs to humans have demonstrated moderately increased ejection fraction and several positive changes in the area of focal scar myocardial changes. However, subsequent numerous, randomized and double-blind clinical trials resulted in failure to reproduce previously obtained results [5, 11]. Bone marrow mesenchymal stem cells (MSCs) have also demonstrated *in vitro* cardiogenic potential and improved cardiac function in animal models of myocardial infarction. However, results of multicentre clinical trials such as POSEIDON revealed only moderate improvement in cardiac function, and further studies demonstrated that MSCs have no ability to differentiate into fully mature cardiomyocytes [12, 13].

Interest of researchers in cardiomyocyte progenitor cells (CMPCs) was driven by the report that these

cells are able to differentiate in three types required for the regeneration of myocardial structures, that is, cardiomyocytes, smooth muscle cells, and endothelial cells. *In vitro* experiments revealed the role of one of the hematopoietic markers on the surface of CMPCs. In several preclinical trials, *c-kit* (the gene encoding kit protein tyrosine kinase receptor) positive CMPCs demonstrated regenerative potential in small and large animal models [14]. First clinical trials, SCIPIO, when patients with ischemic cardiomyopathy received intracoronary autologous c-kit (+) CMPCs, revealed a slight increase in ejection fraction and a decrease in the size of cardiosclerosis area [15]. In the following study, CADUCEUS, a mixed CPC population, with c-kit (+) cells and cardiospheres, was used [7]. It was found that intracoronary infusion of autologous CMPCs during post-infarction period is safe, technically realizable and effective. In particular, there was a significant reduction in scar mass, increase in viable heart mass, and improvement in local contractility compared to the control group. However, there was no significant difference in changes in ejection fraction and end systolic and diastolic volume of LV during treatment with autologous CMPCs in treatment and control groups. More recent animal studies demonstrated that only small amount of c-kit (+) CMPCs is transformed into cardiomyocytes, they were mainly transformed in endothelial cells [16].

According to the results of preclinical studies of cell cultures, skeletal muscle precursor cells localized under the basal lamina of muscle fibers were also considered as a source for myocardial regenerative therapy. However, experiments in animal models and small clinical trials in humans revealed high incidence of ventricular arrhythmias that increased the possibility of developing sudden coronary death [17]. Pathophysiological basis for abnormal ventricular extrasystoles and episodes of paroxysmal ventricular tachycardia was the absence of electromechanical connection between transplanted cells and host cells [18]. The results of MAGIC study demonstrated no effectiveness of the use of skeletal muscle cells in ischemic cardiomyopathy, either in the near or in the long term [19, 20]. A meta-analysis of 667 patients from 11 studies who received autologous MNCs for non-ischemic dilated cardiomyopathy demonstrated good results, mainly for increasing LV ejection fraction and reducing LV end-diastolic volume. Moreover, the group of patients after MNC transplantation demonstrated improvement in the results of six-minute walk test compared with the control group [21].

A number of studies have reported the successful use of CD34+ hematopoietic autologous stem cells derived from peripheral blood along with granulocyte colony-stimulating factor mobilization in patients with dilated cardiomyopathy (DCM). Thus, according to the results of a randomized study that involved 110 patients with DCM, in treatment group there was a significant increase in LVEF, increase in walking distance in 6-minute walking test, and decreased level of N-terminal pro B-type natriuretic peptide that is one of the reliable markers of hypervolemia in CHF. Duration of follow-up for such patients was at least 5 years. Their five-year survival was 2.3-fold higher than in the control group. The increased LV EF directly correlated with the dose of CD34+ cells transplanted into myocardium [22]. However, in contrast to the fairly good results of cell therapy in DCM, its effectiveness in the management of myocardial infarction, focal or diffuse cardiosclerosis is highly controversial. In particular, method of administration of stem cells and their doses require further investigation. It also seems that there is a careful selection of patients in treatment groups considering rigorous criteria for inclusion in protocols [23].

Good results were obtained with intramyocardial use of CD34+ MNCs in patients with exertional angina of 3–4 functional class that is resistant to combined antianginal therapy. A meta-analysis of randomized, double-blind, phase 1 and phase 2 ACT-34 study and phase 3 RENEW study during long-term follow-up demonstrated improved exercise tolerance, decreased intensity and incidence of chest pain, as well as significantly reduced incidence of myocardial infarction and clinically significant CHF in patients who received cell therapy [24]. In regard to the pathogenetic basis of such a good therapeutic effect, the authors mention that cells with CD34+ receptor on their surface are able to trigger the processes of angiogenesis and neovascularization of heart tissues via several mechanisms. First, CD34+ MNCs differentiate into smooth muscle cells and endothelial cells that are the basic structural components of the inner walls of blood vessels. This, in turn, leads to vascular re-endothelialization and myocardial revascularization [25]. Secondly, these cells perform paracrine regulation by producing factors that stimulate angiogenesis and suppress apoptosis of endothelial cells and cardiomyocytes. In addition, factors released by CD34+ MNCs contribute to extracellular matrix remodeling and mobilization of additional progenitor cells [25, 26]. The pro-angiogenic mechanism of cell therapy with CD34+ MNCs is also mediated by the production of so-called exosomes, i.e. membrane-bound nanobubbles. Exosomes carry pro-angiogenic miRNAs that activate the processes of division and differentiation of stem cells [27].

The concept of using embryonic stem cells (ESCs) is attractive due to their pluripotency and ability to differentiate in any type, including functional cardiomyocytes [28]. However, the clinical use of ESCs is limited by ethical issues, as well as by the fact that they are highly immunogenic and can cause rejection reactions. In addition, there is an open question concerning the potential genetic instability of these cells and the development of benign, and possibly malignant neoplasms from them [29, 30].

Cardiomyocytes derived from induced pluripotent stem cells (iPSCs)

Another therapeutic approach involves the use of functional cardiomyocytes obtained *in vitro* from autologous or allogeneic iPSCs [31]. This treatment method was developed after the publication of the results of studies conducted by Takahashi K. et al. [32, 33] on the potential to directly reprogram mouse and human fibroblasts using a combination of four transcription factors: Oct 4, Sox 2, Klf 4 and c-Myc, also known as Yamanaka factors. iPSCs obtained that way share basic morphological and functional characteristics with ESCs and demonstrate the expression of genes of the same type; all this makes them a good alternative to embryonic cells [32–34]. Thus, the discovery of iPSCs helped to solve the existing ethical issues and has great potential for the development of cell regenerative therapy in the time of personalized medicine. Treatment with autologous fibroblasts reprogrammed into cardiac-specific iPSCs also seems to be promising. A group of Japanese researchers reported that transplanted cardiomyocytes derived from allogeneic iPSCs were able to persist in heart tissues in immunosuppressed monkeys for up to 12 weeks. Upon that, improved myocardial contractile function and increased LV EF were observed [35]. During evaluation of adverse effects, the researchers observed high incidence of ventricular arrhythmias that were most likely associated with different degrees of maturity and functional activity of the transplanted cardiomyocytes. Despite the fact that the results of further studies have demonstrated the possibility of obtaining a more mature and homogeneous cell population, the heterogeneity of cardiomyocytes obtained from iPSCs can be one of the significant obstacles to the implementation of this technique in clinical practice [36]. Another challenge is that iPSCs demonstrate pronounced genetic instability and the ability to develop teratomas *in vivo* [37].

Direct reprogramming of myocardial cells

Direct reprogramming of resident scar-forming fibroblasts into cardiomyocytes can change approach to cell therapy for cardiovascular diseases, primarily, myocardial infarction (Figure 1).

It was demonstrated that a combination of several cardiac-specific factors, such as *Gata4* (the gene encoding proteins for "zinc fingers" binding to the "GATA" DNA sequence and playing a role in the differentiation of myocardial cells), *Mef2c* (the gene encoding myocyte-specific enhancer binding factor 2C), and *Tbx5* (the gene encoding T-box transcription factor 5), is able to directly convert fibroblasts into heart muscle cells without passing through stem cell stage [9, 38]. This method allows circumventing the limitations associated with the requirements for the number of transplanted cells, their survival rate and significantly reducing the risk of teratoma development. During the experiment on animals, reprogrammed cardiomyocytes demonstrated good intercellular interaction and structural organization, had global gene expression profiling similar to natural heart muscle cells, as well as electrophysiological potentials and spontaneous contractions. Unfortunately, this combination of factors was found to be insufficient in the studies with human cells [39]. However, despite the low efficiency of reprogramming and the absence of spontaneous beating, these cells demonstrated the ability to mature and contract synchronously when co-growing with mouse cardiomyocytes. Cao N. et al in their papers have demonstrated that human fibroblasts were able to transform into cardiomyocyte-like cells using a combination of nine different chemical compounds [40].

During direct reprogramming of cardiac cells, the following different signaling pathways interact with each other: transforming growth factor-β (TGF-β), Rho-associated kinase (ROCK), WNT pathway proteins (Wnt signaling pathway is one of the mammalian intracellular signaling pathways that regulates embryogenesis and differentiation cells), Notch (transmembrane proteins that regulate cell differentiation and interaction of adjacent cells), and Akt (protein kinase B family proteins). Influence on these pathways at different stages can alter the effectiveness of therapy. It is notable that TGF-β pathway is one of the active pathways in fibroblasts as well. Inhibition of TGF-β and WNT pathways was shown to increase the efficiency of reprogramming [41, 42]. Cellular signals that ensure the normal functioning of fibroblasts probably act as a barrier during attempts to transform them into other cell types and should be suppressed for successful reprogramming. Epigenetic barriers are another obstacle to the direct reprogramming process, in addition to the typical for fibroblasts signaling pathways. For successful reprogramming, cells should be able to use genes that are inactive in a given cell population. Epigenetic factors control their activity with the help of histone methylation, acetylation, and ubiquitination [9]. Research group of Zhou Y. et al. obtained Bmi1 (B cell-specific Moloney murine leukemia virus integration site 1), a protein from the group of proteins that can remodel chromatin that is a critical epigenetic barrier for direct reprogramming of fibroblasts into cardiomyocytes [43]. The authors demonstrated that Bmi1 regulates key cardiogenic genes through direct binding of these loci in fibroblasts, and inhibition of Bmi1 contributes to their activation.

The overall goal of direct reprogramming is to restore damaged myocardium and to improve its functional state by converting endogenous fibroblasts into cardiomyocytes. The authors of several studies reported *in vivo* direct reprogramming by delivering a

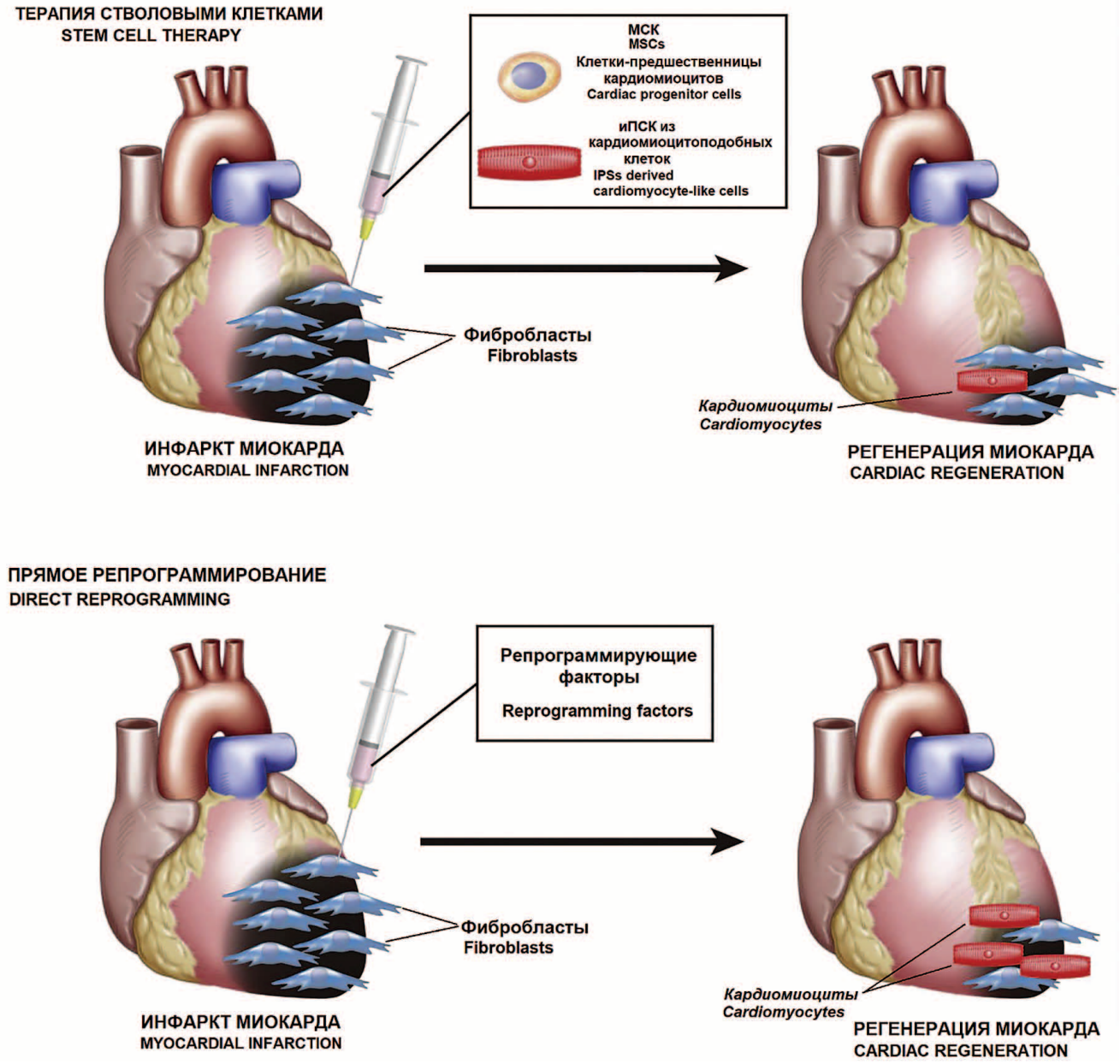

Figure 1. *Strategies for regeneration of damaged myocardium*
Note: MSC-mesenchymal stem cells, iPSCs — induced pluripotent stem cells

set of required factors to the ischemic myocardium of mice [44, 45]. Clone tracing was carried out to demonstrate the origin of these cardiomyocytes from resident cardiac fibroblasts; it allowed to confirm that the obtained cell population was not the result of a fusion with existing myocardial cells. Results of these studies demonstrated that induced cardiomyocytes developed *in vivo* are more similar in regard to their morphological and physiological parameters to endogenous cardiomyocytes in comparison with those obtained *in vitro*. This may be the result of exposure to factors of natural microenvironment, such as extracellular matrix, secreted proteins, and intercellular interactions. Although in vivo reprogramming may improve cardiac function and reduce the severity of fibrotic changes after myocardial infarction, the use of retroviral and lentiviral vectors for the delivery of cardiospecific factors to cells has prevented large-scale clinical trials. Viral vectors can randomly insert in DNA, change its sequence and contribute to insertional mutagenesis. Before the implementation of the methods of direct cardiac cell reprogramming in clinical practice, one should develop methods for controlling these cells that exclude viral integration into DNA. An interesting approach was proposed by a group of Japanese researchers who developed the Sendai polycistronic viral vector (mouse parainfluenza virus) that expressed the cardiospecific factors Gata4, Mef2c and Tbx5 (SeV-GMT). Effectiveness of SeV-GMT was demonstrated in experiments *in vitro* and *in vivo* on

animal models [46]. Sendai virus is a non-segmented RNA virus of the paramyxovirus family that replicates only in cytoplasm and does not integrate into the host genome. It should be mentioned that the use of the new technology resulted in a significant improvement in the contractile function of heart and decreased severity of myocardial scar changes in mice during post-infarction period in comparison with the group of animals that received conventional retrovirus-based treatment.

Conclusion

Known therapeutic approaches to the management of myocardial damage that leads to CHF development cannot completely prevent the development of fibrotic changes in ischemic areas of cardiac muscle and restore their normal functional activity. Cell therapy was proposed for clinical practice as a promising approach to heart muscle regeneration. However, the results of clinical trials in regard to somatic stem cells revealed their moderate effect on contractile function. One of the reasons for this result may be associated to the low engraftment of transplanted cells. Further work on the determination of the optimal doses of cells and the time of their transplantation, routes of administration, as well as the development of new technologies, such as biomatrix-based cell delivery systems and tissue engineering methods, can probably help to overcome these issues. Direct reprogramming of myocardial cells can become one of the main directions of regenerative treatment in chronic circulatory failure. Since the discovery of cardiac-specific factors, the technologies of direct reprogramming of cardiac cells have made a significant progress towards its clinical use. However, several issues should be addressed prior to start clinical trials. First, the efficiency of reprogramming remains low, and generated cardiomyocytes demonstrate heterogeneous maturity. Reprogramming efficiency can be increased by identifying additional transcription factors, miRNAs, finding new active chemical compounds, and developing methods for modifying epigenetic mechanisms of gene regulation. Second, there is a need to develop a standard optimal protocol for cardiomyocyte generation that will allow obtaining comparable research results in this area. Finally, experiments should be conducted directly on CHF models. Almost all experiments and preclinical studies on reprogramming of cardiac cells *in vivo* were carried out in the acute period of myocardial infarction. We do not know whether *in vivo* reprogramming can be applied to CHF models when there is a high demand for regenerative technologies. Regenerative medicine is a high-potential method for the management of chronic circulatory failure, and the widespread use of various types of cell therapy could significantly improve its short- and long-term results and reduce the mortality rate associated with this disease.

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СИМПТОМАТИКА В ОТДАЛЕННОМ ПЕРИОДЕ ПОСЛЕ ПЕРЕНЕСЕННОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ: РЕЗУЛЬТАТЫ ДЛИТЕЛЬНОГО НАБЛЮДЕНИЯ

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Symptoms in the Long Period after the Coronavirus Infection: Results of Long-Term Follow-Up

Резюме

Введение: данные о виде, частоте и продолжительности остаточных симптомов после COVID-19 неоднородны, что связано с методологическими особенностями проведения исследований. **Цель:** оценка частоты и выраженности симптомов в отдаленном периоде после перенесенной новой коронавирусной инфекции. **Материалы и методы:** Проведен телефонный опрос пациентов, госпитализированных в ЛРЦ МЗ РФ в связи с COVID-19 в период 13.04.2020-10.06.2020: 195 пациентов (58,2 % выписанных) через 143 (131-154) дней после дебюта заболевания и 183 (54,6 % выписанных) через 340 (325-351) дней. **Результаты:** Субъективная оценка состояния своего здоровья по 100-балльной шкале до и после перенесенного COVID-19 на первом опросе составила 95 (80-100) и 80 (70-96) баллов (p <0,001 для сравнении оценки до и после заболевания), на втором — 90 (80-100) и 80 (60-90) баллов, (p <0,001 для сравнении оценки до и после заболевания и для сравнения оценки состояния здоровья после COVID-19 на двух этапах опроса). Разнообразные жалобы выявлены у 63 % опрошенных на первом этапе и у 75 % — на втором, количество выявленных симптомов составило 2 (0-6) и 4 (1-8) соответственно. Наиболее частыми жалобами были слабость/утомляемость (31,3 и 47,5 % опрошенных), боли в суставах (31,3 и 47,5 %) и одышка/чувство нехватки воздуха (31,3 и 43,2 %). Рост этих показателей можно связывать с изменением методики опроса. Выраженность лидирующих симптомов на втором опросе при оценке по десятибалльной шкале была низкой: утомляемость 3 (0-6) баллов, боль в суставах, слабость и одышка — 0 (0-5) баллов, чувство нехватки воздуха — 0(0-3) балла. **Заключение:** снижение самочувствия сохраняется в течение длительного времени после перенесенной коронавирусной инфекции у значительной доли пациентов, однако выраженность лидирующих симптомов к 12 месяцу наблюдения достаточно низка.

Ключевые слова: *COVID-19, последствия коронавирусной инфекции, постковид, выраженность симптомов*

Конфликт интересов

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

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Abstract

Background: assessment of type, prevalence and duration of residual symptoms after COVID-19 in recent studies is controversial because of differences in design. **Aim:** to assess the prevalence and severity of symptoms in the long-term period after COVID-19. **Materials and methods:** patients hospitalized with COVID-19 in the period 13.04.2020-10.06.2020 were interviewed by phone: 195 (58,2 %) convalescents at 143 (131-154) days after disease onset and 183 (54,6 %) of them at 340 (325-351) days. **Results:** The subjective assessment of health status with 100-point scale before and after the COVID-19 was 95 (80-100) and 80 (70-96) points, p <0,001, at first interview; 90 (80-100) and 80 (60-90) points, p <0,001, at second one. Various complaints were detected in 63 % of respondents at the first interview and in 75 % at the second, the number of identified symptoms was 2 (0-6) and 4 (1-8) respectively. The most frequent complaints were weakness/fatigue (31.3 and 47.5 % of respondents), joint pain (31.3 and 47.5 %) and dyspnoe/shortness of breath (31.3 and 43.2 %). The growth of these indicators can be associated with a change in the interview methodology. The severity of the symptoms at second interview was low: fatigue — 3 (0-6) points, shortness of breath — 0 (0-3) points; joint pain, weakness and dyspnoe — 0 (0-5) points each. **Conclusion:** a decrease of health status can sustain for a long time after COVID-19. Symptoms persist in a significant proportion of convalescents, but their severity in the end of follow-up is quite low.

Key words: *COVID-19, long covid, post-covid, severity of symptoms*

Conflict of interests

The authors declare no conflict of interests

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ACTIV — Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (Analysis of ComorbidiTies in survIVors), ACVE — acute cerebrovascular event, AV — artificial ventilation, BMI — body mass index, CHD — coronary heart disease, CHF — chronic heart failure, COPD — chronic obstructive pulmonary disease, COVID-19 — new coronavirus infection, ICU — intensive care unit, LMWH — low molecular weight heparin, PCR — polymerase chain reaction, RNA — ribonucleic acid, TRC — Treatment and Rehabilitation Center of the Ministry of Health of the Russian Federation, UFH — unfractionated heparin, p_{MW} — Mann-Whitney test, p_{X2} — χ^2 test, p_W — Wilcoxon test

Introduction

Analysis of the long-term consequences of COVID-19 is important for understanding the course of this disease, evaluation of individual and population-wide need for rehabilitation, predicting the impact of this disease on patients and public health.

Despite a growing number of published papers on residual post-COVID-19 symptoms, data about their types, incidence, duration, and predictors is heterogeneous due to methodological differences between studies. Foreign researchers described the prevalence and characteristics of the consequences of coronavirus infection during different follow-up periods, mainly up to six months: 2 weeks [1], 1–3 months [2–12], 3–6 months [13–18], 6–12 months [19–21]. Results of the largest study comparing the incidence of clinical and laboratory signs in 73,435 patients who recovered from COVID-19 with a cohort of those who had no such disease (n = 4,990,835) during 6 months of follow-up demonstrated high incidence of the signs of respiratory, nervous, articular disorders, as well as a wide variety of other signs of the post-COVID-19 syndrome. These signs caused a significant increase in the administration of drug products, including pain medications and antidepressants. The highest severity of the consequences was described in patients who were hospitalized in Intensive Care Units in the acute phase of COVID-19, however, the signs of post-COVID-19 syndrome are also observed in the patients who have recovered from mild coronavirus infection [22].

Russian researchers have developed the register named “Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients” (ACTIV) in order to study the condition of patients who have recovered from COVID-19 in the Eurasian region. It includes published data on the comorbidity over time and the detection rate of symptoms 3 and 6 months after discharge [23]. A number of differences were reported in the state of Russian patients who recovered from COVID-19 that were possibly related

to the demographic profile of the population, specific features of the organization of medical care, and media representation during the pandemic.

The objective of this study was to assess the incidence and severity of symptoms during the long-term period after new coronavirus infection.

Materials and methods

354 patients received treatment at the Federal State Autonomous Institution "Treatment and Rehabilitation Center" of the Ministry of Health of Russia (TRC) for suspected coronavirus infection or confirmed COVID-19 during the period from 13 APR 2020 to 10 JUN 2020. Data on age, sex, BMI, comorbidities, date of disease onset, results of laboratory tests and instrumental examinations, specific features and treatment duration were retrospectively obtained from medical records. The data on four patients with excluded COVID-19 based on the results of follow-up and on two patients who were hospitalized in the period of long-term effects after previous coronavirus infection were not used in further analysis. 14 patients died during hospital treatment, including one patient with excluded COVID-19.

Table 1. *Main characteristics of patients included in the study*

	Hospitalized due to COVID-19	1st interview	2nd interview
n	**348**	**195**	**183**
Interview timing, day after COVID-19 debut		143 (131-154)	340 (325-351)
Age, years	58,9 (49-70)	56,2 (44,9-64,7)*	56,2 (44,9-65,3)*
Number (%) of women	197 (57 %)	105 (53,8 %)	101 (55,2 %)
BMI, kg/m2	28,4 (24,9-32,1)	29,7 (26,0-32,8)*	29,7 (26,2-33,0)*
Day of illness at the time of hospitalization	8 (6-11)	9 (7-11)	9 (7-11)
Length of stay in hospital (bed days)	17 (14-20)	16 (13,5-19)	16 (13-19)
Number (%) of patients with a positive PCR test	246 (71 %)	138 (71,1 %)	127 (69,8 %)
Hypertonic disease	149 (42,8 %)	86 (44,1 %)	82 (44,8 %)
Diabetes	44 (12,6 %)	29 (14,9 %)	28 (15,3 %)
IHD	27 (7,8 %)	14 (7,2 %)	14 (7,7 %)
Atrial fibrillation	18 (5,2 %)	10 (5,1 %)	8 (4,4 %)
Chronic heart failure	7 (2,0 %)	3 (1,5 %)	3 (1,6 %)
cognitive decline	16 (4,6 %)	11 (5,6 %)	11 (6,0 %)
Postponed stroke	12 (3,5 %)	5 (2,6 %)	5 (2,7 %)
Hypothyroidism (medicated compensated)	22 (6,3 %)	9 (4,6 %)	9 (4,9 %)
COPD or bronchial asthma	12 (3,5 %)	7 (3,6 %)	7 (3,8 %)
Active cancer	45 (12,9 %)	20 (10,3 %)	19 (10,4 %)
Cancer in the past	9 (2,6 %)	5 (2,6 %)	5 (2,7 %)
Number (%) of patients treated in the ICU	59 (17,0 %)	29 (14,9 %)	27 (14,8 %)
Number (%) of patients receiving oxygen therapy	26 (7,5)	14 (7,2 %)	14 (7,7 %)
Number (%) of patients receiving high-flow oxygen therapy	9 (2,6 %)	5 (2,6 %)	4 (2,2 %)
Number (%) of patients receiving ALV	24 (6,7 %)	10 (5,1 %)	9 (4,9 %)
Hydroxychloroquine	260 (80 %)	144 (77,8 %)	134 (76,6 %)
Azithromycin	233 (71 %)	130 (70,3 %)	121 (69,1 %)
Antibiotics other than azithromycin	231 (80 %)	134 (83,2 %)	125 (82,8 %)
Antibiotics, including azithromycin	295 (95 %)	178 (96,2 %)	169 (96,6 %)
UFH or LMWH	267 (82 %)	149 (81,4 %)	140 (80,9 %)
Lopinavir/ritonavir	10 (3,1 %)	5 (2,7 %)	5 (2,9 %)
Glucocorticosteroids	38 (12 %)	23 (12,8 %)	21 (12,4 %)
Tocilizumab	21 (6 %)	13 (7,0 %)	10 (5,6 %)
Sarilumab	7 (2 %)	3 (1,6 %)	3 (1,7 %)
Baricitinib	13 (4 %)	10 (5,3 %)	9 (5,1 %)

Note: IHD — ischemic heart disease, ALV- artificial lung ventilation, BMI — body mass index, UFH — unfractionated heparin, LMWH — low molecular weight heparin, ICU — intensive care unit, PCR — polymerase chain reaction, COPD — chronic obstructive pulmonary disease

As a pilot study, we conducted a telephone survey of 195 (58.2 %) discharged patients 143 (131–154) days after disease onset. In addition to those who died in hospital, patients with known mental disease or dementia, patients who lived in nursing homes, and patients who refused telephone interview were also excluded.

Patients were asked to respond (yes/no) to a question about whether they had the following symptoms: dyspnea, feeling short of breath, feeling of not getting enough air, cough, sputum production, weakness, fatigue, chest pain, lack of smell, lack of taste or abnormal taste, loss of appetite, joint pain, muscle pain, nasal congestion, nasal discharge, headache, dizziness, diarrhea, eye redness, dry eyes, fever, anxiety, low mood, hair loss. For further analysis, the number of symptoms present was used.

We also asked patients to evaluate their general state of health before and after the coronavirus infection using a 100-point scale.

340 (325–351) days after the disease onset, we re-interviewed 183 (54.6 %) discharged patients (93.9 % of those interviewed at the first stage). At the second stage of this study, we detalized the answers to the questions by asking patients to assess the severity of each symptom using a 10-point scale. To compare the data obtained with the results of the previous survey, an answer was considered positive if the patient assessed symptom severity as ≥1 point. For the analysis, we used the number of symptoms present and the sum of points, as well as a 100-point assessment of general state of health before and after COVID-19.

The results obtained were processed using Excel and Jamovi software. Median and interquartile range were used to describe continuous variables. In case of incomplete data, the exact number of patients with a known value of parameter (n) is specified. Independent quantitative variables were compared using Mann-Whitney test (p_{MW}), qualitative variables — using $\chi 2$ test (p_{X2}), dependent variables — using Wilcoxon test (p_W).

Results

Basic characteristics of enrolled patients are presented in Table 1. Diagnosis of COVID-19 was confirmed by at least one positive nasopharyngeal PCR for SARS-CoV-2 RNA during the period of disease in 71 % of hospitalized patients. The presence of CHD was determined by convincing signs of past myocardial infarction, revascularization, high pretest probability, or verified coronary atherosclerosis; CHF was detected by decreased left ventricular ejection fraction of less than 40 %, or by laboratory tests that confirmed the diagnosis before coronavirus infection. High frequency of oncological comorbidity was due to the fact that 39 patients were transferred to LRC from another medical institution where they received chemotherapy and/or radiation therapy for malignant neoplasms.

There were no significant differences in the age of male and female patients during three stages of the study. The respondents were younger compared with the rest of hospitalized patients and also had high BMI; otherwise, the interviewed sample was representative in regard to the inception cohort of hospitalized patients.

Figure 1 presents the results of patients' subjective evaluation of their health state using a 100-point scale before and after COVID-19 during the first and second surveys. There was a statistically significant decrease in scores after the disease that worsened by the time of the second survey. At the same time, assessments of the baseline state of health at different stages of the survey did not differ significantly.

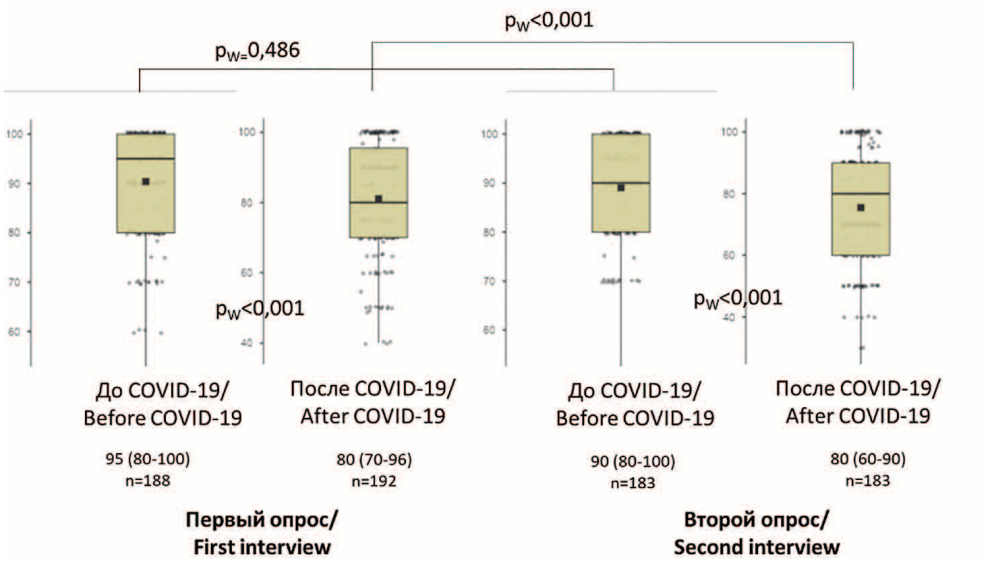

Figure 1. *The subjective assessment of health status with 100-point scale before and after the COVID-19 at first and second interview*

Note: pW- Wilcoxon method, Covid-19 — new coronavirus infection

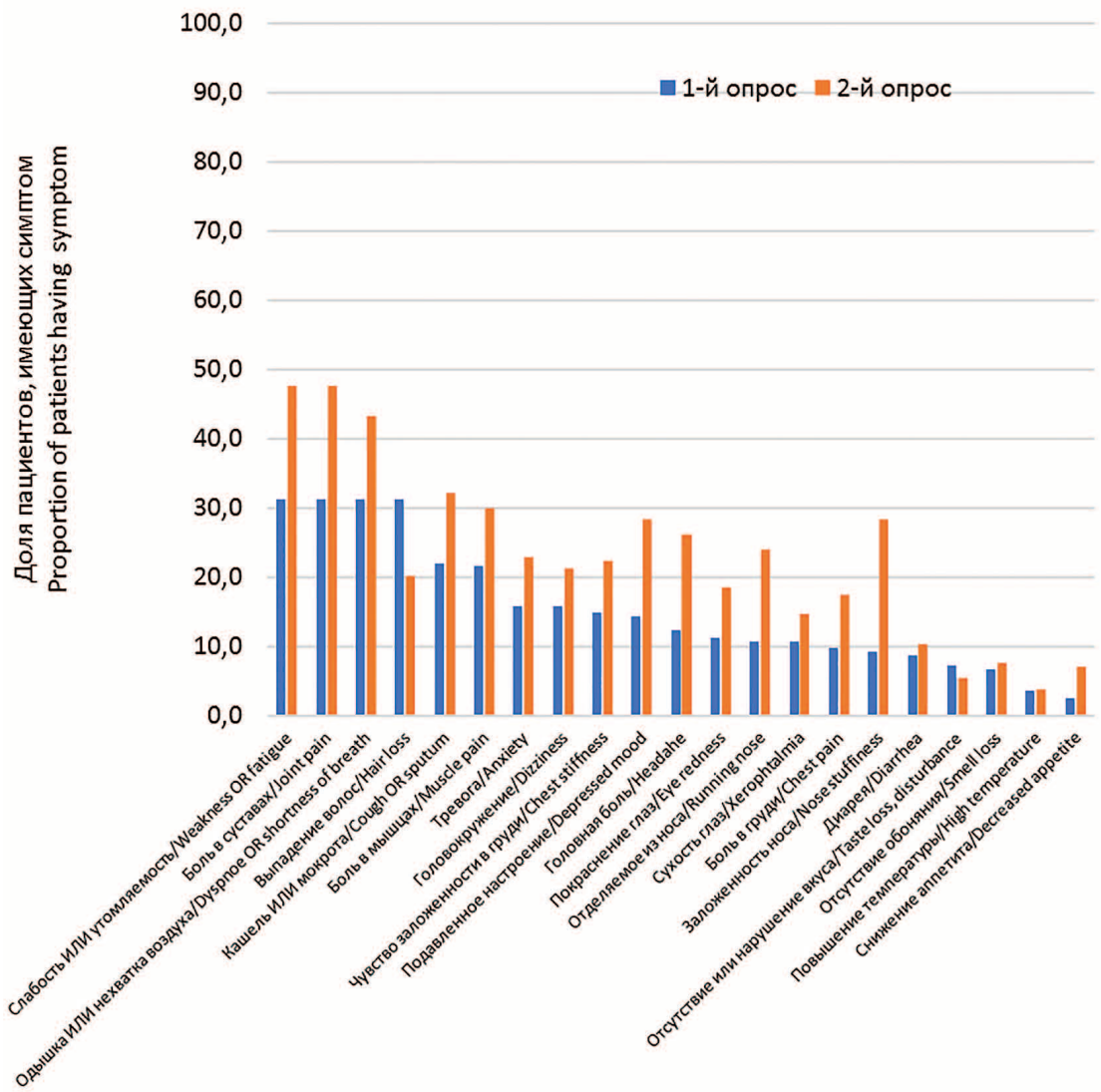

Figure 2. *Prevalence of symptoms at first and second interview*

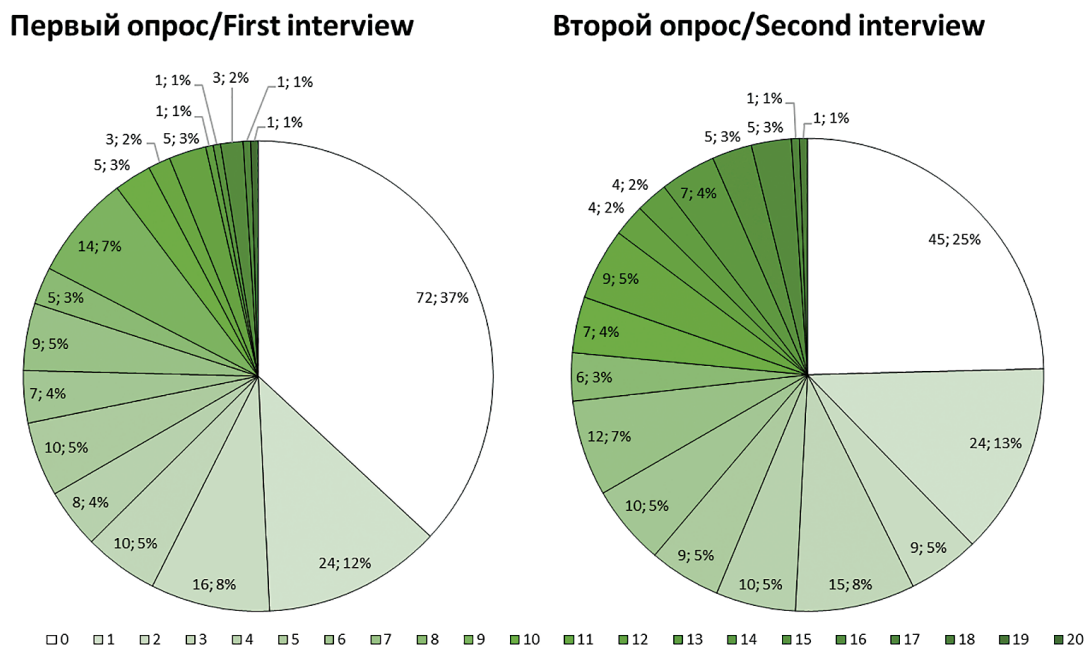

Figure 3. *Number and proportion of interviewed patients with different number of symptoms at first and second interview*

Figure 4. *The average severity of symptoms identified in the second interview (on a 10-point scale). The numbers indicate the median and interquartile range of symptom severity*

Detection rate of symptoms during two stages of the study is presented in Figure 2. Detection rate values for dyspnea/feeling of not getting enough air, weakness/fatigue, and cough/sputum production were combined for visual convenience because the symptoms are interchangeable to a high degree.

The most common complaints were weakness/fatigue (31.3 and 47.5 % of participants in two surveys, respectively), joint pain (31.3 and 47.5 %), and dyspnea/feeling of not getting enough air (31.3 and 43.2 %).

Figure 3 presents the number of patients with different number of complaints. As one can see, 37 % of patients at the first stage of the survey had no symptoms, as well as 25 % at the second stage. The number of symptoms identified in the respondents was 2 (0–6) at the first stage and 4 (1–8) at the second one.

A marked increase in the detection rate of almost all symptoms during the second survey can be explained by a change in the survey method from binary design to a more sensitive ten-point scale. In this regard, no analysis of the statistical significance of differences in the incidence of symptoms at the two stages of the study was performed.

As one can see from Figure 4, the severity of the most common symptoms (fatigue/weakness, dyspnea/feeling of not getting enough air, pain in joints and muscles) assessed by patients using a 10-point scale during the second survey, was quite low.

Discussion

A statistically significant and clinically noticeable decrease in the subjective assessment of one's health using a 100-point scale was revealed that persisted for a year after the recovery from COVID-19. The results of this assessment technique on a similar sample were quite similar: The patients who received treatment for confirmed coronavirus infection on an outpatient basis and in hospital (age 48 (37–57), 44 % female patients) assessed their health at baseline as 85 (75–90) points; at week 16 of follow-up (n = 117) — as 80 (70–90) points; at week 32 (n = 66) — as 80 (75–90) points [24].

63 % of respondents had various complaints 143 (131–154) days after the disease onset, and 75 % — 340 (325–351) days after the disease onset. The most frequent complaints were weakness/fatigue (31.3 and 47.5 %), joint pain (31.3 and 47.5 %) and dyspnea/feeling of not getting enough air (31.3 and 43.2 % of respondents); these results may indicate persistent respiratory failure and asthenia.

When comparing our results with the data of foreign observational studies and the ACTIV register [1–23], one can observe a fairly large range of the incidence of the main detected symptoms (Figure 5). This is due to significant differences in the design of these studies (number, age of patients, part of female patients, part of patients with confirmed diagnosis, part of patients

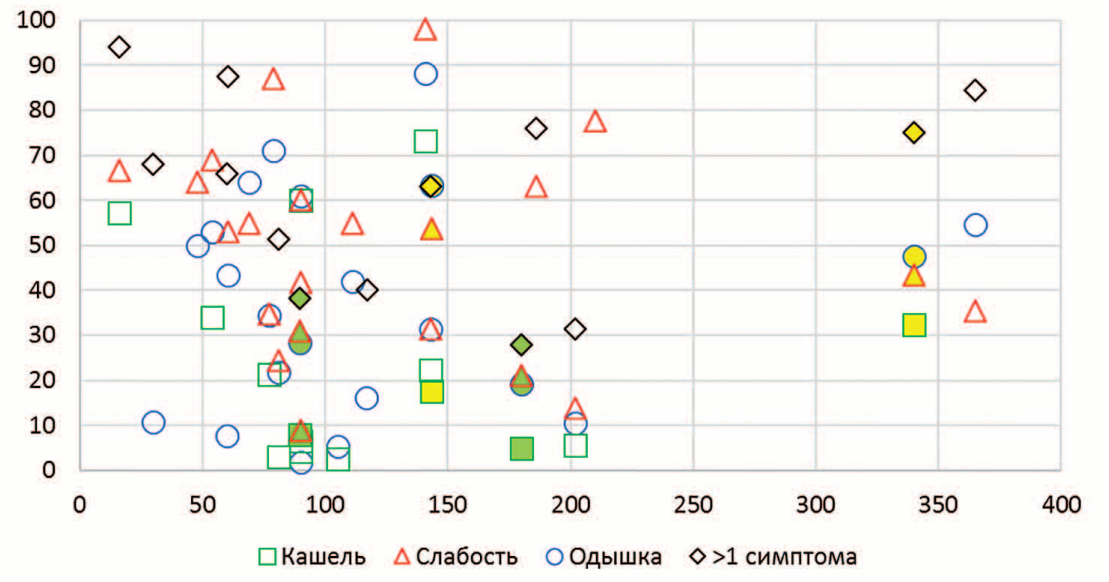

Figure 5. *Frequency of detection and duration of post-COVID symptoms. Comparison of own data (yellow markers) with the results of foreign studies and data from the AKTIV register (green markers) [1-23]*

who required hospitalization in the acute phase of COVID-19, methods for symptom detection, comorbidity of participants). However, it is clear that significant part of patients can demonstrate different of symptoms that worsen state of health for at least 12 months after coronavirus infection.

Enrolled patients received treatment during the acute phase of COVID-19 in one health care facility, and this fact may limit extrapolation of results.

Our study has several limitations associated with the telephone survey design that is characterized by the subjectivity of the self-assessment of symptom severity by patients, and possible variations in the interpretation of the names of these symptoms. In particular, the younger the respondents were, the easier was communication. However, the sample of respondents was representative of all hospitalized patients by sex, the frequency of confirmed coronavirus etiology of the disease, comorbidities and use of various groups of drugs, duration of hospitalization and stay in ICU.

An increase in the detection rate of almost all symptoms during the second survey can be explained by a change in the survey method from binary design to a more sensitive ten-point scale. Low severity of the symptoms identified during the second survey indicates a critical attitude to their clinical significance.

One can not state that the symptoms identified during the interviews are a direct consequence of a past coronavirus infection and are not associated with present comorbidities, since no comparisons were made with a sample of patients comparable in terms of sex, age and comorbidity and who had no COVID-19. In addition, it is not known whether the interviewed patients had any complaints of any severity prior to COVID-19. We were able to partially overcome this limitation in our research due to a retrospective self-assessment of the state of health of patients before coronavirus infection using a 100-point scale. These limitations can be eliminated only within a large prospective comparative study with the participation of patients comparable in terms of sex, age and comorbidity and who had no COVID-19. Under the current circumstances, no such study can be expected.

Spread of new strains, as well as mild course of the disease in vaccinated people can significantly affect the incidence, severity, and characteristics of post-COVID symptoms [25].

Conclusion

Decreased self-assessment of the state of health due to different symptoms persists for a long time after past coronavirus infection in a significant part of patients, however, the severity of the most common symptoms was quite low by month 12 of follow-up. The data obtained on the nature, prevalence, and duration of post-COVID-19 symptoms generally correspond to the results of previous studies.

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УРОВЕНЬ IGA АНТИТЕЛ К CD74 У ПАЦИЕНТОВ СО СПОНДИЛОАРТРИТАМИ И ДЕГЕНЕРАТИВНО-ДИСТРОФИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ ПОЗВОНОЧНИКА

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The Level of IgA Antibodies to CD74 in Patients with Spondyloarthritis and Degenerative-Dystrophic Diseases of the Spine

Резюме

По данным литературы аутоантитела IgA к антигену CD74 рассматриваются в качестве возможного маркера для диагностики аксиальных спондилоартритов (СпА). У пациентов с болью в спине в связи с дегенеративно-дистрофическими заболеваниями позвоночника (ДДЗП) уровень аутоантител к CD74 не изучался. Представляет интерес сопоставление уровня аутоантитела IgA к антигену CD74 у пациентов с хронической болью в спине при различных заболеваниях. **Цель** настоящего исследования — сравнение уровней аутоантитела IgA к антигену CD74 у пациентов со СпА и ДДЗП. **Материалы и методы.** В исследовании включено 87 пациентов (55 мужчин, средний возраст 41 [29; 49] лет) со СпА, отвечающих критериям аксиального спондилоартрита Assessment of Spondyloarthritis International Society (2009), и 39 пациентов (25 мужчин, средний возраст 45 [34; 53] лет) с ДДЗП, верифицированных неврологом (коды МКБ-Х — M 51.1 и M 54.4). Методом

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количественного иммуноферментного анализа измеряли содержание аутоантител IgA к CD74 в образцах сывороток у пациентов со СпА и ДДЗП. **Результаты.** Средний уровень аутоантител IgA к CD74 у пациентов со СпА составил 11,3 [5,4; 19,4] Ед/мл, у пациентов с ДДЗП — 6,9 [4,5; 13,7] Ед/мл (p=0,024). Концентрация аутоантитела IgA к антигену CD74, превышающая пороговое значение, выявлена у 58 (66,7 %) пациентов со СпА и только у 11 (28,2 %) пациентов с ДДЗП (p<0,001). У пациентов с ДДЗП повышение уровня аутоантител IgA к CD74 выявлено у 10 (40 %) из 25 мужчин и у 1 (7,1 %) из 14 женщин (p = 0,029, χ^2 = 4,785). **Выводы.** У 2/3 пациентов со СпА установлено повышение уровня аутоантител IgA к CD74. При этом у пациентов со спондилоартритами значимо повышена концентрация аутоантител IgA к CD74 по сравнению с пациентами с ДДЗП.

Ключевые слова: *IgA антитела к CD74, спондилоартрит, дегенеративно-дистрофические заболевания позвоночника*

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

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Abstract

Background. According to the scientific literature, anti-CD74 IgA antibodies (IgA anti-CD74) are considered as a possible marker for the diagnosis of axial spondyloarthritis (SpA). The level of IgA anti-CD74 in patients with back pain due to degenerative spine disease has not been studied. Therefore, it could be interesting to compare the serum levels of IgA anti-CD74 in patients with chronic back pain in various diseases. **Aim**: to compare the levels of IgA anti-CD74 in patients with SpA and degenerative spine diseases. **Material and methods.** A total of 87 SpA patients (55 male, mean age 41 [29; 49] years) fulfilling the Assessment of Spondyloarthritis International Society (2009) criteria for Axial SpA, and 39 patients (25 male, mean age 45 [34; 53] years) with neurologist-verified degenerative spine diseases (ICD 10 codes — M 51.1 and M 54.4) were enrolled to the study. The serum levels of IgA anti-CD74 were analyzed by enzyme-linked immunosorbent assay (ELISA) in all patients. **Results.** The median levels of IgA anti-CD74 in patients with SpA were 11.3 [5.4; 19.4] U/ml, in patients with degenerative spine disease — 6.9 [4.5; 13.7] U/ml (p=0.024). IgA anti-CD74 serum levels were above the cut-off value in 58 (66.7 %) patients with SpA and only in 11 (28.2 %) patients with degenerative spine disease (p<0,001). The elevated serum levels of IgA anti-CD74 were detected in 10 (40 %) of 25 male patients and in 1 (7.1 %) of 14 female patients (p = 0.029, χ2 = 4.785) with degenerative spine disease. **Conclusion**. Serum levels of IgA anti-CD74 were increased in two-thirds of patients with SpA. IgA anti-CD74 was significantly higher in SpA patients compared to patients with degenerative spine disease.

Key words: *IgA antibodies to CD74, spondyloarthritis, degenerative-dystrophic diseases of the spine*

Conflict of interests

The authors declare no conflict of interests

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ASDAS — the Ankylosing Spondylitis Disease Activity Score, BASDAI — the Bath Ankylosing Spondylitis Disease Activity Index, CRP — C-reactive protein, DDDS — degenerative and dystrophic diseases of the spine, ESR — erythrocyte sedimentation rate, SpA — spondyloarthritis

Introduction

Spondyloarthritis (SpA) is a group of chronic inflammatory diseases of spine, joints, and entheses that are characterized by common clinical, X-ray and/or MRI signs and genetic features [1]. The pathogenesis of SpA is not fully understood. According to current concepts, investigation of the pathogenesis of SpA is based on the theory of the autoimmune nature of this disease, however, no autoantibodies were found that could be used to diagnose this disease, to assess SpA activity, and, in the long term, the effectiveness of ongoing treatment [2]. There are several known types of autoantibodies with not finally determined role in SpA: autoantibodies to beta-2-microglobulin, mutated citrullinated vimentin, sclerostin, CD74, etc. [3]. Over recent years, researchers turned their attention to analysis of the role and diagnostic value of anti-CD74 IgA autoantibodies in patients with SpA. Anti-CD74 autoantibodies that were first identified in 2014 by N.T. Baerlecken et al. [4], are currently considered as a candidate biomarker for the diagnosis of axial SpA, in particular, of non-radiographic axial SpA.

Currently, literature sources have no definitive information about the role and significance of anti-CD74 autoantibodies in the patients with SpA. Thus, a higher diagnostic significance of the combination of HLA-B27 and CD74 for the diagnosis of early axial SpA was observed in the European population compared to the determination of HLA-B27 alone [5]. According to the literature sources, anti-CD74 IgA autoantibodies may become a possible immunological biomarker for the diagnosis of axial spondyloarthritis [6]. However, according to Liu Y. et al., the ambiguity of the data obtained and the discrepancy between the results of studies conducted may be due to ethnic differences in the studied groups of patients, or errors in laboratory tests (perhaps, storage time or the fact of sample freezing) [3]. At the same time, we found no data in available literature on the level of anti-CD74 autoantibodies in patients with back pain caused by degenerative and dystrophic diseases of the spine (DDDS). The use of anti-CD74 IgA autoantibodies level for early diagnosis of SpA, as well as for differential diagnosis of diseases in patients with chronic back pain is of undoubted academic and practical interest. This paper is a pilot study on the comparison of the level of anti-CD74 IgA autoantibodies in the patients with SpA and DDDS.

The objective of this study was to compare the level of anti-CD74 autoantibodies in the patients with SpA and DDDS.

Materials and methods

This study included in total 126 patients aged 28–55, with chronic back pain of different origin. All patients were hospitalized in the Rheumatology or Neurology Department of Saratov Regional Clinical Hospital during the period of 2017–2019 due to persistent intense back pain that could not be managed at the outpatient stage of treatment. All patients signed an informed consent form to enter the study. This study was approved by the Ethics Committee of V.I. Razumovsky Saratov State Medical University of the Ministry of Health of Russia. Patients with oncohematological, rheumatic diseases (except for SpA), acute chronic pathologies, patients with injuries, mental diseases, drug or alcohol abuse, infections (HIV/viral hepatitis), as well as pregnant women were excluded from the study.

The group of patients with SpA included 87 patients (55 men, average age 41 [29; 49]) who were hospitalized in the Rheumatology Department and participated in PROGRESS prospective cohort single-center study (PROGram for monitoRing the activity and functional status of patiEnts with Spondyloarthritis in the Saratov region; registration on the website www.citis.ru, No. 01201376830 from 09 DEC 2013). All patients with SpA met the criteria for axial spondyloarthritis established by the Assessment of Spondyloarthritis International Society (2009). The group of patients with DDDS included 39 patients (25 men, average age 45 [34; 53]); the diagnosis was confirmed by a neurologist (codes M.51.1 and M.54.4 in ICD-10). SpA group included 32 female and 55 male patients; DDDS group — 14 female and 25 male patients. SpA and DDDS groups were comparable in terms of sex, age, and disease duration. SpA activity was assessed by calculating the ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) activity scores [7, 8]. Erythrocyte sedimentation rate (ESR) and highly sensitive C-reactive protein (CRP) levels were determined in all patients. To determine the amount of anti-CD74 (IgA) autoantibodies in the obtained serum samples of patients, a quantitative enzyme immunoassay technique was used using AESKULISA® SpAdetect reagents (AESKU, Germany) according to the instructions attached to the kit (threshold value of normal level was 12 U/mL).

Duration of SpA was 10 [7; 20] years; the age of disease onset was 31.5 [27; 42] years. In patients with DDDS, disease duration was 8 [5; 18] years; the age of disease onset was 36.5 [34; 45] years. Description of patients with SpA and DDDS is presented in Table 1; $p \geq 0.05$ for all parameters. Cardiovascular risk was comparable in patients with SpA and with DDDS.

Statistical processing of obtained data was carried out using Microsoft Office Excel 2007 (Microsoft Corp., USA) and STATISTICA 8.0 (StatSoft Inc, USA). The nature of data distribution was assessed by a graphical method and using Shapiro — Wilk test. Descriptions of parameters other than the normal distribution are presented as Me [Q1; Q3], where Me is the median, Q1 and Q3 are the first and third quartiles. If data distribution was other than normal, nonparametric methods were used: Mann-Whitney test, Wald-Wolfowitz runs test, χ^2 test, Fisher's test, Wilcoxon test.

Results

Average ESR in patients with SpA and DDDS was 11 [6; 20] mm/h and 7 [2; 9] mm/h, respectively ($p = 0.0001$). CRP level in patients with SpA was 10.5 [4.0; 20.0] mg/mL, in patients with DDDS — 4.0 [3.4; 6.5] mg/mL ($p = 0.0001$). The average level of anti-CD74 IgA autoantibodies in patients with SpA was 11.3 [5.4; 19.4] U/mL, in patients with DDDS — 6.9 [4.5; 13.7] U/mL ($p = 0.024$). Increased concentration of anti-CD74 IgA autoantibodies above the threshold value was found in 58 (66.7%) patients with SpA and only in 11 (28.2%) patients with DDDS ($p < 0.001$), Fig.1.

Concentration of anti-CD74 IgA autoantibodies exceeded the threshold value with the same frequency in male and female patients with SpA: in 36 (65.5%) male and 22 (68.8%) female patients. Analysis of data revealed a trend towards increased incidence of elevated levels of anti-CD74 IgA autoantibodies in 10 (40%) male patients compared with 1 (7.1%) female patient with

Table 1. *The main clinical and demographic parameters and characteristics of drug treatment in patients with spondyloarthritis and degenerative spine diseases, included in the study*

Parametr	Patients with spondyloarthritis (n = 87) Me [Q1; Q3] / n (%)	Patients with degenerative spine diseases (n = 39) Me [Q1; Q3] / n (%)
Age, years	43 [36; 51]	47 [38; 55]
Age of onset of the disease	31,5 [27; 42]	36,5 [34; 45]
Men	55 (63,2)	25 (64,1)
Women	32 (36,8)	14 (35,9)
Duration of the disease, years	10 [7; 20]	8 [5; 18]
BMI, kg/m^2	24,2 [18; 32]	25,1 [19; 34]
Obesity	14 (16,1)	7 (17,9)
Totalcholesterol, mmol/L	4,8 [4,0; 5,8]	4,9 [4,1; 6,0]
Arterial hypertension	25 (28,7)	11 (28,2)
	Therapy	
NSAIDs	85 (97,7)	39 (100)
Glucocorticoids	12 (13,8)	-
DMARs, including:		-
Methotrexate	2 (2,3)	-
Sulfasalazine	1 (1,1)	-
bDMARDs	2 (2,3 %)	-

Notes: BMI — body mass index, NSAIDs — non-steroidal anti-inflammatory drugs, DMARs — disease-modifying antirheumatic drugs, bDMARDs — biological disease-modifying anti-rheumatic drugs

DDDS (p = 0.070). Men with DDDS and the level of anti-CD74 IgA autoantibodies above the threshold value demonstrated significantly increased concentration of CRP compared to this parameter in men with DDDS and the level of anti-CD74 IgA autoantibodies below the threshold value (5.8 [4.4; 7.5] and 2.4 [2.2; 4.2] mg/mL, respectively, p = 0.038).

Discussion

Differential diagnosis of chronic back pain is a challenge in clinical practice [9]. Insufficient effectiveness of conventional instrumental examinations and laboratory tests for diagnosing SpA, especially at the early stages of this disease, is the reason for searching new immunological markers for differential diagnosis in patients with back pain [10]. According to research findings, anti-CD74 autoantibodies have the highest clinical and diagnostic significance in SpA [11, 12, 13]. At the same time, anti-CD74 IgA autoantibodies were not studied in patients with DDDS and chronic back pain. Interleukin 6 levels, the activity of cathepsin B, and hyaluronic acid in blood serum were studied as biomarkers of inflammation in patients with DDDS [14, 15]. Results of these studies revealed that patients with DDDS have slightly increased levels of interleukins. In our research, we have found that the concentration of anti-CD74 IgA autoantibodies was significantly higher in patients with SpA than in patients with DDDS. These results are comparable with the results obtained by foreign researchers that demonstrated high sensitivity and specificity of anti-CD74 IgG in patients with SpA what confirms clinical, pathogenetic and diagnostic significance of anti-CD74 autoantibodies in this disease.

Besides, a higher level of CRP was observed in men with DDDS and increased concentration of this immunological marker, than in men with DDDS and the level of anti-CD74 IgA autoantibodies below the threshold value. The data obtained raise questions about the reasons for such a combination in patients with DDDS, as well as about the nature and characteristics of the pathological process, and the need for additional special examination in order to exclude or confirm SpA in this group. Unfortunately, so far, SpA is often diagnosed with delay [9]; the patients with early onset of chronic pain are for a long time treated for DDDS by many doctors, whereas SpA is diagnosed with 7-10 years delay or even later. Such patients suffer from chronic pain, lose working capacity; moreover, they have to undergo repeated resultless examinations with different specialists, as well as diagnostic procedures, including computed tomography; however, SpA is diagnosed only by a rheumatologist. One of the most urgent issues of today is the timely diagnosis of SpA to use "the window of opportunity" and provide time therapy. In this regard, the results obtained are of undeniable academic and practical interest. These data certainly do not allow drawing definite and far-reaching conclusions, however, they allow suggesting that the determination of anti-CD74 IgA autoantibodies can be used in the future in differential diagnostics of patients with chronic back pain, if sufficient evidence is collected.

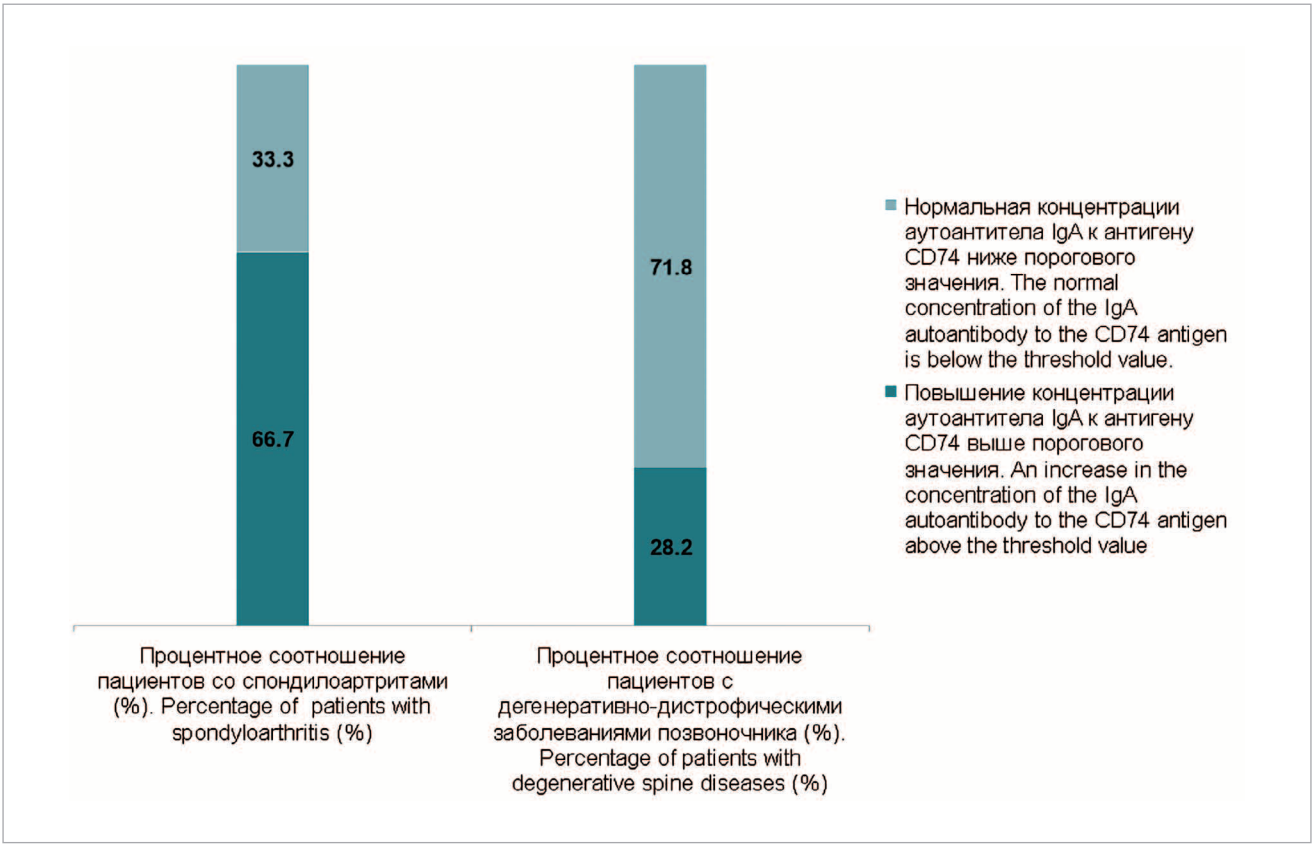

Figure 1. *The patients with spondyloarthritis and degenerative spine diseases with a concentration of IgA to CD74 above and below the threshold level*

Limitations

This study was conducted on a small sample of patients that were included in the study along with different concomitant treatment. Extrapolating the results of this study to all patients with SpA and DDDS should be done with caution.

Conclusion

2/3 of patients with spondyloarthritis demonstrated increased level of anti-CD74 IgA autoantibodies. Moreover, the concentration of anti-CD74 IgA autoantibodies in patients with spondyloarthritis was significantly increased in comparison with patients with DDDS. Determination of the level of anti-CD74 IgA autoantibodies in combination with conventional laboratory tests and instrumental methods of examination seems to be high-perspective for differential diagnosis in patients with chronic back pain; larger studies with specific design are required, with follow-up of patients at the early stages of disease development, i.e. patients with chronic back pain and increased levels of anti-CD74 IgA autoantibodies and CRP.

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КЛИНИЧЕСКИЙ СЛУЧАЙ СИНДРОМА ТАКОЦУБО В РАННЕМ ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ РИНОПЛАСТИКИ

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A Clinical Case of Takotsubo Syndrome in the Early Postoperative Period of Rhinoplasty

Резюме

Синдром такоцубо (СТ) представляет собой острою обратимую дисфункцию миокарда левого желудочка, вызванную эмоциональным или физическим триггером. В периоперационном периоде СТ в некоторых случаях индуцируется различными психологическими факторами, такими как стресс до/после операции, и непсихологическими факторами, например — введение лекарственных препаратов. В данной статье приводится описание клинического наблюдения синдрома такоцубо, развившегося в раннем послеоперационном периоде ринопластики.

Ключевые слова: *вторичный синдром такоцубо, инвертированный тип, ринопластика*

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

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Abstract

Takotsubo syndrome (TS) is an acute reversible left ventricular myocardial dysfunction caused by an emotional or physical trigger. In the perioperative period, TS is in some cases induced by various psychological factors, such as stress before/after surgery, and non-psychological factors, such as drug administration. This article describes the clinical observation of takotsubo syndrome that developed in the early postoperative period of rhinoplasty.

Key words: *acute coronary syndrome, takotsubo syndrome, inverted type, clinical case, rhinoplasty*

Conflict of interests

The authors declare no conflict of interests

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BNP — brain natriuretic peptide, BP — blood pressure, CVG — cardiac ventriculography, ECG — electrocardiography, Echo — echocardiography, EF — ejection fraction, ICU — intensive care unit, LV — left ventricle, MRI — magnetic resonance imaging, ThO — thoracic organs, TS — takotsubo syndrome, VCR — ventricular contraction rate

Introduction

Takotsubo syndrome (TS) is an acute reversible heart disease with clinical presentation and results of laboratory tests and instrumental examinations similar to acute coronary syndrome. A prior significant stressor is a typical feature of TS. According to the International Takotsubo Registry (InterTAK Registry), TS in most cases (36 %) develops as a result of exposure to the so-called "physical" stress: somatic diseases, medical interventions, use of drug products [1]. Emotional stress due to various life situations, both negative and positive, is a less common TS trigger; it is found in 27.7 % of patients; in other cases, TS is either of mixed origin (7.8 %) when a patient had experienced both physical and emotional stress, or a definite trigger cannot be established (28.5 %) [1]. Among the "physical" factors acute respiratory failure is the most common — 20.2 %, with surgical interventions and injuries occupying the second position — 18.4 % [1]. The studies conducted by Guzzo G. et al. (2021) demonstrated that among 305,906 patients who have undergone various types of surgeries in the hospital of Buenos Aires in the period of 2008-2017, TS developed in 21 patients: it occurred during surgery in 6 (29 %) patients, within the first 72 hours in 7 (33 %) patients, and on day 4 and later in 8 (38 %) patients; TS in the perioperative period developed more often in men. Moreover, the author emphasizes the fact that 13 surgeries (60 %) were elective, and 10 surgeries (49 %) were deemed as low or medium risk of TS [2, 3]. According to Brooks JK et al., the literature sources for the period from 1991 to 2018 describe 28 TS episodes that developed during surgical interventions in maxillofacial region, with atypical TS forms in several cases [4]. This article presents a clinical case of inverted (reverse) variant of TS that developed in a 38-year-old man during elective rhinoplasty.

Case report

Patient P., 38 years old, diagnosed with "deviated nasal septum, nasal obstruction syndrome", was admitted to an inpatient department in St. Petersburg for elective rhinoplasty. Pre-operative examinations, as well as laboratory test results, chest X-ray, electrocardiography (ECG), presented no abnormalities. According the patient's history, he had a well-controlled intermittent asthma, chronic gastritis with no exacerbation; no known hereditary diseases; no history of allergies, or epidemiological anamnesis without abnormalities; the patient denied bad habits.

Surgery was performed on the scheduled day under general anesthesia, fentanyl, esmeron and propofol were administered in standard doses without abnormalities, hemodynamics was stable, the patient was intubated. Septoplasty with left sinusectomy was performed. At the final stage of the surgery, in order to prevent postoperative bleeding and edema, 1 mL of 0.1 % adrenaline diluted in 20 ml of saline was injected into the submucosal layer of the nasal septum of the patient. The total duration of the surgical intervention was 1 hour 45 minutes. 20 minutes after adrenaline injection, an increase in blood pressure (BP) up to 210/120 mm Hg was observed, at this time, cardiac monitor demonstrated no rhythm or conduction abnormalities; no changes in repolarization processes, ST segment deviation, or QT interval prolongation were observed. This situation was regarded as an acceptable short-term effect of the local administration of adrenaline. During the next 5 minutes, the patient's blood pressure returned to acceptable values, the patient was extubated (total duration of anesthesia was 2 hours 35 minutes). The patient in clear consciousness was transferred to the intensive care unit (ICU) for follow-up.

In the ICU, the patient almost immediately started to complain of feeling of not getting enough air and constricting discomfort in chest. Physical examination revealed the following: BP 90/60 mm Hg, regular pulse with VCR 100 bpm;RR 20 per minute; heart tones are muffled, no murmurs, harsh breathing, no rales; examination of other organ systems presented no abnormalities. 10 minutes after transfer to the ICU, the patient developed syncope, BP was 80/50 mm Hg, due to unconsciousness and unstable hemodynamics, the patient was re-intubated. ECG demonstrated sinus tachycardia with HR 100 bpm, ST elevation in leads I, II, aVL, V3-V6, corrected QT prolongation (Bazett's formula) up to 465 ms (Fig. 1).

Taking into account the clinical presentation and ECG results, the patient's condition was regarded as an acute coronary syndrome with ST elevation complicated by cardiogenic shock, therefore, the patient was urgently transferred to the vascular unit for cardiac ventriculography (CVG). CVG results demonstrated no hemodynamically significant stenosis of coronary arteries, however, 30 % reduction of left ventricular ejection fraction (LV EF)

and akinesia of all basal segments, as well as hypoakinesia of all midline LV segments were observed (Fig. 2). In view of the persistently severe patient's condition, he was transferred to ICU for further treatment; due to persistent severe hypotension, inotropic support was administered (adrenaline 0.01 μg/kg/min, noradrenaline 0.3 μg/kg/min).

CVG results were in line with of echocardiography (echo) findings: akinesia of all basal segments, hypoakinesia of all LV midline segments, LVEF calculated by Simpson's method was 35 %, with no significant changes in heart valvular apparatus. Complete blood count was indicative of neutrophilic leukocytosis: WBC 33.9×10^9/L, neutrophils 30.9×10^9/L. Among blood chemistry parameters, there was increased troponin I up to 10,376.0 pg/mL (normal up to 26.0 pg/mL), creatine phosphokinase up to 346 U/L (30–200), aspartate aminotransferase up to 43 U/L (5–34), lactate dehydrogenase to 238 U/L (125–220), total bilirubin up to 29.7 μmol/L (3.4–20.5), glucose up to 15.6 mmol/L (3.9–5.5), creatinine up to 90 μmol/L and C-reactive protein up to 9.17 mg/dL (reference range 0–0.5). Coagulogram parameters and blood electrolytes were within reference range, urinalysis presented no abnormalities.

The patient's condition on day 2 in the course of ongoing inotropic support (dopamine 4.5 μg/kg/min; noradrenaline 0.15 μg/kg/min) continued to be severe, hemodynamics was unstable (severe hypotension). Echo: EF 46 %, hypokinesia of LV basal segments persisted; ECG: sinus rhythm with HR 66 bpm, QRS axis in normal position, corrected QT 413 ms, ST elevation in chest leads significantly decreased and was regarded as an early repolarization syndrome, no pathological Q waves, negative T waves were detected in leads I, aVL (Fig. 3); chest (ThO) X-ray: no focal or infiltrative changes, signs of pulmonary interstitial edema; MSCT of the chest: no data for pulmonary embolism; signs of bilateral pulmonary edema.

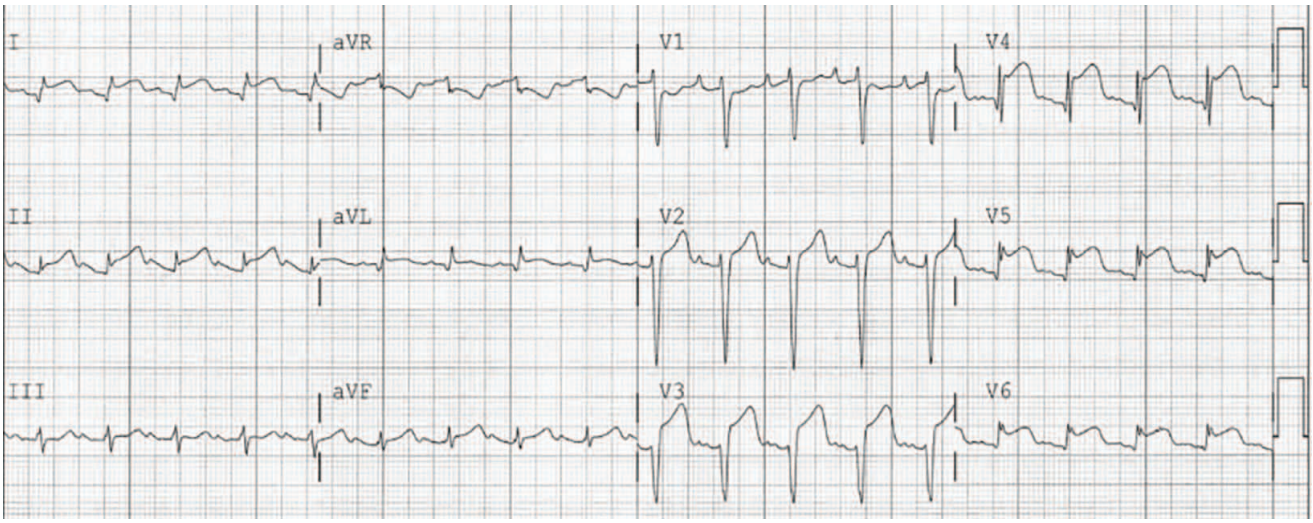

Figure 1. *ECG in the ICU*

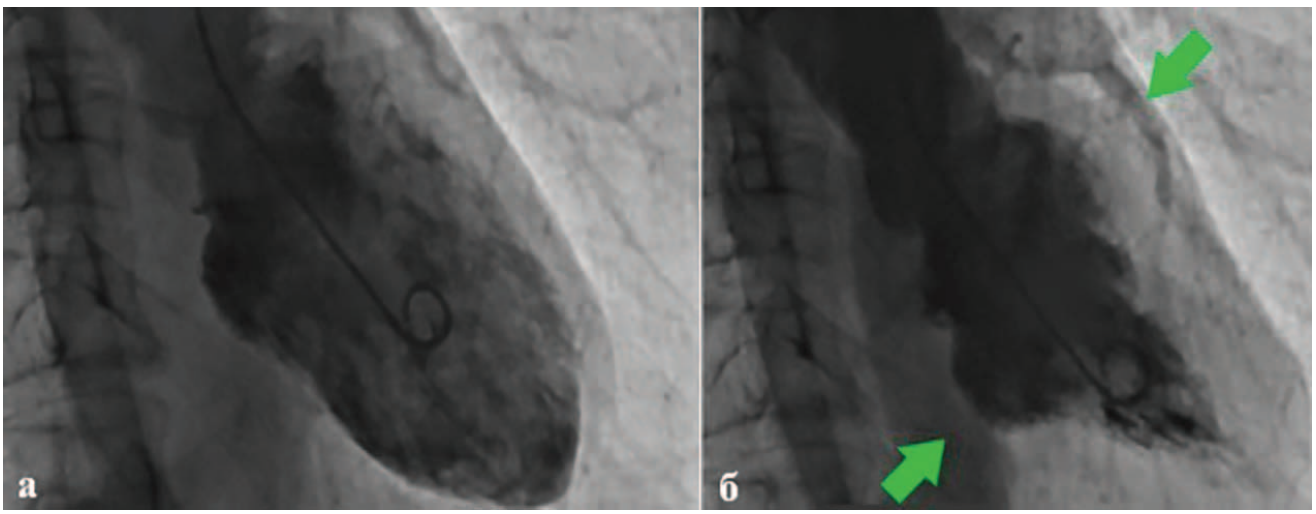

Figure 2. *Coronary ventriculography: a — diastole; b — systole (arrows indicate akinesia of all basal segments, hypo-akinesia of all median LV segments)*

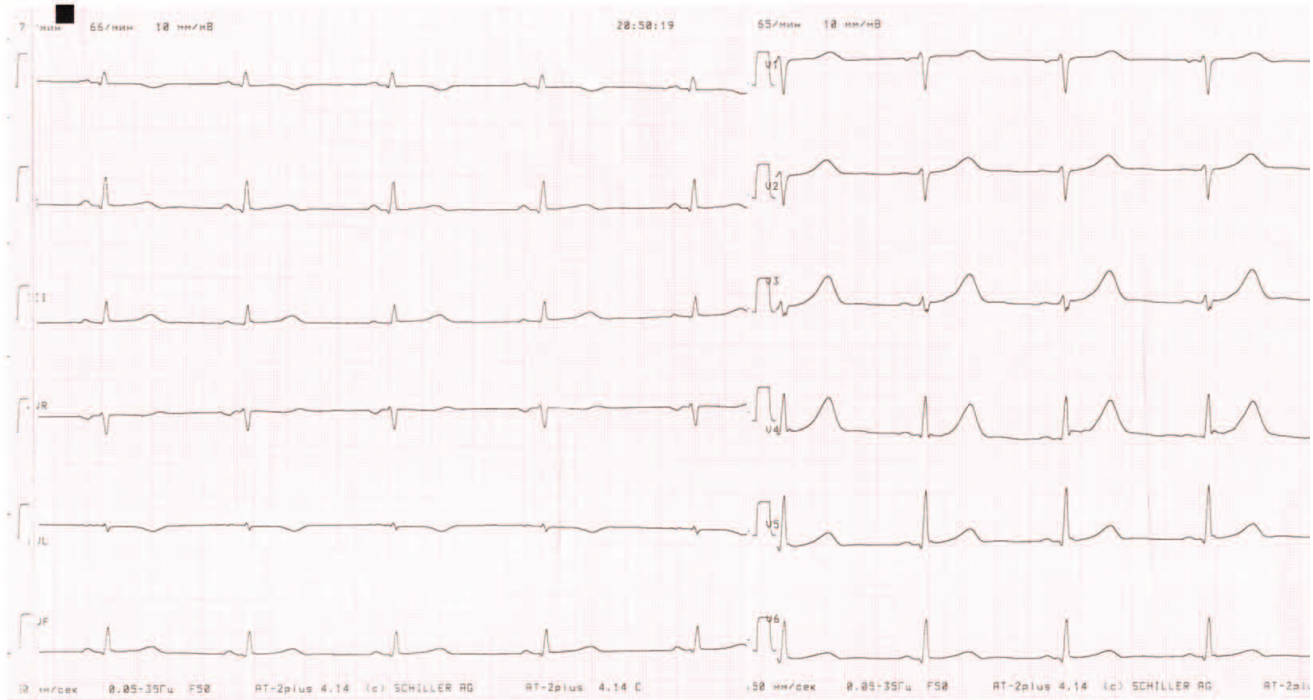

Figure 3. *ECG on day 2*

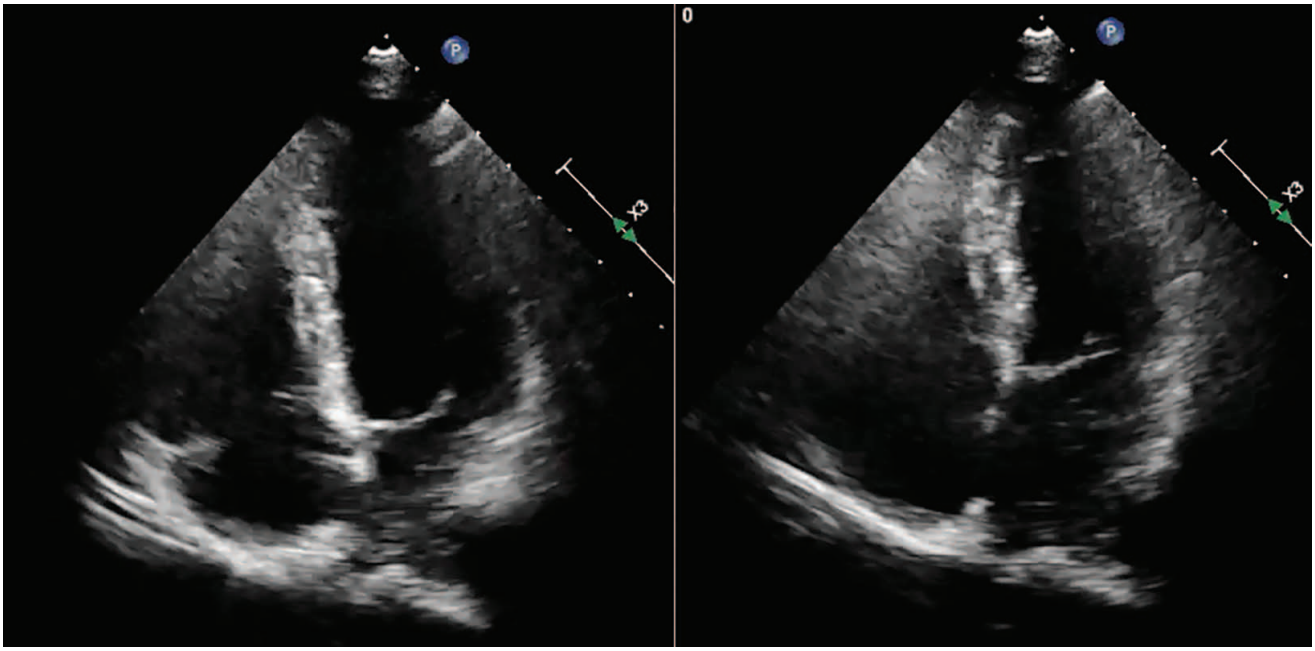

Figure 4. *EchoCG on day 9 (left-systole; right-diastole). Absence of local impairment of LV contractility*

Starting from day 3 of hospitalization, due to the suspicion of TS, vasopressors administration was discontinued (dopamine 5 μg/kg/min; noradrenaline 0.18 μg/kg/min); levosimendan (0.1 μg/kg/min) was prescribed as inotropic support (0.1 μg/kg/min), due to this measure, BP was normalized; on day 4 of the disease, levosimendan was discontinued due to the patient's stabilization.

Over time, on day 9 of hospitalization, all blood parameters returned to normal; chest X-ray demonstrated resolution of interstitial edema; ECG: sinus rhythm with HR of 65–75 bpm, normal position of ORS axis, shortening of corrected QT interval to 350 ms, moderate signs of the early repolarization syndrome of ventricles in chest leads; echo: EF 65 %, restoration of the kinetics of all LV walls (Fig. 3).

Considering clinical signs (dyspnea, chest pain); ECG results (ST elevation in leads I, aVL, V3–V6 with no reciprocal changes); no damage of coronary arteries according to CVG; impaired myocardial kinetics

according to ventriculography and echo-akinesia of all basal segments and hypo/akinesia of all midline segments, followed by normalization of ECG parameters and complete restoration of myocardial contractility by day 9 (Fig. 4), as well as the presence of a provoking stress factor (surgery and adrenaline administration), the patient was diagnosed with inverted TS.

A month after discharge from the hospital, the patient felt good, there were no complaints, no decrease in tolerance to physical activity, results of the examinations of organ systems were within normal. 2 months after TS development, the patient underwent a follow-up echo (EF 63 %, no local contractility impairment was found) and contrast-enhanced cardiac MRI (no impairment of LV myocardial kinetics, no areas of pathological accumulation of a contrast agent were found).

Discussion

In the presented clinical case, both emotional stress reaction to the planned surgical treatment, and all stages of surgery — from anesthesia up to surgical incision — could have triggered TS development. Adrenaline injection into the submucosal layer of the nasal cavity on its own could precipitate the development of TS. Literature describes about 40 cases of adrenaline-induced TS [5–8], in should be noted that adrenaline dose was often relatively low — from 0.3 mg to 1 mg [7].

According to the patient, he did not fear the upcoming surgery; the surgery proceeded smoothly until the injection of adrenaline into submucosal layer of the nasal cavity, therefore, in the presented case, it was probably the local administration of adrenaline that caused TS.

This clinical case demonstrates once again that local administration of adrenaline, even at low doses, should be performed with caution, with thorough monitoring of the patient's the vital functions. If the patient develops sudden hemodynamic disorders following adrenaline administration, ECG demonstrates ST deviation, negative T waves and prolonged QT interval, high troponin and, more typically, proBNP/BNP level, the clinicians should consider the possibility of TS development. In such event, echo as early as practicable and visualization of typical TS presentation will provide early diagnosis and determine patient management approach. The use of vasopressors in TS, including cases of hypotension, should be avoided; the drug of choice is levosimendan [9].

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