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КАНАЛЬЦЕВЫЙ АППАРАТ ПОЧЕК — НАУЧНОЕ И ПРИКЛАДНОЕ ЗНАЧЕНИЕ

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Kidney Tubules — Scientific and Applied Value

Резюме

В настоящее время существует высокий научный интерес к изучению особенностей структуры и функций канальцев почек. Актуальность темы обусловлена потенциальной возможностью выявления разнообразных маркеров нарушения функции канальцев и использования их для ранней диагностики не только тубулопатий, но и гломерулярных нарушений. В клинической практике маркеры канальцевой дисфункции используются недостаточно. В статье представлены сведения об анатомо-функциональных особенностях проксимального и дистального отделов канальцевого аппарата, изложены высокоорганизованные механизмы межмолекулярного взаимодействия, представлены основные биологически активные вещества, изменение концентрации которых является следствием повреждения канальцев. Представленная рукопись является продуктом глубокого анализа и систематизации имеющихся данных в российских и зарубежных информационно-аналитических порталах.

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Abstract

Currently, there is a high scientific interest in studying the features of the structure and functions of the tubules of the kidneys. The relevance of the topic is due to the potential possibility of identifying various markers of tubular dysfunction and using them for early diagnosis of not only tubulopathies, but also glomerular disorders. In clinical practice, markers of tubular dysfunction are used insufficiently. The article presents information about the anatomical and functional features of the proximal and distal parts of the tubular apparatus, outlines highly organized mechanisms of intermolecular interaction, presents the main biologically active substances, the change in the concentration of which is a consequence of damage to the tubules. The presented manuscript is the product of a deep analysis and systematization of the available data in Russian and foreign information and analytical portals.

Key words: *structure and function of renal tubules, markers of tubular dysfunction*

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AKI — acute kidney injury, BAS — biologically active substance, CKD — chronic kidney disease, FABP (L-FABP) — liver fatty acid-binding protein, GFR — glomerular filtration rate, HNF1β — hepatocyte nuclear factor-1β, IL-18, IL-6 — interleukin-18, interleukin-6, IGFBP7 — insulin-like growth factor-binding protein 7, KIM-1 — kidney injury molecule-1, MMP2, MMP9 — matrix metalloproteinases 2 and 9, MRP2/ABCC2 — multidrug resistance protein 2, NAG — N-acetyl-β-D-glucosaminidase, NGAL –neutrophil gelatinase-associated lipocalin, NHE1 — sodium-hydrogen exchanger isoform 1, OAT — organic anion transporter, OCT — organic cation transporter, TIMP-2 — tissue inhibitor of metalloproteinase-2, α-GST — α-glutathione-S-transferase, β_2-MG — β_2 microglobulin, π-GST — π-glutathione-S-transferase

Introduction

The study of renal pathology is of great interest not only for nephrology practice, but also for medicine in general. The high relevance of this issue is conditioned, first of all, by the functions performed by kidneys, as well as by the interaction with heart, blood vessels, brain, gastrointestinal tract, and endocrine system. High morphological organization of kidneys determines their streamlined normal functioning, while the pathological effect of exogenous and/or endogenous factors leads to impaired structure and function of kidneys with the development of the so-called "vicious circle" of kidneys and a co-dependent organ. One of the main functions of kidneys is to maintain the balance of intra- and extracellular fluid in response to changes in external and internal stimuli. Kidneys regulate the activity of organs and systems with the functions of excretion, metabolism and incretion [1]. It is for this reason that renal pathologies initiate the development of continuums with co-dependent organs associated with the increased risk of comorbidities. Functional or organic renal injury most often results in glomerular and tubular functional impairment.

Markers of filtration disorders are well-known and are used to a greater extent to verify chronic processes of primary or secondary renal pathology. The decreased glomerular filtration rate (GFR) indicates glomerular damage due to functional (reversible) or structural (irreversible) remodeling. It is important to emphasize that tubular epithelium has high capacity to regenerate and restore its structure [2, 3]. Thus, it is known that about 70 thousand tubular epithelial cells are excreted in urine per 1 hour, and about 1.5 million cells — per one day [4]. Despite the high regenerative ability, renal tubular cells are highly vulnerable to damaging factors — proteinuria, toxins, metabolic disorders [5]. Long-term, persistent exposure to a trigger factor, i.e. in decreased regeneration processes, or congenital inferiority of tubular apparatus, leads to irreversible structural reorganization of tubules. It is assumed that the damage to the tubular and glomerular apparatus is a single mechanism — the continuum of disease process [6]. Glomerulopathies or tubulopathies primarily affect glomeruli or tubules, and with the disease progression, other parts of nephron become involved in the pathological process [7]. This statement can be illustrated with the increased risk of

developing chronic kidney disease in patients with acute kidney injury (AKI) [8, 9].

The markers of tubular dysfunction are widely used in clinical practice. It is conventionally accepted that tubular dysfunction is a process that characterizes the course of AKI of any etiology or of congenital tubulopathy. In the recent years, there has been an increase in tubulopathies [10, 11] and mortality associated with AKI [12, 13]. Diagnostic significance of the markers of tubular dysfunction in tubulopathies is pathogenetically substantiated. It is supposed that pathological changes in tubules with underlying CKD precede glomerular changes [14] and are key factor in the prognosis of clinical course [15]. This assumption is confirmed by numerous examples — the tubular hypertrophy in CKD [16], especially in the presence of diabetic nephropathy [17, 18], congenital glomerulopathies [19], and involutive nephron loss [20]. It forms a basis for conducting new studies aimed at the review of pathophysiological mechanisms of tubular damage as the early signs of nephron damage.

Specific features of the structure and functioning mechanisms of tubular apparatus

The main function of renal tubules is to maintain homeostasis, i.e. the balance of water-salt status in the body, which is necessary for the functioning of the cells of organs and systems, acid-base balance [21]. Such functioning is possible due to the structure of the tubular apparatus of nephron. Structural features of the epithelial cells of renal tubules provide their main function, that is, transportation (tubular metabolism — reabsorption, secretion, excretion). Most of the proximal tubular epithelium is the simple cuboidal epithelium [22]. The difference between the epithelium of proximal tubules and that of distal ones is the presence of microvilli (brush border) that increase the surface for contact with glomerular ultrafiltrate, thin and long mitochondria at the basal pole and numerous vesicles involved in the transport of 60–80 % of ultrafiltrate [22, 23]. This structure of proximal tubule provides the following functions: reabsorption of trace elements, electrolytes and minerals, reabsorption 60–80 % of sodium and water [24]. Moreover, it is known that renal tubules consist of at least 16 types of epithelial cells, each performing its own functions [25]. In 1988, Renal Commission of the International Union of Physiologic Sciences suggested not to distinguish between the types of epithelial cells, but to determine the segments of renal tubules and their corresponding functions. Dividing proximal renal tubule into segments was based on topographic and anatomical characteristics. This classification allowed studying the mechanisms of the sequential functioning of renal tubules in normal and pathological conditions and using it in the morphological description of renal biopsy samples. Proximal tubule is conventionally divided into three segments: S1, S2, S3. Segments S1 and S2 are considered to be the convoluted proximal tubule, and S3 is the late proximal tubule. The main shortcoming of this classification is the lack of definite boundaries for the transition from one segment to another. S2 is located in cortex, S3 — in medulla, and S1 is the remaining part of proximal tubule. Moreover, it was found that, alongside with the general functions of proximal tubule, S2, in contrast to S1 and S3, secretes organic anions and cations [24].

In the paper by Carney E.F. (2019), it is reported that the ultrastructure of different segments of the proximal tubules has different endolysosomal potential [26]. In her work on an experimental model of kidneys, the author in real time demonstrated the degree and the possibility of absorption of fluorescent ligands in different parts of proximal tubule. It was demonstrated that in the S1 segment, lysozyme, albumin, and dextran were absorbed in the process of receptor-mediated endocytosis, while in the S2 segment, only dextran was absorbed. The author points out the high significance of this study as a further perspective in determining the "target" in differentiated diagnosis and treatment, as well as the need to continue research in order to establish the functioning mechanisms of different epithelial cells of proximal tubules.

The distal tubule of kidney starts from macula densa to the collecting system of nephron and includes 2 main parts: distal convoluted and connecting tubules. Distal tubule can be also divided into early and late parts, according to their function [27].

Distal tubules have a well-ordered structure of epithelial cells, however, near the connecting tubules, epithelium becomes heterogeneous and interspersed with intercalated cells which are responsible for regulating acid-base balance. Epithelial cells in cytosol have a large number of mitochondria, and cell nuclei are located to a greater extent on the apical surface in basolateral membrane which has deep folds [27]. Large number of mitochondria in the cells of distal tubules (the highest density among renal cells) indicates the energy-intense function of distal tubules — transport of electrolytes, such as sodium reabsorption, potassium secretion, maintaining the balance of magnesium and calcium. There are channels and co-transporters for the active transfer of electrolytes throughout distal tubules, as well as receptors that are sensitive to mineralocorticoids. A schematic drawing of proximal and distal tubules is shown in Figure 1.

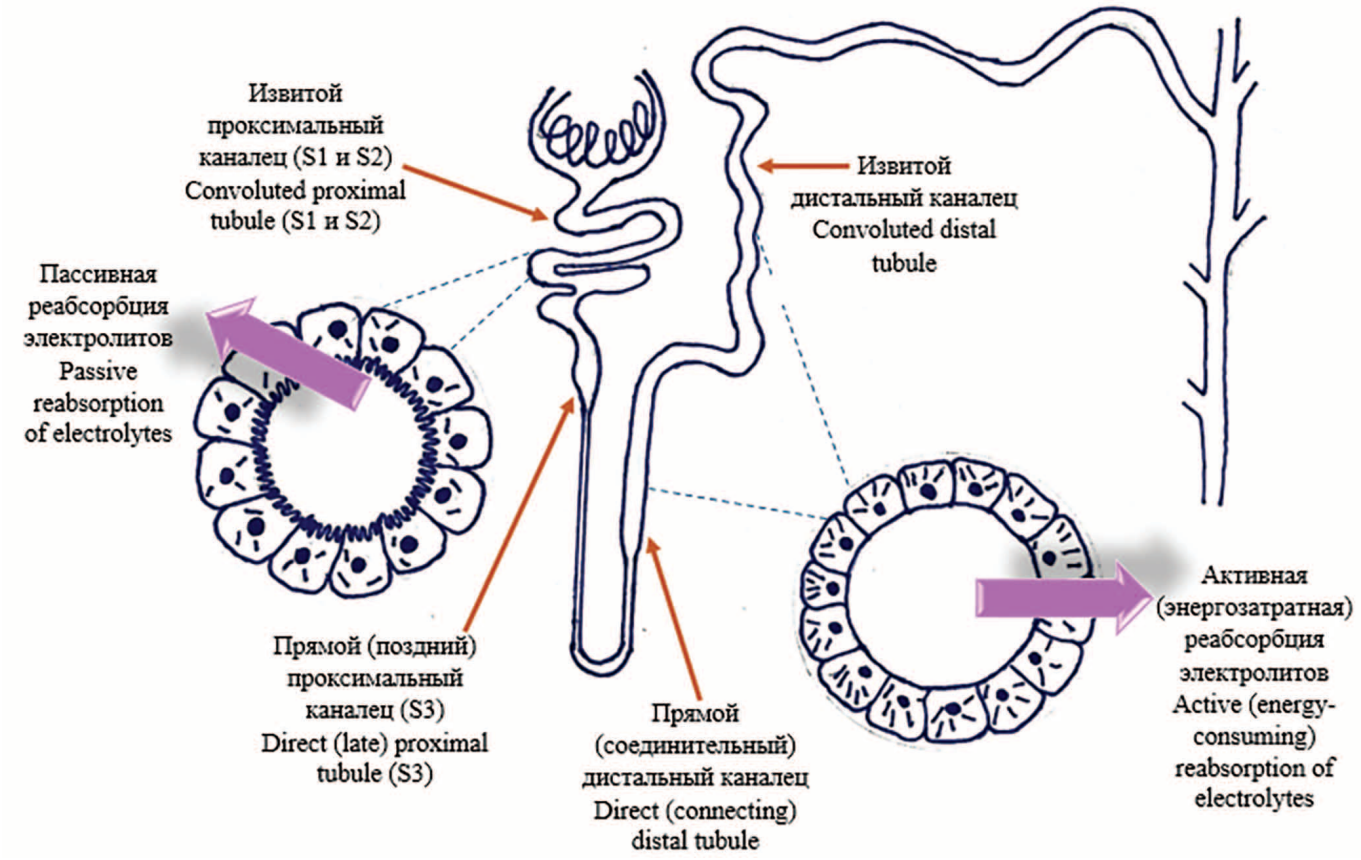

Figure 1. *Schematic representation of the system of proximal and distal tubules of the nephron*

It is important to notice that tubular epithelial cells have polarity and communicate with each other by intercellular junction complexes. Due to cell polarity, the division of plasma membrane into two parts is developed that differ qualitatively in their composition of proteins, lipids and the presence of a sensory organelle on the apical surface, i.e. a primary (non-motile) cilium. The contribution of cilia to the normal functioning of tubular epithelium is high, since this organelle controls, first of all, the signaling pathways required for indirect communication with partner proteins, trace substances, and minerals for the physiological transport of substances in the intercellular space [28]. Signaling pathway molecules and receptors are located within the cilium and separated from cytoplasmic membrane. Moreover, the cilia of tubular epithelium are involved in the regulation of proliferation, regeneration, and cell apoptosis that is of great importance for tubular apparatus [28, 29]. Review of literature sources helped to establish that the pathology of primary cilia is most often associated with the development of cysts in kidneys (single or associated with other diseases), as a rule, of a congenital nature, that is, Bardet–Biedl syndrome, Meckel–Gruber syndrome, Joubert syndrome, Senior–Loken syndrome, autosomal dominant and autosomal recessive polycystic kidney disease [30].

There are microtubules inside the epithelial cells which are important in maintaining the cytoskeleton, the shape and mobility of cells [31]. Microtubules are comprised of heterodimers of α- and β-tubulins. It is worth noting that in some renal pathologies, microtubules act as a mediator leading to acetylation and modification of epithelial cells. It is assumed that the pathology of microtubules can be the cause of the development of a cascade of mechanisms that lead to the damage to tubular apparatus, and subsequently to glomeruli [32]. A schematic drawing of the structure of the proximal and distal tubules of epithelial cell is shown in Figure 2.

It is important to note that renal pathology is not limited to one type of cells, but can be caused by damage both to epithelial and endothelial, mesenchymal, or immune cells [33].

Thus, the high organization of the structure of renal tubules allows performing a consistent series of mechanisms that are responsible for steady intra- and extracellular balance and are required for the effective functioning of organs and systems.

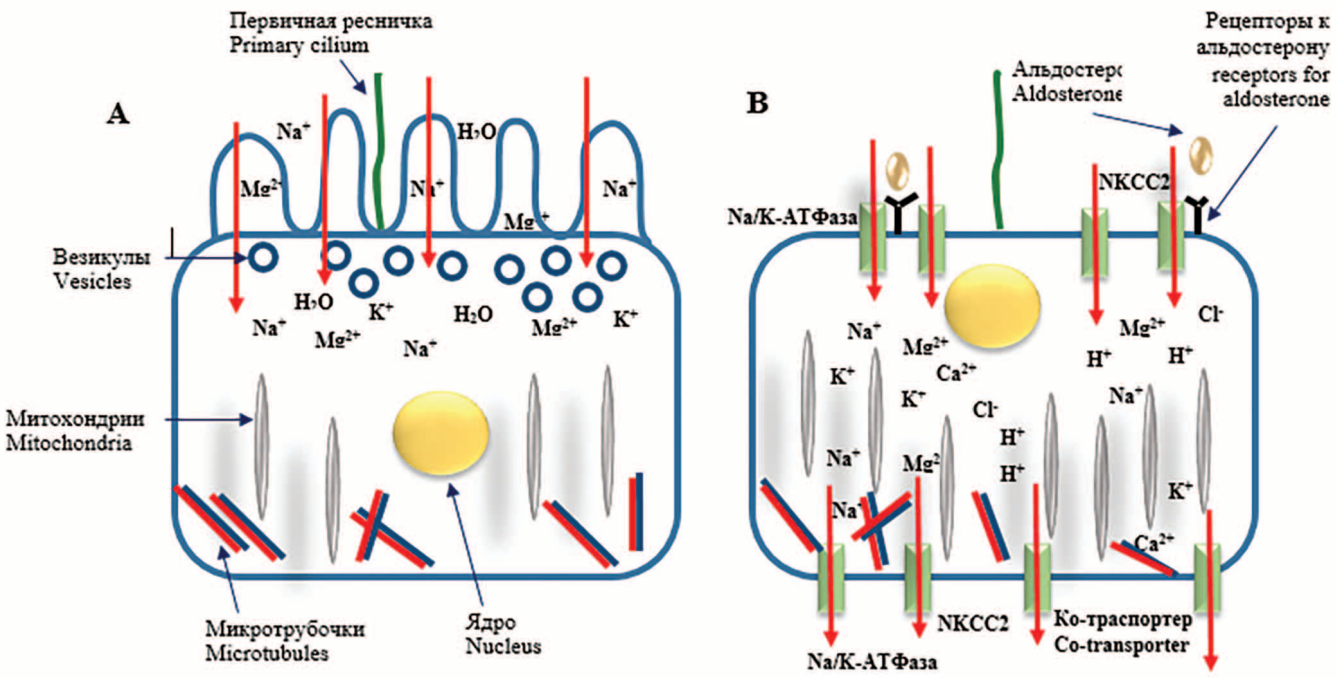

Figure 2. *Schematic representation of the structure of the epithelial cell of the proximal (A) and distal (B) tubules*

Specific features of molecular interactions during the functioning of renal tubules

Well-coordinated functioning of renal tubules is important for maintaining stable blood plasma composition. Many factors are involved in the maintenance of the homeostasis in body fluids depending on endogenous and/or exogenous changes in stimuli. The question arises: what mechanisms in tubular epithelium are involved in developing stimuli that adjust plasma homeostasis? These mechanisms are not fully understood, however, the basic processes and phenomena that contribute to the regulation of homeostasis are known: specific features of the structure of epithelial cells, state of receptor apparatus, molecular pool of interactions that form signaling pathways, and other renal and extrarenal stimuli.

Transporter molecules in proximal tubule help to develop the clearance of toxic substances, mainly uremic toxins, protein/substance complexes that move through glomerular filter, drug metabolites. Thus, it is understood that the process starting in the proximal tubule is a specific "sorting" of reabsorbed and excreted substances that entered tubules after glomerular filtration. The integrity of tubular structure and normal sequential mechanism of transport substances allow performing the effective clearance of glomerular filtrate and maintaining the balance of blood homeostasis.

Intermolecular complexes of transmembrane proteins between epithelial cells develop tight or "loose" contacts complementing cell cytoskeleton, as well as contact with protein compounds of neighboring cells and with cytoplasmic proteins [29]. It is also important to notice that the epithelium of proximal tubules is able to reabsorb substances paracellularly and transcellularly, while the distal tubule transports substances most particularly transcellularly due to the density of epithelial cell contacts. The presence of transmembrane complexes develops the apical polarity of cells and the intercellular flow of substances with urine. Proteins involved in intermolecular interactions are cadherins [29, 33], catenins, nectin, afadin, occludins, junctional adhesion molecules, and claudins [32]. These proteins determine the epithelial phenotype of cells. There are different subtypes of cadherins in kidneys. In particular, membranous or cytoplasmic expression of E-cadherin and β-catenin is observed in distal tubules, while N-cadherin is expressed in the proximal ones [34]. Cadherin/catenin and nectin/afadin complexes are attached to the actin cytoskeleton and microtubules of cells [33]. Complexes develop with the help of Ca^{2+}-mediated mechanism.

Claudins are the basic part of the tight junctions of tubular epithelial cells. They are located along the lateral

membrane of one cell connecting with a similar molecule in another cell. Their main role is making "pores" (barriers) for the passage of the ions of small diameter [35], as well as participation in the signaling pathways of molecular interactions [33]. There are several isoforms of claudins. It is considered that the location of expression of a particular claudin determines cell function and specific features of its permeability. Claudins are expressed in different parts of nephron: tubules, glomeruli, podocytes. Claudin isoforms include 2–4, 7, 8, 10a, 10b, 14 isoforms [35].

Attention should also be paid to integrins, i.e. the substances that are required for the development of cell/extracellular matrix bonds. Integrins account for the most part of the structure of transmembrane receptors located on cell surface. Integrins are primarily considered as adhesive molecules, however, they also act as signaling centers in the transmission of cell metabolism processes, since they determine the sensitivity of a cell to specific microenvironment [33].

The role of microtubules in the pathogenesis of the development of tubular pathology has been stated earlier. It should be noted that CAMSAP3 (Calmodulin-regulated spectrin-associated protein 3) is involved in the correct orientation of microtubules inside a tubular epithelial cell [36]. CAMSAP3 belongs to a family of proteins regulated by calmodulin and spectrin; their main function is to bind the negatively charged poles of tubular epithelial cell.

An important element of intermolecular interactions for tubular functioning is the analysis of the functioning of receptor apparatus in relation to transporting filtrate molecules. The physiology of receptor apparatus which directly or indirectly affects the functions of tubules remains the object of investigation to the present day. Receptors are divided into 3 types — mechanical, chemical and physical, i.e. according to their activation on exposure to a specific stimulus. Mechanical receptors of tubules are the most well-characterized and represent the expression of receptor apparatus on cell surface with a change in filtrate density and rate, i.e. implementation of the "shift" theory. Receptor apparatus activated by chemical factors (filtrate composition — glucosuria, impaired acid-base balance), physical factors (changes in filtrate temperature and environment).

Receptors of renal tubules with normal structure are responsible for paracellular and intracellular diffusion of substances, and their impaired function may be associated with the development of diseases or fatal conditions. Thus, it has been experimentally shown in laboratory animals that genetic deletion of TRPM6 (Transient Receptor Potential Cation Channel Subfamily Member 6) channel is associated with embryonic death in laboratory rats due to the impaired transport of magnesium ions [37]. Or, for example, a genetic defect of TRPM6 in human leads to severe hypomagnesemia and secondary hypercalcemia. TRP (transient receptor potential) channels are a transport route through the hardly permeable plasma membrane of epithelial cell; they are activated in response to the changes of environment. TRP superfamily can be divided into 7 subfamilies which, in turn, are further classified into a number of classes according to their protein structure and function. TRPs are present not only in tubules, but also in glomeruli and podocytes. It should be noted that the control of TRPM6 expression located in tubular epithelium is carried out by several endocrine factors, primarily — insulin, estrogen, and epidermal growth factor. Anticancer treatment with cetuximab often results in hypomagnesemia; this fact can be explained by inhibition of basolateral epidermal growth factor receptors that are required for the functioning of TRPM6 [37]. In addition to endocrine factors, other systems can have an impact on the expression of receptor channel. An example of the physiological control of TRPM6 function is magnesium balance during dieting — low intake of magnesium with food results in channel activation and increasing magnesium reabsorption, and diet with magnesium overdose leads to decreased expression [37]. This example highlights the high importance of tubular function at organ and system levels.

The receptors themselves are important from clinical and scientific points of view in regard to the global performance of tubular function. It is known that blood proteins in small quantities reach the ultrafiltrate due to glomerular filtration. Protein molecules that are transported through glomeruli are reabsorbed by receptor interaction (ligand-associated bonds). In proximal tubular epithelium, there are endocytic receptors represented by cubilin and megalin, i.e. protein structures that bind molecules for their further transportation. Megalin (or autoantigen with underlying Heymann nephritis) is attributed to the class of lipoproteins and is located on the apical surfaces of the epithelial cells of proximal tubules. Cubilin is a receptor (glycosylated extracellular protein) for intrinsic vitamin B12 factor that is originally recognized as a teratogenic factor in the experimental studies in rats. Genetically reduced expression of cubilin leads to hereditary megaloblastic anemia (Imerslund–Grasbeck syndrome, selective vitamin B12 malabsorption with proteinuria). Cubilin is also located in proximal tubules, on their apical surface. Megalin and cubilin can produce complexes with each other bringing into action the receptor mechanism.

There are also other forms of receptors that are involved in the intracellular regulation of ion diffusion.

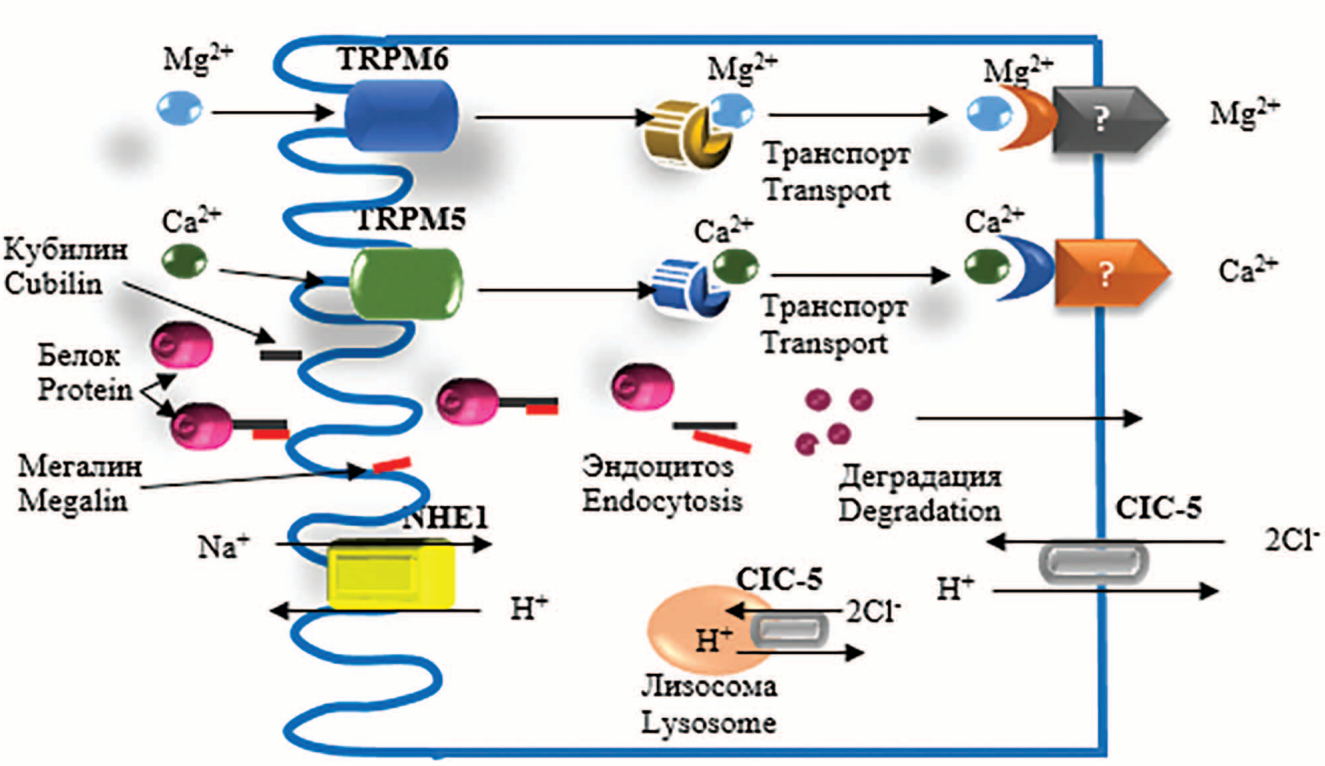

Figure 3. *Scheme of action of the main intracellular transporters in the epithelial cell of the proximal tubule*
Note: TRPM6 — Transient Receptor Potential Cation Channel Subfamily Member, NHE1 — Na-H exchanger 1, CIC-5 — chloride ion channel

Sodium-hydrogen exchanger isoform 1 (NHE1) is a protein expressed by the plasma membrane of tubular epithelial cell. NHE1 plays a key role in maintaining intracellular homeostasis — the balance of sodium and hydrogen ions [38]. In addition, NHE1 cytosolic tail is involved in the development of the cytoskeleton of a tubular endothelial cell, adapts the cell to changing conditions using signaling NHE1-dependent proteins, optimizes cell apoptosis by changing cell pH, and is also a part of signaling pathways that are responsible for the function of tubular epithelial cells [38].

CIC-5 (chloride ion channel) is a protein localized in the apical surface of the epithelial cells of proximal tubules and in the collecting ducts intercalated cells. The main function of CIC-5 is intracellular chlorine-hydrogen exchange; it is also involved in endosome acidification. A genetic mutation of CIC-5 leads to a congenital anomaly — Dent's disease (X-linked pathology of renal tubules) [38].

There are several other proteins that produce complexes with megalin to perform the function of receptor apparatus. This section describes the main components and mechanisms required to the functioning of tubules.

A schematic drawing of the intermolecular interaction in tubular epithelium is shown in Figure 3.

It is also important to note the specific features of molecular transport in the different areas of tubular apparatus. The transport of cations and anions takes place in the basolateral and apical parts of proximal tubular epithelium by the means of transporter molecules — organic anion transporters (OAT) and organic cation transporters (OCT). Transporters have similar structure; they include 12 α-helical transmembrane domains, at least one intracellular domain, and a large extracellular glycosylated loop. OAT and OCT are divides in subclasses depending on the specific features of their structure and function. Basolateral transport does not require ATP hydrolysis; it is carried out using K-Na-ATPase. The exchange messenger for an anion in the OAT complex is intracellular α-ketoglutorate of dicarboxylic acid which binds to OAT releasing the anion. The process of anion transport on the apical surface of cells is energy-intense and is performed through the capture of ATP by transport molecules (multidrug resistance protein 2 (MRP2/ABCC2) producing a complex with an anion [39]. Transport of cations is carried out by means of other transport associations — MATE transporters (multidrug and toxin extrusion) that belong to the SLC transporters family (solute carriers). Currently, several types of MATE transporters

are known (MATE1, MATE2 and MATE2-K. MATE1); among these, MATE2-K has the highest affinity for tubular epithelium, and MATE2 — to a lesser extent. The main function of MATE proteins is cation transport using the antiport mechanism on the apical side of epithelial cells, as well as the metabolites of drug products. It is important to note that MATE forms a complex with OCT localized in basolateral part; it allows performing the transport of a broader spectrum of cations [40].

Energy sources for tubular metabolism. To perform the complex processes of homeostasis in the body, kidneys require energy. It was established that energy processes in tubules are mainly possible due to ATP which is synthesized mainly in the mitochondria of proximal tubular cells. The substrate for ATP is fatty acid oxidation and, to a lesser extent, glucose [41, 42]. Fatty acids enter tubular cells via receptor transport (CD36 is expressed on cytoplasmic membranes), as well as in a complex of fatty acid binding proteins and other transport proteins [41, 42]. Complex fatty acids require binding to carnitine in the form of carnitine palmitoyltransferase 1 with its conversion into isoforms [42]. One of the known mechanisms is peroxisomal oxidation of fatty acids with the production of acetyl-CoA and subsequent transformation in ATP [43].

Markers of tubular dysfunction

Tubular epithelium is not a passive target for injury factors. Epithelial cells perform various functions; the most significant among these are the ability to produce pro-inflammatory factors, i.e. cytokines, chemokines, to develop receptor and signal pathways for signal transmission and, as a result, to coordinate different biological and pathological processes. Reversible or irreversible tubular dysfunction leads to the secretion of biologically active substances and/or decreased tubular reabsorption. In this case, molecules that are normally absent in urine and/or the increased level of nitrogen-containing bases in blood are the markers of acute or chronic tubular dysfunction; this fact is used in clinical practice.

Analysis of literature sources helped to identify a number of molecules that were secreted in increased amount when tubular epithelium was damaged. There are biologically active substances (BAS) produced only (or predominantly) by tubular epithelium. Differentiation of these substances according to the principle of dominant secretion has high applied and scientific significance.

BAS that are secreted and expressed only (predominantly) in tubular epithelium include uromodulin (Tamm–Horsfall protein), kidney injury molecule-1 (KIM-1), T-cell immunoglobulin and mucin domain 1 (TIM-1)). This group can also include glutathione-S-transferase enzymes (α-GST, π-GST), since they are part of the cytoplasm of tubular cells.

BAS, with secretion and expression arising or increasing with the damage of tubular epithelium, however, that can be also expressed in other cells in the body, include neutrophil gelatinase-associated lipocalin (NGAL, lipocalin-2, siderocalin, 24p3), N-acetyl-β-D-glucosaminidase (NAG), hepatocyte nuclear factor-1β (HNF1β, vHNF1, TCF2 and LF-B3), tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor binding protein 7 [IGFBP7, mac25, prostacyclin-stimulating factor (PSF), tumor adhesion factor (TAF), and angiomodulin (AGM)], liver fatty acid-binding protein (FABP, L-FABP, FABP1), gelatinases (matrix metalloproteinases — MMP2, MMP9), interleukin-18 (IL-18).

There are several biologically active substances which are only reabsorbed in renal tubules; if there is a pathology of tubular apparatus, they accumulate in urine. These biologically active substances include β_2-microglobulin (β_2-MG), cystatin C, and interleukin-6 (IL-6).

It is apparent that the tubular function markers are more often associated with the acute pathology of tubular apparatus; in particular, they are used in the diagnosis of AKI. However, with the expansion of the knowledge base about the specific features of tubular damage, many studies are currently being carried out aimed at studying the markers of tubular damage in case of primary or secondary chronic renal pathology.

NGAL was first isolated from neutrophils as a variant of its normal production in neutrophils. This biomarker remains until the destruction of mature neutrophil granules during infectious and inflammatory processes [44]. Further, NGAL expression from other cell types was found, and its main functions were identified, that is, its involvement in migration, proliferation, apoptosis, and differentiation of cells [44, 45]. Further analysis of the specific metabolic features and mechanisms of NGAL secretion allowed establishing that NGAL was secreted and expressed by renal tubular cells, to a greater extent in the area of the ascending part of the loop of Henle and in the collecting ducts in case of their damage [44].

NAG is a lysosome enzyme that is produced by cells of many types. NAG in kidneys is secreted and expressed in the lysosomes of proximal tubule and may be normally present in small amounts in urine [46]. Increased concentration of NAG in urine makes indicates tubular pathology. NAG, being a marker of tubular injury, is used for diagnosis of AKI, chronic renal diseases; there are data on its predictive role in cardiovascular diseases (arterial hypertension, chronic heart failure) and diabetes mellitus [47, 48].

KIM-1 is a glycoprotein receptor with the most significant expression in proximal tubule compared to other molecules. In addition, KIM-1 binds to phosphatidylserine to execute apoptosis. [49, 50]. According to the literature, this compound has the so-called "eat me" function; it means "labelling" of cells to initiate apoptosis. In the context of tubular pathology, not only apoptosis is performed this way, but also the removal of necrotic cell material, oxidized lipids [51].

Uromodulin is one of the most attractive molecules in studying tubular dysfunction and using it in clinical practice. Uromodulin is secreted in the ascending part of the loop of Henle and in distal tubule. The biological role of uromodulin is the binding of calcium oxalate (reducing the risk of kidney stones), with E. coli fimbriae (reducing the risk of urinary tract infections), homeostasis regulation by binding to the co-transporters of sodium (there is a correlation with the development of salt-sensitive arterial hypertension) [52, 53], potassium, chlorine, control the function of magnesium and calcium channels in distal tubules [54]. It was established that uromodulin level in urine corresponds to the mass and function of tubules and has a positive correlation with GFR [54]. There are known mutations of genes encoding the release and quality of uromodulin; the result is the development of renal fibrosis. In the KDIGO consensus report, an autosomal dominant kidney disease due to a mutation in the uromodulin gene was proposed to be called uromodulin-associated kidney disease (UAKD). A number of diseases associated with similar changes in tubulointerstitium, but of different etiology, are conventionally attributed to the group of autosomal dominant tubulointerstitial kidney diseases (ADTKD) [55].

Hepatocyte nuclear factor-1β (HNF1β) is a member of transcription factors family. HNF1β was first isolated in liver, however, it is of greater importance and has predominating secretion localization in kidneys, in particular, in all parts of tubular apparatus. HNF1β is important during embryogenesis for the normal development of kidneys, liver, pancreas, intestine, and genitourinary tract [56]. When tubular apparatus function is normal and there are no HNF1β gene mutations, hepatocyte nuclear factor-1β controls normal metabolism in tubules and transport of solutes by tubular epithelium [57]. Mutation of HNF1β genes is inherited in an autosomal dominant manner resulting in tubulointerstitial fibrosis, renal agenesis or hypoplasia, multicystic dysplastic kidneys, and glomerulocystic disease [57].

β_2-MG is a small protein that is located in all nucleated cells. A specific feature of β_2-MG is its almost complete metabolism via kidneys, with reabsorption through tubules [58]. In this regard, increased β_2-MG level in serum due to non-renal causes also leads to its increased concentration in urine. Clinical use of β_2-MG is reasonable in the cases of the development of renal amyloidosis along with hemodialysis, multiple myeloma, kidney cancer, tumors of extrarenal origin, secondary nephropathies, cardiovascular diseases (coronary heart disease, carotid atherosclerosis, intermittent claudication, etc.) [59–61]. β_2-microglobulinuria also develops with underlying autoimmune diseases, infectious and inflammatory processes [60].

Cystatin C is a low molecular weight protein that is located in all cells of the body, is completely filtered through glomeruli, and is reabsorbed in proximal tubules. Cystatin C is associated with many biological processes in the body, since it is involved in the activation of precursor proteins, protein metabolism, and apoptosis [62, 63]. Since the metabolism of cystatin C takes place in kidneys, its high prognostic value in nephrological practice is established: cystatin C is an indicator of glomerular function and tubular dysfunction in AKI [62]. Moreover, in 2012, KDIGO proposed to use serum cystatin C, both as a single indicator of renal function and, when combined with serum creatinine, in the formulas for calculating GFR in CKD [64]. Formulae that are recommended for use in clinical practice are CKD-EPI formula based on creatinine levels and CKD-EPI formula based on cystatin C and serum creatinine levels.

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are expressed in renal tubules when tubular epithelium is damaged [65]. IGFBP7 is secreted and expressed in the cells of proximal and distal tubules, while TIMP-2 — in distal tubules only. The functions of these biologically active substances include participation in various biological processes in the body, including apoptosis, cell aging, cell cycle, inflammation, and tubular regeneration [66]. Both biologically active substances are protein structures and established markers of early AKI. TIMP-2 is an inhibitor of metalloproteinases. Matrix metalloproteinases are one of the factors that cause damage to renal structure (glomeruli, tubules, vessels) through matrix degradation [67]. TIMP-2 interferes with this process, since it inhibits metalloproteinases and is involved in G1 phase of cell cycle arrest that is considered to be a key component in AKI progression [67]. IGFBP7 is also involved in cell cycle arrest. IGFBP7 is a member of the IGFBP superfamily and is involved in normal cell growth, differentiation, proliferation, and apoptosis; it is also a link in signaling pathways transferring information to receptors, proteins, and proteases [68].

Liver fatty acid binding protein (FABP), also known as L-FABP or FABP1, is a fatty acid protein. FABP is

predominantly expressed in hepatocytes, as well as in many cells, such as enterocytes, proximal tubule cells, and alveolocytes [69]. L-FABP is filtered in glomeruli and reabsorbed in tubules. Damage to tubular epithelium is the result of the excessive reabsorption of L-FABP containing fatty acids [70]. Other damage factors (arterial hypertension, tubular ischemia, infections, toxic effects) are also possible with the increased expression of the gene that controls L-FABP that rapidly accumulates in urine and is used as a marker of tubular epithelium damage [71]. L-FABP, like other members of the FABP family, is currently being actively studied in order to determine their significance in nephrological practice, as well as to clarify the specific features of their metabolism and localization of expression in renal tubules. Fatty acid binding protein 2 (FABP2, I-FABP) is expressed in enterocytes, however, increased FABP expression has currently been found to correlate with the progression of chronic kidney disease in diabetic nephropathy [71].

Gelatinases (matrix metalloproteinases, MMP2, MMP9) are neutral proteinases that can destroy and change the structure of extracellular matrix due to protein degradation [72]. This function is positive because it reduces the process of fibrogenesis and prevents the development and progression of tubulointerstitial fibrosis. However, MMP2 and MMP9 also have other properties that have a damaging effect on renal tubulointerstitium. It was established that MMPs are involved in cell migration, cell–extracellular matrix adhesion, activation of epithelial–mesenchymal transition; they also mediate the activity of growth factors and the release of cytokines, including TGFβ — a primary factor in fibrosis and tissue remodeling [71]. It should be noted that one of the mechanisms for the development of tubular damage in glomerulopathies is MMP9 activation with excessive reabsorption of albumin in proximal tubules. Matrix metalloproteinases can be the markers of both acute and chronic tubular injury [72].

α-GST and π-GST are isoforms of glutathione-S-transferase found in the human body, namely, in proximal and distal tubules, respectively [73]. Based on their localization, it is obvious that these isoforms appear in urine when the integrity of tubular epithelial cells is impaired. Due to this, α-GST and π-GST are early markers of AKI; their significance has been confirmed by many studies [74]. At the same time, persistent low-intensity damage to tubular epithelium is also accompanied by the release of α-GST, π-GST into urine. The predictive value of these enzymes in diabetic nephropathy, glomerulonephritis, obesity-associated nephropathy, and glomerulopathies has been established [73].

IL-18 is a cytokine that plays an important role in the T-helper type 1 and 2 response. Moreover, IL-18 expression leads to the activation of other cytokines that are responsible for the initiation and maintenance of inflammation, i.e., TNF-α and IL-1β. IL-18 is in most cases expressed by tubular epithelial cells, as well as by dendritic cells, macrophages, neutrophils, basophils, keratinocytes, chondrocytes, synovial fibroblasts, cells of adrenal cortex, and osteoblasts [75].

Table 1. *Characterization of renal tubular function markers*

Marker	Place of production	Mechanism in the tubules	Values of normal indicators	Types of pathological conditions
KIM-1	Epithelium of the proximal tubule	Secretion, expression, excretion, reabsorption in small amounts	Urine — 0-2200 pg/ml [79] Blood — not normal	AKI, CHF There is evidence for the predictive role of KIM-1 in CKD
α-GST	The enzyme is localized mainly in the proximal tubule	Expression, excretion	Urine — 2.7-7.6 ng/mg/urine creatinine [80] Blood — not normal	AKI, diabetic nephropathy, other metabolic nephropathy, glomerulonephritis
π-GST	The enzyme is localized mainly in the distal tubule		Urine — 4.1-13 ng/mg/urine creatinine [80] Blood — not normal	
NGAL	NGAL is secreted in neutrophils; in case of kidney damage, it is secreted and expressed by cells of the renal tubules, to a greater extent in the area of the ascending loop of Henle and collecting ducts	When damaged, secretion, expression, excretion, reabsorption. In the absence of damage to the tubules — reabsorption	Daily urine — 17.1-29.7 ng / ml and 21.5 — 32.9 ng / g / creatinine (men) 52.2-75.7 ng/ml, 80.3-99.4 ng/g/ creatinine (women) [81] Blood — 43.0-86.3 mcg / l (men), 38.2-88.9 μg/l (women) [82]	AKI, CKD of any origin

Table 1. *(The end)*

NAG	Secreted in many cells. In the kidneys — in the lysosomes of the proximal tubule.	Secretion, expression, excretion, reabsorption	Urine — 1.6-5.8 U/g creatinine [83], 19.8-22.2 U/l (men), 16.5-20.5 U/l (women) [84] Blood — 270-495 U/l [85]	AKI, CKD, secondary tubulopathies — AH, CHF, DM
HNF1β	Secretion in all parts of the tubular apparatus, liver, bile ducts, thymus, pancreas, tracts, lungs and intestines	Secretion, expression, excretion, reabsorption	No data	Tubulointerstitial fibrosis, renal agenesis or hypoplasia, multicystic renal dysplasia, glomerulo-cystic disease, hyperuricemia, gout, diabetes mellitus, genital tract malformations, hyperparathyroidism
TIMP-2	Secretion in the distal tubules in renal injury. Found in all tissue cells	Secretion, expression, excretion, reabsorption	Urine — 188-244 pmol/l [86] Blood — 109-253 ng/ml [87]	AKI, there is evidence to predict the risk of CKD progression
IGFBP7	Secretion in the proximal and distal tubules in case of kidney damage. Found in all tissue cells	Secretion, expression, excretion, reabsorption	Urine — 2.60-4.09 ng/ml [88] Blood — no data	AKI, there is evidence to predict the risk of CKD progression
L-FABP	Secretion in the cells of the proximal tubules, hepatocytes, as well as in many other cells — enterocytes, alveolocytes	Secretion, expression, excretion, reabsorption	Urine — 0.3-8.4 μg/g creatinine [89] Blood — no data	AKI of any etiology, including ischemic genesis, tubular necrosis. There is evidence to predict the risk of CKD progression
MMP2 MMP9	Secretion of mesangial and epithelial cells of the tubules at an ultra-low level. Increases with damage to the tubules	Secretion, expression, excretion, reabsorption in a small amount is normal	Urine — not normal Blood — 475 to 798 ng/mL [90] Urine and blood — not normal [90]	AKI, CKD of any etiology, including kidney cancer (carcinoma). Any kidney disease characterized by the formation of fibrosis
IL-18	Secretion by epithelial cells in the proximal tubules, distal convoluted tubule, connecting tubules and collecting tubules in case of damage, monocytes, macrophages	Секреция, экспрессия, выведение, реабсорбция	Urine — not normally detected (may be detected in ultra-low concentrations) [91] Blood — less than 70 pg/ml [92]	AKI, ischemic kidney disease, glomerulonephritis, incl. lupus, diabetic and obstructive nephropathy
β_2-МГ	In all nucleated cells, except for erythrocytes	Reabsorbed in proximal tubules	Urine — in trace amounts (no more than 0.1 % of the total content in the body) Blood — up to 0.32 mg/l [93]	Infectious-inflammatory, autoimmune diseases of any etiology, amyloidosis in hemodialysis, kidney cancer, secondary nephropathies, multiple myeloma
Cystatin C	Synthesized by all nucleated cells, 100 % filtered by glomeruli	Reabsorbed in proximal tubules	Urine — not normal Blood — 0.50–0.96 mg/l (in men), 0.57–0.96 mg/l (in women) [94]	AKI, the prospect of use — the risk of progression of tubulopathies of any genesis
IL-6	It is synthesized in many immunocompetent cells. In the kidney tissue, IL-6 is expressed by podocytes, mesengial, and endothelial cells.	Reabsorbed in the tubules	Urine — not normal Blood — 1-2 pg/ml [95]	AKI of any origin, primary and secondary glomerulopathies, secondary nephropathies
Uro-modulin	Secretion and expression in thick ascending loop of Henle	Secretion, expression, excretion, reabsorption in small amounts	Urine — 0.2 to 49.9 μg/mL [96] Blood — not normal	AKI, autosomal dominant tubulointerstitial kidney disease (uromodulo-associated kidney disease), tubulopathies of any genesis

Note: AH — arterial hypertension, IL — interleukin, AKI — acute kidney injury, DM — diabetes mellitus, CKD — chronic kidney disease, CHF — chronic heart failure

Table 2. *Classification of the pathology of the tubular apparatus*

№	Classification sign
I	**According to the etiological factor:** 1. Congenital 2. Acquired
II	**According to the topic of the pathological process:** 1. Pathology of the proximal tubule 2. Pathology of the distal tubule 3. Pathology of the loop of Genle 4. Pathology of the collecting duct 5. Combined forms
III	**According to the damage reaction:** 1. Acute – With complications: ✓ Within the nephron ✓ System ✓ With process timing – Without complications 2. Chronic
IV	**According to the reversibility of the pathological process:** 1. Reversible tubular pathology 2. Irreversible tubular pathology: А. No transformation; Б. With transformation: – autophagy – necrosis – epithelial-mesenchymal transition – atrophy – calcification
V	**According to the pathology of cytoplasmic and intracellular membranes of tubular epithelial cells:** 1. Pathology of tubules of toxic genesis 2. Pathology of tubules of metabolic origin 3. Pathology of tubules of medicinal genesis 4. Pathology of hypertensive origin 5. Pathology of ischemic genesis 6. Pathology of inflammatory genesis: – cytokine reactions – direct influence of infectious (bacterial, viral) facts of pathogenicity (enzymes, exotoxins, etc.) – autoimmune reactions (autoantigens, circulating immune complexes)
VI	**According to the characteristics of the affected structures of the epithelial cells of the tubules:** 1. Membranopathy 2. Co-transport damage 3. Receptor damage – cubilin – megaline – sodium-hydrogen exchanger (NHE1) – Chloride ion channel (CIC-5) 4. Mitochondrial damage 5. Lysosomopathies 6. Primary eyelash pathology; 7. Pathology of the cytoskeleton (microtubules)
VII	**According to the pathology of proteins that form intercellular contacts:** 1. Claudins 2. Integrins 3. CAVSAP3 (Calmodulin-regulated spectrin-associated protein 3)

IL-18 is involved in signaling pathways that take part mainly in the pro-inflammatory response [76]. It should be noted that many acute and chronic diseases are based on the inflammatory process, and IL-18 plays a key role in it. To perform its action, IL-18 requires a specific receptor and a protein that binds IL-18 [76]. IL-18 is used as a marker of tubular damage in cases of renal inflammatory diseases of any etiology, including AKI, autoimmune pathologies (primary and secondary glomerulonephritis), metabolic disorders (diabetic nephropathy), and obstructive kidney diseases [75].

IL-6 is reabsorbed by renal tubules and is found in many immunocompetent cells. In kidneys, IL-6 is expressed by podocytes, mesenchymal, and endothelial cells. IL-6 is a cytokine that provides pro-inflammatory, immune mechanism, as well as immediate response [77]. IL-6 is involved as the key component in several signaling pathways and has specific receptors for interactions with target organ cells, primarily, tubular and blood cells. An important pathological function of IL-6 is increasing the activity of epithelial sodium channel resulting in increasing sodium reabsorption in blood flow; this, in turn, leads to the growing risk of developing arterial hypertension, as well as to the stimulation of renin-angiotensin-aldosterone system [78]. IL-6 may have a prognostic value in the cases of AKI of any origin, primary and secondary glomerulopathies, secondary nephropathies.

Given the variety of markers of renal tubular functioning, it seems to be reasonable to summarize the presented material according to their main characteristics (Table 1.)

This table was drawn up based on the reference values of tubular function markers obtained from the studies conducted with the monitoring of parameters in a cohort of healthy volunteers.

Issues of classification of the pathology of tubular apparatus

Currently, there is no single classification of the pathology of tubular apparatus. The most obvious reason for the lack of systematization and structure of tubulopathies is the complex, highly organized structure of tubules and the variety of processes and mechanisms that are involved in their sequential function. The collaboration of the specialists of different profiles is required to develop a unified classification of tubulopathies that will be used in clinical practice and scientific research.

A deep and detailed review of literature sources allowed us to identify the key aspects that determine possible classification of the pathology of tubular apparatus (Table 2).

Conclusion

This literature review demonstrates the high relevance of further intensive study of the specific features of the highly organized tubular apparatus and of the mechanisms of intermolecular interaction therein. Available clinical data and pathomorphological results of studies gave us an idea on the potential use of the biomarkers of tubular dysfunction in the diagnosis of not only acute kidney injury or acute kidney disease, but also of chronic kidney disease.

It should be noted that a unified classification of tubular apparatus diseases is required for the consistency of terminology, understanding the pathogenetic processes, as well as for diagnostic and therapeutic measures. To address this problem, a working group of the experts in various fields, mainly nephrologists, morphologists, and geneticists should be created. Alongside with structurization, the implementation of such tubular diseases classification in clinical practice will allow to determine the process severity, risk category, possible complications, and to make many other significant assessments.

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ИНТЕРЛЕЙКИН-1 — БИОЛОГИЧЕСКИЙ МАРКЕР ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Interleukin-1 is a Biological Marker in Heart Failure

Резюме

Воспаление является универсальной реакцией живого организма на различные повреждающие факторы и направлено на восстановление целостности тканей и минимизацию гибели клеток. Активными участниками воспалительного ответа являются провоспалительные цитокины, в частности интерлейкины. У пациентов с сердечной недостаточностью воспалительные реакции приводят к повреждению кардиомиоцитов, их апоптозу и активации нейрогуморальных систем, которые способствуют запуску гибернации миокарда и механизмов его ремоделирования. Цель представленного обзора — рассмотреть интерлейкин-1 (IL-1) качестве диагностического и прогностического маркера при сердечной недостаточности, а также влияние лечения рекомбинантной формой IL-1R на течение заболевания.

Ключевые слова: *воспаление, биологический маркер, сердечная недостаточность, цитокины, интерлейкины, анакинра*

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

Inflammation is a universal response of a living organism to various damaging factors and is aimed at restoring tissue integrity and minimizing cell death. Proinflammatory cytokines, in particular interleukins, are active participants in the inflammatory response. In patients with heart failure, inflammatory reactions lead to damage to cardiomyocytes, their apoptosis and activation of neurohumoral systems, which contribute to the initiation of myocardial hibernation and mechanisms of its remodeling. The purpose of this review is to consider IL-1 as a diagnostic and prognostic marker in heart failure, as well as the effect of treatment with a recombinant form of IL-1R on the course of the disease.

Key words: *inflammation, biological marker, heart failure, cytokines, interleukins, anakinra*

Conflict of interests

The authors declare no conflict of interests

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Introduction

As of today, the mortality due to chronic heart failure (CHF) still remains at very high level [1]. According to the large-scale epidemiological protocol EPOCA, the risk of total mortality due to heart failure (HF) exceeds the risk of total mortality in individuals without CHF by more than 10 times, and the average life expectancy in patients with CHF of functional class I–II and III–IV FC (according to the New York Heart Association (NYHA) CHF severity classification) is 7.8 and 4.8 years, respectively [2]. According to the European registry of EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot), mortality in patients with CHF of FC I–II and III–IV was 4.8 % and 13.5 % within one year, respectively [3]. According to the present-day literature sources, survival in CHF is often worse than in malignant tumors [4]. The results of many studies have demonstrated that five-year survival rate after HF diagnosing is about 25–50 % [3].

The search for new biological markers and analysis of the pathophysiological role and changes in their levels under various treatment options allowed understanding many pathogenetic aspects of the development and course of CHF [4]. Over the past twenty to thirty years, significant progress was achieved in the investigation of cardiovascular biomarkers. Determining the concentration of natriuretic peptides (NUP) that were used as biomarkers for the diagnostic and prognostic evaluation of patients with CHF and its implementation in the foreign and Russian clinical practice caused fundamental changes [5]. Currently, the assessment of the level of brain NLP (BNP) and its N-terminal precursor (NT-proBNP) is a kind of "gold standard" for diagnosing HF and predicting its course, however, limitations due to the impact of many factors on the level of these biomarkers, the ambiguity of threshold values, and sufficiently low information content in cases of CHF with preserved left ventricular ejection fraction (LVEF) necessitate further scientific and clinical trials aimed at developing more sensitive and specific laboratory tests [1, 5]. The new biological markers such as copeptin, adrenomedullin, galectin-3 (Gal-3), stimulating growth factor ST2, chemokine CX3CL1, fractalkine, etc., are getting all the closer to being implemented into biomedical practice [6=8].

Inflammation is a common response of a living organism to various damaging factors and is aimed at restoring tissue integrity and minimizing cell death. Initially, oxidized products and proteins of damaged extracellular matrix are released from the damaged or dead cells; they are recognized by sentinel toll-like receptors (TLRs), resulting in the activation of pro-inflammatory response. An active role in inflammatory response is played by pro-inflammatory cytokines (CKs), particularly, interleukins (ILs), tumor necrosis factor-α (TNF-α), chemokines and their receptors, cell adhesion molecules (integrins, selectins, etc.), as well as the acute-phase proteins (C-reactive protein (CRP) and pentraxin 3 (PTX3)). The impact of pro-inflammatory CKs leads to the activation of fibroblasts and cardiac tissue cells in the area of inflammation. Activated cells start producing CKs and growth factors that are potent chemoattractants and play a significant role in enhancing the inflammatory response. Neutrophils and monocytes secrete transforming growth factor-β (TGF-beta), including growth differentiation factor-15 (GDF-15) that attenuates macrophage response and protease production. In the patients with HF, inflammatory reactions result in the damage to cardiomyocytes, their apoptosis, and activation of neurohumoral systems that trigger myocardial hibernation and the mechanisms of its remodeling [9]. The features of inflammatory response in each specific case depend on the interaction of pro-inflammatory and anti-inflammatory CKs [9].

The objective of this review was to consider IL-1 as a diagnostic and prognostic marker in HF, as well as to analyze the impact of treatment with a natural recombinant IL-1R on the course of the disease.

Sourcing methodology

This paper provides the review of relevant publications. The analysis of literature sources was carried out using PubMed, RSCI, MedLine, Google Scholar, Science Direct databases. The authors reviewed both foreign and Russian papers. The search was carried out using the following keywords: biomarkers, heart failure, interleukin-1. This review mainly includes the description of studies conducted over the past 10 years, as well as selected fundamental sources written earlier.

Interleukin-1: structure and physiological functions

Understanding the role of IL-1 in the pathogenesis of inflammation significantly improved after the publication of the paper "Biologic basis for interleukin-1 in diseases" [10]. Blocking IL-1β is currently the standard of care in autoinflammatory diseases [11]. Autoinflammatory conditions often respond to IL-1β blockade, and are much less sensitive to immunosuppressive therapy [11].

The IL-1 family includes 11 CKs and 10 receptors; IL-1β and IL-18 are the best investigated ones [10, 12]. The description of these 11 members, their receptors, co-receptors and their important functions are presented in the Table. There are 4 CKs with anti-inflammatory effect, among these, IL-1Ra (IL-1 receptor antagonist) and IL-36Ra (IL-36 receptor antagonist) are specific, whereas IL37 and IL-38 are nonspecific [13]. The recombinant form of naturally occurring IL-1Ra is anakinra. Anakinra, as already mentioned, is used to treat a wide range of inflammatory conditions, including cardiovascular diseases (CVDs) [14]. IL-36Ra, IL-37, and IL-38 are not currently approved for human use, however, the results of preclinical studies revealed several indications for the management of human autoimmune diseases [15]. Alongside with the anti-inflammatory members of the IL-1 family, extracellular domains called "soluble receptors" also suppress inflammation. For example, soluble IL-1R2 neutralizes IL-1β, and IL-18BP (IL-18 binding protein) neutralizes IL-18 (Table) [16].

Il-1β synthesis and secretion

IL-1β binds to IL-1 type 1 receptor (IL-1R1); then a co-receptor chain, an additional protein (IL-1RAcP), is assembled [13]. This ternary complex recruits the adapter protein MyD88 (myeloid differentiation primary response gene 88) to the Toll-IL-1 receptor (TIR) domain of each receptor. Subsequently, phosphorylation of a part of the kinases occurs; the nuclear factor-κB (nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)) moves into nucleus, and transcription of pro-ILβ occurs [17]. Another "key player" is inflammasome, a cytosolic molecular structure that includes an adaptor protein, procaspase 1, and a sensor molecule. The most well-described inflammasome has a sensor molecule called a nucleotide-binding domain, and a leucine-rich repeat pyrine domain (NLRP3). This sensory molecule can be activated by both infectious stimuli known as pathogen-associated molecular patterns (PAMPs) and non-infectious ones in the form of damage-associated molecular patterns (DAMPs) (cholesterol, amyloid beta, urate crystals, and many others) [13]. This activation is due either to the binding of adenosine phosphate (ATP) to P2X7 receptor and the outflow of potassium into extracellular space, or the production of reactive oxygen species (ROS). After activation of the NLRP3 inflammasome, procaspase 1 turns into an active enzyme [17]. Then, active caspase 1 cleaves the IL-1 precursor in secretory lysosomes or in cytosol followed by the secretion of "mature" IL-1β [18].

Table. *Members of IL-1 family. Adapted from 1. Dinarello C.A. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018; 281:8–27. DOI: 10.1111/imr.12621. [12].*

IL-1 family	Receptor	Coreceptor	Property
IL-1α, IL-1β	IL-1R1	IL-1R3	Proinflammatory
IL-1Receptor Antagonist	IL-1R1	NA	Anti-inflammatory
IL-18	IL-1R5	IL-1R7	Proinflammatory
IL-33	IL-1R4	IL-1R3	Провоспалительная/ Proinflammatory
IL-36 α, β, γ	IL-1R6	IL-1R3	Proinflammatory
IL-36 Receptor Antagonist	IL-1R6	NA	Anti-inflammatory
IL-37	IL-1R5	IL-1R8	Anti-inflammatory
IL-38	IL-1R6	IL-1R9	Anti-inflammatory

IL-1 and heart failure

It was proved that patients with HF have significantly increased levels of various pro-inflammatory CKs, including IL-1 [10, 11]. The inflammatory marker CRP, a known surrogate marker of IL-1 activity, is an independent predictor of adverse outcomes in the patients with acute HF (AHF) and CHF [19]. The cytokine hypothesis of HF suggests that a triggering event induces the activation of pro-inflammatory CKs leading to their negative impact on LV function and to the acceleration of HF progression [11].

Several mechanisms were found to form a correlation between IL-1 concentrations and impaired LV systolic function. IL-1β is proven to reduce the beta-adrenergic response of L-type calcium channels through a cyclic adenosine monophosphate-independent mechanism [20]. Moreover, IL-1β reduces the expression of genes involved in the regulation of calcium homeostasis [21]. IL-1β increases the expression of nitric oxide synthase (NOS) in cardiac myocytes; it leads to increased nitric oxide (NO) activity and decreased myocardial contractility [22].

Several members of the IL-1 family have beneficial effects on myocardium. Two members, IL-33 and ST2, are a ligand and a receptor, and have cardioprotective properties. Two main isoforms of ST2 were identified: ST2L transmembrane receptor and soluble sST2 receptor. Soluble ST2 blocks the protective action of IL-33 contributing to the development of remodeling and fibrosis processes. ST2/IL-33 signaling system is involved in the regulation of inflammatory, neurohormonal activation and prevention of cardiac remodeling [23]. Increased sST2 expression was registered in patients with myocardial hypertrophy, fibrosis, dilatation of cardiac chambers, and reduced ventricular contractility, and is considered to be an independent predictor of one-year mortality in AHF [24]. Besides, it is proven to be a significant predictor of hospitalizations and mortality in stable CHF patients [25]. The patients with elevated sST2, as a rule, have increased LV volumes, reduced LV contractility, and elevated pulmonary artery pressure according to echocardiography (ECHO CG). The individuals with CHF demonstrated better hemodynamic parameters at sST2 concentrations below 35 ng/mL. As a result, the investigators assumed that during the outpatient treatment of patients with HF, this blood sST2 level can be used to monitor the effectiveness of treatment [26].

Healthy mice demonstrated reversible systolic LV dysfunction and decreased LV contractility reserve (measured by the decreased response to isoproterenol) after both single and multiple injections of IL-1β [27]. To investigate the effect of circulating IL-1 activity, mice received injections of plasma obtained from patients with AHF, patients with chronic systolic HF, as well as from healthy volunteers. The results were similar to the exogenous administration of IL-1β as described above: plasma of decompensated HF patients caused significant systolic and diastolic LV dysfunction and decreased cardiac contractility. It is of interest that mice pretreated with anakinra or IL-1β antibody did not show this negative effect [28]; this fact leads to the suggestion that IL-1β has cardiodepressive properties. Rodents injected with plasma from patients with stable systolic HF and elevated CRP levels had normal systolic heart function at rest along with the significantly deteriorated contractile reserve [28].

The experimental study performed in 2010 in the field of cardio-oncology by Zhu J. et al. [29] using rodents demonstrated that IL-1 mediates the cardiotoxicity of doxorubicin. A sequential trial confirmed that blocking IL-1 with anakinra reduced doxorubicin-induced microstructural damage to cardiac tissue and improved LV ejection fraction (LVEF) [29]. Similar data were obtained in the study of radiation-induced cardiopathy in mice and the effect of anakinra on it [30].

First clinical study to evaluate the effect of IL-1 blockade on cardiac function revealed that a single injection of anakinra (150 mg) in patients with rheumatoid arthritis (RA) and without HF significantly improved the parameters of myocardial contractility and relaxation, coronary flow reserve, and endothelial function [31]. American physicians provided data on a female patient with RA and HF with preserved EF (HFpEF) who demonstrated an improvement in NYHA FC and peak aerobic capacity after switching from etanercept (a TNF-α inhibitor) to anakinra; this fact also indicates a positive effect of IL-1 blockade on HF course [32].

A double-blind, randomized, placebo-controlled, cross-over D-HART study was aimed to determine the effects of anakinra IL-1 blockade on aerobic exercise capacity in 12 patients with preserved LVEF and CRP level >2 mg. Anakinra resulted in a statistically significant improvement in maximal oxygen consumption (+1.2 mL/kg/min, $p = 0.009$) and a significant decrease in plasma CRP levels (−74 %, $p = 0.006$). Decreased CRP concentrations correlated with an improvement in maximal oxygen consumption ($r = −0.60$, $p = 0.002$). IL-1 blockade with anakinra during 14 days significantly reduced the systemic inflammatory response and improved aerobic exercise capacity in patients with HFpEF and elevated plasma CRP levels [33].

ADHF study (A Randomized, Double-Blinded, Placebo-Controlled Pilot Study) included 30 patients with AHF, decreased LVEF (40 %), and elevated CRP (≥5 mg/l), who were treated with anakinra or placebo. After 72 hours, anakinra reduced CRP by 61 % from baseline compared with a 6 % reduction in the placebo group ($p = 0.004$). After 2 weeks, patients treated with anakinra demonstrated an increase in LVEF [+10 % (+3, +14)] compared with the placebo group (0 (−16 % to +5 %), $p = 0.020$). The authors summarized that IL-1 blockade with anakinra reduces systemic inflammatory response in patients with AHF [34].

The objective of the study conducted by Imen T. et al. in 2017 was analysis of the correlation between IL-1β-31T/C polymorphism and serum IL-1β levels and the risk of developing AHF in 320 patients with dyspnea (160 with AHF and 160 without AHF) and in 100 healthy volunteers. Genotyping of IL-1β was performed using restriction fragment length polymorphism. IL-1β concentration was significantly higher in patients with HF compared with the group without HF and with the control group. Results of the distribution of IL-1β-31T/C genotypes and allele frequencies revealed no significant difference between three groups. Serum levels of IL-1β were found to be higher in cases of TT genotype than in TC and CC ones [35].

The prognostic stratification of patients with idiopathic dilated cardiomyopathy (DCM) is known to be a complicated task. In 2017, Italian scientists have studied the additive significance of assessing biomarkers of inflammasome activation and systemic inflammation in order to further stratify long-term risk in patients with DCM. 156 outpatients with DCM were examined (mean age 58 years, 77 % males, median LVEF 35 %, mean serum sodium 139 meq/L, BNP median 189 pg/mL, median IL-1 beta (Il-1β) 1.08 pg/mL, median IL-6 1.7 pg/mL, and median IL-10 2.7 pg/mL). During the follow-up period of 89.6 months, 35 patients (22 %) died/underwent heart transplantation. Patients who died/underwent heart transplantation were more likely to have NYHA class III, had atrial fibrillation (AF), lower LVEF, and higher BNP concentrations. Levels of IL-1β, IL-6 and IL-10 did not differ significantly between the groups of patients with good or poor prognosis. There were no significant differences in IL-1β values among either different NYHA classes or LVEF quartiles. However, in a multidimensional model, IL-1β was a strong and independent predictor of all-cause mortality (HR 1.193, 95 % CI 1.056–1.349, p = 0.005 for log-squared values). Other factors associated with poor outcome included: male sex, presence of AF and blood sodium level. The estimated time-dependent ROC curve of multivariate model is AUC 0.74 (95 % CI 0.65–0.86) [36].

In 2017, Tassell B. et al. suggested that the administration of an IL-1 receptor antagonist could suppress inflammatory response and improve peak aerobic exercise capacity in patients with decompensated systolic HF. In the REDHART (Recently Decompensated Heart Failure Anakinra Response Trial) clinical protocol, 60 patients with reduced LVEF (<50 %) and elevated CRP levels (>2 mg/L) were examined. Eight patients withdrew from the study on their own volition. Patients were randomized in three groups: group 1 (16 individuals) 14 days after the discharge from the hospital received anakinra s/c at a dose of 100 mg for 2 weeks, group 2 (18 individuals) received anakinra injections at a dose of 100 mg up to 12 weeks, and group 3 (18 individuals) received placebo. Patients were monitored for maximal oxygen consumption (Vo2, mL/kg per minute) and ventilation efficiency (VE/Vco2 slope indicates the relationship between ventilation and CO2 production). Anakinra therapy had no effect on maximal Vo2 (Vo2 peak) or VE/Vco2 slope in 2 weeks. After 12 weeks, patients who continued anakinra demonstrated an improvement in Vo2 peak from 14.5 (10.5–16.6) mL/kg per minute to 16.1 (13.2–18.6) mL/kg per minute (p = 0.009 for intergroup variations). The rate of death or readmission for HF in 24 weeks was 6 %, 31 %, and 30 % in the patients who received anakinra for 12 weeks, for 14 days, and in placebo group. Larger extension studies are required to confirm the effect of the long-term treatment with the studied agent on maximal Vo2 and readmission for HF [37].

Aerobic capacity, as measured by Vo2, is one of the most powerful predictors of HF prognosis. Inflammation is a key factor that contributes to the change in aerobic capacity, and IL-1 is known to be involved in this process. Apoptosis-associated speck-like protein (ASC) containing a CARD domain is required for the activation of IL-1β and IL-18 inflammasomes. ASC expression is controlled by epigenetic modification; lower ASC methylation is associated with worse outcomes in HF. All this information determined the need for a trial to analyze the relationship between methylation of ASC, IL-1β and IL-18 with Vo2 peak in patients with HF. This study was conducted in North America by the staff of the Department of Cardiology at the University of Alabama, the Department of Cardiology at Stony Brook University, and Emory University. In this paper the relationship between ASC methylation, IL-1β, IL-18, and Vo2 peak was analyzed in 54 stable outpatients with HF. All participants had HF of NYHA FC II and III and were able to complete a treadmill exercise test. Results obtained: mean Vo2 peak was 16.68 ± 4.7 mL/kg/min, Vo2 peak was positively correlated with the average percentage of ASC methylation (r = 0.47, p = 0.001) and negatively associated with IL-1β (r = −0.38, p = 0.007); multiple linear regression models demonstrated that Vo2 peak increased by 2.30 mL/kg/min for every 1 % increase in ASC methylation and decreased by 1.91 mL/kg/min for every 1 pg/mL increase in plasma IL-1β [38].

In 2019, a study was conducted with the objective of analyzing the relationship between IL-1β and sST2 and the prognostic value of the combination of these biomarkers in patients with AHF. As part of the clinical protocol, 316 patients hospitalized with AHF were examined sequentially (age 72 ± 12 years, 57 % males, LVEF 45 ± 17 %). IL-1β concentration on admission was associated with previous hospitalizations for HF, more severe HF, higher concentrations of NT-proBNP and high-sensitivity troponin T. IL-1β levels were higher in patients who died within a year of hospitalization (n = 52, 16.5 %) (p = 0.005). Circulating IL-1β demonstrated positive correlation with sST2 (ρ = 0.65; p < 0.001). Patients with high sST2 and Il-1β levels had a significantly higher risk of death (30 % vs 14 %; hazard ratio: 2.52; 95 % confidence interval: 1.40–4.56; p = 0.002) [39].

In 2021, American investigators evaluated the effect of IL-1 blockade on cardiac remodeling. Transverse narrowing of the aorta was performed in C57BL laboratory mice. Six weeks after the intervention, the progressive decrease in EF and the increase in LV mass and size were reduced after intraperitoneal administration of an IL-1 receptor antagonist (IL-1ra). IL-1ra reduced the expression of collagen-1, tissue inhibitor of metalloproteinases-1 (TIMP1), and periostin. Infiltration of immune cells (macrophages and lymphocytes) was also reduced in mice treated with IL-1ra. In addition, decreased concentrations of cytokines IL-1, IL-18, and IL-6 was observed after the administration of IL-1ra [40].

In the same year, a pooled analysis of three early-phase randomized clinical trials was performed. Endpoints included the pool of all-cause deaths and new-onset HF, and the pool of all-cause deaths and HF hospitalizations during follow-up in one year. The safety of anakinra was also analyzed, including injection site reactions and serious infections. This study included 139 patients with ST-elevation myocardial infarction (STEMI) from three single studies: VCUART (n = 10), VCUART2 (n = 30), and VCUART3 (n = 99). 84 (60 %) individuals of these patients were randomized to anakinra group and 55 (40 %) to placebo group. Treatment with anakinra significantly reduced the incidence of all-cause death or worsening HF (7 (8.2 %) vs 16 (29.1 %), log P = 0.002) and all-cause death or hospitalization for HF (0 (0) vs 5 (9.1 %), log-rank P = 0.007). Patients treated with anakinra had significantly more pronounced injection site reactions (19 (22.6 %) vs 3 (5.5 %), p = 0.016) with no significant difference in the incidence of serious infectious complications (11 (13.1 %) vs 7 (12.7 %), p = 0.435). Treatment with anakinra significantly reduced the area under the curve for highly sensitive CRP from baseline to 14 days (75.48 (41.7–147.47) vs. 222.82 (222.82 (117.22–399.28) mg/day/L, p < 0.001). The researchers concluded that IL-1 blockade with anakinra for 14 days in patients with STEMI reduces the rate of new-onset HF or of hospitalizations for HF after 1 year [41].

The D-HART 2 study is a randomized, double-blind, placebo-controlled, single-center, phase 2, 2:1 clinical trial that included patients with HFpEF, NYHA FC II–III, and with highly sensitive CRP levels >2 mg/L. Patients received anakinra 100 mg once daily or placebo during 12 weeks. The primary endpoints included changes in maximal oxygen consumption and ventilatory capacity at week 12; secondary endpoints were the effects of IL-1 blockade on cardiac performance, systemic inflammation, endothelial function, life quality, nutritional status, and clinical outcomes. This study is completed and its results are upcoming [42].

Conclusion

Currently, there are state-of-the-art technologies for identification of new biological markers, therefore, it would be reasonable to develop a multibiomarker model for diagnosing and predicting the CVDs course. This will definitely require the improvement of bioinformational technologies used for a large database analysis. This literature review indicates the potentially important diagnostic and prognostic value of interleukin-1 assessment. The further scientific and clinical trials are expected to demonstrate the possibility of its use as an additional laboratory method for the diagnosis, risk stratification and prediction of cardiovascular events in the patients with HF. The effect of interleukin-1 blockade on reducing morbidity and mortality in CHF is to be assessed in more detail, of course, taking into consideration the reasonable costs and side effects of the drugs.

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ДИАГНОСТИКА И ЛЕЧЕНИЕ МОНОГЕННЫХ ФОРМ САХАРНОГО ДИАБЕТА: В ФОКУСЕ MODY-ДИАБЕТ

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Diagnosis and Treatment of Monogenic Forms of Diabetes Mellitus: Focus on Mody-Diabetes

Резюме

Диабет зрелого возраста у молодых (MODY) является наиболее распространенной формой моногенного диабета, возникающего в результате мутации одного гена. Он характеризуется легкой гипергликемией, аутосомно-доминантным типом наследования, ранним началом диабета (<25 лет), сохранением эндогенной секреции инсулина, а также наличием подтипов, различающихся клинически и генетически. В настоящее время идентифицировано 14 подтипов MODY, отличающихся частотой возникновения, клиническими особенностями, тяжестью диабета и связанными с ним осложнениями, а также ответом на лечение. Этот тип диабета, зачастую некорректно диагностируется как сахарный диабет типа 1 или типа 2. Причина тому — клиническое сходство с другими типами диабета, высокая стоимость и ограниченный доступ к генетическому тестированию, а также недостаточная осведомлённость клиницистов. В результате несвоевременной диагностики пациенты не получают надлежащего эффективного лечения, отличного от терапии диабета 1 и 2 типов. Цель данного обзора — повысить осведомлённость клиницистов о MODY-диабете, акцентировав внимание на обновленной информации о методах диагностики и лечения 14 подтипов.

Ключевые слова: *сахарный диабет зрелого возраста у молодых; сахарный диабет; генетическое тестирование; генные мутации; HNF1A; глюкокиназа (GCK)*

Конфликт интересов

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

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Abstract

Maturity-Onset Diabetes of the Young (MODY) is the most common form of monogenic diabetes resulting from a single gene mutation. It is characterized by mild hyperglycemia, autosomal dominant inheritance, early onset diabetes (<25 years), persistence of endogenous insulin secretion, and clinically and genetically distinct subtypes. Currently, 14 subtypes of MODY have been identified, differing in incidence, clinical features, severity of diabetes and associated complications, and response to treatment. This type of diabetes is mostly misdiagnosed as type 1 or type 2 diabetes mellitus due to clinical similarities to other types of diabetes, high cost and limited access to genetic testing, and lack of clinician awareness. As a result, thousands of patients do not receive proper treatment. Accurate diagnosis would allow for more effective therapeutic treatments other than those used for type 1 and type 2 diabetes. The purpose of this review is to raise clinicians' awareness of MODY diabetes by focusing on updated information on methods for diagnosing and treating its 14 subtypes.

Key words: *Maturity-Onset Diabetes of the Young (MODY); diabetes; genetic testing; gene mutations; HNF1A; glucokinase (GCK)*

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DPP-4 — dipeptidyl peptidase-4, K-ATP — ATP-sensitive potassium channels, PAP — oral antidiabetic drugs, SSM — sulfonylurea derivatives, SOD — superoxide dismutase, ABCC8 — ATP binding cassette subfamily C member 8, APPL1 — Adaptor protein, phosphotyrosine, interacting with PH domain and leucine Zipper 1, ATP — Binding cassette subfamily C member 8, BLK — B-cell Lymphocyte Kinase, CEL — Carboxyl ester lipase, GCK — Glucokinase, GLP-1 — Ras — агонисты рецептора глюкагоноподобного пептида-1, GLUT2 — Glucose transporter 2, HbA1c — Glycated hemoglobin, hemoglobin A1c, HNF — Hepatic nuclear factor, HNF1A — Hepatocyte nuclear factor 1-α, INS — Insulin, KCNJ11 — K+ channel subfamily J member 11, KLF11 — Krueppel-like factor 11, MODY — Maturity-Onset Diabetes of the Young, NEUROD1 — Neurogenic differentiation factor 1 , NF-kB — Nuclear factor kappa-light-chain-enhancer of activated B cells, PAX4 — Paired box 4, PDX1 — Pancreatic and duodenal homeobox 1, PND — Permanent neonatal diabetes, RCAD — Renal cysts and diabetes, SUR1 — Sulfonylurea receptor -1

Introduction

Maturity-onset diabetes of the young (MODY) is an unusual form of diabetes mellitus resulting from mutations in a single gene [1]. MODY is characterized by β-cell dysfunction; onset at a young age (before the age of 25); autosomal dominant inheritance; mild course that requires no or very little insulin therapy; in most cases, by high sensitivity to sulfonylurea derivatives (SUDs); the presence of clinically and genetically different subtypes; as well as by the absence of insulin resistance [2]. With regard to the latest of the listed specific features of MODY, i. e., the absence of insulin resistance, the researchers have different opinions. This, according to Mohan V. et al. (1987), insulin resistance in MODY patients is not only present, but is even more pronounced than in individuals with classical non-insulin-dependent diabetes [3]. Apparently, defective genes are crucial for the development, function and regulation of β-cells and therefore can cause impaired tissue glucose tolerance and insulin secretion.

Depending on the genes involved, MODY is classified into several subtypes and clinical phenotypes. Currently, there are 14 identified and described MODY subtypes, each of which is caused by a separate gene mutation (Table) [4]. These subtypes differ in gene mutation, age of onset, treatment, and hyperglycemia pattern. Among all 14 MODY subtypes, more than 95 % of cases are caused by mutations in hepatocyte nuclear factor 1-α (HNF1A), glucokinase (GCK), HNF4A and HNF1B; other mutations are rare and uncommon in the Caucasian population [5]. All known mutations underlying MODY vary in their prevalence, clinical features, severity of diabetes and related complications, and response to treatment. Each mutation encodes proteins involved in glucose homeostasis in pancreatic β-cells [6].

Diagnosis of MODY

Advanced genetic testing based on the development of new methods (e.g., next-generation sequencing) and increased availability of genetic testing centers, allow

Table. *Aggregate data on MODY subtypes (gene names, their localization and clinical signs)*

Subtype	Gene name	Locus	Clinical signs	Source
1	*HNF4A*	20q13.12	Mild fasting and postprandial hyperglycemia, sensitivity to sulfonylurea derivatives, low levels of apolipoproteins and triglycerides, neonatal macrosomia, neonatal hypoglycemic events	[6]
2	*GCK*	7p13	Mild fasting hyperglycemia, impaired glucose tolerance, HbA1c typically 7.3-7.5 %	[6]
3	*HNF1A*	12q24.31	Decreased renal threshold for glucosuria, sensitivity to sulfonylurea derivatives, transient neonatal hyperinsulinemic hypoglycemia	[17]
4	*PDX1*	13q12.2	Pancreatic agenesis, permanent neonatal diabetes in homozygotes	[5]
5	*HNF1B*	17q12	It is characterized by kidney damage and the development of anomalies of the genitourinary system in females, dysfunction of the exocrine part of the pancreas, hyperuricemia	[53]
6	*NEUROD1*	2q31.3	Characterized by obesity and insulin resistance, neonatal diabetes, childhood or adult-onset diabetes, neurological abnormalities	[11,19]
7	*KLF11*	2p25.1	Associated with the development of malignant neoplasm in the pancreas	[11]
8	*CEL*	9q34.13	Associated with endocrine and exocrine pancreatic dysfunction, lipomatosis, and fibrosis	[11]
9	*PAX4*	7q32.1	This gene encodes a transcription factor that is essential for the development and survival of insulin-producing β-cells	[11]
10	*INS*	11p15.5	Associated with neonatal diabetes	[53]
11	*BLK*	8p23.1	Helps control beta signals	[53]
12	*ABCC8*	11p15.1	Associated with renal diabetes	[53]
13	*KCNJ11*	11p15.1	Associated with renal diabetes	[53]
14	*APPL1*	3p14.3	Associated with Wolfram syndrome	[53]

Notes: GCK: Glucokinase (glucokinase); HNF1A, HNF4A, HNF1B: Hepatic nuclear factor alpha/beta (hepatocyte nuclear factor alpha/beta); PDX1: Pancreatic and duodenal homeobox 1 (pancreatic and duodenal homeobox 1); NEUROD1: Neurogenic differentiation factor 1 (neurogenic differentiation factor 1); KLF11: Krueppel-like factor 11 (Krueppel-like factor 11); CEL: Carboxyl ester lipase; PAX4: Paired box 4 (paired box 4); INS: Insulin (insulin); BLK: B-cell Lymphocyte Kinase (tyrosine protein kinase); ABCC8: ATP binding cassette subfamily C member 8; KCNJ11: K+ channel subfamily J member 11 (K+ channel subfamily J member 11); APPL1: Adapter protein, phosphotyrosine, interacting with PH domain and leucine Zipper 1

clinicians to make correct molecular diagnoses, thereby, avoiding the misdiagnosis of type 1 diabetes mellitus (DM1) or type 2 diabetes mellitus (DM2) [7]. Furthermore, several extrapancreatic signs can be used as specific MODY subtypes markers (e.g., macrosomia and neonatal hypoglycemia in the HNF4A-MODY subtype, or renal cysts in the HNF1B-MODY subtype). It should also be known that several MODY subtypes are characterized by a stable blood glucose level throughout the patient's life, others — by a progressive deterioration in insulin secretion and glucose control, and still others are predisposed to the development of micro- and macrovascular complications.

MODY can be distinguished from other types of diabetes by the age of the disease onset. However, it should be considered that MODY subtypes with different age of onset, low penetrance, or atypical signs may not meet the diagnostic criteria of the disease [8]. Furthermore, while a family history of diabetes is highly suggestive of MODY, several mutations in MODY-associated genes may occur at high frequency in individuals with no family history of diabetes [9].

According to the MODY diagnostic guidelines, genetic testing should be performed in individuals diagnosed with diabetes at a young age (25 years), as well as in individuals with the family history of diabetes, signs of endogenous insulin secretion as determined by C-peptide levels, and negative antibody results [10]. Direct sequencing with sensitivity approximating 100 % and next-generation sequencing can be successfully used to detect mutations in the MODY gene [1]. According to the model proposed by Shields B. M. et al. (2010), the onset under the age of 30 is an important differentiating factor between MODY and type 2 DM, while diabetes in parents increases the probability of a later change in a previously diagnosed type 1 DM to MODY 23-fold [5].

Clinical relevance of MODY diagnosis

Patients with MODY are often misdiagnosed with DM1 or DM2, and it leads to incorrect treatment [11]. The reason is not only the overlapping clinical signs common in diabetes mellitus; the high price and limited availability of genetic testing, as well as the lack of clinician awareness are also relevant. Exact diagnosis of MODY and its subtypes is crucial for patients and their families allowing them to choose the optimal

therapeutic approach that differs significantly from that used in DM1 and DM2 [4]. Thus, the patients treated for DM1 can shift to oral medications (e.g., SUDs) that will improve their life quality and glycemic control [12]. Similarly, patients with HNF1A-MODY (MODY 3) and HNF4A-MODY (MODY 1) may avoid unnecessary insulin therapy, as the results of studies have demonstrated that oral sulfonylurea agents are the optimal choice [13]. The diagnosis of MODY is the key to providing accurate consultation for predictive clinical outcome and genetic screening of family members [14].

MODY subtypes and management

HNF4A-MODY (MODY 1). MODY 1 is caused by a mutation in the hepatocyte nuclear factor 4A (*HNF4A*) gene that is expressed predominantly in liver, as well as in pancreas and kidneys. *HNF4A* gene regulates the expression of genes involved in lipid metabolism and gluconeogenesis in liver [15]. The mutations in *HNF4A*, associated with autosomal dominant inheritance lead to decreased insulin production [16]. Heterozygous mutations in this gene cause dysfunction of β-cells, impaired glucose-stimulated insulin secretion, and contribute to the development of atherogenic dyslipidemia [16]. MODY 1 can be associated with fetal macrosomia, transient neonatal hyperinsulinemic hypoglycemia, progressive development of hyperglycemia, and onset of diabetes mellitus in late adolescence or by the age of 25 [17]. During the first decade of life, patients with MODY 1 show normal glucose tolerance [15]. At the time of diagnosis and at the early stages of the disease, the patients with MODY 1 can control their glycemia just with diet, despite the elevated postprandial glucose levels after eating carbohydrate-rich food [18]. However, in most patients, β-cell function deteriorates over time requiring drug treatment [19]. Individuals with HNF4A-MODY are sensitive to sulfonylurea [19]; the best treatment is this compound in low doses rather than insulin [12]. However, in the later stages of the disease or during pregnancy, insulin therapy is usually required [15].

GCK-MODY (MODY 2). Glucokinase (GCK), also known as hexokinase IV or D, belongs to hexokinase family. *GCK* gene plays an important role in glucose-stimulated insulin secretion in pancreas, facilitating glucose uptake and its conversion to glycogen in liver [20, 21]. Mutations of *GCK* gene underlie the development of MODY 2 [21] and have been shown to cause abnormal sensitivity of β-cells to glucose that contributes to the development of a higher threshold for the start of glucose-stimulated insulin secretion. Glycated hemoglobin (HbA1c) levels are usually under 7.3–7.5 %. The vast majority of patients with MODY 2 have slightly elevated fasting plasma glucose levels, with no postprandial hyperglycemia, indicating adequate insulin production in response to elevated postprandial blood glucose levels [19]. Patients with confirmed GCK-MODY do not require any treatment other than recommendations on diet as their long-term outcomes are comparable to those in healthy individuals [20]. However, insulin should be administered during pregnancy to reduce the risk of fetal macrosomia [22]. Fetal genotype is not always known, therefore, series ultrasound measurements can be used to determine the height. If there is evidence of increased abdominal circumference on series ultrasound, then it can be assumed that the fetus has no GCK mutation and maternal hyperglycemia in this case should be managed to reduce the risk of macrosomia. If no signs of accelerated growth are found, then there is reason to suggest that the fetus has inherited the GCK gene mutation, and, in this regard, no treatment for maternal hyperglycemia is provided [23].

HNF1A-MODY (MODY 3). MODY 3 is a common variant of maturity-onset diabetes of the young and is caused by mutations in *HNF1A* gene [20]. *HNF1A* gene was found in liver, kidneys, intestine, and pancreatic β-cells and has been shown to control the expression of insulin genes in mature β-cells, as well as of the GLUT2 glucose transporter genes [4]. Mutations in *HNF1A* gene can cause impaired dimerization processes that, in turn, leads to the impaired metabolism of carbohydrates and the development of diabetes mellitus. HNF1A-MODY has a glycemic pattern that includes moderate fasting hyperglycemia and extremely high glucose levels after glucose administration [15]. HNF1A-MODY is characterized by transient neonatal hyperinsulinemic hypoglycemia, progressive hyperglycemia throughout the childhood, and the onset of diabetes mellitus at the age of 25 [17]. Insulin secretion in patients with HNF1A-MODY gradually decreases, glucose control upon that deteriorates over time and requires treatment. In addition, 63 % of patients develop diabetes under the age of 25, 79 % — under the age of 35, and 96 % — under the age of 55 [15]. Treatment of patients with HNF1A-MODY is carried out depending on their age and HbA1c level [24]. HNF1A-MODY is initially managed with a low-dose diet and sulfonylurea agents, however, insulin is required at the later stages of the disease or during pregnancy [15]. Glucagon-like peptide-1 receptor agonists (GLP-1 Ras) have been shown to effectively control HNF1A-MODY [25].

PDX1-MODY (MODY 4). Pancreatic and duodenal homeobox 1 (PDXI) is a homeodomain-containing transcription factor that regulates insulin gene expression and pancreatic development [20]. PDX1-MODY is a rare type of MODY that is caused by heterozygous mutations in *PDX1* gene that is important for the regulation of genes encoding the enzymes of glucagon, insulin, glucose transporter 2 (GLUT2), and glucokinase (GCK) [26]. *PDX1* gene acts as a main switch for the hormonal and enzymatic functions of pancreas [27]. Heterozygous mutations in *PDX1* gene can lead to impaired insulin

secretion, while homozygous mutations cause permanent neonatal diabetes (PND) and exocrine pancreatic insufficiency [28]. Patients with PDX1-MODY have type 2 diabetes with early onset and no extrapancreatic involvement. Metformin [29] and dipeptidyl peptidase-4 (DPP-4) [30] inhibitors have been shown to be effective in clinical cases. Diet, oral antidiabetic drugs (OADs), and insulin are all treatment options for individuals with MODY 4 [15].

HNF1B-MODY (MODY 5). MODY 5 is a rare type of the disease caused by mutations in *hepatocyte nuclear factor 1B* (*HNF1B*) gene [20]. *HNF1B* is a transcription factor of the superfamily of homeodomain-containing transcription factors and is found in a wide range of tissues such as liver, intestine, stomach, lungs, and pancreas [15, 20]. It is involved in many processes, including the development of nephron and embryonic pancreas [31]. Patients with HNF1B-MODY often have significant histologic abnormalities such as renal cysts and diabetes (RCAD). Variable multisystem phenotypes with a wide range of pancreatic and extrapancreatic clinical signs are observed in HNF1B-MODY [15]. Severe renal disease is caused by mutations in *HNF1B* that may start before the onset of glucose intolerance [32]. MODY 5 can cause such complications as vaginal aplasia, rudimentary uterus, hyperglycemia, gout, and low birth weight (900 g) [31]. Patients with HNF1B-MODY demonstrate hepatic insulin resistance [12] and resistance to sulfonylurea therapy, thus, early insulin administration may be required [33].

NEUROD1-MODY (MODY 6). Neurogenic differentiation factor 1 (NEUROD1) is a transcription factor with a basic loop and helix structure that is expressed in neurons and pancreatic cells. NEUROD1 is essential for pancreatic and neuronal development and has an effect on pancreatic morphology and neuronal differentiation [34]. NEUROD1 plays a role in the activation of insulin transcription by binding and activating the promoters of the sulfonylurea receptor 1 (SUR1), GCK, and PAX6 (a protein related to the catalytic subunit of glucose-6-phosphatase) [15]. Mutations in *NEUROD1* gene lead to the development of MODY 6 [20], and heterozygous mutations of this gene result in the dysfunction of β-cells [35]. Although insulin therapy is a standard treatment option, it should be kept in mind that patients with MODY 6 have diabetes with incomplete penetrance. This fact explains the possibility of obtaining benefits from both OADs and diet in half of patients with MODY 6 [36].

KLF11-MODY (MODY 7). Krueppel-like factor 11 (KLF11)-MODY is a result of heterozygous mutations in *KLF11* gene. *KLF11* gene encodes a transcription factor from the KLF/Sp1 family that is found in all human tissues [20, 37]. KLF11 regulates the expression of free radical scavengers such as catalase and superoxide dismutase (SOD) that are required for pancreatic β-cell function [20, 34]. Heterozygous mutations in *KLF11* gene ultimately lead to the dysfunction of β-cells and impaired insulin secretion [37]. KLF11-MODY is a type of diabetes with the onset at an early age and is managed with either OADs or insulin [15].

CEL-MODY (MODY 8). MODY 8 is caused by mutations in *carboxyl ester lipase* gene (CEL) that regulates pancreatic exocrine and endocrine functions. This gene is usually found in mammary glands and acinar tissue of pancreas [20, 38]. CEL is important in infants as it contributes to milk digestion and hydrolysis of food esters in duodenum [39]. Heterozygous mutations in *CEL* are associated with early pancreatic atrophy and subsequent exocrine failure, pancreatic lipomatosis, and endocrine dysfunction caused by carboxyl ester lipase misfolding and cytotoxic aggregation [38]. CEL-MODY manifests as adult-onset diabetes. Insulin appears to be the most appropriate treatment option for MODY 8; however, oral antidiabetic drugs can also be used [15, 38].

PAX4-MODY (MODY 9). MODY 9 develops as a result of heterozygous mutations in paired box *4* gene (PAX4) that encodes a transcription factor required for the formation, differentiation, development, and survival of insulin-producing β-cells [15, 20]. At the early stages of embryonic development, PAX4 is expressed in endocrine promoter cells, and then in β-cells [40]. Ketosis-prone diabetes was associated with mutations in *PAX4* gene [41]. At the early stages, patients with MODY 9 are treated using dietary agents or OADs [42]. However, at later stages of the disease, patients may require insulin administration [43].

INS-MODY (MODY 10). *Insulin* gene (*INS*) encodes proinsulin, and its mutation can lead to primary defects in nuclear factor kappa-B (NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells) [20]. Heterozygous gene mutations in *INS* gene result in MODY 10 which is characterized by decreased β-cell mass, gradually decreased insulin secretion, and diabetes mellitus with variable onset. Although dominant misfolding mutations in *INS gene* are a common cause of isolated permanent neonatal diabetes, the age of disease onset varies [44]. These mutations lead to a severe folding defect, an abnormal response to unfolded proteins, and β-cell apoptosis [45]. Diet or OADs can be used to treat patients with MODY at the time of diagnosis, however, patients eventually become insulin-dependent [44].

BLK-MODY (MODY 11). MODY 11 is caused by heterozygous mutations in *tyrosine protein kinase* gene (*BLK*, *B cell lymphocyte kinase*). *BLK* gene belongs to the SRC family of proto-oncogenes and encodes a tyrosine receptor protein that stimulates β-cells to produce and secrete insulin [20]. *BLK* gene is expressed in β-cells and is required for thymopoiesis in immature T-cells [46].

BLK-MODY has incomplete penetrance, so not all carriers develop diabetes. Heterozygous mutations in this gene reduce the expression and/or activity of BLK; it leads to PDX1 and NKX 6.1 deficiency, impaired glucose-stimulated insulin secretion, and decreased β-cell mass [47]. Environmental and genetic factors are suggested to play a role in the development of BLK-MODY, with overweight being the most important cause of hyperglycemia [48]. Pregnancy can also affect hyperglycemia [49]. Although the vast majority of patients require insulin, some of them can be treated with diet or OADs [15].

ABCC8-MODY (MODY 12). MODY 12 is based on heterozygous mutations of *ATP-binding cassette subfamily C member 8* gene (*ABCC8*) that encodes the sulfonylurea receptor 1 (SUR1), a subunit of the ATP-sensitive potassium (K-ATP) channel found in β-cell membranes [20, 34]. ABCC8 is responsible for the secretion of insulin that controls blood glucose levels [50]. Mutations in *ABCC8* gene can lead to congenital hyperinsulinism which can be caused by dominantly inherited inactivating mutations. Moreover, mutations in *ABCC8* gene (activating or recessive loss-of-function mutations) can cause the development of permanent or transient neonatal diabetes [50]. Most patients with MODY 12 are misdiagnosed with diabetes of another type and mistreated with insulin; it results in poor control and episodes of hypoglycemia [15]. Rafiq M. et al. (2008) suggested that in adulthood, all carriers of the ABCC8 mutation can be switched to sulfonylurea drugs [51].

KCNJ11-MODY (MODY 13). MODY 13 is caused by heterozygous mutations in *KCNJ11* gene that encodes Kir6.2 protein, one of the subunits of ATP-dependent potassium channels that regulate the flow of potassium ions across the cell membrane in pancreatic β-cells and play an important role in the regulation of glucose-stimulated insulin secretion [4]. This gene mutation results in the development of severe conditions such as inactivation of potassium channels due to the impaired interaction of subunits. This disorder has been found to be associated with Arg301 mutations that commonly lead to hyperinsulinism and possibly — to neonatal diabetes [34]. Patients with KCNJ11-MODY are best treated with high doses of a sulfonylurea for a long period of time [15].

APPL1-MODY (MODY 14). MODY 14 is a rare subtype caused by mutations in an adapter protein *phosphotyrosine* and *leucine lightning 1* gene (*APPL1*, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1) that regulates cell proliferation and the interaction between adiponectin and insulin signaling pathways [52]. Heterozygous loss-of-function mutations in this gene lead to impaired insulin secretion in response to glucose stimulation and decreased survival of β-cells [52]. *APPL1* mutations can induce apoptosis in the tissues with high expression; overexpression causes dysmorphic phenotypes and developmental delay [52]. Diet, oral antidiabetic drugs, and insulin are all possible treatments options for APPL1-MODY [15].

Conclusion

MODY is a rare type of diabetes mellitus that in many cases leads to the delayed diagnosis. As a result, patients often receive ineffective treatment that can aggravate the disease course. Molecular diagnostics is crucial for finding the optimal management in most patients with MODY. Clinicians should be aware of MODY pathogenesis and biomarkers, as this information is crucial for diagnosis verification, individual case management, and family screening.

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ОСТРЫЙ ОСТЕОПОРЕТИЧЕСКИЙ ПЕРЕЛОМ ПОЗВОНОЧНИКА. ЧАСТЬ 2. ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА ПО ДАННЫМ ВИЗУАЛИЗИРУЮЩИХ МЕТОДОВ. КОНСЕРВАТИВНОЕ И ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ

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Acute Osteoporotic Vertebral Fracture. Part 2. Differential Diagnostics According to the Data of Imaging Methods. Conservative and Surgical Treatment

Резюме

Остеопороз — широко распространенное метаболическое заболевание скелета среди лиц старше 50 лет. 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 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, дифференциальная диагностика*

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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, differential diagnosis*

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CT — computed tomography, DXA — Dual energy X-ray absorptiometry, KP — kyphoplasty, MM — multiple myeloma, MPS — myofascial pain syndrome, MRI — magnetic resonance imaging, OP fracture — osteoporotic fracture, T1-WI — T1-weighted image, T2-WI — T2 — weighted image, VP — vertebroplasty

Acute osteoporotic vertebral fracture (OP fracture) is one of the most common structural injuries of spine in elderly individuals. In most cases, such a fracture is accompanied by pronounced pain syndrome and a significant decrease in patient's motor activity. Such nonspecific clinical manifestations require careful verification of fracture, as well as differential diagnosis with other diseases that can lead to vertebral fracture. Acute OP fracture can be managed using conservative and surgical treatment methods.

Differential diagnosis of acute OP fracture based on the results of imaging studies

A low-energy vertebral fracture can develop due to osteoporosis or have other causes, including vertebral hemangioma, metastatic lesion, or primary malignant tumor in vertebral body (including multiple myeloma).

Fractures that are a result of these diseases are clinically indistinguishable, since they are present as nonspecific signs: acute pain in the area of injured vertebra and secondary limited range of motion. Diagnostic imaging can confirm the presence of fracture and are the first step in differential diagnosis determining the need for further examination and its direction.

Vertebral hemangioma

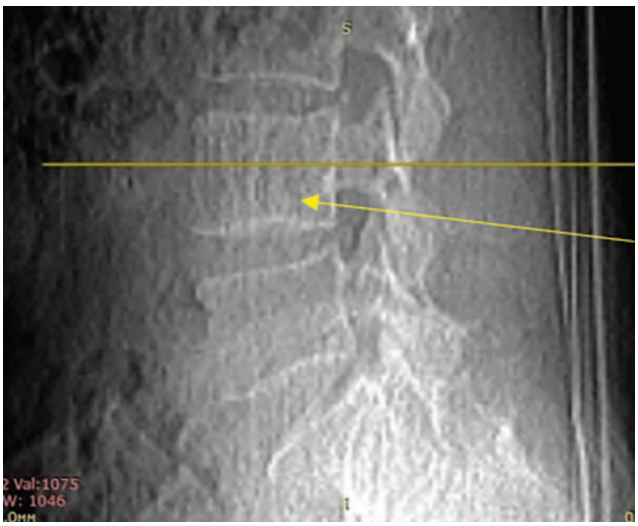
Vertebral hemangioma is a common benign vascular tumor and the most common neoplasm of spinal column; it occurs in 10–20 % of adults [1]. In most cases, hemangiomas are asymptomatic and are found incidentally. Hemangiomas can be single and multiple. Typically, they are rounded lesions with sharp contours, several millimeters in diameter, however, they may be large and cover the entire vertebral body. It is these hemangiomas that can cause a pathological fracture of vertebral body.

Histologically, hemangiomas include thin-walled vessels and sinuses lined by a layer of endothelial cells interspersed with sparse bone trabeculae oriented along the spinal axis. Adipose stroma is located between the vessels [2].

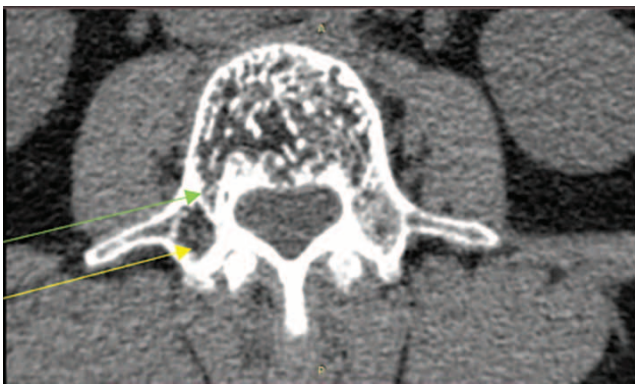
An X-ray image reveals typical longitudinal striation of the vertebral body in the presence of rare and thickened bone trabeculae ("honeycomb" appearance) [3]. Computed tomography (CT) demonstrates hemangioma

as low-density focus with the inclusion of rare bone trabeculae; the tissue of vertebral body on axial sections resembles honeycomb. According to magnetic resonance imaging (MRI), in the T1-weighted image (T1-WI), there is increased signal intensity due to the adipose tissue in lesion. In T2-weighted mode (T2-WI), the signal intensity is also increased due to the high water content, and this signal is usually more intense than the signal from adipose tissue, which distinguishes hemangioma from local fat deposits [4].

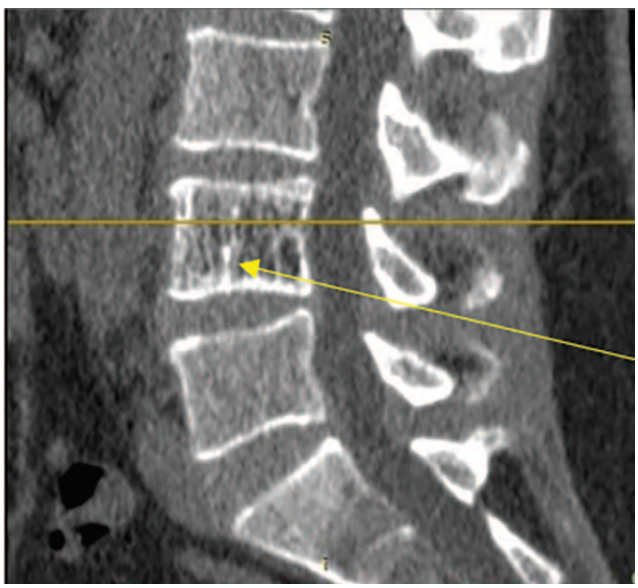
A vertebral body fracture due to a large hemangioma has no clinical differences from an OP fracture. In several cases differential diagnosis can be performed using MRI and CT imaging, however, most often, this diagnosis can be established only if the patient has a known history of hemangioma or results of previous studies. As a rule, the final diagnosis can be established after a bone biopsy performed during reconstructive surgery. The examples of hemangiomas demonstrated with the help of imaging techniques are shown in Figure 1.



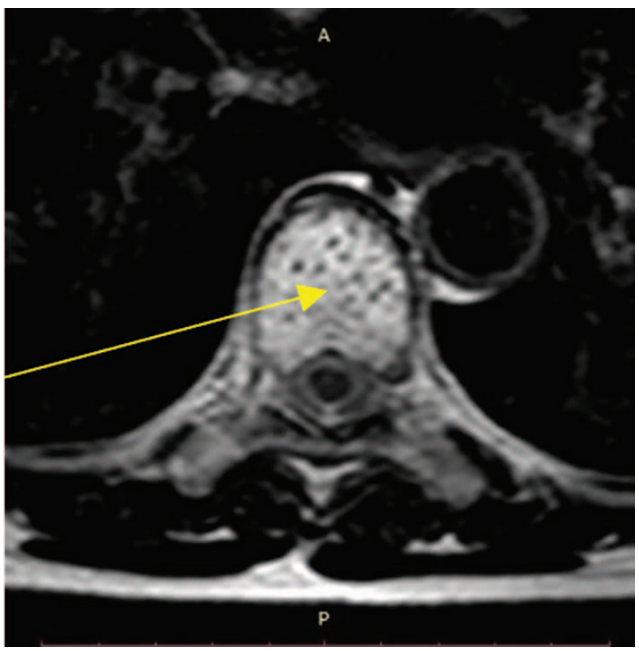
Picture 1a. *Radiography in lateral projection. Thickened longitudinally oriented trabeculas ("corduroy sign") are visible on the background of increased transparency of the bone tissue of the vertebral body*



Picture 1в. *CT, axial slice through the L4 vertebral pedicle. The hemangioma occupies over a half of the vertebral body and expands to the right pedicle and the articular process of the vertebra. Cross section through the hemangioma appears as a polka-dot pattern*



Picture 1б. *CT, sagittal reconstruction. Thickened longitudinally oriented trabeculas ("corduroy sign") are visible on the background of increased transparency of the bone tissue of the vertebral body. "Corduroy sign" is much better visualized than by radiography*



Picture 1г. *MRI T2 WI, axial slice through the middle of the Th8 body. Aggressive hemangioma, honeycomb pattern*

Figure 1. *Hemangioma of the L4 vertebral body (Observation by I.A. Borshenko)*
Abbreviation: CT — computed tomography, MRI — magnetic resonance imaging, T2 WI — T2 weighted imaging

Multiple myeloma

Multiple myeloma (MM) is a B-cell malignant tumor with the morphological substrate of plasma cells that produce monoclonal immunoglobulin [5]. Thus, MM refers to peripheral B-cell lymphoid tumors and is characterized by the bone marrow infiltration with plasma cells, the presence of monoclonal immunoglobulin in serum and/or urine, and osteolytic bone lesions. MM accounts for approximately 1 % of all malignant tumors and up to 10–15 % of all tumors of the hematopoietic and lymphoid tissues. This disease develops predominantly in elderly individuals. The average age of new patients is about 70 years. In 2020, the incidence of MM in Russia was 2.64 per 100,000 of population [6].

Bone marrow damage in the presence of MM can be both diffuse and focal.

The main clinical signs of MM is the bone pain. One of the typical localizations of myeloma is vertebrae; in most cases thoracic and lumbar spine regions are affected. Therefore, the decreased growth due to vertebral compression deformation and acute compression fractures can develop. Laboratory tests reveal normochromic normocytic anemia, pronounced acceleration of erythrocyte sedimentation rate (ESR), increased total protein level, dysproteinemia with M-gradient (paraprotein, monoclonal immunoglobulin), hypercalcemia, proteinuria [5].

The results obtained by imaging techniques help to provisionally identify four main MM patterns; the first three are the most relevant in terms of differential diagnosis of acute OP fracture [7]:

- disseminated form with multiple, well-defined demarcated lytic lesions,
- disseminated form of diffuse osteopenia type,
- solitary plasmacytoma (single lesion in vertebral body or in pelvic bones),
- osteosclerosing myeloma.

Diagnosis of MM is based on the results of laboratory tests, as well as on the data of morphological, immunohistochemical and cytogenetic tests of bone marrow biopsy material. However, in the case of an acute vertebral compression fracture in a patient without the known history of MM, the first step in diagnosis is likely to be the assessment of imaging results.

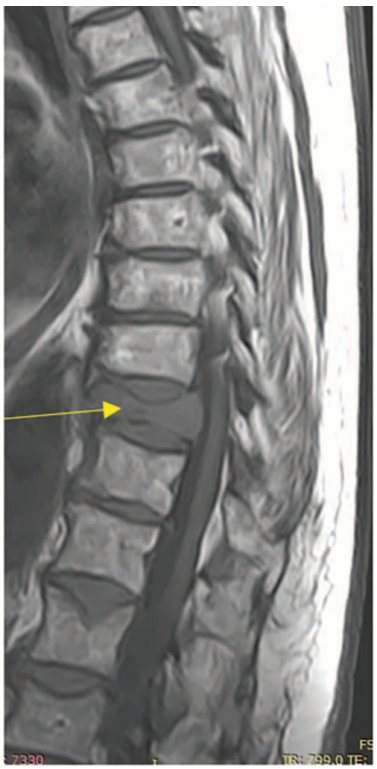


Figure 2a. *MRI, T1 WI, sagittal slice. Low signal intensity from the vertebral body, significant decrease in height over the entire area of the vertebral body, flat shape of the vertebra (vertebra plana), bulging posterior wall of the vertebral body*

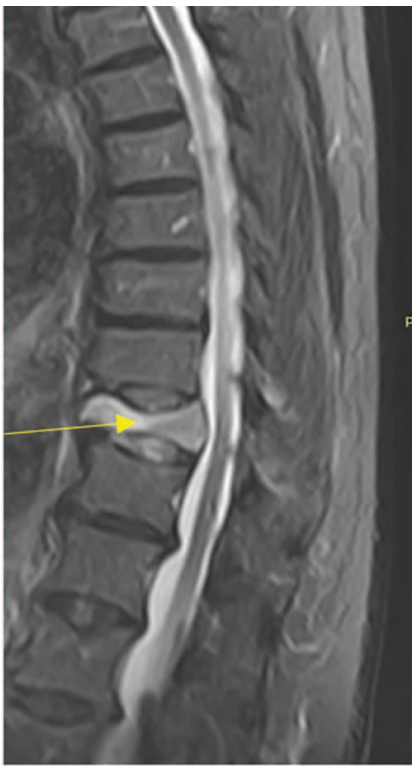


Figure 2б. *MRI, T2 WI, sagittal slice. Mixed signal from the vertebral body, bulging of the posterior wall of the vertebral body*

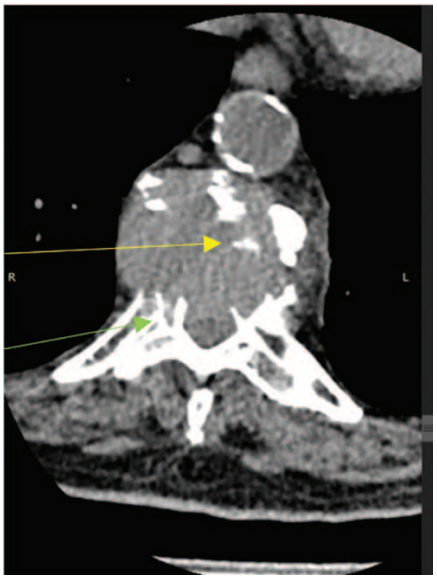


Figure 2в. *CT, axial slice. Destruction in the vertebral body and pedicles, as well as the posterior wall of the vertebral body*

Fugure 2. *Compression pathological fracture of the Th 10 vertebral body in a patient with focal myeloma (Observation by I.A. Borshenko, V.V. Lyalina)*

Abbreviation: CT — computed tomography, MRI — magnetic resonance imaging, T1 WI — T1 weighted imaging, T2 WI — T2 weighted imaging

X-ray generally has low sensitivity detecting no more than 60 % of myeloma lesions [7]. X-ray results suggest MM only if there are multiple "stamped" lytic bone lesions. However, this signs also cannot be specific. In all other respects, X-ray imaging will confirm, but not differentiate, the presence of osteopenia, fracture, and/or multiple vertebral compression deformities.

On MRI, myeloma focus is visualized as a rounded area of low intensity T1-WI signal and high intensity signal on T2-WI with fat suppression. In diffuse MM form, a uniformly low signal from the affected bones on T1-WI and a uniform, slightly inhomogeneous increased signal on T2-WI is observed [8]. Moreover, MR-imaging provides detailed examination of the condition of arches, transverse and spinous processes that can also be involved in the myeloma process, as well as of the epidural space of spine that may include epidural soft tissue component leading to the compression of spinal cord and its roots.

One of the MM types is solitary vertebral plasmacytoma that is defined on MRI as a typical "mini brain" appearance. [9].

However, one should understand that the differential diagnosis of an OP fracture and a MM-related fracture can be difficult in the case of acute vertebral fracture. First of all, this is due to the fact that the appearance of the damaged vertebra is non-specific and is mainly represented by deformity and pronounced bone edema. In some cases, MM may be suspected based on such typical changes as diffuse focal lesions of other vertebrae or the presence of epidural component. However, in the case of a diffuse osteopenic type, the MRI presentation will be low-informative, and in the case of an acute fracture due to a solitary plasmacytoma, differential diagnosis based on MRI results will be impossible. The final diagnosis of MM is based on the results of biopsy and laboratory tests. An example of a pathological fracture in the presence of focal myeloma obtained with the help of imaging techniques is shown in Figure 2.

Vertebral metastatic lesion

The most osteotropic types are breast, prostate and lung cancers, as well as kidney, adrenal, thyroid and ovarian cancer [10]. The presence of metastases is often complicated by a compression vertebral fracture. The most typical localizations of metastases in spine are the lower thoracic and upper lumbar regions; fractures most often occur in these regions, as it happens in osteoporosis [11]. Metastases can be divided into osteolytic, osteoblastic and mixed [10].

X-ray cannot reveal small lytic lesions, as well as does not provide adequately detailed visualization of the structures of spinal canal. Damage to the posterior parts of vertebra, including pedicles, is typical ("missing pedicle", or "winking owl sign" that is assessed on the frontal image); this fact can be useful in several cases for the differential diagnosis of fractures. However, it should be kept in mind that this symptom is non-specific [9].

CT presentation depends on the degree of metastasis mineralization. Lytic metastases (the most common form) appear as a lesion of hypointense signal with uneven contours. Destruction of the posterior cortical plate and asymmetric insertion of plus-tissue into the spinal canal are typical signs. Sclerotic metastases look like an area of hyperintense signal and, as a rule, do not spread beyond the vertebra. Typical features also include impaired trabecular structure of the vertebral body, the presence of destruction foci in the spongy substance, as well as in anterior and posterior cortical plates where asymmetric fractures are developed, partial destruction of endplates, insignificant changes in the anteroposterior size of vertebral body [8].

MRI is the most high-sensitive method for detecting metastases (more than 90 %), including the early stage of metastatic process; it also allows detailed analyzing of the state of spinal canal. *Lytic* metastasis is characterized by a hypointense signal on T1-WI and hyper- or isointense signal on T2-WI; *osteoblastic* metastasis is hyperintense in T1- and T2-WI; *mixed* metastasis is hypointense on T1-WI and hypo- and/or hyperintense on T2-WI. Process spreading to vertebral posterior structures is also well visualized, as well as its paraspinal spreading [9].

The presentation of a metastasis-related vertebral fracture is non-specific. The metastatic origin of the fracture can be clearly defined by such typical signs as damage to the posterior parts of vertebra, spreading of plus-tissue, destruction of posterior cortical plate (that sometimes looks like a "bulge" into the spinal canal), damage to other vertebrae [10]. However, the differential diagnosis of an OP fracture and a metastatic fracture in the absence of these signs is difficult. A distinctive feature of a "benign" from a "malignant" fracture is a change in signal characteristics during dynamic MRI: in cases of a "benign" fracture, the signal returns to normal range in 1–3 months. However, this sign is not reliable, since bone marrow edema and the associated signal change in an OP fracture can persist for more than three months. Final diagnosis is established based on the results of morphological study. [12, 13].

An example of L1 metastatic lesion according to the results of imaging techniques is shown in Figure 3.

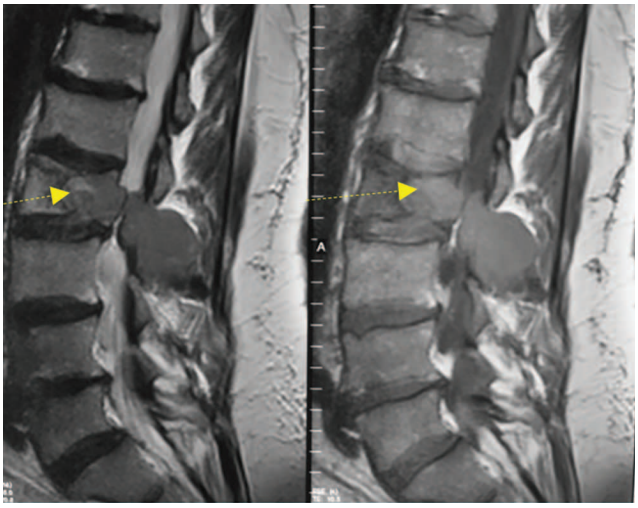
Treatment

Treatment of a patient with an acute OP fracture can last up to three months or more and involves drug and non-drug conservative treatment, and, in certain cases, surgical treatment as well.

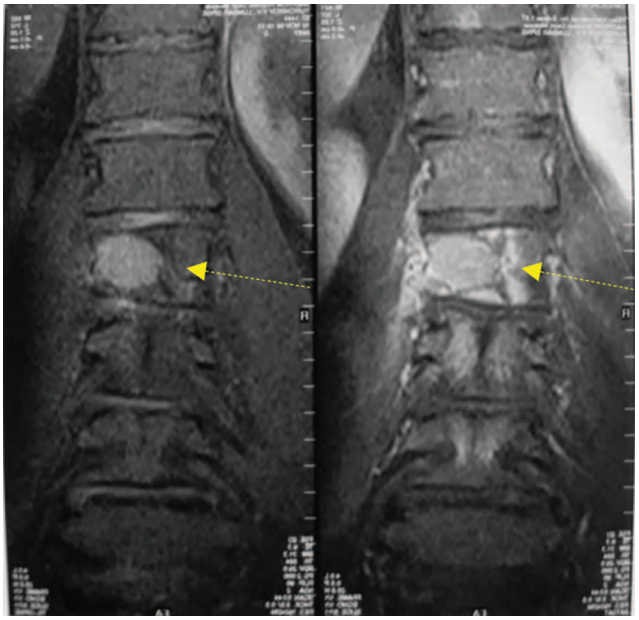
Non-drug treatment methods

Physical activity and wearing corsets

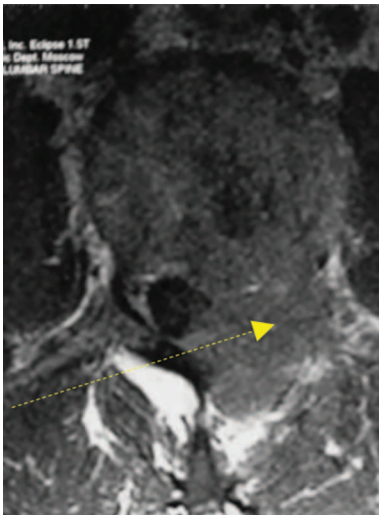
Patients are recommended to restart physical activity as soon as possible. Long-term bed rest is not



Picture 3а. *MRI, T2 WI (left), T1 WI (right) sagittal slice. Metastatic growth in the L1 vertebral body involves the left pedicle, expands into the spinal canal, compresses and displaces the dural sac, affects the posterior structures of the vertebra, arch and intervertebral joint and forms of a paravertebral mass in the spinal muscles*



Picture 3б. *MRI, T2 WI (left), T1 WI (right) frontal slice. There is a focal lesion of the left half of the L1 vertebral body with a expansion to the left side of the vertebral arch, into the lumen of the spinal canal and beyond the vertebra into the paravertebral tissues on the left*



Picture 3в. *MRI, T1 WI axial slice. There is a focal lesion of the left half of the L1 vertebral body with an expansion to the left side of the vertebral arch, into the lumen of the spinal canal and beyond the vertebra into the paravertebral tissues on the left*

Figure 3. *Metastatic lesion of the L1, MRI visualization, T1 WI, T2 WI (observation by Solomin V.D.)*
Abbreviation: CT — computed tomography, MRI — magnetic resonance imaging, T1 WI — T1 weighted imaging, T2 WI — T2 weighted imaging

recommended. Vertebral OP fracture significantly limits the overall physical activity of the patient; this fact results in the risk of pulmonary and thrombotic complications, contributes to the further loss of bone mass and muscle strength, and general detraining. In this regard, it is recommended, if possible, to start gymnastics literally from the first day of fracture using adequate anesthesia. The patients who have to temporarily stay in bed due to a fracture, on day 4–8, are recommended to turn from side to side with adequate anesthesia; then, if their condition allows, it is recommended to get out of bed with back support with a corset (corset should be put on in supine position) for short time (for 10 minutes up to 10 times a day). 3 weeks after fracture and for the next 10 weeks, patients should comply with the regimen of "intermittent rest in horizontal position": 2 hours in vertical position followed by 20 minutes in lying position [13, 14]. Physical exercises to improve balance and adequate strength training are recommended as prescribed by an exercise therapy physician.

Rigid/semi-rigid lumbar or thoracolumbar corset facilitates patient's verticalization, reduces pain severity by limiting the motion of the affected spine, and contributes to the early restart of physical activity [15]. However, many patients with previous pronounced deformity (kyphoscoliosis with torso shortening and decreased

costo-iliac distance) experience significant difficulties and discomfort from wearing a corset that diminish its therapeutic effect. An important negative aspect of the use of corsets is the development of muscle atrophy, so their use is recommended during the first three months after fracture, but not longer.

Drug treatment

Drug treatment includes pain relief and specific treatment for osteoporosis [5].

Treatment for osteoporosis

Primary osteoporosis is managed with bone resorption modulators (bisphosphonates, RANKL inhibitors receptor activator of nuclear factor-kappa B ligand), teriparatide), as well as vitamin D agents (cholecalciferol and alfacalcidol). Management of secondary osteoporosis also requires compensation for the underlying disease. If the fracture appeared during treatment with one or another bone resorption modulator, then a question should be raised whether it is reasonable to continue taking or replacing this agent.

Anesthesia

The choice of drug products depends primarily on the intensity and type of pain syndrome.

In most cases, pain syndrome is represented by vertebral and myotonic components. In this regard, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol), muscle relaxants, and lidocaine patches are recommended as first-line agents for mild to moderate pain (Table 1) [16]. Drug pain relief is often not effective enough or is poorly tolerated. Given the wide variability in individual efficacy and tolerability, it is recommended to select NSAIDs and muscle relaxants using agents belonging to different chemical groups. If the pain is still not reduced within one to two weeks, then tramadol and/or calcitonin may be used, as well as a decision on surgical treatment should be made.

If myofascial trigger points were found, therapeutic blockades are recommended.

In the case of the prevalence of radicular pain, the development of radiculopathy signs and other neurological symptoms, an individual decision on further treatment strategy is recommended. [17]. Conservative pathogenetic treatment of radicular syndrome can

Table 1. *Drugs for pain relief in acute vertebral osteoporotic fracture*

Medications	Dosing	Side effects
Paracetamol	500-100 mg q4-8h (daily doses up to 3 g/day may be used)	Nephropathy, anemia, thrombocytopenia, hepatotoxicity, hypersensitivity, acute renal tubular necrosis
Non-steroidal anti-inflammatory drugs	Ibuprofen 200-800 mg q8h Naproxen, 200-500 mg q12h	Atrial fibrillation, bleeding, cardiovascular disease, edema, gastritis, gastrointestinal bleeding, heart failure, hypertension, kidney disease, gastric ulcer
Calcitonin	200 UI q24h intranasal 2-4 weeks. Alternate nostrils from one day to the next	Decreased appetite, dizziness, flashes, gastrointestinal disorders, headache, hypertension, hypocalcemia, rash, rhinitis, weight gain
Lidocaine patch 5 %	Stick on the affected area for 12 hours	Dermatitis, edema, exacerbation of pain, skin depigmentation, urticaria
Myorelaxants	Tolperisone — 50 mg q8-12h, then gradually increase the dose to 150 mg q8-12h	Dizziness, drowsiness, sedation, vomiting, dry mouth, constipation, headache
	The initial dose of tizanidine is 2 mg 3 times a day, then a gradual increase in the daily dose by 2-4 mg at intervals of 3-7 days to 12-24 mg/day, divided into 3-4 doses at regular intervals. Do not exceed 36 mg/day. Do not abruptly withdrawal	
Opioid analgesics	Tramadol — 50-200 mg/day Maximum daily dose — 400 mg	Dependence, confusion, drowsiness, dizziness, tachycardia, orthostatic hypotension, dry mouth, nausea, vomiting, increased sweating, miosis
Central analgesics	Nefopam Per os — 30-90 mg q8h; IM — 20 mg q6-8h; IV in NaCl 0,9 %– 20 mg q6-8h Maximum daily dose — 120 mg P.S. During the administration of the drug and within 15-20 minutes after the injection, the patient must be in the supine position	Dizziness, drowsiness, sleep disturbances, nervousness, thinking disturbances, a feeling of a veil over vision, nausea, vomiting, dry mouth, increased sweating, tachycardia, urinary retention. In rare cases — euphoria, hallucinations, convulsions
	Flupirtine* 200-600 mg/day. Maximum daily dose — 600 mg.	Dizziness, heartburn, nausea, vomiting, constipation or diarrhea, flatulence, abdominal pain, dryness of the oral mucosa, anorexia, depression, sleep disturbances, sweating, anxiety, nervousness, tremors, headache

Note: * currently not available in Russia

be used that includes neurotropic agents (lipoic acid, B vitamins, medications that improve microcirculation), or agents aimed at reducing neuropathic pain can be administered (gabapentin, pregabalin, etc.). In cases with the development of compressive radiculopathy — it often develops when a compression fracture is combined with degenerative spinal stenosis — injection of epidural steroid to the compressed root under X-ray monitoring can be used to relieve pain.

For patients with pronounced radiculopathy, inadequate effectiveness of conservative treatment, decompensated spinal stenosis, or developed neurogenic intermittent claudication syndrome, a decision should be made in regard to the microsurgical expansion of spinal canal (microdecompression) [18].

Signs of cauda equina syndrome are always an indication for urgent decompression of the nerve structures of cauda equina, since prolonged compression of these nerve structures leads to irreversible neurological deficit, especially — to the dysfunction of pelvic organs [19].

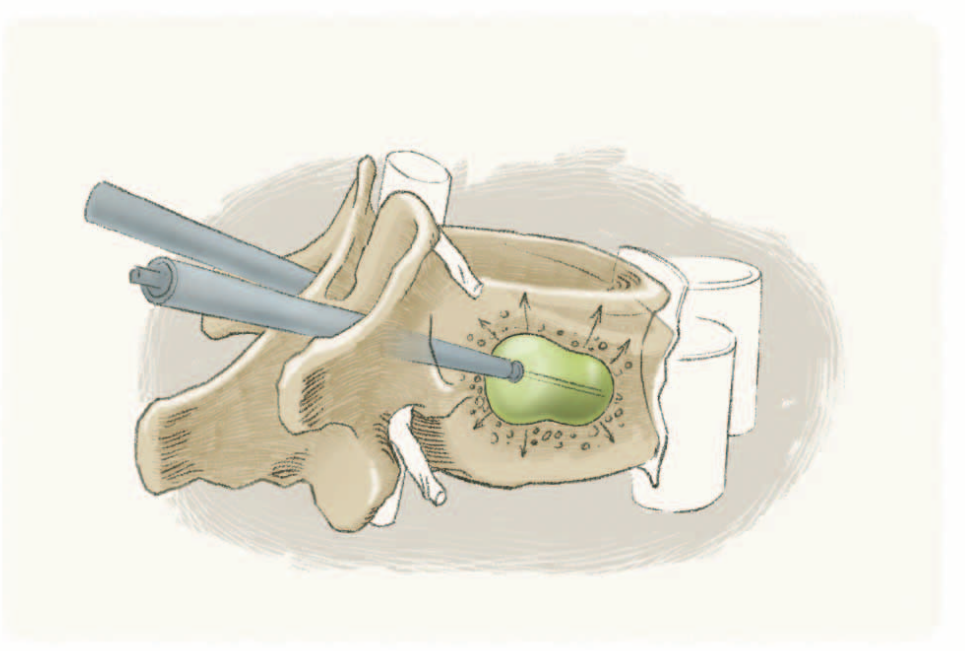
Pain facet syndrome is observed quite often in elderly patients, in particular, in the presence of osteoporosis [20]. However, the clinical presentation of acute vertebral fracture is usually stronger, and treatment for facet arthropathy is usually started several months after the compression fracture was healed. In such cases, blockades of the posterior medial branch of spinal nerve that innervates these joints are widely used, often combining local anesthesia with topical steroids [20]. If such blockades are effective, the technique of radiofrequency or endoscopic denervation of facet joints can be applied that allows achieving long-term pain relief.

Surgical management of acute vertebral fracture

In cases of choosing a surgical technique, vertebroplasty or kyphoplasty is commonly used. The purpose of these surgeries is to reduce pain and to correct or stabilize the shape of vertebrae.

In 1987, P. Geliber et al. described the management of a vertebral body tumor by injecting cement (polymethyl methacrylate) into the affected vertebra [21]. This procedure was called "vertebroplasty" and is actively used to manage various vertebral fractures (osteoporotic, traumatic, tumor). Vertebroplasty does not imply correction of vertebral shape; it only helps to "fix" the existing shape. During vertebroplasty (VP), methacrylate-based bone cement is injected into the spongy substance of vertebral body; it hardens within 10–15 minutes and prevents further vertebral deformation [22].

Afterwards, balloon kyphoplasty (KP) was developed: one or two balloons are inserted into a broken vertebral body [23]. When these balloons are inflated, endplates are moved apart, thereby reducing the kyphotic deformation of vertebra (that is, a kind of "straightening" and restoration of vertebral shape is achieved); a cavity in vertebral body is also made for the following injection of cement. KP mechanism is presented in Figure 4. Both surgeries (both VP and CP) are performed under the monitoring using image intensifier. As a rule, 5–7 ml of cement is injected into the ventral and central part of vertebral body. It should not be filled "tightly", as this does not always correlate with the analgesic effect, however, increases the risk of cement leakage.

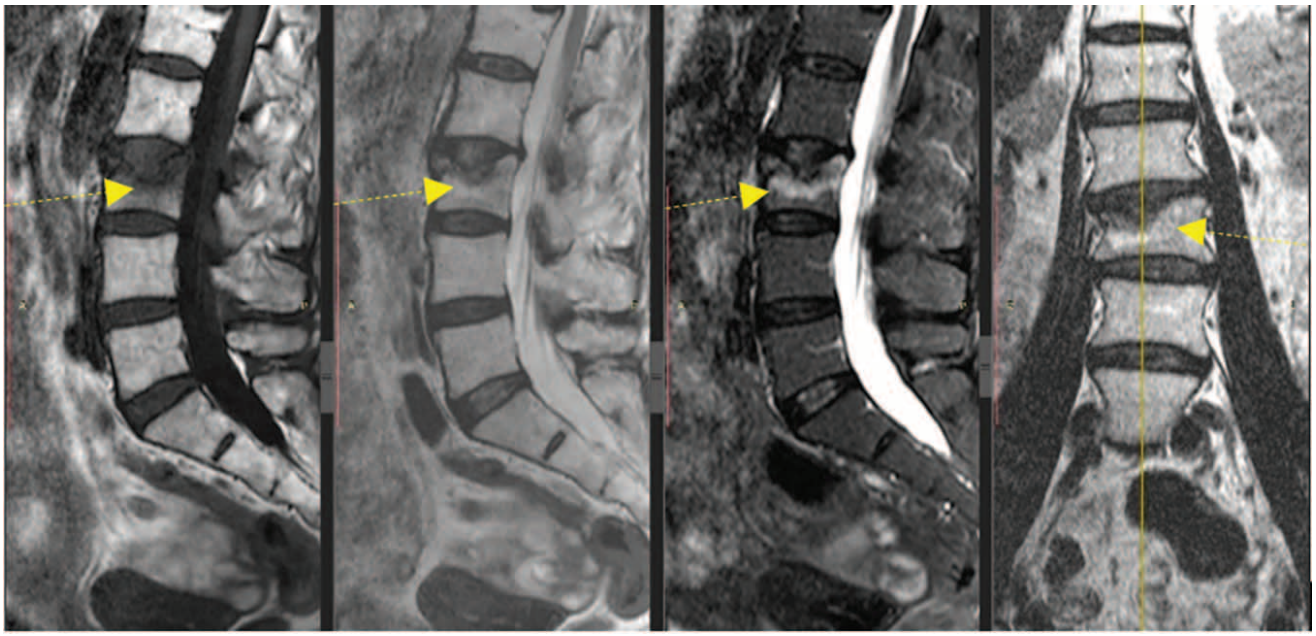


Picture 4. *Balloon kyphoplasty. Illustrator A.K. Rudykh*
Comments: the process of inflating a balloon in a fractured vertebral body to detect a cemented formation in the form of a cavity

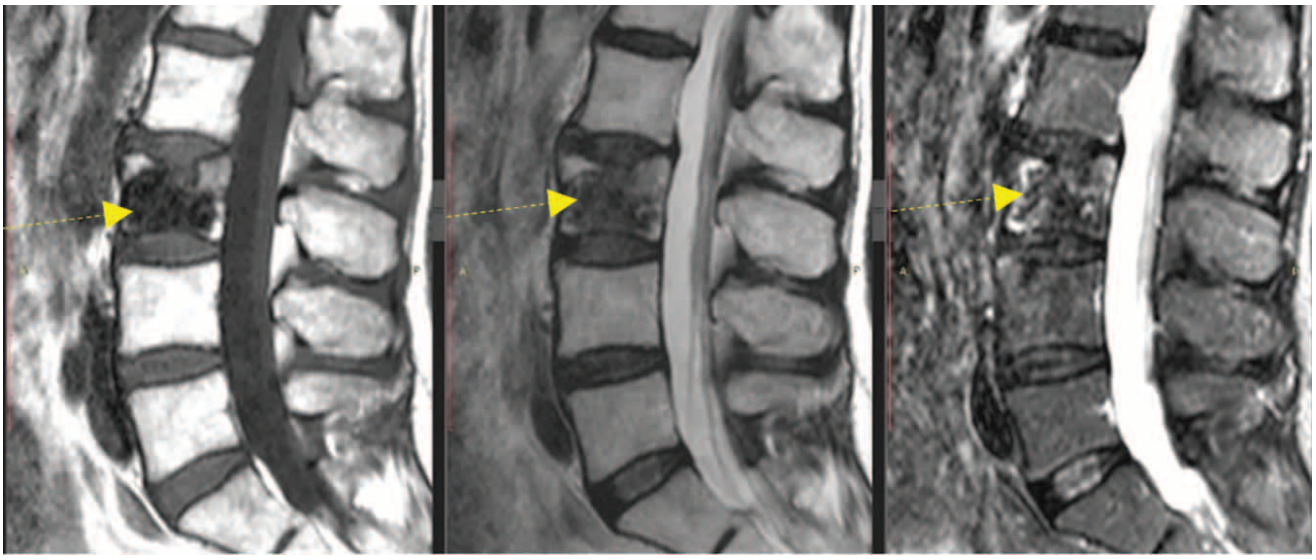
The advantage of KP is the lower risk of cement leakage due to the preliminary making a cavity in vertebral body. However, KP requires a fairly wide tunnel in vertebral pedicle (5–6 mm) for balloon placement that can cause technical difficulties for the surgeon, especially in cases of vertebral compression-comminuted fracture, causing iatrogenic displacement. Thus, a comminuted fracture of vertebral body and thin pedicles make this surgery difficult, so, in such cases VP is preferable [2] {Борщенко, 2014, Практика спинальной хирургии в условиях частной клиники}. The results of surgical treatment are shown in Figure 5.

VP/KP surgery with the strengthening of one vertebra lasts about 30–40 minutes. If cement is injected into two or more vertebrae, the duration of intervention increases. Most often, one or two vertebrae are treated.

Basic anesthetic technique for this intervention is local anesthesia. Potentiation in the form of ataralgesia



Picture 5a. *MRI of the lumbar spine. Hypointensive signal in T1 WI, areas of increased signal intensity in T2 WI. Significant increase in signal intensity in STIR mode as a manifestation of acute bone edema. Schmorl's hernia formation in the body of the L3 vertebra and decreased signal intensity along the line of bone compression*



Picture 5б. *MRI of the lumbar spine, 3 years after the fracture and puncture vertebroplasty of the L3 vertebra. An irregularly shaped area with a low signal in all modes — bone cement. The height of the vertebral body and normal spinal axis are preserved. No increase in the size of Schmorl's hernia in the body of L3 vertebra*

Figure 5. *Acute vertebral compression fracture of the L3, results of the vertebroplastic*
Abbreviation: MRI — magnetic resonance imaging, STIR — Short tau inversion recovery, T1 WI — T1 weighted imaging, T2 WI — T2 weighted imaging

is possible. Anesthesia with intradural administration of fentanyl in lumbar spine proved to be effective. In this case, fentanyl selectively binds to the segmental opioid receptors of spinal cord causing high-quality pain relief without affecting the motor functions of lower extremities.

Since the cement hardens already in the operating room 10–15 minutes after mixing and injection into vertebra, the patient can be activated almost immediately after returning to the ward. The verticalization of patient usually starts 30–60 minutes after the injection of cement. At this moment, the patient often notes a significant regression in vertebral pain syndrome.

Surgical indications in the acute period of vertebral OP fracture

Indications for performing VP/KP in case of a vertebral fracture are determined by the time elapsed after fracture, pain syndrome severity, and the presence of signs of fracture consolidation.

The severity of a vertebral fracture is primarily due not only to the time that has passed since the alleged vertebral injury, but also to the degree of bone tissue restructuring. Acute fracture process is associated with crushing of the bone trabeculae of the spongy substance of vertebral body. This can be observed on high-quality X-ray or CT images. On MRI, this situation is visible as the signs of the bone edema of vertebral body (decreased signal intensity on T1-WI, increased — on T2-WI, increased signal in the fat suppression mode (STIR mode)). An additional MRI sign of an acute fracture may be the line of the actual fracture with no bone trabeculae that can be observed as a line of reduced signal on T1-WI and T2-WI. On CT and X-ray images, a step-like deformation of a cortical plate is the sign of an acute fracture; it indicates a short period after the fracture when this "step" had no enough time to smooth out and transform.

If on X-ray or CT images there are established bone trabeculae in the area of vertebral deformation, and there are no MRI signs of bone edema, then such a fracture is considered chronic or consolidated.

Thus, the indication for VP/KP is a combination of two signs: the presence of an acute vertebral fracture in combination with a pronounced pain syndrome that is resistant to conservative treatment within 1–3 weeks [24, 25].

Actually, the time after fracture is not a criterion for surgery, since with low bone metabolism and delayed fracture consolidation, signs of an acute fracture may remain on MRI or CT for 1–6 months. Therefore, even 4-6 months after an OP fracture, if the signs of vertebral bone edema in combination with pain persist, an effective VP/KP can be performed. Such surgeries are performed on average 1–3 months after the fracture. At the same time, later than 6 months after the fracture, as a rule, vertebral remodeling is carried out and the reasonability of this type of surgical treatment becomes doubtful [2].

High pain tolerance, good physical activity of patient, effective analgesics and other conservative methods of treatment may be a relative contraindication for VP/KP surgery.

The degree of vertebral anatomical deformity is also not a criterion for determining indications for VP/KP, since even the first degree of vertebral compression can result in an extremely pronounced pain syndrome, and vice versa, complete compression crushing (vertebra plana) may not be accompanied by significant pain. However, a first-degree compression fracture in the transition zone where the inactive thoracic and highly mobile lumbar spine meet (Th11-L2 vertebrae) has a risk of deformity progression with the transition to higher degrees of compression. In this case, the risk of spinal kyphotic deformity increases that can lead to the development of a hump and chronic pain syndrome associated with the overload of spinal muscular and ligamentous apparatus. Therefore, in the case of an acute compression Th11-L2 fracture, it is recommended to expand the indications for VP/KP to prevent such biomechanical complications, even in the case of moderate primary pain syndrome [26–28].

Indications for surgery in delayed period

A compression fracture leads to the compaction of bone tissue (crushing of bone trabeculae). This in combination with natural reparative processes results in the spontaneous healing of fracture within 4–6 months while maintaining vertebral deformity. Therefore, VP/KP is most likely not indicated later than 6 months after fracture. However, osteoporosis can slow down reparative processes, so fracture healing may not occur, and bone loss and vertebral lysis may continue. In such cases, strengthening the vertebra with cement and performing VP/KP even later than 6 months after fracture can have a positive effect, i.e. significant decrease in pain and increased motor activity [29, 30].

The condition of vertebra is assessed by MRI and clinical signs. Signs of the process of crushing bone tissue, i.e. of the *ongoing fracture,* are decreased signal intensity from vertebral body on a T1-weighted image and increased signal intensity on a T2-weighted image. When drawing up a treatment plan, one should also keep in mind such signs of process severity as pain in the spinous process of damaged vertebra on palpation or percussion. The decision on the reasonability of VP/KP is made considering all the above factors [2].

Moreover, other surgical interventions are used in certain situations: neurological deficit (nerve roots compression), spinal instability according to the imaging, progression of kyphosis.

Conclusion

Differential diagnosis of an acute OP fracture based on clinical data is very difficult due to its non-specific signs and requires the use of medical imaging techniques, including CT and MRI. The treatment for acute OP fracture involves conservative and surgical methods that should be chosen in each individual case based on the results of thorough examination and ongoing monitoring of the patient.

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ВЗАИМОСВЯЗЬ ФЕНОТИПА ОКИСЛИТЕЛЬНОГО МЕТАБОЛИЗМА И АКЦЕНТУАЦИИ СВОЙСТВ ТЕМПЕРАМЕНТА С ПРИВЕРЖЕННОСТЬЮ К ТЕРАПИИ У ПАЦИЕНТОВ С ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНЬЮ

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Relationship of Clinical Picture, Phenotype of Oxidative Metabolism, Accentuation of Temperament Properties and Compliance in Patients with Gastroesophageal Reflux Disease

Резюме

Цель исследования. Установить взаимосвязь акцентуации свойств темперамента, клинической картины заболевания и приверженности к терапии у пациентов с гастроэзофагеальной рефлюксной болезнью с различным фенотипом окислительного метаболизма. **Материалы и методы.** Для реализации поставленной цели было проведено исследование в дизайне «случай-контроль» 156 пациентов обоих полов в возрасте от 21 до 55 лет (101 мужчина и 55 женщин, средний возраст 38 лет (IQR 29-46)) с верифицированной гастроэзофагеальной рефлюксной болезнью с оценкой клинической картины, сопутствующей патологией, выраженности симптомов с помощью визуально-аналоговой шкалы, приверженности к терапии, фенотипа окислительного метаболизма с помощью препарата-маркера эуфиллина, определением личностных психофизиологических особенности с использованием теста акцентуации свойств темперамента. Статистический анализ проводился согласно целям исследования и особенностям совокупности данных. **Результаты.** У пациентов с гастроэзофагеальной рефлюксной болезнью были выделены три основных типа личности: гипертимный (29;19 %), смешанный (61;39 %) и эмоционально-нестабильный тип (66;42 %). По фенотипу окислительного метаболизма 156 пациентов подразделялись на быстрые (51; 33 %), промежуточные (82; 52 %) и медленные метаболизаторы (23; 15 %). Мультиномиальный логистический регрессионный анализ показал, что у пациентов с быстрым метаболизмом, в отличие от промежуточных и медленных метаболизаторов, следует ожидать низкую интенсивность болевого синдрома (p=0,014). Влияния на клиническую картину свойств темперамента не выявлено (p=0,063). При изучении с помощью мультиномиальной логистической регрессии зависимости приверженности к терапии от свойств темперамента и уровня метаболизма пациента, у пациентов с гипертимным типом акцентуации свойств темперамента вероятность высокой приверженности к терапии составила более 65 % у быстрых и промежуточных ме-

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таболизаторов и 100 % у медленных метаболизаторов (p=0,006), у пациентов со смешанными типами вероятность высокой приверженности к терапии наблюдается только у медленных метаболизаторов (p=0,006), у пациентов с эмоционально-нестабильным типом высока вероятность низкой приверженности к терапии вне зависимости от уровня метаболизма (p=0,006). **Заключение.** Для прогнозирования приверженности к терапии пациентов с гастроэзофагеальной рефлюксной болезнью целесообразно определять уровень окислительного метаболизма и тип акцентуации свойств темперамента.

Ключевые слова: *гастроэзофагеальная рефлюксная болезнь, фенотип окислительного метаболизма, свойства темперамента, приверженность к терапии*

Конфликт интересов

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

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Abstract

The purpose of the study is to establish the relationship between the accentuation of temperament properties, clinical picture of disease, and adherence to therapy in patients with gastroesophageal reflux disease with different phenotype of oxidative metabolism. **Materials and methods.** To achieve this goal, a case-control study was conducted in 156 patients aged 21 to 55 years (101 men and 55 women, mean age 38 years (IQR 29-46))with verified gastroesophageal reflux disease with assessment of the clinical picture, assessment of the severity of symptoms using a visual analogue scale, concomitant pathology, adherence to therapy, phenotype of oxidative metabolism with the eufillin marker drug, determination of personal psychophysiological features using a temperament accentuation test. Statistical analyses were performed according to study objectives and data set features. **Results.** In patients with gastroesophageal reflux disease, 3 main personality types were identified: hyperthymic (n = 29; 19 %), mixed (n = 61; 39 %) and emotionally unstable type (n = 66; 42 %). By oxidative metabolism phenotype, 156 patients were divided into rapid (n = 51; 33 %), intermediate (n = 82; 52 %) and slow metabolizers (n = 23; 15 %). Analysis of multinomial logistic regression showed that in patients with rapid metabolism, in contrast to intermediate and slow metabolizers, low pain syndrome intensity should be expected (p = 0.014). There was no effect on the clinical presentation of temperament properties (p = 0.063). When studying the dependence of adherence to therapy on the properties of temperament and the patient`s metabolic level by multinomial logistic regression in patients with a hyperthymic type of accentuation of temperament properties, the probability of high adherence to therapy was more than 65 % in fast and intermediate metabolizers and 100 % in slow metabolizers (p = 0.006), in patients with mixed types the probability of high adherence to therapy is observed only in slow metabolizers (p = 0.006), patients with emotionally unstable type have a high probability of low adherence to therapy regardless of metabolic level (p = 0.006).**Conclusion.** To predict adherence of patients with gastroesophageal reflux disease to therapy, it is advisable to determine the level of oxidative metabolism and the type of accentuation of temperament properties.

Key words: *gastroesophageal reflux disease, phenotype of oxidative metabolism, temperament properties, compliance*

Conflict of interests

The authors declare no conflict of interests

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ARDs — acute respiratory diseases, APTT — accentuation of personality traits test, CVHC — chronic viral hepatitis C, GERD — gastroesophageal reflux disease, GERD-Q — gastroesophageal reflux disease questionnaire, GIT — gastrointestinal tract, GSRS — Gastrointestinal Symptom Rating Scale, HetEM — heterozygous extensive metabolizers (intermediate oxidative metabolism genotype), HomEM — homozygous extensive metabolizers (fast oxidative metabolism genotype), NSAIDs — non-steroidal anti-inflammatory drugs, PM — poor metabolizers (slow oxidative metabolism genotype), QAA-25 — quantitative assessment of adherence, VAS — visual analogue scale, WHO — World Health Organization

Rationale

The prevalence of gastroesophageal reflux disease (GERD) varies across countries and regions and remains quite high. The prevalence of GERD in the United States is approximately 20 %, while the prevalence of this disease in the Russian Federation is from 11 to 15 % [1].

Quite detailed approaches to the management of patients with GERD are described in the guidelines [2].

Based on the publications in PubMed from 1985 to 2015, Patti M.D. et al. (2015) demonstrated that lifestyle modification, proton pump inhibitors, and laparoscopic fundoplication are reliable methods of GERD treatment. Based on this review, the authors conclude that GERD is a very common disease, and the best results after its diagnosis can be achieved by a multidisciplinary team providing personalized treatment [3].

However, there are factors that reduce the effectiveness of drug therapy, for example, the difference in the metabolic rate between patients; currently, there are single scientific papers on the study of the metabolic rate in GERD patients. Mayev I. V. et al. (2011) found that among 267 examined patients with GERD, significantly predominating are the patients with fast oxidative metabolism genotype (HomEM) — 84 %, whereas the share of patients with intermediate metabolism (HetEM) was significantly lower — only 14 % of patients, and only four patients had slow metabolism (PM) [4]. Personalization of therapy often requires the knowledge of oxidative metabolism phenotype rather than its genotype, since the correlation between genotype and phenotype is not indicative: 50 % of erroneous predictions are reported [5]. One of solutions to this issue would be to determine individual differences in drug product metabolism using xenobiotics as markers [6].

Various questionnaires and scales are used to assess the effectiveness of GERD management; they allow to objectify the effect of treatment, both on the clinical presentation and on the life quality (assessment of the severity of gastroenterological symptoms using Gastrointestinal Symptom Rating Scale (GSRS), SF-36) [7, 8]. It should be noted that it is quite convenient to use in clinical settings a simpler method for assessing the clinical presentation with the help of a ten-point visual analog scale (VAS).

Another factor affecting the effectiveness of treatment is the adherence to therapy, i.e. the voluntary compliance of a patient with the prescribed treatment regimen. Zimmerman Ya.S. et al. in their paper (2015) on acid-related diseases mentioned the importance of following the prescribed recommendations in order to improve the effectiveness of treatment, including lifestyle modification, abandoning bad habits, adopting dietary restrictions, avoiding stressful situations, as well as adherence to prescribed doses of drugs, regimens, and treatment duration. Besides, the authors highlight the importance of cooperation between the physician and the patient in the management of acid-related diseases (gastroesophageal reflux disease, peptic ulcer, etc.) and the ways to improve it [9].

One of the reasons for the decreased adherence to the therapy and, consequently, its ineffectiveness, may be personality traits of the patient. To study personality traits, temperament models were developed and several methods were proposed (by V.M. Rusalov, H. Eysenck, A. Thomas and S. Chess, J. Strelau, etc.) [10]. A common technique for studying personal psychophysiological characteristics in routine clinical practice in patients with somatic disorders is the accentuation of personality traits test (APTT) (D.V. Plotnikov et al., 2001) [11]. It should be noted that in available literature sources there are almost no studies of the impact of personality traits on the adherence to therapy in patients with GERD.

In view of this, it is of interest to identify the correlation between individual differences in the rate of oxidative metabolism that determine the antisecretory effect of drugs and the accentuation of personality traits and their effect on adherence to therapy in patients with GERD.

The objective of this study was the establishment of the correlation between the accentuation of personality traits, the clinical presentation of the disease, and adherence to therapy in patients with gastroesophageal reflux disease with different phenotypes of oxidative metabolism.

Materials and methods

Study design to achieve the objective, a case–control study was performed; the analysis included results of clinical examination of 156 patients of the Gastroenterological Department of the Kursk Regional Clinical Hospital; the study included the patients with gastroesophageal reflux disease, at the age between 21 and 55 years (mean age of 38 (IQR 29–46)) (Table 1). There were 101 male and 55 female patients (male to female ratio 2:1). The inclusion criteria were: the presence of gastroesophageal reflux disease with or without esophagitis, the diagnosis of GERD was confirmed by GERD-Q questionnaire [12], alginate test, and/or fibroesophagogastroduodenoscopy (Table 1). The exclusion criteria were: Barrett's esophagus, gastric and/or duodenal ulcerative process, including this associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), refusal of the patient to participate at any stage of the study, chronic diseases in the acute or decompensation

Table 1. *Distribution of GERD patients by sex and esophagogastroduodenoscopy findings*

Nosology	Total amount	Sex	
		Men, amount	Women, amount
Gastroesophageal reflux disease without esophagitis	129 (83 %)	88 (57 %)	41 (26 %)
Gastroesophageal reflux disease with esophagitis	27 (17 %)	13 (8 %)	14 (9 %)
Total	156 (100 %)	101 (65 %)	55 (35 %)

stage. The patients with suspected acute respiratory disease (ARD) were included in this study, since the signs of laryngitis can be caused by GERD.

Before enrollment, all patients filled out a voluntary informed consent form with the information about the goals, objectives and description of the study. The abstract for this study with the protocol and the content of the informed consent form was approved by the Regional Ethics Committee of Kursk State Medical University.

The review of comorbidities in the examined population revealed the following patterns (Fig. 1). The most common comorbidities in patients were the symptoms of rhinitis and cough without fever (acute respiratory diseases) — in 28 patients (18 %), coronary heart disease — in 27 patients (17 %), and hypertension — in 22 patients (14 %). Among the GI comorbidities observed in 20 patients (13 %) were: functional dyspepsia, irritable bowel syndrome, fatty liver, and biliary dyskinesia.

The patients underwent clinical examination in accordance with the guidelines for GERD diagnosis and management. GERD was diagnosed in accordance with the WHO classification and recommendations of the Russian Gastroenterological Association [2].

Evaluation of the clinical presentation (severity of heartburn and pain syndrome) in patients with GERD was carried out using a ten-point visual analog scale (VAS). 1 point corresponded to the minimal manifestations of symptoms, 10 points — to their maximal manifestations. The results below 4 points were defined as mild heartburn or pain, 4–7 points — as moderate heartburn or pain, 8+ points — as severe heartburn or pain. The results of the clinical presentations evaluation were compared in patients with GERD with different metabolism and type of personality traits accentuation.

To study the adherence to therapy, the authors used a questionnaire proposed by Kolesnikova I.Yu. et al. (2005) [13] that included 5 items: taking medicines prescribed by a physician; satisfaction with treatment; dieting; smoking. Scores of the questionnaire range from 1 point (negative) to 3 (positive, no bad habits). The total score was also calculated; the sum from 5 to 10 was considered as low adherence, from 11 to 15 points — as high adherence [13]. This questionnaire was originally composed in the Russian language and validated for patients with acid-related diseases. No other questionnaires were used due to the large number of questions (QAA-25) as well as due to the fact that the questionnaires were validated mainly for patients with hypertension, coronary heart disease, type II diabetes mellitus, and not for patients with acid-related diseases. The difference between the amount of preparation handed out to the patient and the amount returned by the patient was not calculated. Additionally, information about the drugs taken was registered in the patient's protocol, and their average price in the pharmacies of Kursk was calculated; the frequency of administration per day, daily rate and duration of drug action were also recorded.

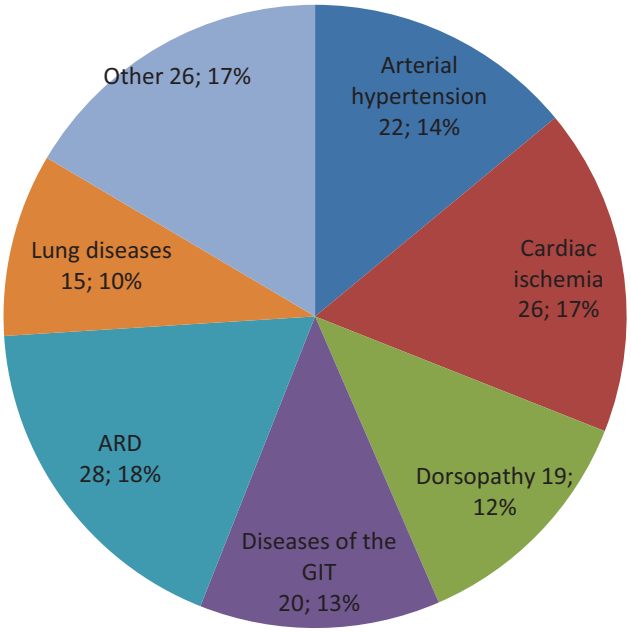

Figure 1. *Comorbidities in GERD patients*
Note: GERD — gastroesophageal reflux disease, ARD — acute respiratory diseases, GIT — gastrointestinal tract

The phenotype of oxidative metabolism in the examined population was studied according to the technique developed by the Pharmacokinetic Laboratory of Kursk State Medical University [6]. In particular, patients received oral aminophylline at a dose of 150 mg; its concentration during 24h in saliva was determined by the method of high-performance liquid chromatography. According to the method, patients were divided into the groups of fast metabolizers (half-life of aminophylline T½ < 9 hours), intermediate metabolizers (T½ = 9–15 hours) and slow metabolizers (T ½ > 15 hours).

The psychophysiological personality traits of patients with GERD were analyzed using the APTT questionnaire that includes 125 questions that should be answered "yes" or "no". The type of the accentuation of personality traits was established based on the previous factorial analysis of APTT scales as follows. Initially, APPT scales of accentuation were identified in the individual profile of each subject. Scale increase up to 8 STENs was regarded as a moderate accentuation of the trait, and three STENs were considered as a moderate deficiency of the measured trait. 9 and 2 STENs indicated a pronounced accentuation or deficiency of the measured trait. Maximum accentuation or deficiency of a trait was characterized by 10 and 1 STENs. It should be noted that the same patient may have accentuation on different scales. Then it was found out which of the generalized personal trait group includes accentuated scales. In accordance with this, the following types of accentuation were defined: hyperthymic, dysthymic, emotionally labile, inert, hyperthymic-labile, dysthymic-labile, inert mixed [11].

It was analyzed which of the generalized personal trait group includes accentuated scales, according to these, the type of accentuation was defined: hyperthymic, dysthymic, emotionally labile, inert, hyperthymic-labile, dysthymic-labile, inert mixed. The study was conducted once at the start of treatment course [11].

Statistical data analysis was carried out using the IBM SPSS Statistics Standard Edition 17.0 software package. Quantitative and qualitative ordinal characteristics (with more than 5 ranks) were represented by medians (Me) and quartiles (lower, Q1, and upper, Q3); qualitative characteristics — in the form of the absolute number of observations (n) and the percentage (%) of the total number of patients in the group. As a result of a preliminary data evaluation using the Kolmogorov–Smirnov test, it was revealed that the distribution of datasets differed from the normal one, therefore, in order to analyze the effect on the severity of the clinical presentation of metabolic rate and personality traits, as well as to assess the effect of the metabolic rate, treatment costs, frequency of drug administration, rate and duration of drug action on adherence to therapy, multinomial logistic regression was used [14].

Results

Accentuation of personality traits test in 156 patients with GERD revealed that 11 patients (71 %) has an accentuation in "neuroticism", "emotional inertia" and "emotional lability" scales (56; 36 % and 45; 29 %, respectively); the scales with the lowest representation were "aggressiveness" (39; 25 %), "vigorousness" (33; 21 %), "social activity" (36; 23 %), "sensitivity" (33; 21 %), "timidity" (28; 18 %).

Analysis of the results of the APTT questionnaire confirmed the heterogeneity of personality traits of the surveyed contingent: Hyperthymia with social and objective activity occurred (up to 8–10 STENs) in 29 patients (18.6 %). Emotional lability was expressed by increased score in APTT scales "neuroticism", "sensitivity", "timidity", "aggressiveness", "emotional lability" in 66 patients (42.3 %). Hyperthymic-labile, dysthymic-labile, inert mixed and emotional inert types were observed in 8 (5.1 %), 20 (12.8 %), 26 (16.7 %) and 1 (0.7 %) patients, respectively. Dysthymia, as opposed to hyperthymia (1, 2, 3 STENs), was observed in 6 (3.8 %) patients. No other combinations of APTT scales were found. It should be noted that the prevalence of emotional lability was revealed in patients with GERD.

Thus, according to the frequency of incidence, 3 main personality types were identified in patients with GERD: 1) hyperthymic type that is characterized by accentuation of scales indicating social and subject activity (29, 19 %); 2) mixed types combining the strengthening in scales indicating emotional lability, and scales indicating both social and objective activity and passivity; all other patients with GERD were assigned there (61, 39 %) 3) emotionally labile type with the accentuation in scales of asthenic emotions (66, 42 %).

At the next stage, the analysis of changes in the daily concentration of oral marker aminophylline in saliva in 156 patients with GERD revealed the following results: 51 patients (33 %) had fast oxidative metabolism phenotype, 82 patients (52 %) had an intermediate phenotype, and 23 patients (15 %) had slow oxidative metabolism phenotype.

Among the examined population, all 156 patients complained of heartburn, and only 119 patients (76 %) experienced pain in the lower third of sternum area. The severity of symptoms was checked using the VAS scale (Table 2).

To check the hypothesis about the correlation between the severity of clinical manifestations, the phenotype of oxidative metabolism and personality traits in patients with GERD, data were analyzed using multinomial logistic regression. Dependent variables included the results of the perception of heartburn and pain according to the VAS scale in points, the type of the accentuation of personality traits, and metabolism rate in each patient; they were determined as factors and denoted by nominal numbers.

As a result, the effect of metabolic rate ($p = 0.662$) and the type of the accentuation of personality traits ($p = 0.069$) on the severity of heartburn according to the VAS scale in patients with GERD was not confirmed (significance of the entire model $p = 0.163$). However, the results of multinomial logistic regression analysis performed for confirming the hypothesis of the effect of metabolism rate and personality traits on the clinical presentation, confirmed the difference in the assessment of pain syndrome in patients with different phenotypes of oxidative metabolism (chi-square = 25.093, p=0.014), however, no significant difference was found in the perception of pain in the patients with different types of personality traits accentuation (p=0.263).

It should be noted that the multinomial regression analysis when calculating the observed and predicted

Table 2. *The severity of clinical symptoms in patients with gastroesophageal reflux disease*

Name of indicator (n; MQR)	Number of patients with different intensity of heartburn and pain syndrome (n (%))		
	Low intensity ≤4 points	Middle intensity 4-7 points	Highintensity ≥8 points
The severity of heartburn according to the VAS (n=156, MQR 6-8 points)	3 (1,9 %)	81 (51,9 %)	72 (46,2 %)
Pain severity according to the VAS (n=119, MQR 3-6 points)	51 (42,9 %)	62 (52,1 %)	6 (5 %)

frequencies (cell probabilities) (Table 3) showed that the probability of detecting pain in fast metabolizers with weak intensity (below 4 points) was 41.4 %, and the probability of the incidence of pain intensity of 4–7 points according to VAS was 58.6 % (p = 0.014). At the same time, the probability of detecting low-intense pain syndrome in patients with GERD with intermediate and fast metabolism is 16.2 % and 18.7 %, respectively; the probability of detecting pain of moderate intensity (4–7 points according to VAS) was 74.2 % and 81.2 %, respectively (p = 0.014); and pain syndrome with the intensity over 7 points can develop only in the group of intermediate metabolizers, in 9.7 % of cases (p = 0.014).

For a deeper understanding of the effect of the analyzed factors (type of the accentuation of personality traits, metabolic rate) and conventional parameters (frequency of drug administration per day, rate and duration of action, as well as drug costs per treatment day) on the adherence to therapy, an analysis was carried out by the method of a multinomial logistic regression. The dependent variable "adherence to therapy" was determined in points by the total value (low adherence — the sum of points from 5 to 10, high adherence — from 11 to 15).

Results of this analysis showed that the costs of drugs (p = 0.094), frequency of administration per day (p = 0.063), rate (p = 0.316) and duration of drug action (p = 0.068) could be excluded as statistically insignificant. Multinomial logistic regression analysis demonstrated that in patients with GERD there is a significant dependence of the adherence to therapy on the patient's metabolic rate and personality traits (p = 0.006).

During calculating the observed and predicted frequencies (cell probabilities), the probability of high or low adherence to therapy was determined depending on metabolism rate and personality traits:

- in patients with hyperthymic type of the accentuation of personality traits, the probability of high adherence to therapy (11+ points) was 66.5 % for fast metabolizers, 65.3 % for intermediate metabolizers, and 100 % for slow metabolizers;
- in patients with mixed types of the accentuation of personality traits and fast metabolism, the probability of high adherence to therapy was 21.9 %, in patients with intermediate metabolism — 29.0 %, in slow metabolizers — 100 %;
- in patients with an emotionally labile type of the accentuation of personality traits, the probability of low adherence to therapy was 100 %, regardless of metabolism rate.

Thus, high adherence to therapy should be expected in patients with GERD, with a hyperthymic type of the accentuation of personality traits and with different phenotypes of oxidative metabolism, as well as in patients with mixed types of the accentuation of personality traits and slow metabolism. At the same time, patients with an emotionally labile type of the accentuation of personality traits have a high probability of low adherence to therapy, regardless of metabolism rate.

Table 3. *Observed and predicted frequencies of the influence of the level of metabolism on the severity of pain syndrome*

Metabolitic rate	Pain assessment on the VAS	Frequency			Percentage	
		Observed	Predicted	Pearson residual	Observed	Predicted
Quick	2,00	11	11	0	26,8 %	26,8 %
	3,00	6	6	0	14,6 %	14,6 %
	4,00	9	9	0	22,0 %	22,0 %
	5,00	12	12	0	29,3 %	29,3 %
	6,00	3	3	0	7,3 %	7,3 %
	7,00	0	0	0	0 %	0 %
	8,00	0	0	0	0 %	0 %
Intermediate	2,00	4	4	0	6,5 %	6,5 %
	3,00	6	6	0	9,7 %	9,7 %
	4,00	9	9	0	14,5 %	14,5 %
	5,00	16	16	0	25,8 %	25,8 %
	6,00	12	12	0	19,4 %	19,4 %
	7,00	9	9	0	14,5 %	14,5 %
	8,00	6	6	0	9,7 %	9,7 %
Slow	2,00	2	2	0	12,5 %	12,5 %
	3,00	1	1	0	6,3 %	6,2 %
	4,00	3	3	0	18,8 %	18,7 %
	5,00	6	6	0	37,5 %	37,5 %
	6,00	2	2	0	12,5 %	12,5 %
	7,00	2	2	0	12,5 %	12,5 %
	8,00	0	0	0	0 %	0 %

Table 4. Factors affecting adherence to therapy

Name of indicator	Data		
Total points — adherence to therapy Me (MQR, min-max)	13 (IQR 11-13, min9-max 13)	10 (IQR 9-10, min 8-max 12)	9 (IQR 6-9, min 5-max 12)
Type of accentuation of temperament properties	Hyperthymic type 29 (19 %)	Mixed types 61 (42 %)	Emotion allyunstable type 66 (39 %)
Metabolitic rate			
Fast metabolizers n=51 (32,7 %)	12(7,7 %)	23(14,7 %)	16(10,3 %)
Intermediate metabolizers n=82 (52,6 %)	9(5,8 %)	31(19,9 %)	42(26,9 %)
Slow metabolizers n=23 (14,7 %)	8(5,1 %)	7(4,5 %)	8(5,1 %)
The daily cost of the drug, rubles		от 3 до 50 Me 6 (IQR 3-10)	
Frequency rate of admission per day, number of times		от 1 до 6 Me 2 (IQR 1-6)	
Performance (number of people who answered YES)		116 (74,3 %)	
The effectiveness and duration of the drug (number of people who answered YES)		121 (77,6 %)	

Note: The cost of the administered drug product was calculated per one day during the month preceding the study

Discussion

In this study, for the first time, the psychophysiological characteristics of patients with GERD were analyzed using the accentuation of personality traits test, as well as the effect of the metabolic rate and personality traits on clinical presentation and adherence to therapy.

Evaluation of the clinical presentation in patients with GERD with different phenotypes of oxidative metabolism and different types of the accentuation of personality traits demonstrated the following patterns: a direct dependence of the level of pain syndrome on metabolism rate was established (p = 0.014); in fast metabolizers the perceived pain syndrome, assessed using VAS scale, was lower than in intermediate and slow metabolizers. However, personality traits of examined subjects had no effect on the perception of pain syndrome (p = 0.263).

These patterns can be explained by the fact that in patients with GERD, due to the chronic damage to esophageal mucosa by gastric contents, there is not only a nociceptive, but also an inflammatory component of pain [2]. In response to inflammation, immune cells release histamine in blood that binds to its receptors, and the subsequent cascade of biochemical interactions triggers membrane depolarization and conduction of pain impulse. Histamine can be metabolized in two ways: by oxidative deamination with diamine oxidase produced by the apical membrane of enterocytes, and by methylation with histamine-N-methyltransferase [15]. In fast metabolizers, histamine can be more rapidly destroyed in the liver with a decrease in its blood concentration, thereby, it can lead to a decreased intensity of pain syndrome.

It should be noted that the authors of APTT method describe individuals with hyperthymic type of the accentuation of personality traits as individuals with the following behavior pattern: extraversion, sociability, cheerfulness, good mood most of the time, free movements, activity, quick thinking. Such individuals are subjective and have adequate self-regulation in order to monitor their health [11]. At the same time, signs of emotional lability in patients with GERD, i.e. psychovegetative instability, somatic distress, aggressive reactions and self-doubt, can be associated with inadequate self-regulation and low self-control that can lead to the patient's poor attention to follow the physician's recommendations [11]. In this regard, our study, with the help of multinomial logistic regression analysis, revealed the following patterns: in patients with a hyperthymic type of the accentuation of personality traits, regardless of metabolism, high adherence to therapy should be expected (probability from 65 to 100 %, p = 0.006); in patients with an emotionally labile type of the accentuation of personality traits and with different phenotype of oxidative metabolism low adherence to therapy is observed (p = 0.006). Similar results on patients with emotional lability and viral hepatitis C (CVHC) were obtained by Maksimova M.Yu. et al. (2014). In this study, it was found that 69.66 % of the examined patients with chronic hepatitis C have pronounced personality deviations that in 39.3 % of cases reached the level of personality disorder, and in 30.33 % of patients corresponded to the level of accentuations. At the same time, patients with emotional lability demonstrated low adherence to therapy, and patients with a high level of adherence to therapy predominated in the group of CVHC patients with anxiety disorders [16].

Our study demonstrated that metabolism rate also affected the adherence to therapy: the highest adherence to therapy can be expected in slow metabolizers with hyperthymic and mixed types of the accentuation of personality traits. In intermediate and fast metabolizers, the probability of high adherence to therapy is observed only with hyperthymic type of the accentuation of personality traits ($p = 0.006$). Apparently, this is due to the fact that the effectiveness of drugs in standard doses was pronounced in slow metabolizers, and patients did not refuse to take drugs.

These factors (personality traits and metabolism) are unchangeable ones, however, the effect of temperament can be changed by psychological methods, and the dosage of proton pump inhibitors can be increased in order to increase their effectiveness. These assumptions require further analysis and confirmation. Training physicians in the ability to develop trusting relationships with the patient can also play a not unimportant part.

Conclusion

1. Clinical signs of gastroesophageal reflux disease in the form of pain in patients with fast metabolism are less pronounced than in patients with GERD and intermediate or slow phenotype of oxidative metabolism.

2. High adherence to therapy should be expected in GERD patients with hyperthymic type of personality traits accentuation and different oxidative metabolism phenotypes, as well as in the patients with mixed types of personality traits accentuation and slow metabolism, regardless of other factors (the price of drugs, administration frequency, the rate and duration of action).

3. In patients with GERD with emotionally labile types of accentuation, regardless of metabolism rate, a decrease in the possible fulfilling physician's prescriptions should be expected.

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Author Contribution

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

Kalugin A.A. (ORCID ID: https://orcid.org/0000-0002-8339-3369): participation in design development, basic collection, data analysisand interpretation, final approval of the manuscript for publication, creation of critical intellectual content, willingness to accept responsibility for all aspects of the work

Stepchenko A.A. (ORCID ID: https://orcid.org/0000-0001-5672-9341): design development, mathematical analysis and data interpretation

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ВЗАИМОСВЯЗЬ РИСКА ПАДЕНИЙ С ОСОБЕННОСТЯМИ КОГНИТИВНОЙ ФУНКЦИИ И ЭМОЦИОНАЛЬНОГО СТАТУСА (СТРАХА ПАДЕНИЙ) У ЛИЦ СТАРШЕГО ВОЗРАСТА

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The Relationship of the Risk of Falls with the Features of Cognitive Function and Emotional Status (Fear of Falls) in Older People

Резюме

Цель. Оценить частоту падений, связь страха падения и риска падений у лиц в возрасте 60 лет и старше. **Материал и методы.** В открытое одномоментное исследование включены 51 амбулаторный пациент (49 женщин, 2 мужчин) в возрасте от 61 до 90 [70 (67; 75)] лет. Проводился общепринятый физикальный осмотр, клинический и биохимический анализ крови, скрининг старческой астении (опросник «Возраст не помеха»), оценивался риск падений (анамнез, тест «Встань и иди»), страх падений («Краткая шкала оценки страха падений», «Шкала эффективности падений»), когнитивные функции (КФ) (монреальская шкала когнитивной оценки — МоСа-тест). **Результаты.** Высокий риск старческой астении выявлен у 38 %, преастении — у 31 % пациентов. Падения в анамнезе наблюдались у 75 %, страх падений — у 78 %, нарушение КФ — у 49 % (24,3±2,9 баллов) пациентов. Установлена взаимосвязь между страхом падений и фактом падений в анамнезе (отношение шансов [ОШ] 9,92, p=0,003, 95 % доверительный интервал [ДИ] 2,20-44,63); между страхом падений и наличием двух и более сопутствующих заболеваний (ОШ 10,86, p=0,013, 95 % ДИ 1,66-71,09); между тестом «Встань и иди» более 10 сек и МОСА менее 25 баллов (ОШ 8,57, p=0,001, ДИ 2,4-30,3); результатом по шкале эффективности падений и МОСА менее 25 баллов (ОШ 5,6, p=0,018, ДИ 1,34-23,36). Оптимальное значение теста «Встань и иди» для предсказания падений составило 10.5 сек и выше (площадь под кривой 0,753±0,083, p=0,019), теста МОСА — 24,5 баллов и менее (площадь под кривой 0,792±0,065, p <0,001); шкалы эффективности падений для предсказания страха падений — 72,5 баллов и более (площадь под кривой 0,743±0,092, p=0,014); теста «Встань и иди» — 9,5 секунд и более (площадь под

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кривой 0, 708±0,098, p=0,036). **Заключение.** Страх падений ассоциировался с фактом падений в анамнезе, коморбидностью, низкой функциональной активностью и снижением КФ, что подтверждает многофакторность происхождения страха падений в пожилом и старческом возрасте и требует учёта при разработке комплексных лечебно-профилактических программ.

Ключевые слова: *пожилые пациенты, падения, факторы риска, страх падений, когнитивные функции, коморбидность*

Конфликт интересов

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

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Abstract

Objective. To assess the frequency of falls, the relationship between fear of falling and the risk of falls in people aged 60 years and older. **Material and methods.** The open cross-sectional study included 51 outpatients (49 women, 2 men) aged 61 to 90 [70 (67; 75)] years. A conventional physical examination, clinical and biochemical blood tests, screening for fragility (the "Age is not a hindrance" questionnaire), the risk of falls (history, the "Get up and go" test), fear of falls ("Short scale for assessing the fear of falls", "Scale of effectiveness falls"), assessment of cognitive function (CF) — Montreal scale of cognitive assessment — MoCa-test). **Results.** A high risk of senile asthenia was found in 38 %, preasthenia — in 31 %, a history of falls — in 75 %, fear of falls — in 78 %, impaired CF — in 49 % (MOCA 24.3±2.9 points) of patients. An association was found between fear of falls and history of falls (odds ratio [OR] 9.92, p=0.003, 95 % confidence interval [CI] 2.20-44.63), 2 or more comorbidities (OR 10.86, p=0.013, 95 % CI 1,66-71,09); between the "Get up and go" test for more than 10 seconds and MOCA less than 25 points (OR 8.57, p=0.001, CI 2.4-30.3); scores less than 25 on the Fall Effectiveness Scale and MOCA (OR 5.6, p=0.018, CI 1.34-23.36). The optimal value of the "Get up and walk" test for predicting falls was 10.5 seconds or more (area under the curve 0.753±0.083, p=0.019), the MOCA test was 24.5 points or less (area under the curve 0.792±0.065, p <0.001); the fall effectiveness scale for predicting fear of falls — 72.5 points or more (area under the curve 0.743±0.092, p=0.014); test "Get up and go" — 9.5 seconds or more (area under the curve 0.708±0.098, p=0.036). **Conclusion.** Fear of falls was associated with a history of falls, comorbidity, low functional activity, and a decrease in CF, which confirms the multifactorial origin of the fear of falls in older age and requires consideration in the development of comprehensive treatment and prevention programs.

Key words: *elderly patients, falls, risk factors, fear of falls, cognitive functions, comorbidity*

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AH — arterial hypertension, BP — blood pressure, BMI — body mass index, CF — cognitive function, CHD — coronary heart disease, CI — confidence interval, CKD — chronic kidney disease, GFR — glomerular filtration rate, MOCA — Montreal Cognitive Assessment, OR — odds ratios, VAS — visual analogue scale, WHO — World Health Organization. AUC — area under the curve

According to the forecasts of the United Nations Organization, the elderly is expected to grow to reach more than 2 billion people by 2050 [1].

Currently, there are more than 30 million elderly and senile people in Russia, and their number increases by about 1 million per year [2]. In this regard, the relevance of predicting complications and their medical and social consequences associated with complex pathology and geriatric syndromes is obvious.

Locomotive falls are common and serious problem in elderly and senile people, regardless of the place and conditions of living. Every year, there are 646,000 fatal falls worldwide [3]. Experts from many countries agree that people 65+ are at high risk of falls, and the fear of falls is recognized as significant health problem and risk factor for falls in elderly age group; it allows to refer this category of patients to a fall risk group [4].

Senile asthenia can contribute to falls, and falls, in turn, cause and accelerate the progression of senile asthenia, therefore creating the "vicious circle".

Due to the consequences of injuries from fall and chronic pain syndrome, patients significantly reduce

their motor activity; it results in their dependence on assistance, maladaptation in everyday life, and the development of fear of a possible fall [5].

One of the important factors that affects the life quality of elderly patients and their functional capacities is the fear of falls. Up to 70 % of individuals shortly before a fall, and up to 40 % of those who had no falls, reported of the fear of falling. Up to 50 % of people who experience the fear of falls limit or completely terminate their social and physical activity. Approximately two-thirds of people experienced such fear after falling, and about a half tried to avoid intense activity in the future due to the fear of falls [6].].

At present, the relationship between the risk of falls and the frequency of falls in elderly people depending on their cognitive and emotional status (fear of falls) has not been adequately studied. A thorough assessment of the history and clinical functioning of elderly people, the analysis of the correlation between the risk of falls and psycho-emotional status will help to stratify patients according to the risk of falls, to improve their clinical condition, quality of life, and to develop preventive measures; it provides the background of this study.

Objective

To assess the frequency of falls, the correlation between the fear of falls and the risk of falls in people 60+ who are observed on an outpatient basis.

Materials and methods

This open-label, cross-sectional study included 51 patients (49 females, 2 males) aged 61 to 90 years and observed on an outpatient basis.

Inclusion criteria: age 60+; males and females; the ability to understand the study procedure and to sign an informed consent form.

Exclusion criteria: age under 60; fatal chronic diseases or life expectancy of less than one year; severe cognitive impairment.

The clinical condition of patients was evaluated taking into consideration history and demographic data and the results of standard physical examination.

Comorbidity was considered if the patient had a combination of at least any two chronic diseases that reduce functional capacities [7].

Obesity was defined according to WHO body mass index (BMI) classification: BMI of 25–29.9 kg/m^2 was considered as overweight, 30 kg/m^2 and more — as obesity.

The criterion for anemia was decreased hemoglobin level less than 130 g/L in men and less than 120 g/L in women [8]; the criterion for arterial hypertension (AH) was blood pressure (BP) ≥140/90 mm Hg when examining a patient during his/her visit to a physician, with at least three measurements on both arms according to the Russian guidelines for the management of patients with AH-2020 [9].

Pain was assessed using visual analog scale (VAS) [10]. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (2011). Chronic kidney disease (CKD) was diagnosed according to the KDIGO guidelines-2012 [11]. The 10-year absolute fracture risk was assessed using the Fracture Risk Assessment Tool (FRAX). [1] Screening of senile asthenia was carried out using "Age is not a hindrance" questionnaire: patients with 3 or more positive answers were considered to have high risk for the presence of senile asthenia [12].

The risk of falls was assessed by collecting history, including clarification about falls, their number, symptoms before falls, the presence of injuries and other consequences of falls. The patients were asked 3 questions: "*Have you had a fall-related injury or non-injury fall during a year? Do you feel instability when you stand up and walk? Are you afraid of falls?"* Patients with a positive answer to at least one of these three questions underwent the "Stand up and go" test; the result of more than 14 seconds indicated the risk of falls [13, 14].

Fear of falls was assessed using Short Scale of Falls Fear Assessment: 7–8 points indicated low, 9–13 points — moderate, and 14-28 points — high fear of falls [15]; the Falls Efficacy Scale was also used which evaluates the grade of fear that the patient experiences when performing everyday activities; fear of falls is determined with points ≥70 [16].

The state of cognitive function (CF) was assessed using the Montreal Cognitive Assessment scale (MOCA-test) [17]. CF was considered to be normal at 25+ points, moderately reduced at 19–24 points, severe cognitive dysfunction was found at less than 19 points.

All patients underwent full blood count and biochemical assay.

All patients signed informed consent form for the voluntary participation in the study. The study was approved by the local Ethics Committee of N.I. Pirogov Russian National Research Medical University (Pirogov Medical University) on May 17, 2021, protocol No. 208.

Patients were enrolled in the study from March 2021 to September 2021 on the basis of the city polyclinic No. 134 of the Moscow Health Department.

Statistical data processing was performed using SPSS 16.0 and Statistica 6.0 software packages.

Descriptive statistical information on continuous quantitative data with a normal distribution is presented as the mean and its standard deviation; in cases of a non-normal distribution — as a median and interquartile range (25th percentile; 75th percentile). Discrete variables are presented as a percentage of the total number of patients in the group. To compare them, we used the analysis of contingency tables using χ^2 criterion adjusted for continuity or Fisher's exact test, when the number of observations in one of the table cells did not exceed 5.

[1] URL: https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=rs

The correlation between continuous parameters was assessed using Spearman's rank correlation coefficient. The association between fear of falls and analyzed factors was assessed using odds ratios (OR) and 95 % confidence interval (CI) in multiple logistic regression analysis. Differences were considered significant at two-sided $p < 0.05$.

Results

The age of patients included in the study was 70 (67; 75) years, the level of systolic BP was 130 (130; 140) mm Hg, of diastolic BP — 80 (80; 90) mm Hg, heart rate was 66 (60; 70) bpm, BMI — 27.2 (22.7; 31.6) kg/m^2.

49 (96 %) patients had comorbidities: 38 (76 %) had AH, 14 (29 %) — coronary heart disease (CHD), 16 (31 %) — obesity, 15 (30 %) — osteoporosis, 43 (88 %) — osteoarthritis, 8 (16 %) — diabetes mellitus, 22 (41 %) — CKD; no patients demonstrated any signs of anemia. 35 (92 %) patients with AH were on constant antihypertensive therapy: angiotensin-converting enzyme inhibitors were taken by 30 patients (85.7 %), angiotensin II receptor antagonists — by 5 patients (14.2 %), slow calcium channel blockers — by 15 patients (42.8 %), thiazide and thiazide-like diuretics — by 16 patients (45.7 %), beta-blockers — by 10 patients (28.6 %), fixed combinations of two or three drug products — by 24 (68.6 %) patients.

A high risk of senile asthenia in accordance with "Age is not a hindrance" scale was identified in 19 (38 %) patients, preasthenia — in 16 (31 %) patients.

Table 1 presents general characteristics of patients.

38 (75 %) patients had a history of falls, with the average number of falls 2.0 (0.0–3.0) per person in the past year (Table 2).

30 patients (59 %) had fall-related injuries, or falls without injury during the past year, 35 patients (69 %) had a feeling of instability when standing up or walking, 40 patients (78 %) had fear of falls.

The result of "Stand up and go" test was 10.7 ± 2.7 seconds: 26 (51 %) individuals completed the test in 10 seconds or less, 15 (29 %) individuals required 11–13 seconds, 10 (20 %) — 14+ seconds. Functional mobility was reduced by 0.8 seconds in patients aged 70–79, and by 1.8 seconds in patients aged 80–99; these results indicate the risk of falls.

According to the Falls Efficacy Scale, the fear of falls was detected in 40 (78 %) individuals; the result corresponded to 72.5 ± 10.0 points.

According to the Short Scale of Falls Fear Assessment, low fear of falls was detected in 13 (25 %) patients, moderate one — in 17 (33 %), and high — in 21 (41 %) patients.

Impaired CF was present in 25 (49 %) patients; the result on the MOCA scale corresponded to 24.3 ± 2.9 points. Correlation analysis of the fear of falls with a number of parameters is presented in Table 3.

In individuals with the history of multiple falls (3 or more), a correlation was established with a decrease in MOCA questionnaire score (p = 0.023, r = 0.37). A correlation was found between decreased CF by MOCA and the fear of falls (according to the results of the "Stand up and go" test) (p < 0.001, r = 0.49), according to the results of the Short Scale of Falls Fear Assessment (p = 0.028, r = 0.46) and of Falls Efficacy Scale (p = 0.012, r = 0.35) — with a decrease in hemoglobin level (p = 0.014, r = 0.40). Parameters that are associated with the fear of falls in elderly and senile patients are presented in Table 4.

A correlation was found between the "Stand up and go" test with more than 10 seconds and MOCA result of less than 25 points (OR 8.6, p = 0.001, 95 % CI 2.4–30.3); between Falls Efficacy Scale score and MOCA of less than 25 (OR 5.6, p = 0.018, 95 % CI 1.3–23.4).

Table 1. *General characteristics of the included patients*

Indicator	Number of patients, n
Elderly	35 (69 %)
Senile age	15 (29 %)
Centenarians	1 (2 %)
Men	2 (4 %)
Women	49 (96 %)
Higher education	26 (51 %)
Disability group	19 (37 %)
Working patients	6 (12 %)
Marital status married / married	37 (73 %)
Bad habits	2 (4 %)
Availability of a social worker	3 (6 %)
Lives at home with family	45 (87 %)
Family history of cardiovascular disease	30 (58 %)
History of skeletal fractures	21 (41 %)

Table 2. *Fall characteristics Indicator Number of patients, n*

Indicator	Number of patients, n
History of falls	38 (75 %)
Pre-fall symptoms: dizziness	18 (47 %)
Pre-fall symptoms: palpitations	2 (4 %)
Pre-Fall Symptoms: Chest Pain	2 (5 %)
Circumstances of falls: slippery	24 (63 %)
Circumstances of falls: dark	14 (37 %)
Place of fall: at home	12 (32 %)
Place of fall: outdoors	26 (68 %)

Table 3. *Fear of falling: correlation analysis Spirmen*

Indicator	r	
History of falls	0,46	0,001
Number of falls in history	0,47	0,001
Two or more comorbidities	0,40	0,004
Dizzy before falling	0,32	0,050
Time to pass the «Get up and go» test	0,28	0,048
High risk of frailty	0,45	0,001

Table 4. Indicators associated with fear of falls in elderly and senile patients

Indicator	Odds ratio	Confidence interval	p
History of a fall	9,92	2,20-44,63	0,003
Two or more comorbidities	10,86	1,66-71,09	0,013
Get up and walk test over 10 sec.	6,02	1,16-31,88	0,032

The optimal result of the "Stand up and go" test for predicting falls in patients 60+ was 10.5 seconds or more according to the analysis of the ROC curve (AUC 0.75 ± 0.08, p = 0.019, 95 % CI 0.59–0.92), with a sensitivity of 77 % and a specificity of 63 %.

The optimal result of the MOCA test for predicting falls in patients 60+ was 24.5 points or less (AUC 0.792 ± 0.065, p < 0.001, CI 0.66–0.92) with a sensitivity of 72 % and a specificity of 77 %.

The optimal result of the Falls Efficacy Scale for predicting the fear of falls was 72.5 points or more (AUC 0.743 ± 0.092, p = 0.014, 95 % CI 0.56–0.92) with a sensitivity of 72.5 % and a specificity of 72.7 %, and of the "Stand up and go" test — 9.5 seconds or more (AUC 0.708 ± 0.098, p = 0.036, 95 % CI 0.52–0.89) with a sensitivity of 70 % and a specificity of 73 %.

Discussion

The objective of this study was to assess the frequency of falls, the fear of falls and to analyze the correlation between the fear of falls and the risk of falls in outpatients aged 70 (67; 75). Most of the patients were elderly (69 %), female (96 %), had a higher education (51 %), were married (78 %), had comorbidities (96 %) with the predomination of osteoarthritis (88 %) and AH (76 %). High risk of senile asthenia was found in 38 %, falls — in 38 (75 %), history of fractures — in 41 % of patients.

Obtained results are consistent with the data obtained by other researchers. According to a study involving 628 patients aged 76.9 ± 15.5, falls in the past year were observed in 56.5 % of individuals. Women fell statistically significantly more frequently (58.62 % of cases, 95 % CI 80.2–88.6) compared to men. The highest frequency of falls (61.36 %, 95 % CI 10.5–21.8, p < 0.001) occurred in patients aged 85+ [18, 19].

Currently, a fall is considered to be a complex multifactorial phenomenon. To understand the mechanism of falls, one should be remember the basic mechanisms that are responsible for normal gait. Cerebellum and basal ganglia are the main subcortical nuclei, which, in interaction with cerebral cortex, carry out motor and cognitive functions of brain. Normal functioning and effective coordination of the musculoskeletal system, proper processing of sensory information (while maintaining vision, hearing, proprioception, etc.) along with adequate cognition and concentration, are also required to prevent falls and to maintain normal gait [20]. It is not surprising that many of these functions at least somewhat decline with age increasing the risk of falls. For example, balance problems are one of the most common cause of falls, and the corresponding complaint in patients with falls is dizziness.

According to the Falls Efficacy Scale, the fear of falls was found in 78 % of patients who participated in our study. At the same time, according to the Short Scale of Falls Fear Assessment, low fear of falls was detected in 25 % of patients, moderate — in 33 %, high — in 41 % of patients. In a study of 5,560 patients aged 65+, the fear of falls was found in people who had fallen in the previous year (48.8 % vs 24.8 %, p < 0.001) and in individuals with recent falls (previous month: 46.8 % vs 31.0 %, p < 0.001). Regardless of the time of the fall, the fear of falls remains almost the same [21].

In a study of 125 geriatric patients (110 females, 88 %) aged 75.66 ± 7.98 years who had at least one fall in the past year, the risk of falls was assessed using the Morse scale and the self-assessment risk scale for falls. The number of falls during one year was 2.42 ± 1.90 per person, 71 (56.8 %) individuals had more than 2 falls. Falls partially occurred at home (44.8 %), about the same number — outdoors (42.4 %), in 12.8 % of cases, patients fell both outdoors and at home. According to the Scale of Self-assessment of the Risk of Falls, high risk was revealed in 104 (83.2 %) cases, and low one — in 21 (16.8 %) cases [5]. Moreover, the prevalence of comorbidity and polypharmacy that contribute to the risk of falls increases with age; logistic regression analysis revealed an association between the fear of falls and comorbidity (OR 10.86, p = 0.013).

Gait normally changes with age; the changes include decline in gait speed and stride length, as well as decreased strength of lower extremities. These changes are most pronounced when elderly people walk on uneven surfaces. Falls are usually the result of an interaction between long-term or short-term predisposing factors and short-term triggers (such as travel, acute disease, or adverse drug reaction) in the person's environment. According to our study, slippery roads (63 %) and poor lighting (37 %) were the common causes of falls, with most falls occurred outdoors (68 %), not at home (32 %).

Analysis of the place of falls in 355 patients aged 65+ revealed that patients aged 65–74 more often (in 66.25 % of cases) fall outdoors; patients aged 75–84 fall at home and outdoor with a frequency of 34.88 and 48.84 %, respectively; and patients aged 85+ fall more often at home [22].

In a study of 655 patients (81 % female) aged 75.1 ± 8.2 years, it was demonstrated that 33.1 % of patients fell at home, 44.6 % — outdoors, the other –both at home and

outdoors. As the immediate cause of their fall, patients considered balance problems (2 %), dizziness (4.2 %), instability when walking (8.1 % slipped, 7.7 % stumbled), loss of consciousness (2.4 %), joint pain (3 %), dangerous environment (ice on road) (1.8 %); 69 % of patients could not determine the cause of their fall [23].

According to our data, most of the falls occurred outdoors, possibly due to the younger age of the patients included in the study (69 % of patients aged 60–75 years); this fact indicates their adequate activity.

Our study confirmed the contribution of decreased CF and altered emotional status (the fear of falls) into the occurrence of falls. The association of the fear of falls and the very fact of falls in history (OR 9.92, p = 0.003) confirms the contribution of the fear of falls to the development of the latter. The most vulnerable group of elderly patients in regard to the development of the fear of falls includes individuals with low functional mobility based on the results of the "Stand up and go" test (OR 6.02, p = 0.032).

The association between the time to complete the "Stand up and go" test and the MOCA score less than 25 points (OR 8.6, p = 0.001), as well as the results on the Falls Efficacy Scale and MOCA score less than 25 points (OR 5.6, p = 0.018) allows us to consider decreased CF as the most important risk factor for the fear of falls.

The optimal result of the "Stand up and go" test for predicting falls was 10.5 seconds or more, of the MOCA test — 24.5 points or less; and a cut-off value of the Falls Efficacy Scale of 72.5 points or more, with a sensitivity of 72.5 % and a specificity of 72.7 %, may indicate the fear of falls in outpatients 60+.

A study performed by Levedan A. et al. (2002) revealed that patients 75+ with a history of falls were 2.5 times more likely to have the fear of falls than those who had not fallen in the past year. It was found that patients with the fear of falls are predominantly female, with comorbidity, functional limitations, symptoms of depression, however, in contrast to our results, there was no association with a worse cognitive status [24]. However, an association between the fear of falls and cognitive impairment was previously reported in a study with age-matched participants [25].

The fear of falls should not be considered as just a consequence of the falls themselves. The fear of falls is a predictor of future falls [26]; it has a significant adverse effect on the quality of life, reduces activity, physical and cognitive functioning, increases the risk of disability and should be considered as an separate factor for specific measures.

Conclusion

75 % of outpatients aged 60+ had a history of falls; they were predominantly female (96 %) and those living at home with their families (87 %). Most of them had comorbidities (96 %), every third had a high risk of senile asthenia (38 %), 49 % had decreased CF, 59 % — fall-related injuries or falls without injury during the past year. Slippery roads (63 %) and poor lighting (37 %) were common causes of falls; most part of falls occurred outdoors (68 %). 78 % of patients had the fear of falls: 25 % — low; 33 % — moderate; 41 % — high.

The fear of falls was associated with a history of falls, comorbidities, low functional activity, and decreased CF.

The results of the "Stand up and go" test of 10.5 seconds or more and of the MOCA test of 24.5 points or less can be considered for fall risk stratification; 72.5 points or more on Falls Efficacy Scale — for the fear of falls in outpatients 60+.

The fear of falls is a psychological problem, however, the origin of such fear in elderly patients is multifactorial. The associations with comorbidity, senile asthenia, decreased mobility, and CF demonstrated in our study should be taken into account when developing comprehensive treatment and prevention programs for elderly patients with falls.

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ХАРАКТЕРИСТИКИ ВАРИАБЕЛЬНОСТИ ГЛЮКОЗЫ У ПАЦИЕНТОВ С GCK-MODY

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Characteristics of Glycemic Variability in Patients with GCK-MODY

Резюме

GCK-MODY — один из самых распространённых вариантов сахарного диабета (СД) типа MODY (40–60 %) в европейской популяции. При диагностировании GCK-MODY возможно использование систем непрерывного мониторинга глюкозы (НМГ), что позволяет проводить углубленный анализ вариабельности глюкозы (ВГ) с использованием математических индексов и детально оценивать гликемический профиль. Цель исследования — изучить особенности вариабельности уровня глюкозы у лиц молодого возраста с GCK-MODY диабетом. У 20 пациентов (7 мужчин и 13 женщин, медиана возраста при диагностировании СД была 28,0 [18,0; 36,0] лет) с подтвержденной молекулярно-генетическим исследованием мутацией в гене глюкокиназы проведено суточное исследование уровня глюкозы с использованием портативных систем НМГ и анализ индексов вариабельности глюкозы с помощью специализированной компьютерной программы GLINVA.

При определении рутинных показателей углеводного обмена (глюкозы плазмы натощак (ГПН) и гликированного гемоглобина) у большинства пациентов с GCK-MODY наблюдаются целевые значения, что определяет тактику ведения пациентов из данной группы пациентов (рациональное питание или минимальные дозы пероральных сахароснижающих препаратов). Однако после проведения НМГ и изучения индексов ВГ, определено, что у некоторых пациентов индексы были выше референсных значений при нормальных показателях гликированного гемоглобина и ГПН, что требует коррекции терапии. Полученные результаты при изучении ВГ у лиц с GCK-MODY показывают низкую ВГ в течение суток, что, вероятно, обуславливает меньшую частоту развития диабетических осложнений и определяет тактику ведения пациентов.

Ключевые слова: *GCK-MODY диабет, вариабельность глюкозы, непрерывный мониторинг глюкозы*

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Abstract

GCK-MODY is one of the most common MODY variants (40–60 %) in the European population. It is possible to use continuous glucose monitoring systems (CGMS) when diagnosing GCK-MODY which allows for an analysis of glucose variability (GV) using mathematical indices and a detailed assessment of the glycemic profile. The purpose of this abstract is to investigate the features of GV in young people with GCK-MODY. A daily study of glucose levels was performed using portable systems for CGMS in 20 patients (7 men and 13 women, median age at diagnosis of DM was 28.0 [18.0; 36.0] years) with a mutation in the glucokinase gene confirmed by molecular genetic testing. There was also performed an analysis of glycemic variability indices with the specialized GLINVA program.

Most patients with GCK-MODY have target values when determining routine indicators of carbohydrate metabolism (fasting plasma glucose (FPG) and glycated hemoglobin), they determines the tactics of managing patients from this group of patients (rational nutrition or minimal doses of oral hypoglycemic drugs). However, after conducting CGMS and studying the GV indices it was determined that in some patients the indices were higher than the reference values with normal levels of glycated hemoglobin and FPG, and it is this group of patients that needs therapy correction. The results demonstrate a flat glycemic profile during the day which probably causes a lower incidence of diabetic complications and determines the tactics of GCK-MODY patient management.

Key words: *GCK-MODY, glycemic variability, continuous glucose monitoring*

Conflict of interests

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BG — average daily blood glucose level, CGM — continuous glucose monitoring, CMD — carbohydrate metabolism disorders, DM — diabetes mellitus, FPG — fasting plasma glucose, GAD — anti-glutamic acid decarboxylase autoantibody, GCK — glucokinase, GV — glucose variability, HbA1c — glycated hemoglobin, HBGI — high blood glucose index, IA-2A — antibodies to tyrosine phosphatase, ICA — islet-cell antibodies, LBGI — low blood glucose index, MAGE — mean amplitude of glycemic excursion, MODY — maturity-onset diabetes of the young, NGS — next generation sequencing, OHGD — oral hypoglycemic drugs, SD — standard deviation

Introduction

GCK-MODY (Glucokinase-maturity-onset diabetes of the young) is one of the most common variants (40–60 %) of MODY-type diabetes mellitus (DM) in the European population [1]. Most patients diagnosed with GCK-MODY demonstrate no clinical manifestations of diabetes mellitus (DM), and carbohydrate metabolism disorders (CMD) in such cases are found during routine tests [2]. Hyperglycemia associated with glucokinase defects is usually moderate and may be either intermittent or stable over months, or even years. The severity of fasting hyperglycemia in GCK-MODY patients increases very slowly; glycated hemoglobin (HbA1c) level varies from 5.9 % to 7.6 % [3, 4].

When diagnosing GCK-MODY, continuous glucose monitoring (CGM) systems can be used; they allow performing a comprehensive analysis of glucose variability (GV) using mathematical indices, as well as detailed assessment of glycemic profile [5]. These measures help to determine the most optimal and effective approach for managing such patients, since they do not always require insulin therapy and oral hypoglycemic drugs (OHGD); in most cases, dietary recommendations are sufficient. Moreover, using the CGM technique in the proband's relatives allows diagnosing them with carbohydrate metabolism disorders at preclinical stages, predicting the course of the disease, and prescribing a pathogenetic therapy. Thus, modern diagnostic methods can help to reduce the rate of medical errors in the diagnosis and management of patients with such a rare type of DM as GCK-MODY; it improves their life quality and is an important issue in endocrinological practice.

The objective of this study was to analyze the specific features of glucose variability in young patients with GCK-MODY diabetes mellitus.

Materials and methods

The study was performed at the Research Institute for Treatment and Preventive Medicine (RITPM), a branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (C&G SB RAS). At the first stage of the study, the patients (n = 66) who were previously observed with a diagnosis of "diabetes mellitus, type to be clarified, possibly MODY" underwent a complete clinical examination; the following parameters of carbohydrate metabolism were assessed: fasting plasma glucose (FPG), C-peptide, HbA1c level and antibodies (to pancreatic β-cells, to glutamate decarboxylase, to tyrosine phosphatase). Criteria for inclusion in the group of patients with GCK-MODY phenotypic signs: age of hyperglycemia diagnosis from 18 to 45 years; signed informed consent to participate in the study; carbohydrate metabolism disorder, twice confirmed by laboratory test results (DM diagnosis was verified on the basis of two laboratory tests of fasting blood glucose ≥ 6.1 mmol/L for whole capillary blood (7.0 mmol/L for venous plasma) and/or 2 hours after oral glucose tolerance test, or random determination of glucose in whole capillary or venous blood ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5 %;); no antibodies to pancreatic β-cells (ICA), glutamate decarboxylase (GAD), tyrosine phosphatase (IA-2A); normal or slightly reduced C-peptide level; no absolute need for insulin therapy; no ketoacidosis at the time of disease onset. Exclusion criteria: history of tuberculosis of lungs or other organs; history of human immunodeficiency virus infection; present infectious disease due to hepatitis B virus or hepatitis C virus that requires antiviral treatment; administration drug products that cause hyperglycemia, including glucocorticoids; confirmed neonatal diabetes mellitus in the proband; phenotypic signs of other genetic syndromes in the proband, with the symptom complex including hyperglycemia.

At the next stage, all patients underwent molecular genetic analysis using targeted high-throughput next-generation sequencing (NGS) technique. The mutations found were verified using direct automated Sanger sequencing. According to the study results, GCK-MODY was confirmed in 43 (65.1 %) out of 66 examined patients. To study glucose variability in young patients with GCK-MODY diabetes mellitus, a random sample of 20 patients (7 male and 13 female patients, median age at the time of being diagnosed with DM was 28.0 [18.0; 36.0]) was selected. Median DM duration was 2.0 [1.0;4.0] years. Baseline parameters of the studied group of patients are presented in Table 1.

At the time of enrollment, patients had no overweight or obesity, cardiovascular diseases, diabetic retinopathy, or nephropathy.

At the third stage, the studied group of patients received a CGM system — portable Medtronic MiniMed (USA). For the study, the portable systems in each patient were programmed to measure glucose level every 5 minutes for at least 5 days. The median CGM duration was 6.0 [5.0; 13.0] days. The monitoring results were integrated into the Medtronic CareLink®Pro software. To analyze GV, the following values were assessed: average daily glucose level (BG, blood glucose), standard deviation (SD), mean amplitude of glycemic excursion (MAGE), high blood glucose index (HBGI), low blood glucose index (LBGI). For the subsequent mathematical processing of the data obtained and for the calculation of GV parameters selected for interpreting

Table 1. *Characteristics of patients with GCK-MODY (n=20)*

Indicators (reference values), units of measurement	Index (median)
Gender	65.0 % female patients; 35.0 % male patients (p = 0.08)
The average age of diagnosis verification, years	28,0 [18,0; 36,0]
The median duration of diabetes, years	2,0 [1,0;4,0]
FPG (3,3–6,0), mmol/l	6,1 [5,8; 7,0]
HbA1c (less than 6.5), %	6,0 [4,5;6,6]
C-peptide (0.7–1.9), ng/m	0, 8 [0,4;1,7]
Body mass index (weight, kg/height, m^2)	28,3 [21,7; 29,4]
LDL-C, mmol/l	2 [1,7;2,9]
HDL-C, mmol / l	1,3 [1,0;1,4]
Общий холестерин, ммоль/л/ Total cholesterol, mmol/l	4,5 [4,3;5,1]
Триглицериды, ммоль/л/ Triglycerides, mmol/l	1,2 [1,0;1,5]
Отягощенный анамнез по ССЗ/ Burdened history of CVD, n (%)	4 (20,0)
Отягощенный анамнез по СД/ Burdened history of diabetes, n (%)	2 (10,0)
Курение/ Smoking, n (%)	7 (35,0)

Примечание: данные приведены как Me (25-й процентиль — 75-й процентиль), n (%); ГПН — глюкоза плазмы натощак; СД-сахарный диабет; ССЗ-сердечно-сосудистые заболевания; ЛПВП — липопротеиды высокой плотности; ЛПНП-липопротеиды низкой плотности
Note: data are given as Me (25th — 75th percentile); FPG — fasting plasma glucose; CVD — cardiovascular disease; LDL -C — low density lipoproteins; HDL-C — high density lipoproteins

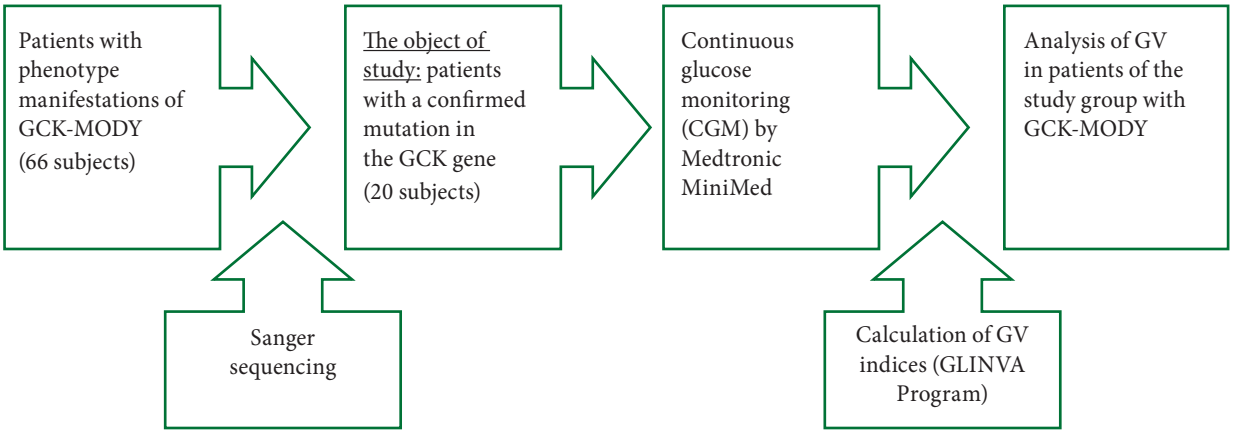

Figure 1. *Research design*
Note: GCK gene — Glucokinase gene, CGM — Continuous glucose monitoring, GV — Glycemic Variability, GCK -MODY — Glucokinase maturity onset diabetes of the young

the results of this study, a specialized calculator software GLINVA (Russia) was used. The GLINVA calculator software was developed at RITPM, a branch of the C&G SB RAS (computer software state registration certificate No. 2019660636 dated August 9, 2019; patent for an invention No. 2746830 dated April 21, 2021). The design of this study is provided in Figure 1.

Statistical processing of the results was carried out using IBM SPSS Statistic 23 software (USA). Since the distribution of quantitative characteristics differed from the normal one, non-parametric methods of analysis were used: median (Me) was determined, with the 25th and the 75th percentiles in the Me format [Q25; Q75].

Results and discussion

The results of the study revealed that most patients (19; 97.0 %) with GCK-MODY achieved the target levels of FPG and HbA1c (Table 2). C-peptide median level was within the reference values in 100.0 % of cases; it indicates the preserved insulin secretion by pancreatic b-cells. GV parameters were assessed in all patients of the studied group; the results are presented in Table 2; one can compare the values in individuals with no DM and in GCK-MODY patients.

The SD parameter is used in many research papers and describes the dispersion of glycemic values. Mean daily glucose (BG, blood glucose) is calculated automatically by the CGM system; in this study it was 7.5 mmol/L that confirms mild hyperglycemia in GCK-MODY patients. The MAGE score was developed to assess postprandial hyperglycemia. In individuals with normoglycemia, this value ranges from 0 to 2.8 mmol/L. Similar values were observed in patients with GCK-MODY; it indicates low GV and is probably associated with a low risk of micro- and macrovascular complications. The risks of hypo/hyperglycemia can be assessed by calculating HBGI (hyperglycemia risk) and LBGI (hypoglycemia risk). In GCK-MODY patients, the risk of hyperglycemia is within the reference range, as well as in individuals with normoglycemia. The increased LGBI value indicates the possibility of hypoglycemia in the studied group. Analysis of the CGM curves of all 20 patients revealed that they had no nighttime (00:00–06:00) hypoglycemia episodes. Based on the data obtained, it was found that even individuals with GCK-MODY who have achieved the target levels of FPN and HbA1c require CGM to determine the indications for treatment adjustment.

There are few published data on the CGM in individuals with MODY. In 2017, Moscow researchers conducted a similar study with 312 patients (162 male, 150 female patients) aged from 3 months to 25 years, suspected of MODY [6]. It was found that the most

Table 2. *Indicators of glycemic variability in patients with GCK-MODY (n=20)*

Different Indexes of Glycemic Variability (M)	Reference values of GV parameters in individuals without DM	GV scores in individuals with GCK-MODY
BG (blood glucose), mmol/l	<5,6	7,5
MAGE (mean amplitude of glycemic excursions), mmol/l	0 — 2,8	2,5
HBGI (high blood glucose index)	0 — 7,7	1,6
LBGI (low blood glucose index)	0 — 6,9	9,0
SD (standard deviation)	0 — 2,8	1,5

Note: GV — glucose variability, DM — diabetes mellitus

common MODY subtype in the Russian population is GCK-MODY. According to the results of our study, GCK-MODY was confirmed in 65.1 % of the subjects. Median glycated hemoglobin in the above work was 6.4 [4.5; 7.7] %; it did not differ from the median HbA1c level at the time of diagnosis that indicates a non-progressive course of carbohydrate metabolism disorders in GCK-MODY. One of the typical signs of the studied diabetes type is the moderate fasting hyperglycemia. All patients had fasting hyperglycemia at the time of CMD detection, and it is comparable to the results of our study.

The results of scientific studies revealed that, despite a long history of hyperglycemia in patients (the mean duration was 48.6 years) with mutations in GCK gene, the prevalence of micro- and macrovascular diabetic complications in them was the same as in the general population [7; 8]. The risk of developing cardiovascular diseases (CVD) in individuals with GCK-MODY is similar to the population risk [9]. Some other studies provide similar data, that although β-cell and hepatocyte function in GCK-MODY is altered, hyperglycemia associated with glucokinase defects is usually moderate. Nevertheless, mutation carriers have CMD since birth [10]; they can be detected as early as in the first years of life and, in almost all individuals, by the end of sexual maturation [11]. The severity of fasting hyperglycemia increases very slowly: HbA1c level in patients with GCK-MODY is 5.9–7.3 % in the age group up to 40 years, and 5.9–7.6 % in the age group 40+. A more aggressive course of this type of DM is observed in cases when a GCK mutation is accompanied by insulin resistance and obesity [7].

Turkish scientists performed glucose level monitoring in 8 patients with mutations in the *GCK* gene with a glycated hemoglobin level of up to 7 %. They found that daily glucose values were above the normal range in half of patients. Thus, the individuals with GCK-MODY do not present high glucose levels, however, they should be adjusted with dietary and lifestyle changes [12]. The results of this study are consistent with the data obtained during the research work in our clinic; they demonstrate the reasonability of dietary interventions and hypoglycemic therapy for individuals with GCK-MODY, since several patients do not achieve their target values. Thus, the assessment of glucose variability using modern portable systems has been successfully used to analyze the course of a monogenic type of diabetes mellitus.

Conclusion

1) Most patients with GCK-MODY had target values of the routine carbohydrate metabolism (FPG and HbA1c) parameters, however, CGM results revealed that the values in several patients are higher than the reference ones; therefore, the treatment should be adjusted.

2) The patients with GCK-MODY had low daily glucose variability that probably causes a lower frequency of diabetic complications than in the patients with other DM types.

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

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КЛИНИЧЕСКИЙ СЛУЧАЙ ГЕНЕРАЛИЗОВАННОГО САРКОИДОЗА С ПРЕИМУЩЕСТВЕННЫМ ПОРАЖЕНИЕМ СПИННОГО МОЗГА

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A Clinical Case of Generalized Sarcoidosis with a Predominant Lesion of the Spinal Cord

Резюме

Саркоидоз, как системный эпителиоидно-клеточный гранулематоз, может сопровождаться поражением не только внутригрудных лимфатических узлов и лёгких, но и других органов, в частности, центральной нервной системы и периферических лимфатических узлов. В спектре экстраторакальных поражений саркоидоз спинного мозга встречается лишь в 6-8 % случаев всех поражений мозга. Представленный клинический пример иллюстрирует поражение спинного мозга на уровне грудного отдела, хотя в литературе чаще описывается поражение шейного отдела. Заболевание сопровождалось саркоидозом внутригрудных лимфатических узлов с быстрой спонтанной регрессией и саркоидозом надключичного лимфатического узла. Диагноз был подтвержден после биопсии периферического лимфоузла. Саркоидоз спинного мозга у данного пациента характеризовался быстрой регрессией на фоне парентерального введения дексаметазона в течение 14 дней с последующим переводом на таблетированные формы преднизолона. Положительная динамика саркоидоза спинного мозга опровергла предположение о наличии саркоидной реакции в лимфатических узлах на фоне опухоли спинного мозга. Использование курса реабилитационных методик способствовало восстановлению работоспособности.

Ключевые слова: *генерализованный саркоидоз, саркоидоз спинного мозга, саркоидоз центральной нервной системы, реабилитация.*

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

Sarcoidosis, as systemic epithelioid cell granulomatosis, can be accompanied by damage not only to the intrathoracic lymph nodes and lungs, but also to other organs, in particular, the central nervous system and peripheral lymph nodes. In the spectrum of extrathoracic lesions, spinal cord sarcoidosis occurs only in 6-8 % of cases of all brain lesions. The presented clinical example illustrates the lesion of the spinal cord at the level of the thoracic region, although the literature more often describes the lesion of the cervical region. The disease was accompanied by sarcoidosis of the intrathoracic lymph nodes with rapid spontaneous regression and sarcoidosis of the supraclavicular lymph node. The diagnosis was confirmed after a peripheral lymph node biopsy. Spinal cord sarcoidosis in this patient was characterized by rapid regression against the background of parenteral administration of dexamethasone for 14 days, followed by transfer to tablet forms of prednisone. The positive dynamics of spinal cord sarcoidosis refuted the assumption of the presence of a sarcoid reaction in the lymph nodes against the background of a spinal cord tumor. The use of a course of rehabilitation techniques contributed to the recovery of working capacity.

Keywords: *generalized sarcoidosis, spinal cord sarcoidosis, central nervous system sarcoidosis, rehabilitation.*

Conflict of interests

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ACE — angiotensin-converting enzyme, ALT — alanine aminotransferase, APTT — activated partial thromboplastin time, AST — aspartate aminotransferase, BMI — body mass index, BP — blood pressure, CD — cluster of WBC differentiation, CEA — carcinoembryonic antigen, CT — computed tomography, ENMG — electroneuromyography, ESR — erythrocyte sedimentation rate, FDG — fluorodeoxyglucose, HIV — human immunodeficiency virus, HR — heart rate, INR — international normalized ratio, L — lumbar, Max — maximum, MRI — magnetic resonance imaging, PSA — prostate specific antigen, PET — positron emission tomography, RF — respiratory failure, RR — respiratory rate, RV — reference values, S — sacral, SUV — standardized uptake value, T3 — triiodothyronine, T4 — thyroxine, Th — thoracic, TSH — thyroid stimulating hormone

Introduction

Sarcoidosis, as a systemic epithelioid granulomatous disease, may not be limited to only the respiratory system; it may be localized in other organs, such as skin, subcutaneous tissue, peripheral lymph nodes, bones, joints, kidneys, myocardium, eye, or nervous system. Extrathoracic signs of sarcoidosis generally include skin manifestations, however, the lesions of central nervous system and peripheral nerves are found in 5–10 % of cases [1]. Among the patients with a generalized process with the nervous system involvement the predominating group are both middle-aged female patients aged 35–60 with stage 2 or 3 pulmonary sarcoidosis, often with the disease relapse, and young male patients up to 35, with new onset stage 1 or 2 pulmonary sarcoidosis. In such cases, other localizations of the disease are often found only in cervical or submandibular peripheral lymph nodes [1]. Most case reports on central nervous system sarcoidosis describe predominant brain lesion, however, changes in spinal cord are found in 6-8 % of patients [2]. At the same time, there are no descriptions of a generalized damage to the central nervous system due to sarcoidosis. According to the literature sources, clinically intact lesions of the nervous system were detected during autopsy in 15–25 % of patients with generalized sarcoidosis. 10–20 % of patients probably had isolated neurosarcoidosis, however, in 84 % of cases, neurosarcoidosis was the first sign of the disease with the subsequent development of symptoms typical of a generalized process [3]. Sarcoidosis of the spinal cord is considered to be a rare disease. N. Soni (2019), using the sample of 18 individuals, concludes that the detection of this pathological condition is more often accompanied by the changes found in cervical region (up to 76 %); lepto- and pachymeningeal lesions are found in 61 % of patients; intramedullary lesions — in 46 % [4]. The clinical signs of spinal cord sarcoidosis depend on the localization and may develop gradually, for example, with radiculomyelopathy. The damages to the spinal cord membranes cause, first of all, hyperalgesia, radicular syndrome, followed by anesthesia, and pareses. Localized or diffuse intramedullary process results in the signs of motor and sensory dysfunction, as well as symptoms of compression that require differential diagnosis with tumors. In vast majority of cases, no spinal lesions are found in spinal cord sarcoidosis. Some researchers specified an increased ratio of CD4/CD8 and interleukin-6 in the cerebrospinal fluid of patients with neurosarcoidosis compared with the other inflammatory diseases of central nervous system. The analysis of angiotensin-converting enzyme level in the cerebrospinal fluid in neurosarcoidosis patients does not allow interpreting the increase in this parameter as a reliable diagnostic criterion due to its low sensitivity and specificity [5]. The increased level of angiotensin-converting enzyme in peripheral blood, CD4/CD8 ratio in bronchoalveolar lavage and peripheral blood is of great importance for the diagnosis of generalized sarcoidosis [1].

Isolated spinal cord sarcoidosis requires histologically verified diagnosis, although the literature sources describe the single cases of direct intravital spinal cord biopsy [5]. According to the criteria developed by J.P. Zajicek (1999), when all other causes of damage to the central nervous system are excluded, neurosarcoidosis with its corresponding clinical signs and examination results can be described as possible (no histological confirmation), probable (with histological confirmation of systemic sarcoidosis), or definitive (with histologically confirmed damage to the nervous system due to sarcoidosis). Descriptions of definitive spinal cord sarcoidosis in the literature are rare. Most works include the analysis of probable sarcoidosis damage to spinal cord. Thus, in the study by N. Soni (2019), only 5 patients out of 18 had a definitive diagnosis, and 8 patients had a probable one. It should be mentioned that there is no description of the cases of discrepancy in diagnosis or medical error in probable spinal cord sarcoidosis [4].

The management of spinal cord sarcoidosis involves methylprednisolone for the first 3-5 days at a dose of 1 g (preferably parenterally); then the patient is switched to oral drug at an initial dose of 1 mg/kg of body weight with gradual dose tapering associated with clinical improvement within 12 months. Glucocorticosteroid therapy is effective in most patients, however, in cases of intolerance and ineffectiveness, methotrexate or azathioprine can be prescribed, as well as tumor necrosis factor-α inhibitors [3]. Complete regression of tomographic changes in the spinal cord associated with resolution of clinical symptoms of the disease occurs rarely. In most cases, several residual focal changes with sharp outlines persist. The possibility of spinal cord sarcoidosis relapse is significantly reduced if there is small amount of residual changes and long basic treatment course [5].

Sarcoidosis is a systemic granulomatous disease, therefore, the first symptoms of the disease in any organ may cause the patient to visit a relevant medical specialist, however, the complete examination and diagnosis justification with the choice of adequate therapeutic approach requires the cooperation of all involved specialists [1]. Focus on a narrow clinical issue can lead to a chronic course of the disease or to irreversible consequences of other initially asymptomatic manifestations. We would like to present the following case report.

Case report

Patient S., male, 31, presented with complains of general weakness, lack of sensitivity in lower limbs, no movements in lower limbs, no urge to urinate or defecate.

The patient is a coach for a children's football team. After a back injury in February 2021, he began to notice progressive muscle weakness, then — decreased sensitivity in lower limbs starting from the feet. In April, he was unable to move, with a complete loss of sensitivity in lower limbs, and pelvic organ dysfunction. According to the patient, no previous history of tuberculosis, HIV, hepatites, syphilis, oncological diseases. No past surgical interventions. The patient does not drink alcohol, denies smoking and substance use. About 20 years ago, the patient's mother had stage 2 pulmonary sarcoidosis and was treated with corticosteroids; there are residual changes in her lungs of the type of the areas of pulmonary fibrosis on both sides.

Physical examination of the patient revealed the general condition of moderate severity. The patient is oriented in space and time. Skin and visible mucous membranes are normally colored, no rash. Subcutaneous tissue is developed normally. BMI 18.2 kg/m^2. No peripheral edema. Peripheral lymph nodes are not palpable. Thyroid gland is not enlarged. No pathological changes found on palpation, percussion and auscultation. RR 16/min. BP 120/75 mm Hg. HR 76 bpm. Urination is spontaneous, painless, uncontrolled. Stool is regular, formed, uncontrolled.

Neurological status: fully conscious, cooperated, oriented. No meningeal signs. Palpebral fissures and pupils are symmetrical, direct and consensual pupillary reflexes are brisk. Eyeball movements are in full, painless. No nystagmus or diplopia. Sensitivity of face is remained. Tenderness of thoracic spinous processes during percussion. Tendon reflexes are brisk with the increased reflexogenous zones of lower limbs. Lower limb paraparesis up to 3 points. Heel-to-shin test is performed with significant dysmetria. Sensitive ataxia. The patient moves in a wheelchair.

Complete blood count: RBC 4.47×10^{12}/L (RV 4.28-5.78×10^{12}/L), hemoglobin 136 g/L (RV 130-170 g/L), WBC 12.2×10^9/L (RV 3.9-10.9×10^9/L), stab neutrophils 1 % (RV 1-5 %), segmented neutrophils 80 % (RV 40-70 %), lymphocytes 16 % (RV 20-45 %), monocytes 3 % (RV 3-8 %), ESR 3 mm/h (RV 2-16 mm/h).

Urinalysis: specific gravity 1015 g/L (RV 1015-1025 g/L), pH 6.5 (RV 5-9), protein 0 (RV 0-0.033 g/L), glucose 0 (RV 0-0.8 mmol/L), WBC 2-3 PFV (RV 0-6 PFV), RBC not found (RV 0-2 PFV), oxalates (RV none).

Biochemical assay: AST 23.5 U/L (RV 0-37 U/L), ALT 11.5 U/L (RV 0-45 U/L), creatinine 79.3 μmol/L (RV 62-115 μmol/L), bilirubin 16.2-13.3-2.9 μmol/L (RV 3.4-20.1 μmol/L, 2.4-12.2 μmol/L, 1-7.9 μmol/L), uric acid 3.86 μmol/L (PV 210-420 μmol/L), seromucoid 0.255 U (RV 0.13-0.2 U), C-reactive protein (CRP) 10.21 mg/L (RV 0-5 mg/L), glucose 4.49 mmol/L (RV 3.3-5.5 mmol/L), potassium 3.61 mmol/L (RV 3.5-5.5 mmol/L), sodium 140.8 mmol/L (RV 136-145 mmol/L), chlorine 100.8 mmol/L (RV 98-107 mmol/L), calcium 2.45 mmol/L (RV 2.25-3.0 mmol/L), ACE 14.6 ACE unit (RV 20-70 ACE unit).

TSH 0.548 μIU/L (RV 0.4-4 μIU/L), T3 4.82 pmol/L (RV 3.1-6.8 pmol/L), T4 0.54 ng/dL (RV 0.89-1.76 ng/dL).

APTT 34.5 s (RV 24.6-31.2 s), antithrombin III 100 % (RV 75-125 %), D-dimer 315.0 ng/mL (RV < 440 ng/mL),

INR 1.41 s (RV 0.85-1.15 s), Quick prothrombin 49.2 % (RV 70-130 %), thrombin time 17.2 s (RV 15.8-24.9 s), fibrinogen 4.0 g/L (RV 1.7-4.2 g/L).

Immunohematology. Antigen of the Kell (K) system not found (RV negative); antigens of the Rh system (C, c, E, e) C-E+c+e+ (RV negative); antibodies to RBC antigens not found.

Tumor markers. PSA: total 1.41 ng/mL (RV < 4 ng/mL), free (free PSA) 0.141 ng/mL (RV 10 % of total value); CEA 0.5 ng/mL (RV < 5 ng/mL).

Intradermal test with recombinant tuberculosis allergen — negative.

Ultrasound examination: signs of reactive lymphadenopathy of the neck on the right side. Abdominal organs without pathological findings. Small diffuse changes in thyroid parenchyma. No thrombosis of the veins of lower limbs.

Whole body 18-FDG PET/CT (Figure 1): in the right palatine tonsil, there is pathological metabolic activity, with SUV max 5.3, with no reliably detectable changes related to contrast enhancement; in a single right hypervascular supraclavicular lymph node, there is pathological metabolic activity, with SUV max 6.2, in size; there is pathological metabolic activity, with SUV max 24.0,

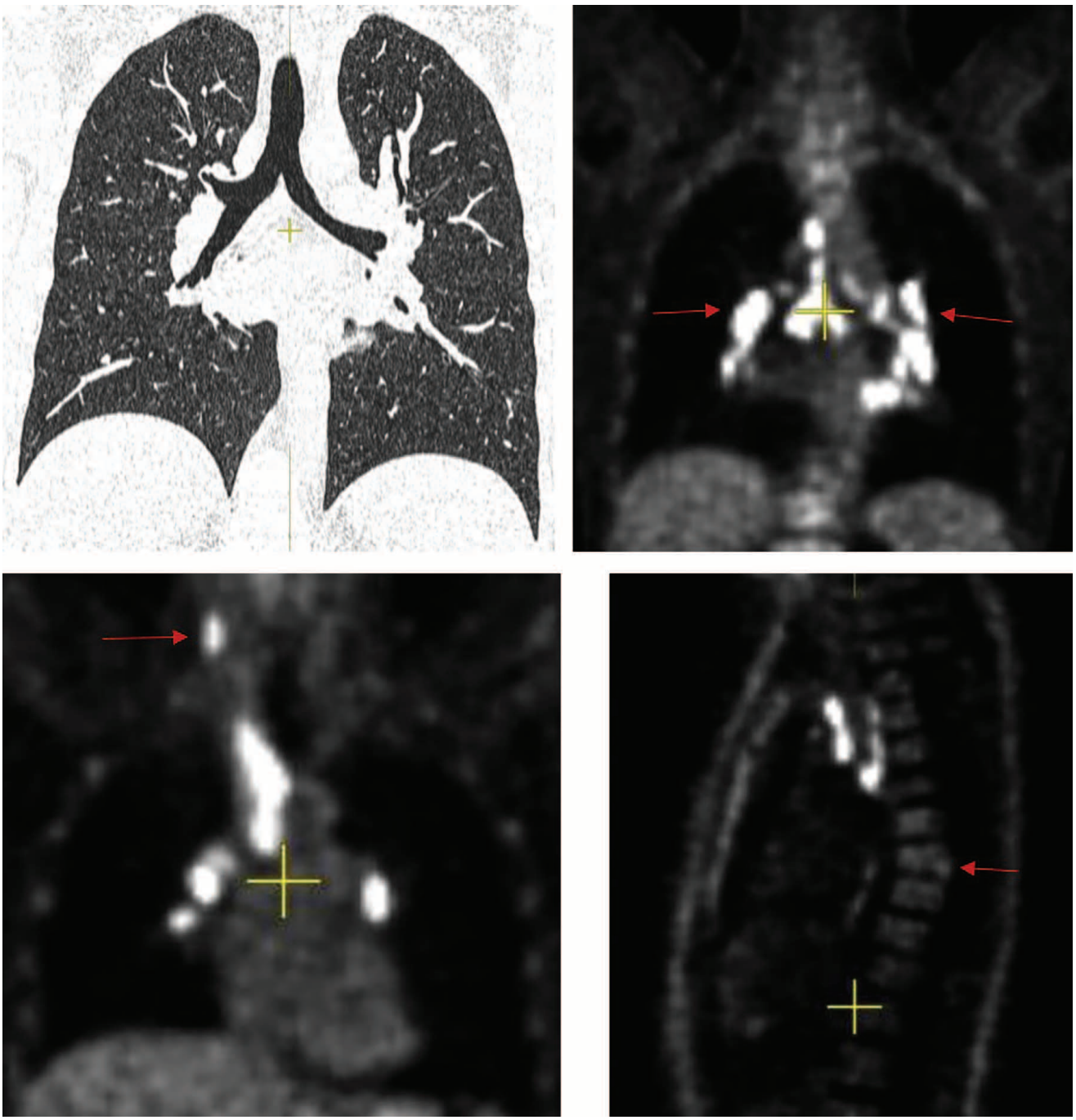

Figure 1. *PET/CT scan with 18-FDG of the chest of patient C. Pathological metabolic activity of SUV in enlarged intrathoracic lymph nodes, in enlarged right supraclavicular lymph node and in the spinal cord*

in paratracheal, bifurcation, bronchopulmonary, tracheobronchial lymph nodes that are enlarged from 15 to 22 mm; in spinal cord at Th8 endplate level, there is a focus of increased metabolic activity, with SUV max 3.1, 13x8 mm in size. Conclusion: findings suggestive of metabolically active neoplastic tissue in pathologically enlarged intrathoracic lymph nodes and right supraclavicular lymph node; the focus of increased metabolic activity in the spinal cord at Th8 endplate level requires additional examination.

MRI of thoracic spine with intravenous contrast enhancement (Fig. 2) in T1, T2, DWI, STIR, FAT SAT modes: degenerative changes and intervertebral disc height loss. The height of vertebral bodies is not changed. Bone endplates are sclerotic and visualized irregularly. Multiple Schmorl's nodes in Th7–Th12. Thoracic kyphosis is preserved. No listhesis of vertebral bodies was found.**1**Spondylosis changes are visible at the levels of Th7-Th12. Spinal canal is not narrowed. An intramedullary zone with altered MR signal was found, 18*5 mm in size (in sagittal plane). Spinal subarachnoid spaces are not deformed, not narrowed. After i/v contrast enhancement, its weak uptake by the pathological focus was observed. In DWI mode, the focus has a hyperintense signal. The roots of cauda equina are not deformed, not displaced. Conclusion: MRI signs of an intramedullary focal lesion at Th8-9 level.

ENMG of lower limbs: impaired function of impulse conduction along the left peroneal nerve and the left sural nerve. The lesion is of axonal-demyelinating type. There are signs of reinnervation along the sciatic nerve at the proximal level.

Considering the results obtained, an opinion was given about the need for the lymph node biopsy. However, during the examination of the patient, there was a significant regression of intrathoracic lymphadenopathy. An excisional biopsy of the right supraclavicular jugular lymph node was performed. Microscopic description: sections with the fragments of a lymph node with an inapparent structure pattern due to granulomatous inflammatory process. Cellular composition of the granuloma is represented by epithelioid cells and single multinucleated giant cells. The granuloma has quite sharp contours, with lymphocytic infiltration along the periphery. A developing reticular stroma of the granuloma with sharp contours was found; this fact (along with the absence of caseosis) allows speaking on a sarcoid granuloma. Conclusion: sarcoidosis of a lymph node.

After a multidisciplinary team meeting, the following diagnosis was established:

Generalized sarcoidosis: Sarcoidosis of intrathoracic lymph nodes and lungs, stage 1, active phase. Sarcoidosis of spinal cord, active phase. Sarcoidosis of peripheral lymph nodes, active phase. RF0. Central lower paraparesis. Dysfunction of pelvic organs. Lumbosacral spine osteochondrosis. Herniated discs L4-S1.

Considering the recommendations of all involved specialists, the following treatment was prescribed: dexamethasone 4 mg i/m 2 times a day; thioctacid 600 mg

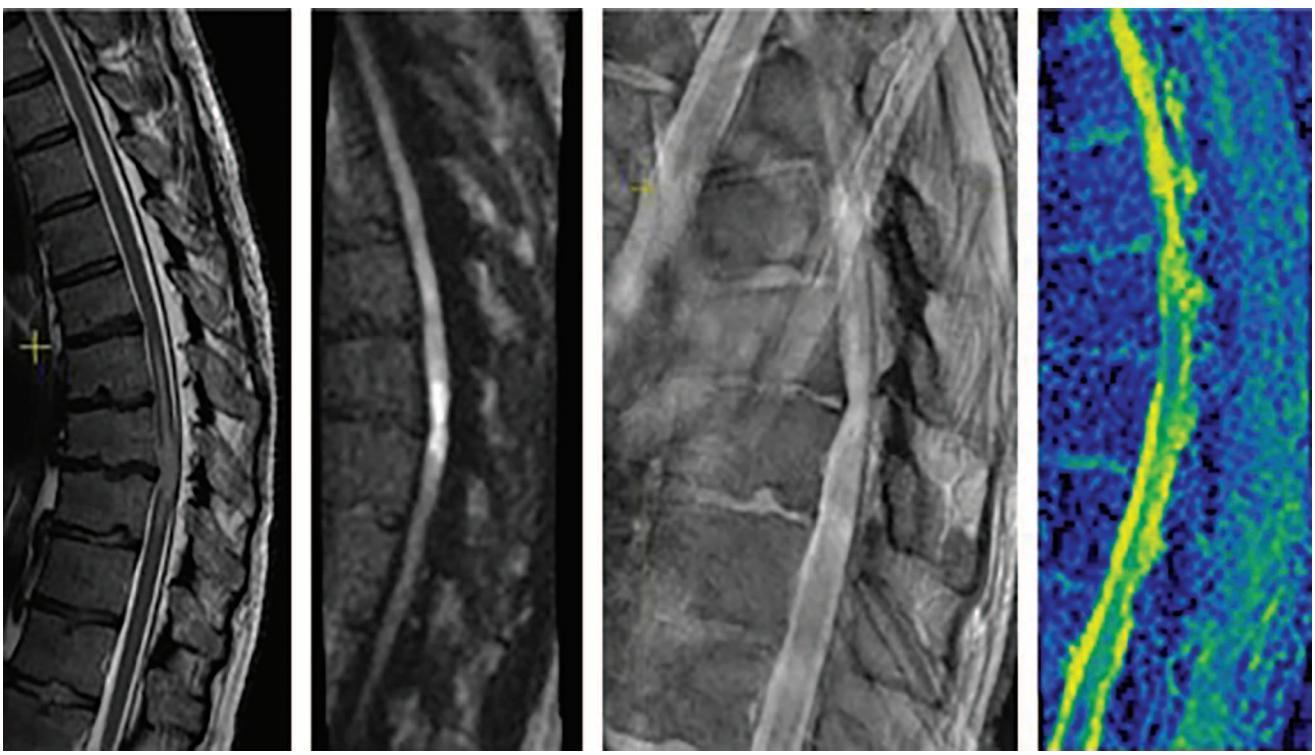

Figure 2. *MRT of the thoracic spine with intravenous contrast, performed in different modes. Signs of intramedullary focal formation in the spinal cord at the level of the Th8-9 vertebrae*

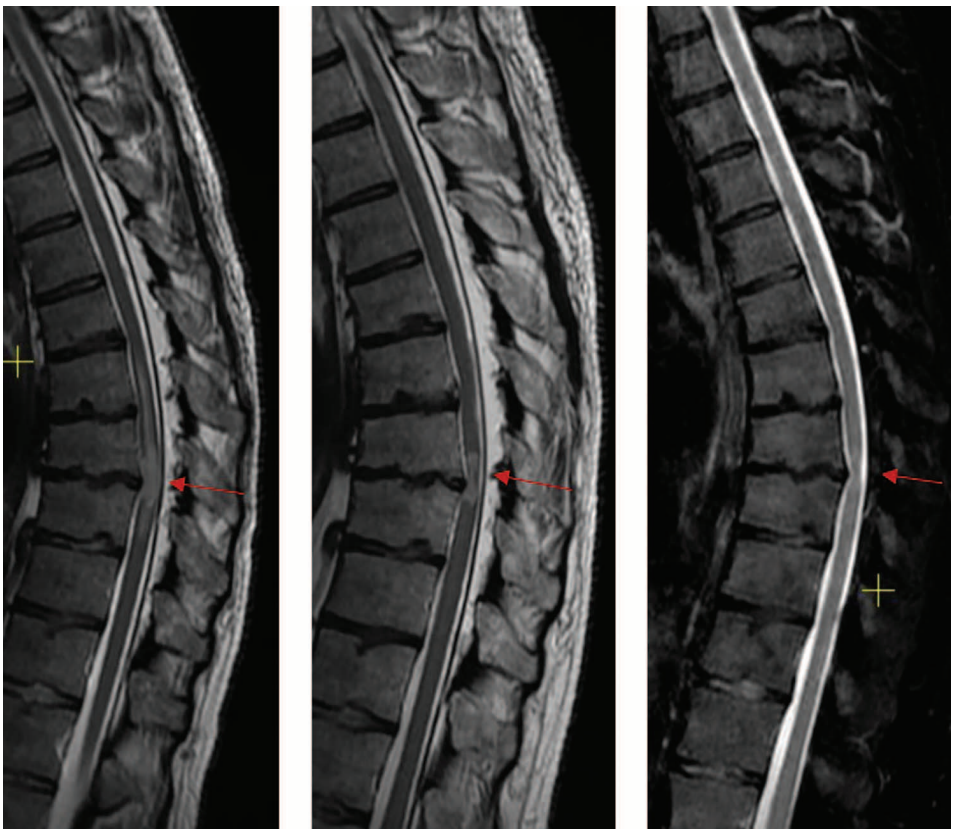

Figure 3. *Control MRT of the thoracic spine with intravenous contrast after 2 months and after 10 months of corticosteroid therapy. There is a decrease in the size of the intramedullary focus in the spinal cord at the level of the Th8-9 vertebrae*

orally once a day; actovegin 800 mg orally; omeprazole 20 mg orally; ipidacrine hydrochloride 20 mg 2 times a day.

14 days after the start of dexamethasone, positive changed in clinical presentation were observed: gradual restoration of sensitivity and movements in lower limbs. The patient was recommended to switch to oral prednisolone at a daily dose of 40 mg (30 mg in the morning and 10 mg in the afternoon). After 60 days of treatment with corticosteroids, complete restoration of sensitivity of lower extremities was achieved, as well as restoration of the pelvic organs function; the patient could move unassisted, first — using walking aids, later — without them. Control MRI of thoracic spine with intravenous contrast enhancement after 2 months and after 10 months of treatment with corticosteroids revealed decreased in size intramedullary lesion in spinal cord at Th8-9 level and the regression of perifocal edema (Fig. 3).

Adverse effects of treatment with corticosteroids included moon face, 5 kg weight gain, and acne.

Subsequently, a gradual dose tapering of prednisolone (by 5 mg per month) and two rehabilitation courses were performed (therapeutic exercises according to an individual method for lower paraparesis, 10 procedures; therapeutic swimming using a lift, 10 procedures; a course of mechanotherapy with Ortorent, Corvit, Detensor devices, 10 procedures; whirlpool pine bath for lower limbs, 10 procedures; programmable multi-channel electrical stimulation of the muscles of lower limbs, 5 procedures). The patient was fully recovered and returned to work. No relapse of sarcoidosis was observed.

Discussion

This case report confirms that sarcoidosis with a predominant involvement of intrathoracic lymph nodes can be asymptomatic, especially in young male patients, and tends to spontaneously regress. However, without timely diagnosis and adequate treatment, the extrathoracic signs of the process often tend to progress. One example is the lesions of central nervous system. Some researchers who dealt with the cases of isolated spinal cord sarcoidosis could observe early rapid regression of changes in intrathoracic lymph nodes at the time of the manifestation of cerebral symptoms. In such situations, the search for changes in peripheral lymph nodes is reasonable, as the process there tends to regress more slowly, as well as the analysis of ACE level — although in our case this parameter was within normal values — and blood CRP.

The clinical hypothesis about the possibility of a sarcoid reaction in connection with a tumor was confirmed by many reports on the possibility of sarcoidosis changes in lymph nodes combined with a local neoplastic process, or of their development that precedes a tumor. However, sarcoid reaction in tissues and lymph nodes is always localized and affects only one anatomical group of lymph nodes that is on the path of lymph outflow from the corresponding organ. As a rule, sarcoid reaction has no tendency to spontaneous regression. Our patient demonstrated generalized involvement of intrathoracic lymph nodes in combination with enlarged supraclavicular node, with a tendency to regression.

To confirm sarcoidosis, a tissue biopsy is reasonable in such cases, although the selection of an organ for biopsy in generalized process can be difficult. In our case, it was a peripheral lymph node. In many case reports on spinal cord sarcoidosis, researchers considered the results of a biopsy of a peripheral lymph node, so, the diagnosis was probable; while no cases of diagnostic errors were described. Direct biopsy of spinal cord is rare and is performed only in the absence of typical sarcoid lesions in any other organs. Histological results in our case report confirmed the presence of distinct non-caseous epithelioid cell granulomas with moderate lymphocytic infiltration. Although in some cases the histological conclusion is not always so unambiguous, there may be cases of obtaining a result of present lymphocytic infiltration with no typical granulomas in the early stages of the process. In such situations, a repeat biopsy is required.

However, is the following combination possible: sarcoidosis of intrathoracic and peripheral lymph nodes with a neoplastic lesion of spinal cord? We have found no such cases in the literature sources; sarcoidosis is usually combined with tumors of breast, thyroid gland, uterus and ovaries, or lungs. The patient was diagnosed with systemic inflammatory response in the presence of a normal level of tumor markers according to laboratory tests, as well as with maximum pathological metabolic activity of SUV 24.0 in enlarged intrathoracic and peripheral lymph nodes, and pathological metabolic activity of SUV 3.1 in spinal cord at Th8 endplate level. Considering the histological results of peripheral lymph node biopsy, the diagnosis of generalized sarcoidosis with a predominant lesion of spinal cord became probable, and the approach with a course of intensive corticosteroid therapy with a subsequent assessment of changes seemed to be adequate.

In all cases of spinal cord sarcoidosis that are described in the literature sources, the effectiveness of parenteral methylprednisolone or prednisolone during the first month was mentioned, followed by oral agents for a period of at least 12 months. Our case is interesting due to the fact that we used dexamethasone injections for 14 days, and then prednisolone in tablets at an initial dose of 40 mg; such treatment resulted in the rapid regression of clinical and radiological signs with no pronounced adverse effects.

Present-day treatment programs for sarcoidosis of all localizations include rehabilitation procedures. In the above clinical case, medical rehabilitation courses including mechanotherapy, balneotherapy, electrical stimulation, and exercise therapy led to a rapid recovery of the patient's ability to work.

The case of our patient is also interesting due to his history with the indication of past sarcoidosis in his mother. There are reports on cases of familial sarcoidosis in the literature sources. In our practice, we have observed the cases of sarcoidosis in siblings, a mother and a son, a mother and a daughter. The disease process commenced in relatives at different times and was characterized by no uniformity of clinical signs or course. In the described case, the patient's mother had pulmonary sarcoidosis with pronounced fibrotic changes at the age of 38. Her son fell ill under the age of 35; the process was characterized mainly by extrathoracic manifestations.

Conclusion

Generalized sarcoidosis may initially be represented by stage 1 or 2 pulmonary sarcoidosis, however, later on, it is often accompanied by the clinical signs of extrathoracic disease localizations. Systemic granulomatous lesions may be localized in spinal cord. The procedure for confirming the diagnosis of spinal cord sarcoidosis is demonstrated in Figure 4.

Regardless of the main symptoms, the correct diagnosis and adequate treatment require a comprehensive examination, with consideration of the recommendations of involved specialists and biopsy results. Corticosteroids are effective in the management of spinal cord sarcoidosis; the treatment takes many months and the initial use of parenteral drugs.

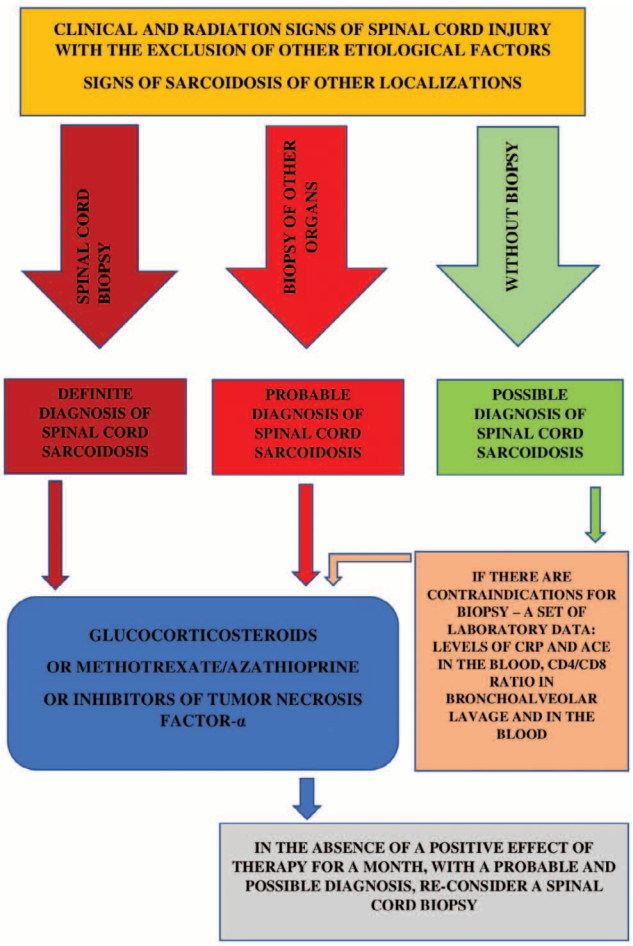

Figure 4. *Algorithm for confirming the diagnosis of spinal cord sarcoidosis*

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Кабанова С.А.: сбор, анализ и интерпретация данных

Дьяков А.В.: проверка критически важного интеллектуального содержания и окончательное утверждение для публикации рукописи

Author Contribution:

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

Chernikov A.Y. (ORCID ID: https://orcid.org/0000-0002-2045-9607): contribution to the development of the concept and design, justification and writing of the manuscript

Kabanova S.A.: contribution to the collection, analysis and interpretation of data

Dyakov A.V.: contribution to the verification of critical intellectual content and final approval for publication of the manuscript

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