Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

ИЮНЬ 2023 (№ 3(71))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
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Подписано в печать 22.05.2023 года
Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»
ООО «Сам Полиграфист»
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru

Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Урал-Пресс Округ» 87732

DOI: 10.20514/2226-6704-2023-3

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
JUNE 2023 (№ 3(71))

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107076, Moscow, Korolenko str., 3A, of. 18B
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Signed for printing on 22.05.2023
Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»
«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Ural-Press Okrug» 87732

DOI: 10.20514/2226-6704-2023-3

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DOI: 10.20514/2226-6704-2023-13-3-165-174
УДК 616-006
EDN: ENSMNZ

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МЕТОД ВИРУСНОЙ МИМИКРИИ В ОНКОЛОГИИ И ПЕРСПЕКТИВЫ ЕГО РАЗВИТИЯ

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The Method of Viral Mimicry in Oncology and Prospects for its Improvement

Резюме

Клетки злокачественных новообразований характеризуются эволюцией клонов, устойчивых к применяемым противоопухолевым препаратам и уклонением от воздействия иммунной системы. В связи с этим перспективным и многообещающим направлением в современной онкологии является стимуляция иммунного ответа против новообразований. Данный способ может быть использован в комбинации с другими противоопухолевыми препаратами и самостоятельно. Клетки опухолей вырабатывают контрольные точки CTLA4 (CTLA4 — cytotoxic T-lymphocyte protein 4) и PD-1 (programmed cell death), подавляющие активность Т-лимфоцитов и выработку ими противоопухолевых цитокинов. В клинике применяются антитела против CTLA4, PD-1 и PD-L1, монотерапия которыми повышает эффективность применяемой химиотерапии, но значительно усугубляет развитие нежелательных реакций, что ограничивает их назначение. Монотерапия анти-PD/PD-L1 показала низкую эффективность и также высокий риск осложнений со стороны легких, печени и щитовидной железы. В связи с этим необходима разработка новых способов иммунотерапии опухолей. Наиболее перспективен в данном отношении метод вирусной мимикрии, когда в качестве триггера для выработки интерферона и активации Т-киллеров служат двуцепочечные РНК, образованные из транскриптов ретроэлементов. Для искусственной активации ретроэлементов используют ингибиторы ДНК-метилтрансфераз, деацетилаз и метилтрансфераз гистонов. Поскольку ретроэлементы располагаются в интронах генов, вирусная мимикрия может быть использована в сплайсосомной таргетной терапии. Необходимо отметить, что транспозоны служат драйверами канцерогенеза, поэтому, помимо их искусственной активации, в онкологии используются методы сайленсинга ретроэлементов с помощью ингибиторов обратной транскриптазы. Применение для этого неспецифических метилтрансфераз и ингибиторов деметилаз гистонов может привести к подавлению экспрессии других генов, с возможным провоцированием побочных эффектов. Поэтому данная методика наиболее перспективна с использованием гидов, направляющих ферменты модификации гистонов в локусы расположения генов ретроэлементов в геноме. Гиды могут быть использованы также для активации наиболее значимых ретроэлементов в развитии иммунного противоопухолевого ответа и исключения экспрессии элементов, участвующих в инициации и поддержании канцерогенеза. В качестве гидов могут быть использованы микроРНК, длинные некодирующие РНК и антисмысловые олигонуклеотиды.

Ключевые слова: *антисмысловые олигонуклеотиды, вирусная мимикрия, злокачественные новообразования, канцерогенез, микроРНК, ретроэлементы, таргетная терапия, транспозоны*

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

Статья получена 20.12.2022 г.
Принята к публикации 10.04.2023 г.

Для цитирования: Мустафин Р.Н. МЕТОД ВИРУСНОЙ МИМИКРИИ В ОНКОЛОГИИ И ПЕРСПЕКТИВЫ ЕГО РАЗВИТИЯ (ОБЗОР ЛИТЕРАТУРЫ И РЕКОМЕНДАЦИИ ДЛЯ ПРАКТИКИ). Архивъ внутренней медицины. 2023; 13(3): 165-174. DOI: 10.20514/2226-6704-2023-13-3-165-174. EDN: ENSMNZ

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Abstract

Malignant neoplasms cells are characterized by clonal evolution that is resistant to the applied antitumor drug and evasion from the effects of the immune system. Therefore, a promising direction in modern oncology is the stimulation of the immune response against neoplasms. This method can be used in combination with other anticancer drugs and alone. Tumor cells produce CTLA4 (CTLA4 — cytotoxic T-lymphocyte protein 4) and PD-1 (programmed cell death) checkpoints that inhibit the activity of T-lymphocytes and their production of antitumor cytokines. The clinic uses antibodies against CTLA4, PD-1 and PD-L1, monotherapy with which increases the effectiveness of the chemotherapy used, but significantly aggravates the development of adverse reactions, which limits their use. Monotherapy with anti-PD/PD-L1 showed low efficacy and also a high risk of pulmonary, hepatic, and thyroid complications. In this regard, it is necessary to develop new methods of tumor immunotherapy. The most promising in this regard is the method of viral mimicry, when double-stranded RNA formed from transcripts of retroelements serve as a trigger for the production of interferon and activation of T-killers. For artificial activation of retroelements, inhibitors of DNA methyltransferases, deacetylases, and histone methyltransferases are used. Since retroelements are located in gene introns, viral mimicry can be used in spliceosomal targeted therapy. Transposons serve as drivers of carcinogenesis, therefore, in addition to their artificial activation, oncology uses methods for silencing retroelements using reverse transcriptase inhibitors. The use of non-specific methyltransferases and inhibitors of histone demethylases for this can lead to suppression of the expression of other genes, with possible side effects. Therefore, this technique is the most promising with the use of guides that direct histone modification enzymes to the loci of the location of retroelement genes in the genome. Guides can also be used to activate the most significant retroelements in the development of the immune antitumor response and exclude the expression of elements involved in the initiation and maintenance of carcinogenesis. MicroRNAs, long non-coding RNAs, and antisense oligonucleotides can be used as guides.

Key words: *antisense oligonucleotides, viral mimicry, malignant neoplasms, carcinogenesis, microRNA, retroelements, targeted therapy, transposons*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 20.12.2022
Accepted for publication on 10.04.2023

For citation: Mustafin R.N. The Method of Viral Mimicry in Oncology and Prospects for its Improvement. The Russian Archives of Internal Medicine. 2023; 13(3): 165-174. DOI: 10.20514/2226-6704-2023-13-3-165-174. EDN: ENSMNZ

AZA — 5-aza-2-deoxycytidine, CTLA4 — cytotoxic T-lymphocyte protein 4, HERV — human endogenous retrovirus, LINE — long interspersed nuclear element, MAVS — mitochondrial antiviral-signaling protein, ORR — objective response rate, PD-1 — programmed cell death (programmed cell death checkpoints), PD-L – programmed cell death ligand, SINE — short interspersed nuclear element, TLR3 — toll-like receptor 3, TNF-α — tumor necrosis factor alpha, ASO — antisense oligonucleotide, HDM — histone demethylase, lncRNA — long non-coding RNA, dsDNA — double-stranded DNA, MN – malignant neoplasm, DNMT — DNA methyltransferase, HDACi — histone deacetylase inhibitors, DNMTi — DNA methyltransferase inhibitors, NRTI — nucleoside reverse transcriptase inhibitors, NNRTI — non-nucleoside reverse transcriptase inhibitors, ncRNA — non-coding RNA, RE — retroelements, STT — spliceosome-targeted therapy, TNBC — triple negative breast cancer

Introduction

One of the factors for malignant neoplasm (MN) progression can be immune evasion by tumor cells due to affected secretory and regulatory function of T lymphocytes, antigen presentation, and a change in the production of immunosuppressive mediators. These mechanisms can be utilized for the targeted action of anticancer agents through their stimulation (for example, stimulation of T cells producing cytotoxines and interferon-γ) or inhibition (inhibition of immunosuppressive mediators such as transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), interleukins IL-1, IL-6, IL-8, IL-10, colony-stimulating factor (CSF-1), and type I interferon) [1]. MN cells effectively suppress the immune response by activating negative regulatory pathways called “checkpoints.” Tumors use these checkpoints to evade detection by the host’s immune system. There are known checkpoints of programmed cell death (PD-1) and cytotoxic T-lymphocyte protein 4 (CTLA4) [2]. The PD-1 cell surface receptor is expressed by T lymphocytes being activated during priming or expansion and binds to one of two ligands PD-L1 or PD-L2, which are produced by normal and tumor cells under the influence of cytokines (such as interferon-γ). When PD-L1 or PD-L2 binds with PD-1 receptors, a signal inhibiting the T lymphocyte activity is generated. CTLA4 also acts as a negative regulator, which controls T cell activation due to competition with co-stimulating molecule CD28 to bind common ligands CD80 and CD86. Antibodies blocking the PD-L1/PD-1 interaction have anticancer effect due to activation of immune response to MN cells [3].

Antibodies to α-PD-1 (anti-PD-1), including nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab, zimberelimab, prolgolimab, and dostarlimab, as well as antibodies to α-PD-L1 (anti-PD-L1) atezolizumab, durvalumab, and avelumab have found their clinical use in the treatment of hemoblastosis and solid tumors [4]. According to the meta-analysis data, anti-PD-1/PD-L1 can enhance the efficacy of the conducted chemotherapy in cancer patients when combined with CTLA4 inhibi-

tors [5], in patients with gastric and gastroesophageal cancer [6], stage 3/4 melanoma [7], and nasopharyngeal carcinoma [8].

Meta-analyses of trials in cancer patients have demonstrated that the PD-L1 and PD-1 inhibitors alone or in combination with other anticancer agents can significantly increase the risk of hepatotoxicity [9], immune-related pneumonitis [10], thyroid dysfunction (especially, hypothyroidism) [11], and rash (especially when anti-PD-L1 and anti-PD-1 are used in combination) [12]. Concomitant use of anti-PD-L1/PD-1 and BRAF and MEK inhibitors significantly increases the risk of fever, asthenia, myalgia, arthralgia, hypothyroidism, liver injury (with a change in ALT and AST levels) [7]. Therefore, combination of anti-PD-L1/PD-1 and chemotherapy in MN can be related to the risk of complications, which restricts their use. At the same time, anti-PD-L1/PD-1 inhibitors alone are not highly effective. For example, in the treatment of nasopharyngeal carcinoma, the objective response rate (ORR) is 19 % for nivolumab, 23.3 % for JS001, 26.3 % for pembrolizumab, 34.1 % for camrelizumab [8]. For α-PD-1 inhibitors, ORR was 1.33 on average, regardless of tumor type [5]. The meta-analysis of anti-PD-L1/PD-1 use in elderly (older than 75 years) patients with solid tumors did not show their efficacy (except for the treatment of melanoma) when used alone [13]. In this regard, the search for new methods of MN immunotherapy having more specific targets involved in carcinogenesis seems promising.

Retroelements in the immunotherapy of malignant neoplasms

One of the directions in anticancer therapy is the method of viral mimicry, which triggers antiviral response due to activation of retroelements (RE) present in the human genome [14]. Since the formation of 5-methylcytosine is associated with heterochromatization and transcriptional repression [15], DNA methyltransferase inhibitors (DMTi) can be used for this purpose, which unlabel 5-methylcytosine at RE loci and promote their expression. Consequently, this enhances immune transmission of antiviral protection signals and triggers cytosolic recognition of double-stranded RNA (dsRNA) of human endogenous retroviruses (HERV) with subsequent cell apoptosis under the action of interferon. Mitochondrial antiviral-signaling proteins (MAVS) and toll-like receptor 3 (TLR3) can be used as dsRNA sensors [16]. HERV transcription products are also recognized by T-killers that destroy MN cells [17], which may be used for DNA vaccination based on adenoviral or other vectors [18].

Retroelements are mobile genetic elements (transposons), specific DNA regions able to move inside the genome. A thorough analysis of the human DNA sequences has demonstrated that transposons constitute the major part of nucleotide sequences in the human genome (69 %) [19]. In addition to REs, the human genome contains DNA transposons, which are moved using the cut-and-paste mechanism, making up to 3 % of all genome sequence. Retroelements replicate through reverse transcription of their RNA and integration of the cDNA into another locus. REs are subdivided into those containing long terminal repeats (LTR) of HERV (constituting 8 % of genome), and REs non-containing LTR (more than 35 % of genome): autonomous long interspersed nuclear elements (LINE) and non-autonomous short interspersed nuclear elements (SINE) [20].

Viral mimicry can be induced by 5-aza-2-deoxycytidine (5-AZA) and 5-azacytidine (5AC), which were first used in the clinical practice in 1979 for the treatment of chronic myeloleukemia [21]. In 2015, the phenomenon of viral mimicry under the influence of AZA was described in preclinical studies of breast cancer cells [22] and colorectal cancer cells [23]. Non-nucleoside DMTi include such epigenetic regulators as epigallocatechin, curcumin, RG-108, isoxazoline, hydralazine, procaine, which are reversibly binding to the catalytic domain of DMT [24]. Clinical trials conducted in 2017 demonstrated the efficacy of non-nucleoside DMTi of guadecitabine (SGI-110) in patients with acute myeloblastic leukemia [25].

In addition to DMTi, the exposure on histone-modifying enzymes can be used for RE activation in viral mimicry. An example of this is tazemetostat, EZH inhibitor, which is a component of the Polycomb Repressive Complex 2 (PRC2), placing histone H3 lysine 27 methylation marks (H3K27me). The efficacy of tazemetostat in clinical trials for the treatment of mesothelioma, epithelioid sarcoma and large B-cell lymphoma [26] has become the basis for the use of EZH2 inhibitors in the treatment of chemotherapy-resistant breast cancer [27], as well as prostate cancer (in combination with anti-PD-1) [28]. The combination of DMTi and histone deacetylase inhibitors (HDACi) shows the most remarkable antitumor effect. In the experiment with mouse models of non-small cell lung cancer, this method enhanced antigenic presentation through increased dsRNA expression, with stimulation of type I interferon. This also included the activation of CCL5 (a T cell chemoattractant) and inhibition of MYC oncogene. Consequently, the tumors became representative for the immune response, with their infiltration by T-killers [29]. The combination of DMTi and HDAC showed a pronounced antitumor effect in mice with epithelial ovarian cancer, most significantly in combination with anti-PD-1 [30].

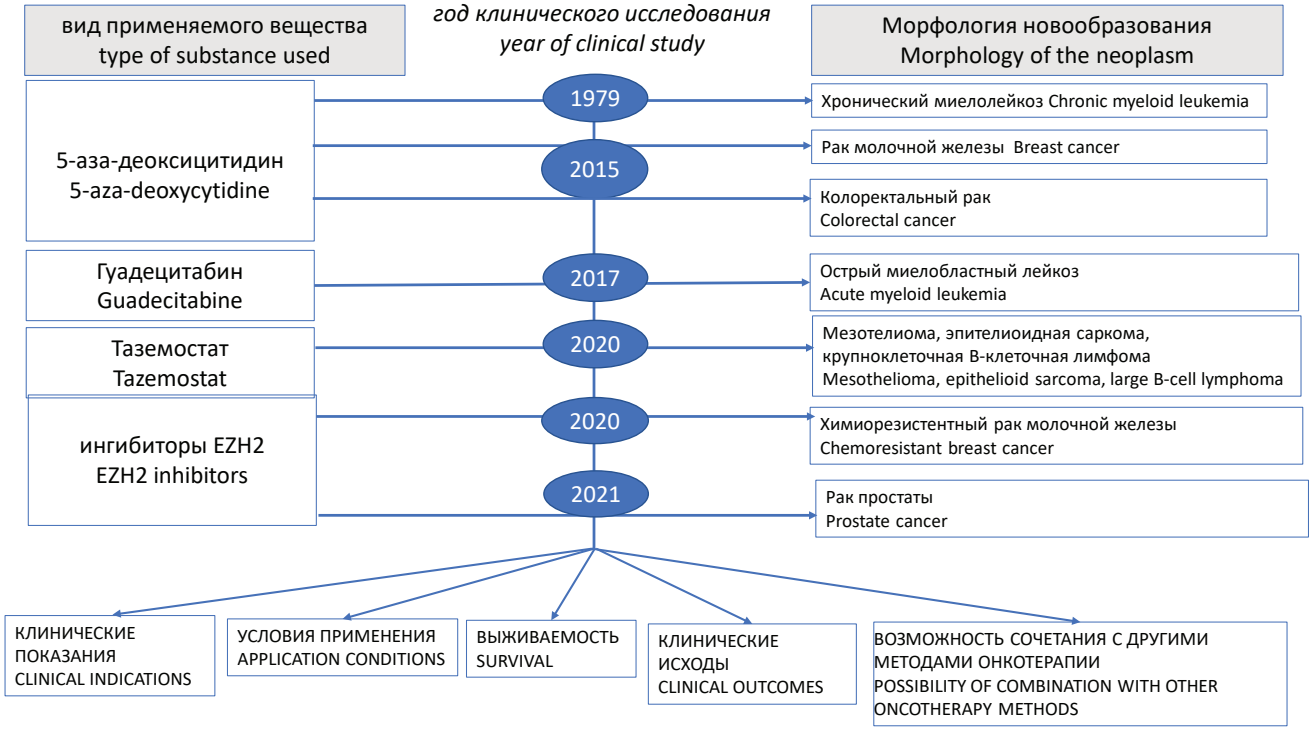

Figure 1. *Algorithm for applying the method of viral mimicry in oncology with examples*

The effect of viral mimicry may be achieved by inhibition of histone methyltransferase (trimethylation of H3K9me3, a RE repressive mark). An example of this is the use of SENDB1 histone methyltransferase inhibitors in the treatment of acute myeloblastic leukemia, which causes the formation of heterochromatin in RE loci using KAP1 or human silencing hub complex (HUSH) [31]. G9a histone methyltransferase inhibitors demonstrated their efficacy against ovarian cancer cells [32]. A promising target for viral mimicry in anticancer treatment is SUV39H1 histone methyltransferase, which is recruited by FBXO44 in the RE locus [20]. Depletion of another SETDB1 histone methyltransferase causes RE activation, inducing expression of viral response genes and SETDB1-medicated death of acute myeloblastic leukemia cells [33]. Figure 1 shows an algorithm for virus-mimicking drugs in the oncology with examples.

Role of virus-mimicking targets in carcinogenesis

Since DMTi, HDACi, and methyltransferase inhibitors used in the clinical practice and developed in viral mimicry are not selective towards activation of specific REs, possible consequences caused by their effects should be considered, since REs are drivers of carcinogenesis (Figure 2). The role of abnormal activation of LINE-1 in tumor initiation in MN is confirmed [34, 35]. In meta-analyses, reliable activation of Alu elements [36] and LINE-1 [37] has been identified in the tissues of various MN. In large-scale trials, RE insertions in the genomes were demonstrated in 35 % [38] to 87 % (for certain MN types) of tumor samples with activation of proto-oncogenes under the influence of integrated promoters HERV and LINE-1 [39]. The grade of RE activation also influences the survival rate of patients with MN, which is indicative of RE significance in tumor progression mechanisms [40]. Therefore, it may be safer to use the methods that affect strictly defined REs, carrying no potential risk of secondary tumors in humans. This strategy may be implemented with specific guides: synthetic oligonucleotides or non-coding RNA, that is complementary to RE. Since most long non-coding RNA (lncRNA) genes [41] and microRNAs [42] evolved from transposons, an analysis of their relationships may be promising for the development of targeted therapy for MN using viral mimicry.

The data on the involvement of specific ncRNAs derived from RE in carcinogenesis are in favor of the proposed approach to the use of guides. LncRNA TROJAN evolved from HERV is used in the mechanisms of triple negative breast cancer (TNBC) progression [43]. HERVs have proven to be sources of HCP5 [44], PRLH1 [45], and lncMER52A [46] lncRNAs involved in carcinogenesis. LncRNA processing can lead to the development of specific microRNA involved in carcinogenesis: in breast cancer, lncRNA LOC554202 is expressed, processing in

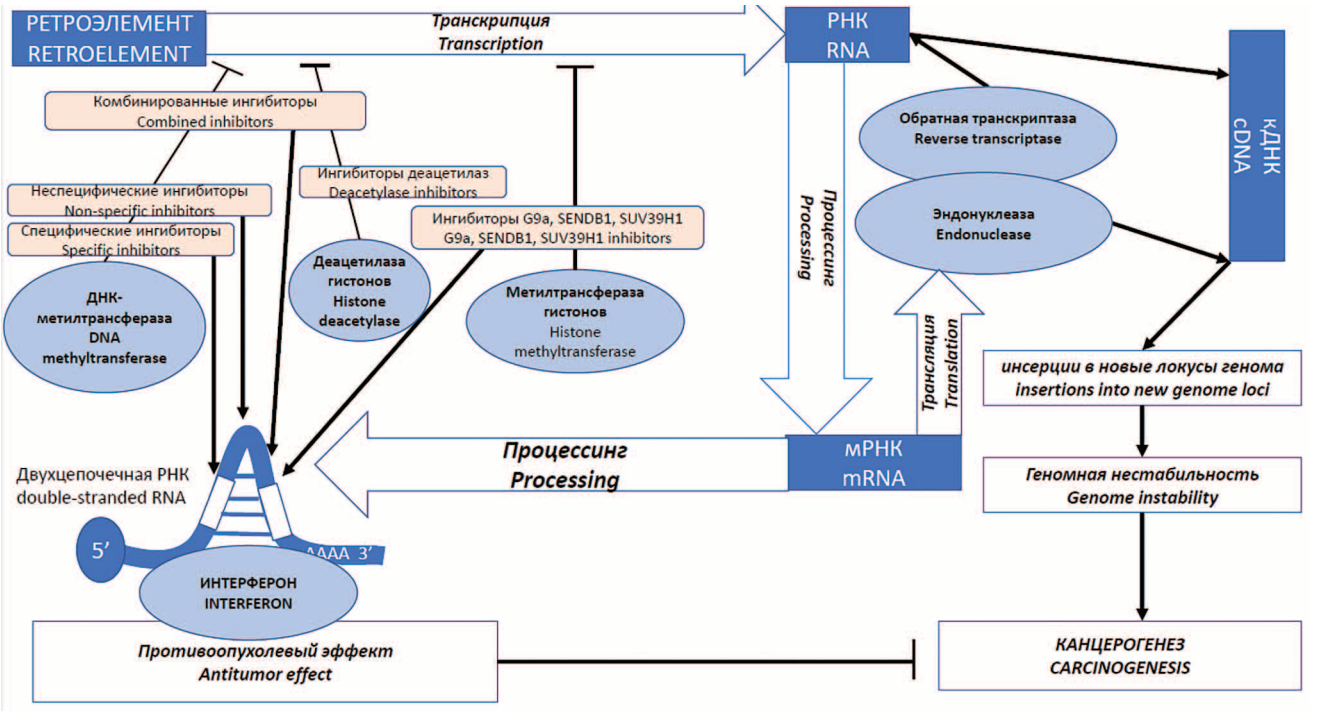

Figure 2. *Scheme of used variants of viral mimicry and the role of retroelements in carcinogenesis*

miR-31 [47], and lncRNA H19 in miR-675 [48]; lncRNA MIR497HG generates pri-miR-497, precursor of miR-195 and miR-497 (binding with ribosomes and producing tumor suppressive peptide miPEP497) [49]. According to the literature data, 94 specific microRNA derived from transposons take part in the development of various MN [42].

Role of retroelements in the spliceosome-targeted therapy of tumors

The viral mimicry phenomenon may be used with regard to the RE genes located in the introns, as well as the sequences of the introns, that evolved from RE [50]. This technique is part of the spliceosome-targeted therapy (STT) of tumors. Inhibition of spliceosome components leads to defective splicing, resulting in the formation of double-chain loops of mRNA molecules (Figure 3) and becoming targets for the body's antiviral systems. The resulting interferon causes tumor cell apoptosis. In STT, various splicing components are affected, including SF3B1 protein that stabilizes binding of small nuclear RNA U2 with branch point sequence; protein U2AF1, recognizing AG dinucleotide in 3'-splice site; SRSF2 binding mRNA exonic splicing enhancer motifs; ZRSR2, spliceosome components, required to recognize 3'-splice sites [51].

Since the immunogenicity of REs is the highest, dsRNAs of SINE transcripts, which are often located in introns, have been proposed as targets for viral mimicry in STT [15]. The efficacy of STT was demonstrated in the experiment on MYC-positive cells of TNBC. In this case, dsRNAs formed from incorrectly spliced mRNA, which were perceived by the body's antiviral defense systems, were used as the targets. For this purpose, agents SD6 and H3B-8800 targeted to SF3B1 spliceosome component were used [52]. Prostate cancer cells are characterized by high sensitivity to the spliceosome inhibitor E7107, which also targets the SF3B complex [53].

It should be noted that mutations of the splicing factors or molecules affecting it can play an important role in the MN etiopathogenesis. For example, mutations in *SF3B1, SRSF2, U2AF1, ZRSR2* genes can be associated with acute myeloblastic leukemia, while a mutation in the *U2AF1* gene is found in hairy cell leukemia [51]. Therefore, one of STT options can be based on a completely opposite principle: restoration of spliceosome component function to eliminate the mechanisms of tumor development. In renal cell carcinoma, microRNA miR-30a-5p and miR-181a-5p suppress expression of SRSF7 (serine/arginine-rich splicing factor 7). Consequently, splicing of apoptosis regulators and tumor suppressors is disrupted, which leads to carcinogenesis [54]. Retinoic acid-induced miR-10a and miR-10b repress SRSF1, leading to differentiation of neuroblastoma cells [55].

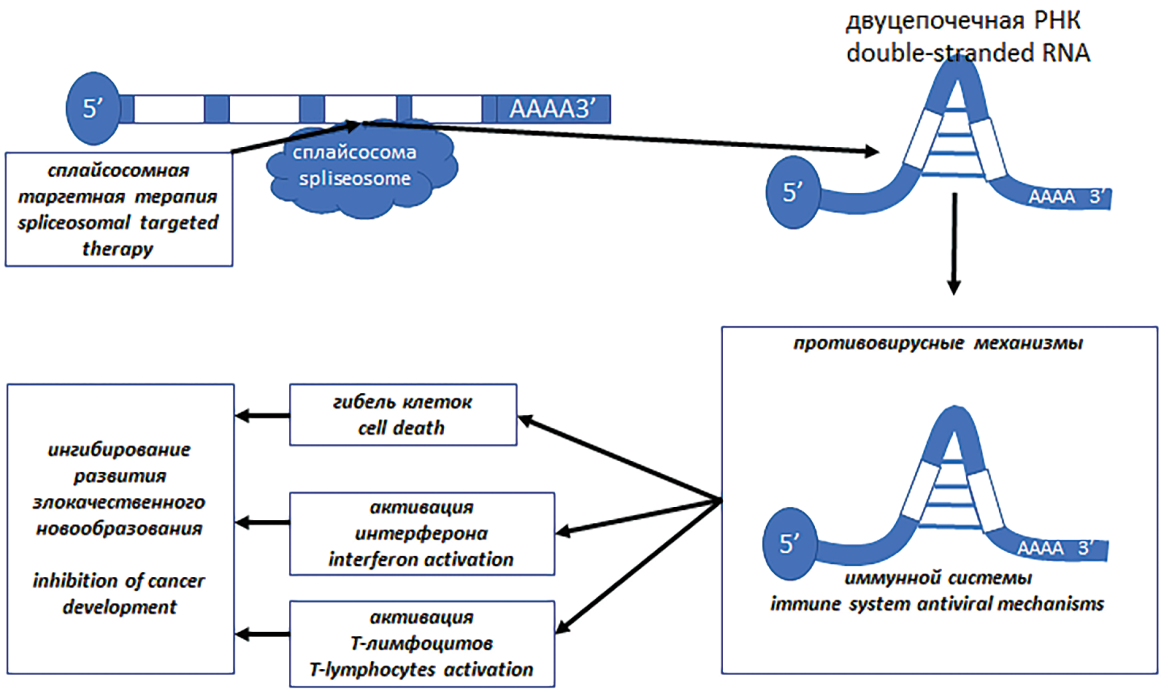

Figure 3. *Scheme of immune response activation against the tumor using spliceosomal targeted therapy*

Inhibition of retroelements in anticancer treatment

It should be taken into account that the use of viral mimicry in anticancer treatment can have negative effects, since MN is characterized by abnormal activation of REs, which cause genomic instability and carcinogenesis. Therefore, similarly to STT, a strategy aimed at suppressing RE expression, which is completely opposite to viral mimicry, can be used in MN treatment with regard to REs. Inhibition of histone demethylases (HDM) characterized by hyperexpression in MN with loss of heterochromatin and RE activation can be used for this purpose. A target for RE inhibition can be HDM KDM1A (LSD1), which suppresses HERV expression and genes containing LTRs in their promoters through demethylation of H3K9 and increased acetylation of H3K27 and methylation of H3K4 [56]. Increased levels of HDM KDM5A/B/C/D subfamily members, JARID1 family, demethylating H3K4me2 and H3K4me3, are also detected in various tumor types. Selective HDM inhibitors include CPI-455 and 1,7-naphthyridines, which are effective against chemotherapy-resistant MNs [57].

A specific histone methyltransferase SETDB1 (ESET, KMT1E), acting on H3K9me3 in an HDM-independent manner through interactions with the KRAB-containing zinc-finger protein, could be a promising target for RE inhibition in anticancer treatment [58]. However, the studies show that in addition to RE splicing, SETDB1 prevents functioning of transcription factors CDX2, ELF3, HNF4G (hepatocyte nuclear factor 4 gamma), PPARG (peroxysome proliferator-activated receptor), VDR (vitamin D receptor). Therefore, depletion of SETDB1 in the experiment contributed to the transition of colorectal cancer stem cells into a postmitotic state with restoration of normal morphology and global gene expression profile of differentiated cells [59]. Consequently, SETDB1 activation to inhibit REs abnormally activated in tumors can cause other pathways of carcinogenesis. It is necessary to consider these mechanisms when developing targeted anticancer therapy. Therefore, the effect on specific REs that are carcinogenesis inductors using the microRNA or lncRNA complementary to these REs as molecule guides seems promising (Figure 4). The use of reverse transcriptase as a target can be another alternative option of RE inhibition.

Clinical studies demonstrated a significant efficacy of nucleoside reverse transcriptase inhibitor (NRTI) in patients with colorectal cancer. In addition to eliminating the genomic instability caused by retroelements, NRTI induced DNA damage and antitumor interferon response [35]. Antitumor efficacy of NRTI is determined with regard to hormone resistance prostate cancer [34].

In the breast cancer cell line, the use of NRTIs such as abacavir and stavudine was shown to be associated with a significant increase in the number and rate of cell death and inhibition of their migration ability, especially in combination with paclitaxel [60]. Meta-analyses also demonstrated a reduced risk of hepatocellular carcinoma in patients treated with NRTI tenofovir in patients with chronic viral hepatitis B [61].

The use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) is also promising. They include efavirenz, which showed its antitumor activity in pancreatic cancer cells [62]. NNRTI etravirine, which caused AGR2 degradation (anterior gradient homolog 2 protein), suppressed proliferation, migration and tumor-cell invasion in vitro. In mouse models, the combination of paclitaxel and etravirine demonstrated more effective inhibition of ovarian cancer progression [63]. It should be noted that a pronounced expression of telomerase reverse transcriptase was associated with a poor clinical response to immune checkpoint inhibitors [64], due to which NNRTIs can be recommended in combination with these agents.

Antisense oligonucleotides (ASOs), RNA sequences of 12 to 25 nucleotides long, which inhibit gene expression by binding to cellular mRNAs, as well as microRNAs and long non-coding RNAs, can be used as tools for RE inhibition [65]. Since REs are key evolutionary sources (therefore, they contain identical sequences) of lncRNA [41] and microRNA [42] genes, the use of these ASOs may influence REs. In addition to non-coding RNAs, the targets of ASOs are molecular members of splicing, RNA translation, mRNA degradation, and sequestered protein release [65]. The modern scientific literature contains no information on the use of RE-targeted ASOs in oncology. However, there is evidence of the use of ASO targeting Alu in age-related macular degeneration [66], targeting SVA (SINE-VNTR-Alu) RE in Fukuyama muscular dystrophy [67], targeting HERV HML-2, which participated in the pathogenesis of amyotrophic lateral sclerosis [68].

The design of ASOs targeting specific REs may be based on the existing information on the use of ASOs targeting microRNAs (which may have evolved from REs) [42], oncogenes or oncosupressors (since they are characterized by a close relationship with REs in oncology [69]. For example, there are ASOs targeting exon 11 of *NF2* tumor suppressor gene in type 2 neurofibromatosis [70], FLT3-ITD (FMS-like tyrosine kinase-3) and microRNA miR-125b in acute myeloblastic leukemia [2], microRNA miR-17 (for μ-17-ON), miR-21 (for μ-21-ON) and miR-155 (for μ-155-ON) in lymphosarcoma [71], oncogenes IGF1R (insulin-like growth factor receptor) [72], tumor suppressors Smad7 [73], Stat3 in hepatocellular carcinoma [74], oncogene transforming growth factor TGF-β2 in lung cancer [75] and TNBC [76].

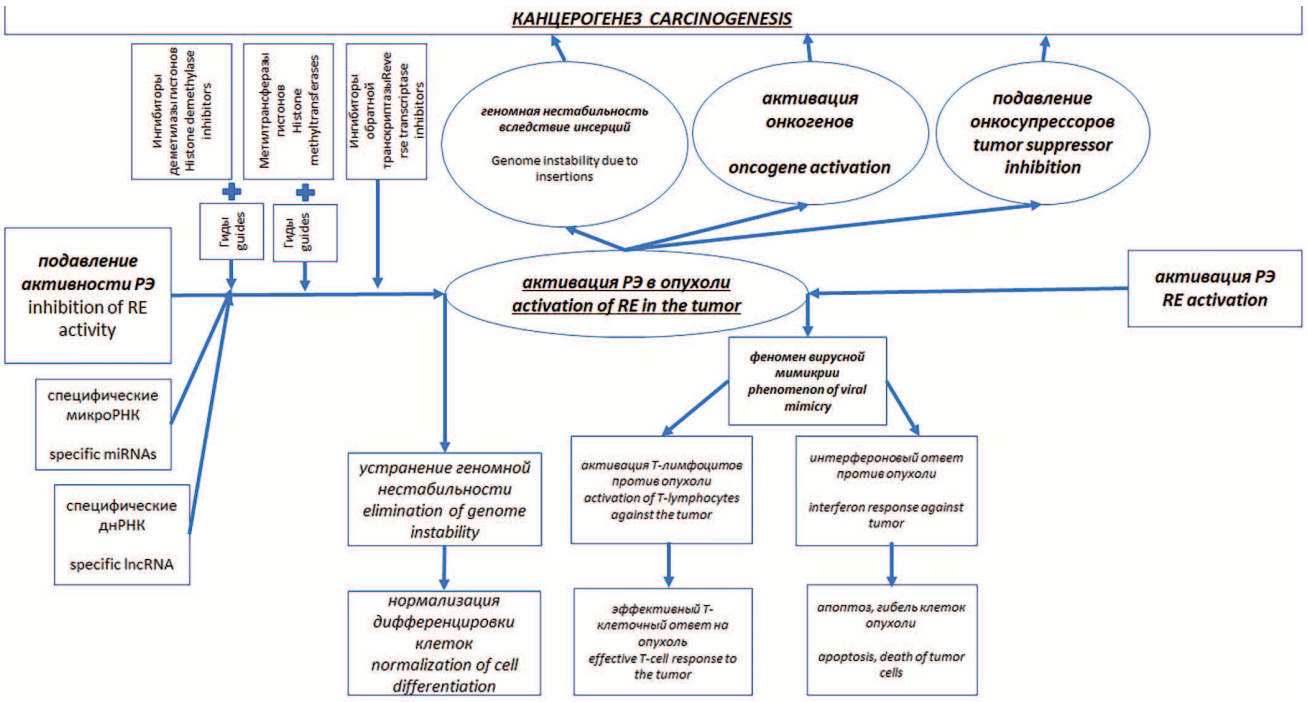

Figure 4. *Scheme of retroelement-targeted antitumor therapy*

Conclusion

Since the anti-PD-1/PD-L1 method is ineffective when used alone, and in combination with anticancer agents, it leads to serious complications, the search for more effective and fewer toxic options is required. The method of viral mimicry is based on activation of RE expression in the tumor, which stimulates the MN immune response. For this purpose, DNA methyltransferase, histone deacetylase and histone methyltransferase inhibitors are used to activate RE and trigger an antitumor interferon response. Splicing targeting therapy is a variant of viral mimicry, in which the targets for the immune response are introns inserted into REs or introns evolved from REs. Since abnormal activation of REs plays a significant role in MN etiopathogenesis, the method of viral mimicry may be most safe when used in combination with agents suppressing the activity of specific REs and their insertion. Reverse transcriptase inhibitors, which are used in clinical practice, can be also used for this purpose. The use of histone demethylase and histone methyltransferase inhibitors, as well as the method of viral mimicry, can be most promising when used in combination with guides (microRNA, lncRNA or ASO) that can recruit histone modification enzyme and DNA into the RE loci playing a certain role in tumor etiopathogenesis (in RE inhibition) or having the greatest clinical significance in the immune response (in RE activation).

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DOI: 10.20514/2226-6704-2023-13-3-175-180
УДК 616.1/.9-085.212-06:616.831-009.7
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ЛЕКАРСТВЕННО-ИНДУЦИРОВАННАЯ ГОЛОВНАЯ БОЛЬ (ОБЗОР ЛИТЕРАТУРЫ И РЕКОМЕНДАЦИИ ДЛЯ ПРАКТИКИ)

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Medication-Overuse Headache (Review of Literature and Recommendations for Practice)

Резюме

Лекарственно-индуцированная головная боль (ЛИГБ) является распространенной вторичной цефалгией, развивающейся у пациентов с частыми и хроническими головными болями при злоупотреблении анальгетическими препаратами и приводящей к значительному ухудшению качества жизни пациентов. Терапия ЛИГБ требует высокой степени комплаентности в отношениях врач-пациент и не всегда приводит к удовлетворительному результату. Поэтому важной задачей является профилактика излишне частого применения симптоматических средств для купирования головной боли. В обзоре представлены современные данные о ЛИГБ, ее лечении и профилактике.

Ключевые слова: *лекарственно-индуцированная головная боль; анальгетические препараты; лечение; профилактика*

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

Статья получена 26.01.2023 г.
Принята к публикации 10.04.2023 г.

Для цитирования: Старикова Н.Л. ЛЕКАРСТВЕННО-ИНДУЦИРОВАННАЯ ГОЛОВНАЯ БОЛЬ (ОБЗОР ЛИТЕРАТУРЫ И РЕКОМЕНДАЦИИ ДЛЯ ПРАКТИКИ). Архивъ внутренней медицины. 2023; 13(3): 175-180. DOI: 10.20514/2226-6704-2023-13-3-175-180. EDN: FEKKPE

Abstract

Medication-overuse headache (MOH) is a highly prevalent secondary headache, developing in patients with frequent and chronic cephalalgias due to excessive use of "acute" medications for headache, and significantly affecting patients' quality of life. Treatment of MOH demands high compliance physician-patient, and the result is satisfactory not in all cases. For this reason, the prophylaxis of overuse of symptomatic medications for headaches is important. The review presents contemporary data on MOH, its treatment and prophylaxis.

Key words: *medication-overuse headache, analgesic medications, treatment, prophylaxis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 26.01.2023
Accepted for publication on 10.04.2023

For citation: Starikova N.L. Medication-Overuse Headache (Review of Literature and Recommendations for Practice). The Russian Archives of Internal Medicine. 2023; 13(3): 175-180. DOI: 10.20514/2226-6704-2023-13-3-175-180. EDN: FEKKPE

fMRI — functional MRI, HA — headache, DIHA — drug-induced headache

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Introduction

The accessibility of medicinal products for symptomatic treatment of pain caused the spread of their uncontrolled use by patients with variously localised pains and aches. Considering the high incidence of headaches in the population (all types of headache: 47 %, migraines: up to 11–20 %, tension headache: approx. 42 % [1, 2]), their significant effects for patient's daily life as well as emotional and individual traits of persons with primary cephalalgia, the problem of drug-induced headache (DIHA) is gaining in significance. Frequent uncontrolled use of symptomatic agents for headache (HA) management causes more frequent cephalalgia episodes, reduced efficacy of symptomatic painkillers, and transformation of ocassional headache into chronic headache.

In the third edition of the International Classification of Headache Disorders [3], drug-induced headaches are described in Section 8.2.

Diagnostic criteria for DIHA [3]:

A. Chronic headache lasting for 15+ days per month in a patient with previous headaches

B. Regular abuse of one or several painkillers for symptomatic management of headaches for over three months

C. Headache cannot be explained by any other diagnosis from the International Classification.

Drug abuse means taking painkillers for 10 (triptanes, ergotamines, combined pain killers) or 15 (simple painkillers and NSAIDs) days per month, depending on teh drug.

DIHAs are classified according to abuse of certain painkillers and can develop in case of frequent use of any of them — ergotamines, triptanes, non-opioid analgesics, paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (including aspirin), combined painkillers. Sub-section 8.2.6. of the Classification is of special interest; it is dedicated to abuse of several drug classes without abuse of each of them. What is meant here is a common clinical case when a patient alternates several medications.

Considering that DIHA develops in the patient with existing headache, the patient is diagnosed with both clinical diagnosis — primary cephalalgia and DIHA.

Epidemiology

The incidence of drug-induced headaches in the population is 1–7 % [4, 5], teh condition prevails in women with a ratio of 4:1 [6]. However, the incidence of DIHA in patients with headaches, especially with chronic migraines, is significantly higher [5].

According to international study results, DIHA is a global issue affecting daily life of approx. 60 million of patients, while social and economic implications of DIHA (disability, drug therapy, medical assistance) are three times higher than in migraines [7]. Of note, according to the World Health Organisation, migraines are among the top 10 conditions affecting patient's life.

Etiology

DIHA usually develops as a result of progression of frequent occasional or chronic headaches. The main cause of DIHA is chronic migraine leading to frequent use of symptomatic painkillers, including triptanes and combined painkillers; however, DIHA can be caused by other variants of frequent and chronic cephalalgia (tension headache, headache associated with vascular diseases, etc.).

In 2020, Salhofer-Polanyi S, et al. published results of a 32-year retrospective analysis of drugs abused by 787 patients of a specialised headache center, who had DIHA. In 2004–2015, patients usually used ordinary painkillers (54.4 %) and simple painkillers (33.5 %), triptanes (31.9 %) and ergotamines (8.2 %) were less common. At the same time, 53 % of patients were diagnosed with abuse of two or more drug classes [8]. The risk of DIHA from a new class of antimigraine agents — ditans (not registered in Russia) has also been studied [9].

It is worth mentioning that the structure of this list of drugs has gradually changed: ergotamines are now used less frequently; there are more and more patients with abuse of triptanes (also in Russia, resulting from teh availability of cheaper generics) or of several classes of painkillers.

NSAIDs and paracetamol are associated with a lower risk of DIHA, whereas triptanes easily cause DIHA. However, headaches caused by abuse of triptanes react to therapy better and have a shorter withdrawal headache period [8, 10, 11].

DIHA pathogenesis is still not clear. It is assumed that a certain role is played by genetics, in particular by polymorphism of dopaminergic system genes (DRD4, DRD2, COMT, SLC6A3) and genes associated with addictive state mechanisms [12]. However, the number of study subjects and the quality of evidence did not allow making clear conclusion from the metaanalysis [12].

It is believed that frequent and excessive use of medications is facilitated by emotional and personal factors, e.g. [13]:

1. Desire to reduce pain and have normal daily activities
2. Fear/anxiety because of pain
3. Presence of withdrawal headache

4. Comorbid depression and anxiety
5. Presence/susceptibility to addictive states.

As a result, patients start taking painkillers not only at onset of headache, but also in advance, believing it to be for prevention purposes.

DIHA pathophysiology is not clear. Probably, painkillers provide a basis for DIHA by interacting with neurotransmitter systems [5]. It is assumed that excessive use of painkillers for headaches causes dysregulation of descending nociception inhibiting control [14,15], impaired functional links in the brain with formation of abnormal neuronal networks and changes in nociception information processing [16], lower pain threshold, and increased expression of 5HT2a serotonin receptors in the cortex and trigeminal ganglion [11].

A major part in development of chronic pain syndromes is played by central sensitisation, i.e., a long-term (however reversible) increase in neuron irritation in the central nociceptive structures as a result of repeated nociceptive stimulation. The mechanisms of this phenomenon include imbalance between excitatory and inhibitory neurotransmitters, neuronal and synaptic plasticity, and impaired glia–neuron connections [15]. Central sensitisation syndromes can also include chronic cephalalgia (chronic migraine, chronic tension headache, and DIHA) [17]. A clinical marker of central sensitisation is dermal allodynia (dermal pain from non-pain stimuli), observed in 50–80 % of patients with migraine and it is a predictor of condition perpetuation [11].

Since not all patients with abuse of painkillers in accordance with the International Classification develop DIHA, a primary task for further studies is development of a marker (either a biochemical or neuroimaging), that could help in identification of patients with true or potential DIHA [18]. Morphometric studies demonstrated that patients with DIHA (vs. healthy subjects) have a larger amount of cerebrum in ventral striatum (an area participating in behavioural activities of reward and addiction) [19] and a smaller amount in frontoorbital area (an area of the mesocortical-limbic system also involved in addictive behaviour) [20]. Functional MRI (fMRI) showed higher neuronal activity in thalamus [21].In magnetic resonance spectroscopy, Niddam et al. observed several markers (N-acetyl aspartate, myo inositol) in patients with DIHA and concluded that they could contribute to disease development [22].

Unfortunately, currently neither structural nor biochemical markers have clinical application.

Factors associated with DIHA development

It is still not clear why DIHA develops in some patients with primary cephalalgia and does not affect others. Viana M, et al. [23] reported results of an examination of 318 patients with long-lasting (over 10 years) migraines. DIHA was observed in a half of them (162 patients); mean migraine duration was similar both with and without DIHA. Factors associated with DIHA development were reported both as highly expected (low physical activity, history of depression, insomnia, brain injury) and unexpected, e.g., marital status (DIHA was more frequent in married and divorced persons than in single subjects) and younger age at migraine onset. In this study, we have not found any correlation between DIHA and patient sex, body weight index, coffee and alcohol consumption or smoking [23]. Also, another risk factor is lower level of education and chronic gastrointestinal conditions.

The most significant risk factor for DIHA is the frequency of primary headache episodes [24]. Therefore, there is still a point of issue: Is the frequent use of painkillers a cause or a consequence of headache perpetuation [18, 23]? However, it has been proven that an efficient therapy for DIHA is withdrawal of contributing painkillers; therefore, their role in condition pathogenesis has been verified.

At the same time, discussions of the role of depression and anxiety in development of chronic cephalalgia, particularly of DIHA [13, 25], have been observed in literature. According to COMOESTAS study results, high levels of anxiety were found in 57.7 % and depression — in 40 % out of 492 patients with DIHA [26]; however, no association was observed between anxiety/depression and number of days of headache duration. According to Park H-K et al. [27], depression was diagnosed in 83 % out of 229 patients with DIHA, anxiety — in 62 %.

DIHA is a biobehavioural disorder facilitated by personal traits and behavioural patterns of patients [28, 29]. It was noted that up to 50 % of patients with DIHA demonstrate addictive behavior, reduced or lost control of the use of painkillers [5], i.e., they take painkillers as a ritual [11].

Therapeutic strategy in DIHA

For DIHA management, it is essential to create trust relationship between the doctor and the patient and to clearly explain to the patient the mechanism of abnormal association between drug intake and increased frequency of headaches.

During an information talk, it is recommended to tell the patient about the following aspects [13]:

1. The role of excessive use of symptomatic painkillers in higher frequency and severity of pain and in potential reduction in the efficacy of other therapies.

2. Possible DIHA development even if painkillers are taken 2–3 times a week
3. Discussion of withdrawal headache, i.e., temporary deterioration of patient's condition when contributing medications are discontinued
4. Information on the maximum frequency of symptomatic painkillers and inadmissibility of the use in anticipation of headache.

The objective of DIHA treatment is reduction of the frequency of headaches, reduction in the use of painkillers, and improved therapeutic response to preventive and symptomatic therapy. Treatment includes discontinuation (single-step or gradual) of contributing drugs, a course of preventive therapy, and arrest of withdrawal symptoms.

Drugs can be discontinued in a single step or their frequency can be gradually reduced. Both strategies have advantages and disadvantages. A single-step withdrawal is more efficient and usually causes marked withdrawal symptoms resulting in reduced compliance. Gradual withdrawal is easier for a patient, however, it bears a risk of voluntary increase in the frequency of drugs and return to the previous abuse pattern. Nielsen M, et al. [30] evaluated results of drug discontinuation (complete withdrawal or reduced frequency, follow-up duration: 6–12 months) in 72 patients with DIHA and concluded that complete withdrawal from symptomatic painkillers is most efficient. At the same time, researchers demonstrated that the mean efficiency of the painkiller discontinuation program is still low, just approx. 30 % [31]. Therefore, the search for the ways to increase efficiency has continued.

In addition to withdrawal from contributing drugs, patients are also recommended to undergo a course of preventive therapy with proven efficiency. A list of drugs depends on the primary headache: topiramate, beta-blockers, amitriptyline in migraines; antidepressant drugs (primarily cyclic ones) in tension headaches [18,32]. According to the international multicenter analysis of DIHA register, in real life, most common are antiepilepsy drugs (25 %), beta-blockers (13 %), tricyclic antidepressants (12 %), botulinum toxin A (9 %), monoclonal anti-CGRP antibodies (7 %), calcium-channel blockers (6 %), angiotensin II receptor blockers (2 %), and selective serotonin reuptake inhibitors (1 %) [27]. Medications with the highest level of evidence in DIHA are topiramate and onabotulinumtoxin A [18], as well as monoclonal anti-CGRP antibodies (fremanezumab, frenumab), which are new target drugs for the treatment of episodic and chronic migraine, including with DIHA [33]. Of note, neurometabolic drugs commonly used in Russia are not indicated in DIHA or primary cephalalgia.

Specific time limits for preventive therapy are to be discussed. It can start on the first day following painkiller discontinuation or at a later date [18, 32]. Delayed therapy initiation may be due to the fact that later approximately a half of patients do not need it [34]. Patient management and support in their efforts to overcome medication abuse are essential.

It is also recommended to arrange for detoxication therapeutic programs [32], that include, in addition to discontinuation or limitation of painkillers, a course of preventive therapy, corticosteroids (prednisolone), and fluid resuscitation [34-36]. Such programs can be organised either in outpatient or inpatient settings. A short-term inpatient treatment is especially indicated for patients with depression and anxiety and chronic stress situations [8]. During first days after symptomatic drug discontinuation, naprosine, acetaminophen, promethazine, metoclopramide can be prescribed to relieve withdrawal symptoms. There are reports of long-term efficacy of detoxication programs when patients are followed up for 6 months [26] and 5 years [37].

As far as non-drug non-invasive methods of chronic headache management are concerned, most interesting are repetitive transcranial magnetic stimulation [38], feedback methods (computer-aided biocontrol and mobile apps for behavior therapy) [39] and transcutaneous trifacial electrical stimulation — Cefaly [40].

Prognosis

Therapeutic measures in DIHA do not always ensure long-term success. Prospective studies demonstrate that 20–30–50 % of patients continue abusing medications [5, 23, 41]; there is also a 25–45 % probability of DIHA recurrence in years after successful discontinuation of contributing painkillers [18,42]. Usually recurrences develop within a year after withdrawal; in case of a recurrence, a majority of patients continue abusing the same medications they used before their diagnosis [43]. Another attempt to discontinue medications usually causes a negative reaction from patients. This is another proof of the need in long-term and regular follow-up of patients after therapy [44]. Moreover, it is essential to identify and correct comorbid anxiety, psychological dependence, pain catastrophizing [11].

Prognostically favourable factors are successful discontinuation of contributing drugs and absence of chronic headache by the end of the first year after withdrawal [41, 43].

DIHA prevention consists of identification of a drug dependence risk group and face-to-face work with the patient including educational measures [5]. It is believed that a majority of DIHA cases can be avoided with the help of timely preventive measures. Patients should be advised to minimise symptomatic medications for

headache. The national DIHA prevention program initiated in Denmark includes not only face-to-face work with patients, but also development of awareness on admissible use of painkillers through mass media, online resources, pharmacies, and primary healthcare professionals [7]. In Russia, the TV slogan "headache cannot be tolerated" should be declared incorrect, and patients should receive appropriate information. Another important prevention method is timely prescription of a course of headache prevention with proven efficacy. Studies show that, before going to a specialised center, just 21–38 % of patients undergo preventive therapy for cephalalgia [8,27]; lack of preventive therapy eventually results in chronic headaches.

Conclusion and practical recommendations

Drug-induced headache is a common secondary cephalalgia leading to a poorer quality of patients' life. DIHA therapy requires good compliance and not always gives satisfactory results. Therefore, it is essential to prevent excessively frequent use of symptomatic agents to manage headache. The most important part of this work is making the community aware of unfavourable consequences of frequent use of painkillers. Patients should be aware that, in accordance with international standards, the highest frequency of symptomatic medications for headaches is 2 days per week and that not all types of headaches are indications for painkillers.

The objective of this publication is to inform GPs of drug-induced headaches.

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DOI: 10.20514/2226-6704-2023-13-3-181-195
УДК 616.127-007.61-036-07
EDN: GGLHPG

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ОСОБЕННОСТИ ДИАГНОСТИКИ И ТЕЧЕНИЯ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Features of Diagnostics and Course of Hypertrophic Cardiomyopathy in Real Clinical Practice

Резюме

Введение и цель. Гипертрофическая кардиомиопатия (ГКМП) характеризуется наличием утолщения стенки левого желудочка (ЛЖ), не связанного с увеличением постнагрузки (артериальной гипертензией и стенозом устья аорты). В большинстве случаев ГКМП обусловлена мутациями в генах саркомерных белков и наследуется по аутосомно-доминантному механизму. В ряде случаев ГКМП может быть обусловлена накоплением в миокарде таких веществ, как амилоид, гликоген и др. Целью нашей работы стало проанализировать особенности диагностики и течения ГКМП в реальной клинической практике. **Материал и методы.** Проведен ретроспективный анализ медицинской документации 80 пациентов (56,3 % мужчин) с ГКМП, диагностированной в многопрофильном стационаре г. Москвы в период с 2007 по 2021 год. Диагноз ГКМП у всех пациентов был установлен на основании данных эхокардиографии. Медиана (здесь и далее в скобках указаны 25- и 75-процентили) возраста составила 57 (48,5; 63) лет. Продолжительность госпитализации составила 8 (6; 12,5) дней. **Результаты.** Причиной госпитализации являлись синдром стенокардии у 35 %, подозрение на острый коронарный синдром у 16,3 %, пароксизм фибрилляции предсердий (ФП) у 11,3 %, другие нарушения ритма у 2,5 %, декомпенсация хронической сердечной недостаточности у 11,3 %, обмороки у 7,5 %, гипертонический криз у 3,8 %, необходимость проведения коронароангиографии у 3,8 %, постановки электрокардиостимулятора у 2,5 %, имплантации кардиовертера-дефибриллятора у 1,2 %, медицинского освидетельствования для решения вопроса о годности к воинской службе у 1,2 %, острое нарушение мозгового кровообращения у 1,2 %, гипотония у 1,2 %, лекарственная брадикардия у 1,2 % пациентов. До анализируемой госпитализации инфаркт миокарда в анамнезе был диагностирован у 15 %, артериальная гипертензия — у 53,8 %, хроническая сердечная недостаточность — у 77,6 %, хроническая болезнь почек — у 21,3 % пациентов. Толщина стенки ЛЖ ≥1,5 см выявлена у 91,2 %. Симметричная форма гипертрофии ЛЖ имела место у 22,1 %, апикальная — у 5,2 %, гипертрофия папиллярной мышцы — у 1,3 %, ассиметричная гипертрофия межжелудочковой перегородки — у 71,4 % пациентов. Постоянная обструкция выносящего тракта ЛЖ (ОВТ ЛЖ) выявлена у 62,8 % (9,0 % пациентов была выполнена септальная редукция в анамнезе), преходящая ОВТ ЛЖ — у 1,3 %, необструктивная ГКМП — у 35,9 %. Фракция выброса (ФВ) ЛЖ (по Симпсону) составила 63 (55-70)%, ХСН со сниженной ФВ ЛЖ <40 % выявлена у 3,8 %, с умеренно сниженной ФВ ЛЖ (40-49 %) — у 5 %, с сохраненной ФВ ЛЖ — у 68,8 % пациентов. У 47,5 % имело место переднесистолическое

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движение передней створки митрального клапана, у 7,14 % описано пролабирование передней створки митрального клапана. Митральная регургитация зарегистрирована у 75 % пациентов. Фибрилляцией предсердий (ФП) страдали 45 % пациентов с ГКМП: постоянной формой 15 %, пароксизмальной 23,8 %, персистирующей 6,2 % пациентов. За время госпитализации желудочковая тахикардия зарегистрирована у 7,5 %, наджелудочковая тахикардия — у 3,8 %. Нарушения проводимости отмечены у 36,3 % пациентов, из них атриовентрикулярная блокада у 6,3 %, блокада правой ножки пучка Гиса у 21,3 %, левой ножки — у 15 %, синдром Вольффа–Паркинсона–Уайта — у 1,3 %. Имплантация электрокардиостимулятора в анамнезе была у 5 %, в том числе в связи с приступами Морганьи-Эдамса-Стокса — у 3,8 % пациентов. За время наблюдения, медиана которого составила 87 (интерквартильный размах 45-131,5) месяцев, умерло 13,8 % пациентов с ГКМП. У умерших пациентов достоверно чаще встречалась ОВТ ЛЖ (у умерших 100 %, у живых 58,2 %, p = 0,006) и ФП (у умерших 72,7 %, у живых 40,6 %, p=0,047). Генетическое тестирование и исключение фенокопий ГКМП не было проведено во время госпитализации и не было рекомендовано ни одному больному. **Заключение.** В реальной клинической практике в большинстве случаев проводится лишь фенотипическая диагностика ГКМП по данным эхокардиографии, не проводится скрининг на генетические мутации и инфильтративные заболевания сердца, фенотипически неотличимые от ГКМП. Необходимо широкое внедрение генетического тестирования и скрининга на инфильтративные заболевания сердца для своевременной диагностики патологии, требующей назначения специфической патогенетической терапии для улучшения прогноза пациентов.

Ключевые слова: *инфильтративные заболевания сердца, гипертрофическая кардиомиопатия, хроническая сердечная недостаточность, фенокопии, генетика, вторичная ГКМП, амилоидоз, болезнь Фабри*

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

Статья получена 10.07.2022 г.
Принята к публикации 15.02.2023 г.

Для цитирования: Резник Е.В., Нгуен Т.Л., Дикаева М.С. и др. ОСОБЕННОСТИ ДИАГНОСТИКИ И ТЕЧЕНИЯ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ. Архивъ внутренней медицины. 2023; 13(3): 181-195. DOI: 10.20514/2226-6704-2023-13-3-181-195. EDN: GGLHPG

Abstract

Introduction and purpose. Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular (LV) wall thickening not associated with increased afterload (hypertension and aortic stenosis), is usually caused by mutations in sarcomeric protein genes, and is inherited in an autosomal dominant manner. Unlike HCM, myocardial hypertrophy in its phenocopies is associated with the accumulation of substances such as amyloid, glycogen, etc. in the myocardium. The aim of our work was to analyze the features of the diagnosis and course of HCM in real clinical practice. **Material and methods.** A retrospective analysis of medical records of 80 patients (56.3 % of men) discharged with a diagnosis of HCM from a multidisciplinary hospital in Moscow in the period from 2007 to 2021 was carried out. The diagnosis of HCM in all patients was established on the basis of echocardiography data. The median age (25th and 75th percentiles are indicated in brackets) was 57 (48.5; 63) years. The duration of hospitalization was 8 (6; 12.5) days. **Results.** The reason for hospitalization was angina syndrome in 35 %, suspicion of acute coronary syndrome in 16.3 %, paroxysmal atrial fibrillation (AF) in 11.3 %, decompensation of chronic heart failure in 11.3 %, syncope in 7.5 % %, hypertensive crisis in 3.8 %, coronary angiography in 3.8 %, pacemaker implantation in 2.5 %, consultation with an arrhythmologist in 2.5 %, implantation of a cardioverter-defibrillator in 1.2 %, medical examination to resolve the issue of fitness for military service in 1.2 %, acute cerebrovascular accident in 1.2 %, hypotension in 1.2 %, drug bradycardia in 1.2 % of patients. Before hospitalization, a history of myocardial infarction was diagnosed in 15 %, arterial hypertension — in 53.8 %, chronic heart failure — in 77.6 %, chronic kidney disease — in 21.3 % of patients. Prior to the analyzed hospitalization, a history of myocardial infarction was diagnosed in 15 %, arterial hypertension in 53.8 %, chronic heart failure in 77.6 %, chronic kidney disease in 21.3 % of patients. LV wall thickness ≥1.5 cm was detected in 91.2 %, symmetrical form of hypertrophy — 22.1 %, apical — 5.2 %, papillary muscle hypertrophy — 1.3 %, interventricular septum — 71.4 % of patients. Permanent obstruction of the LV outflow tract (LVOTO) was detected in 62.8 % (9.0 % of patients had a history of septal reduction), transient LVOTO — in 1.3 %, non-obstructive HCM — in 35.9 %. The ejection fraction (EF) of the LV (according to Simpson) was 63 (55-70) %, CHF with reduced LV EF <40 % was detected in 3.8 %, with a moderately reduced LV EF (40-49 %) — in 5 %, with preserved LV EF — in 68.8 % of patients. Anterior systolic movement of the anterior leaflet of the mitral valve occurred in 47.5 %, prolapse of the anterior leaflet of the mitral valve was described in 7.14 %. Mitral regurgitation was registered in 75 % of patients. 45 % of patients with HCM suffered from AF: permanent 15 %, paroxysmal 23.8 %, persistent 6.2 % of patients. During hospitalization, ventricular tachycardia was registered in 7.5 %, supraventricular tachycardia — 3.8 %, conduction disturbances were noted in 36.3 % of patients, of which atrioventricular block in 6.3 %, blockade of the right bundle branch block in 21.3 %, left bundle branch block in 15 %, and Wolff-Parkinson-White syndrome in 1.3 % . Implantation of a pacemaker in history was in 5 %, including in connection with Morgagni-Adams-Stokes attacks — in 3.8 % of patients. During a median follow-up of 87 (interquartile range 45–131.5) months, 13.8 % of patients with HCM died. In deceased patients, LVOTO was significantly more common (in the dead 100 %, in the living 58.2 %, p = 0.006) and AF (in the dead 72.7 %, in the living 40.6 %, p = 0.047). Genetic testing and exclusion of HCM phenocopies was not performed during hospitalization and was not recommended for any patient. **Conclusion.** In real clinical practice, in most cases, only phenotypic diagnosis of HCM is carried out according to echocardiography, and screening for genetic mutations and HCM phenocopies is not performed. It is necessary to widely introduce genetic testing and screening for HCM phenocopies for the timely diagnosis of pathology that requires the appointment of specific pathogenetic therapy to improve the prognosis of patients.

Key words: *infiltrative heart disease, hypertrophic cardiomyopathy, chronic heart failure, phenocopies, genetics, secondary HCM, amyloidosis, Fabry disease*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 10.07.2022
Accepted for publication on 15.02.2023

For citation: Reznik E.V., Nguyen T.L., Dikaeva M.S. et al. Features of Diagnostics and Course of Hypertrophic Cardiomyopathy in Real Clinical Practice. The Russian Archives of Internal Medicine. 2023; 13(3): 181-195. DOI: 10.20514/2226-6704-2023-13-3-181-195. EDN: GGLHPG

HCM — hypertrophic cardiomyopathy, LV –left ventricle, EF — ejection fraction, CHF — chronic heart failure, CHFpEF — chronic heart failure with preserved ejection fraction, ECG — electrocardiogram, EchoCG — echocardiography, NT-proBNP — N-terminal pro brain natriuretic peptide, hsTn — high sensitive troponin, LVH — left ventricular hypertrophy, AF — atrial fibrillation, CAG — coronary angiography, AH — arterial hypertension, GFR — glomerular filtration rate, LVOTO — left ventricular outflow tract obstruction

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease worldwide. Its prevalence in the general population is 1 per 500 people [1]. This heart disorder is characterized by unexplained left ventricular hypertrophy (LVH) in the absence of other cardiac and noncardiac conditions that could lead to its development [1]. Hypertrophic cardiomyopathy caused by mutations of genes encoding the sarcomere proteins or associated to it account for more than half of all disease case [1]. There have been 1,500 mutations identified in at least 15 genes encoding the sarcomere proteins [1].

One of the criteria for HCM diagnosis in adults is increased wall thickness ≥15 mm in one or more LV segments (determined by any visualization methods: EchoCG, MRI/CT), which cannot be explained by an increase in pressure load alone [1]. In some patients, atypical HCM is reported, which is manifested as less pronounced LVH, concentric LVH, apical hypertrophy, left ventricular outflow tract obstruction with systolic anterior motion of the anterior mitral leaflet, provided that a high risk of sudden death persists [1]. In some cases, it is difficult to differentiate HCM from hypertensive or athlete's heart.

Moreover, a pronounced increased LV wall thickness can be observed in some infiltrative heart diseases, which are called HCM phenocopies. They include several disorders such as glycogen storage disorders, mucopolysaccharidosis, amyloidosis, Fabry disease, etc. [1–3] Hypertrophic cardiomyopathy and its phenocopies differ both in hypertrophy pathogenesis and clinical features, course, and prognosis, due to which both clinical and molecular genetic diagnosis is required to establish HCM in clinical practice.

The study is aimed at analyzing the specificity of HCM diagnosis and course in real-life clinical practice.

Materials and methods

A prospective, cross-sectional study was performed. The analysis included all cases of HCM diagnosis following the results of electronic database of the multi-speciality hospital for the period 2007 through 2021 and medical records of the specified 80 patients (43.7 % women, 56.3 % men) with HCM. The HCM diagnosis was established based on echocardiographic (EchCG) data. Maximum LV wall thickness at diastole ≥15 mm, unexplained by abnormal pre- and postload [4], or LV wall thickness at diastole ≥13 mm in relatives of persons with HCM or in persons with a positive genotype[5] were used as diagnostic criteria for HCM.

The median age in patients with HCM was 57 years (hereinafter, an interquartile range 48.5; 63 is given in the brackets). Among patients with HCM, men slightly prevailed: 56.3 % (n = 45). Causes of hospitalization in patients with HCM were diverse, including angina pectoris in 28 (35 %), acute coronary syndrome in 13 (16.3 %), paroxysmal atrial fibrillation (AF) in 9 (11.3 %), decompensated chronic heart failure (CHF) in 9 (11.3 %), syncope and presyncope in 6 (7.5 %) patients (Figure 1).

A post hoc analysis of EchoCG findings obtained by highly qualified specialists using ultrasonic diagnostic apparatuses of expert class. All LV measurements were performed in accordance with the guidelines of the American Society of Echocardiography. LV ejection fraction (EF) was measured using the biplane method of disks (modified Simpson method). The left ventricular outflow tract obstruction (LVOTO) was diagnosed using the Doppler echocardiography at maximum (peak) pressure gradient in the left ventricular outflow tract ≥30 mm Hg at rest or during provocative testing. Asymmetrical septal HCM was diagnosed at interventricular septum (IVS) thickness ≥15 mm and the ratio of IVS/LV posterior wall thickness ≥1.3 [1]. Apical HCM was diagnosed in patients with LV hypertrophy limited to left ventricular apex [1]. Images for papillary muscle measurements were obtained from the parasternal short axis projection. The maximum diameters of the anterolateral and posteromedial papillary muscles were measured at the midline in the parasternal short axis view at the end of diastole. The horizontal diameter was measured in parallel with a line drawn between the center of the LV cavity and the papillary muscle at the point of its attachment to the LV wall. The vertical diameter was measured perpendicular to the above-described line.

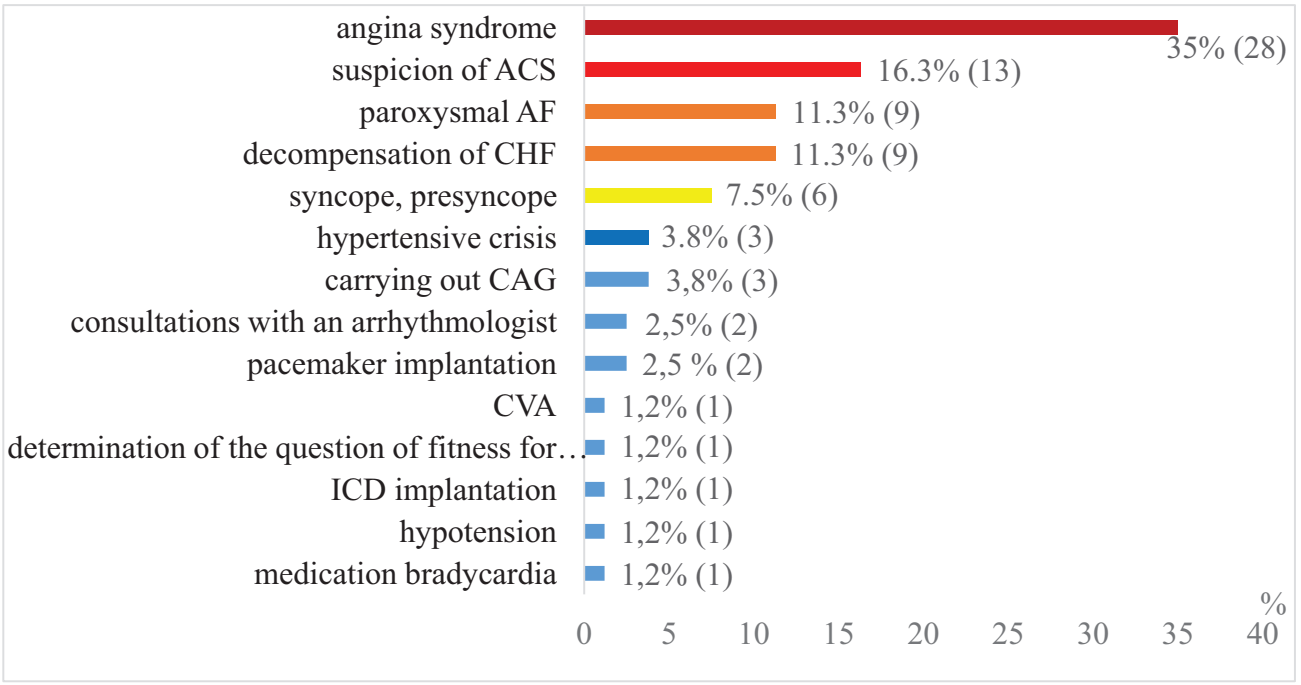

Figure 1. *Reasons for hospitalization in patients with HCM*
Note: ACS — acute coronary syndrome, AF — atrial fibrillation, CHF — chronic heart failure, CAG — coronary angiography, CVA — acute cerebrovascular accident, ICD — implantable cardioverter-defibrillator

According to the Kobayashi criteria, papillary muscle hypertrophy was defined by a diameter ≥11 mm of at least one papillary muscle in the horizontal or vertical direction or in both directions [5]. The pulmonary artery systolic pressure (PASP) was estimated noninvasively using transthoracic echocardiographic data on peak tricuspid regurgitation rate, taking into account the diameter of inferior vena cava and its collapse during inspiration. Pulmonary hypertension was diagnosed at values >30 mm Hg.

The analysis included all available electrocardiograms (ECG); Cornell criteria, Sokolow-Lyon index, and electrocardiographic QRS voltage were assessed. The voltage in extremity leads <5 mm or precordial leads <10 mm was considered low [2]. QRS complex that are ventricular in origin and artifacts were disregarded.

The glomerular filtration rate (GFR) was calculated using the CKD-EPI formula to assess the functional state of the kidneys. The presence and severity of proteinuria were evaluated based on the urinalysis findings. The data obtained in the laboratory investigations conducted during and before the index hospitalization were regarded. A clinical and instrumental criterion for chronic kidney disease (CKD) was a persistent decrease in GFR <60 mL/min/1.73 m^2 and/or urine markers of kidney injury for 3 months or more. The levels of N-terminal pro brain natriuretic peptide (NT-proBNP), serum troponin, and urinary albumin excretion were not assessed for technical reasons.

In real-life clinical practice, no genetic testing or exclusion of HCM phenocopies was performed in any patient. In 2020-2022, to exclude HCM phenocopies in 55 patients with LVH (including 5 (9.1 %) of the patients analyzed above), genetic testing was performed as part of the research work at the Department of Propaedeutics of Internal Medicine, Faculty of Medicine, N.I. Pirogov Russian National Research Medical University, Ministry of Health of the Russian Federation.

Patients' prognosis was assessed via telephone calls and analysis of available medical records 87 (45–131.5) months later. The endpoint was all-cause mortality.

Statistical analysis was performed using SPSS 26 software. Since some of the obtained data did not follow the normal distribution law, non-parametric methods were used. The central tendency and attribute variance are presented as the median and the interquartile range. Intergroup differences in two independent groups were assessed using the Mann–Whitney test. In the qualitative data analysis, the absolute and relative frequencies were determined for each attribute value. When comparing the relative frequencies of the attribute in two groups and the correlation coefficients, hypotheses of their equality were tested using a two-tailed statistical significance test. The chi-square test (maximum likelihood method) was used to compare groups by qualitative characteristics. The patients' survival rate was assessed using the Kaplan–Meier survival curves. The level $p<0.05$ was considered statistically significant.

Results

Over the period 2007 to 2021, in one of the multispeciality hospitals in Moscow, HCM was diagnosed in 80/560,901 hospitalized patients (0.0143 %; 14.3/100,000 patients/year, 1:6,993 of hospitalized patients a year). All patients with HCM were discharged from the Cardiology Department (Table 1).

On admission to hospital, complaints of angina pain/heaviness in the chest in 44 (55 %) patients with HCM; dyspnea in 41 (51.3 %); weakness and/or fatigue in 30 (37.5 %); palpitation, impaired cardiac function in 25 (31.3 %), fainting/presyncope in 10 (12.5 %), lower extremity edema in 7 (8.8 %) patients.

According to the patients' medical history, 12 (15 %) patients had previously diagnosed miocardial infarction (MI), without significant coronary artery stenosis on coronary angiography in 6 (50 %), with evidence-based coronary artery stenosis in 3 (3.8 %) of them; stenting of the infarct-related artery was performed in 2 (2.5 %) of them.

43 (53.8 %) of patients had a history of arterial hypertension (AH): grade 1 in 6 (7.5 %), grade 2 in 9 (11.3 %), and grade 3 in 28 (35 %) patients. On admission, arterial hypertension was detected in 1 (1.3 %) patient.

14 (17.5 %) of patients with HCM had a history of type 2 diabetes mellitus (DM); impaired glucose tolerance was detected on admission in 10 (12.5 %) patients.

The diagnosis of CHF was recorded in 62 (77.6 %) of patients with HCM: 71.1 % had New-York Heart Association (NYHA) functional class II/III; 61.8 % had stage IIA CHF according to the Vasilenko-Strazhesko classification. Among the signs of CHF, hydrothorax was detected in 5 (8.1 %) patients, of whom 3 (4.8 %) had right-sided hydrothorax; 2 (3.2 %) had bilateral hydrothorax; 7 (11.3 %) had hepatomegaly; 1 (1.6 %) had ascites.

On EchoCG, IVS thickness was 1.8 (1.4–2.3) cm; basal IVS segment thickness was 2.06 (1.8–2.3) cm; LV posterior wall thickness was 1.4 (1.2–1.6) cm. IVS and/or LV posterior wall thickness >1.5 cm was detected in 91.2 % patients with HCM. Symmetric form of HCM in 22.1 %, apical form in 5.2 %, papillary muscle hypertrophy in 1.3 %, IVS hypertrophy in 71.4 % of patients. Obstructive HCM was diagnosed in 64.1 % (latent LV ventricular outflow tract obstruction (LVOTO) was detected in 1.3 %); nonobstructive form was diagnosed in 35.9 % of patients with HCM. A history of septal reduction surgery was recorded in 9.0 % of patients. The median maximum pressure gradient in the left ventricular outflow tract (LVOT) in patients with LVOTO was 53 (28–105) mm Hg; the mean pressure gradient in (LVOT) was 30 (15–49) mm Hg. The left atrium anteroposterior diameter was 4.5 (4.0–5.2) cm; its volume was 102.5 (63–140) mL; the right atrium area was 16 (14.5–22.5) cm^2. The left ventricular end-diastolic diameter was 4.3 (4.0–4.8) cm; its end-diastolic volume was 80 (70–100) mL. LV EF was 63 (55–70)%. Chronic heart failure with reduced LV ejection fraction <40 % was diagnosed in 3 (3.8 %), with moderately reduced LV EF in 4 (5 %), with preserved LV EF(CHFpEF) in 55 (68.8 %) patients (Figure 2).

Table 1. *Frequency of diagnosing HCM in a multidisciplinary hospital for the period from 2007 to 2021*

Year	Number of patients treated in hospital	Number of patients diagnosed with HCM	% of patients diagnosed with HCM among those treated in a hospital	HCM diagnostic frequency/ 100 thousand people/year
2007	20212	6	0,0297	29,70
2008	26134	5	0,0191	19,10
2009	30268	6	0,0198	19,82
2010	28855	8	0,0277	27,72
2011	30569	4	0,0131	13,09
2012	29720	5	0,0168	16,82
2013	30078	6	0,0199	19,95
2014	39735	3	0,0076	7,55
2015	42024	9	0,0214	21,42
2016	46047	4	0,0087	8,69
2017	45909	4	0,0087	8,71
2018	49604	10	0,0202	20,16
2019	47027	5	0,0106	10,63
2020	45206	3	0,0066	6,64
2021	49513	2	0,0040	4,04
2007-2021	**560901**	**80**	**0,0143**	**14,26**

Note: HCM — hypertrophic cardiomyopathy

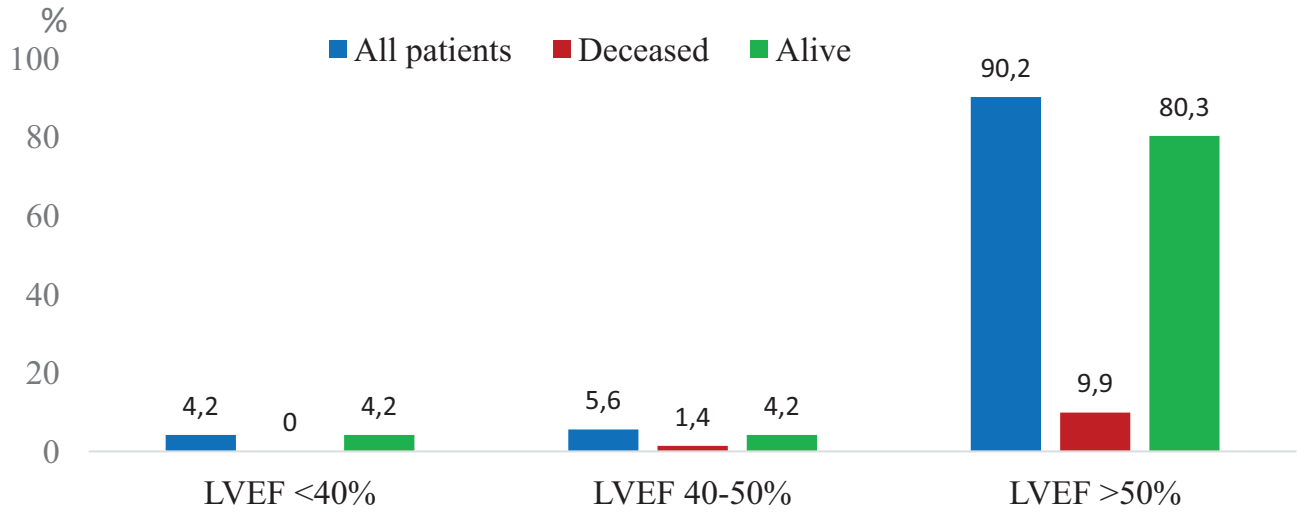

Figure 2. *Systolic function of the left ventricle in patients with HCM*
Note: LVEF — left ventricular ejection fraction

Systolic anterior motion of the mitral leaflet was recorded in 38 (47.5 %) patients. Mitral valve prolapse was recorded in 7.14 % patients. Secondary mitral regurgitation was registered in 60 (75 %) patients.

EchoCG findings revealed calcinosis of cardiac structures in 13 (16.3 %) patients: only calcinosis of mitral valve leaflets in 3 (3.8 %); only calcinosis of aortic valve in 2 (2.5 %); calcinosis of both mitral and aortic valves in 8 (10 %).

Diffuse left ventricular (LV) hypokinesis was detected in 5 (7.2 %) patients, local hypokinesis in 5 (7.2 %); akinesis was detected in 1 (1.4 %) patient (all these patients had a history of myocardial infarction); 2 (2.9 %) patients had LV apical dissynergy against a background of complete left bundle branch block.

Signs of pulmonary hypertension were detected in 21 (35 %) patients, for whom mean pulmonary arterial pressure (MPAP) was calculated; in 20 (33.3 %) patients, MPAP was not recorded in the EchoCG protocol. In patients with HCM, 14 (23.3 %) had grade 1 pulmonary hypertension (MPAP <50 mm Hg), 5 (8.3 %) had grade 2 PH (MPAP 50–80 mm Hg), and 2 (3.4 %) had grade 3 PH (MPAP >80 mm Hg).

Diastolic LV dysfunction was detected in 37 (51.4 %) patients with HCM: 24 (33.3 %) had relaxation disorder, 12 (16.7 %) had pseudonormalization, 1 (1.4 %) had restriction; 5 (6.9 %) had normal diastolic function in their medical records. In 30 (41.7 %) patients, diastolic LV function was not assessed (Figure 3).

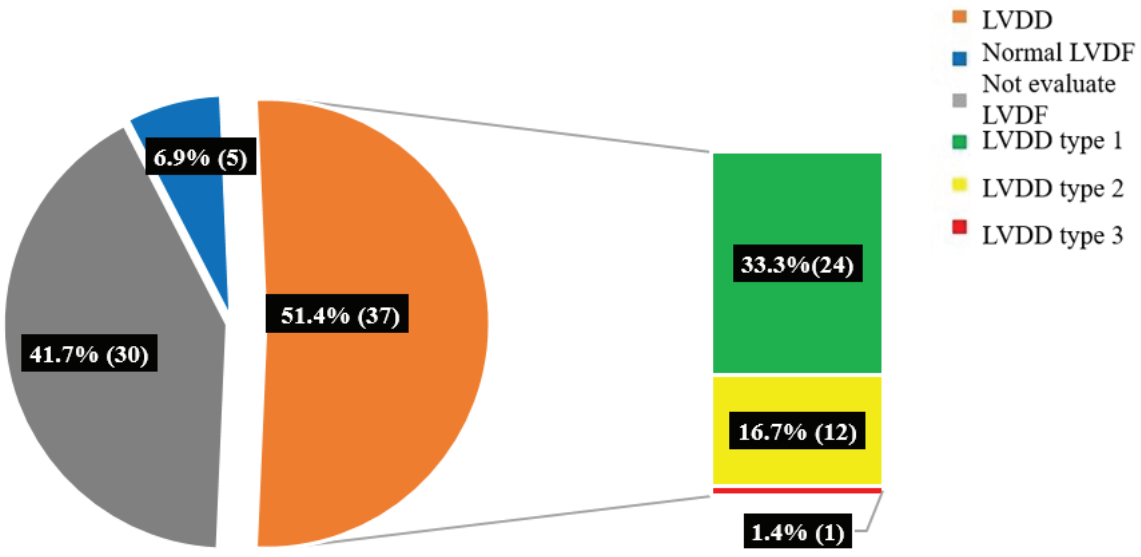

Figure 3. *Diastolic function of the left ventricle in patients with HCM*
Note: LVDD — left ventricular diastolic dysfunction, LVDF — left ventricular diastolic function

Pericardial effusion was detected in 9 (12.5 %) patients.

The analysis of available ECG data recorded during the last hospitalization revealed voltage signs of LVH in 36 (48 %), low-voltage on ECG in 1 (1.3 %) patient (Figure 4). A negative T wave in precordial leads (often in V2–V6) was recorded in 36 (48 %) patients. An abnormal Q wave on ECG was recorded in 8 (10 %) patients (all of them had a history of MI/postinfarction cardiosclerosis (PICS)): 4 (5 %) in inferior leads, 1 (1.3 %) in lateral leads, 2 (2.5 %) in anteroseptal leads and LV apex, 1 (1.3 %) in inferior and lateral leads.

Atrial fibrillation was detected in 36 (45 %) patients with HCM: permanent AF in 12 (15 %), persistent AF in 5 (6.2 %), and paroxysmal AF in 19 (23.8 %).

During hospitalization, ventricular tachycardia was reported in 6 (7.5 %) patients: of whom, unstable ventricular tachycardia was recorded during 24-hour Holter ECG monitoring in 4 (5 %) patients and on 12-lead ECG in 2 patients. Supraventricular tachycardia was detected in 3 (3.8 %) patients with HCM: in 2 (2.5 %) during 24-hour Holter ECG monitoring, in 1 (1.3 %) on 12-lead ECG (Figure 5).

Cardiac conduction disorders were revealed in 29 (36.3 %) patients: atrioventricular (AV) blockage in 6 (6.3 %) patients, including degree 1 AV blockade in 2 (2.5 %), degree 3 AV blockade in 3 (3.8 %); right bundle branch block in 17 (21.3 %), left bundle branch block in 12 (15 %) patients. Wolff–Parkinson–White syndrome was detected in (1) 1.3 % patient (Figure 6). Morgagni–Adams–Stokes attack was reported in 3 (3.8 %) patients with HCM. 4 (5 %) patients had a history of cardiac pacemaker implantation. Implantation was caused by degree 3 atrioventricular blockade in 3 (3.8 %) patients after ventricular septal resection, bradycardiac permanent AF in 1 (1.3 %) patient.

In patients with HCM, the glomerular filtration rate (GFR) was 65 (56–78.8) mL/min/1.73 m2 (n=71). Chronic kidney disease was reported in 22 (31 %) patients, provided that most of them had stages 3a and 3b (Figure 7). Proteinuria was detected in 17 (25 % of patients, n=68), proteinuria >1 g/L was detected in 3 (4.4 %), and nephrotic syndrome was detected in 1 (1.5 %) patient with HCM (Figure 8).

The hospitalization duration in patients with HCM was 8 (6; 12.5) days. 87 (45–131.5; min 1, max 180) months after discharge, 11 (13.8 %) patients died. In the dead patients, the time from HCM diagnosis to death was 10 (3–12, min 0, max 17) years.

dead patients were more likely to have a history of LVOTO and AF compared to alive patients (X^2=10.09; p=0.006 and X^2=3.96; p=0.047, respectively) (Figure 9, 10).

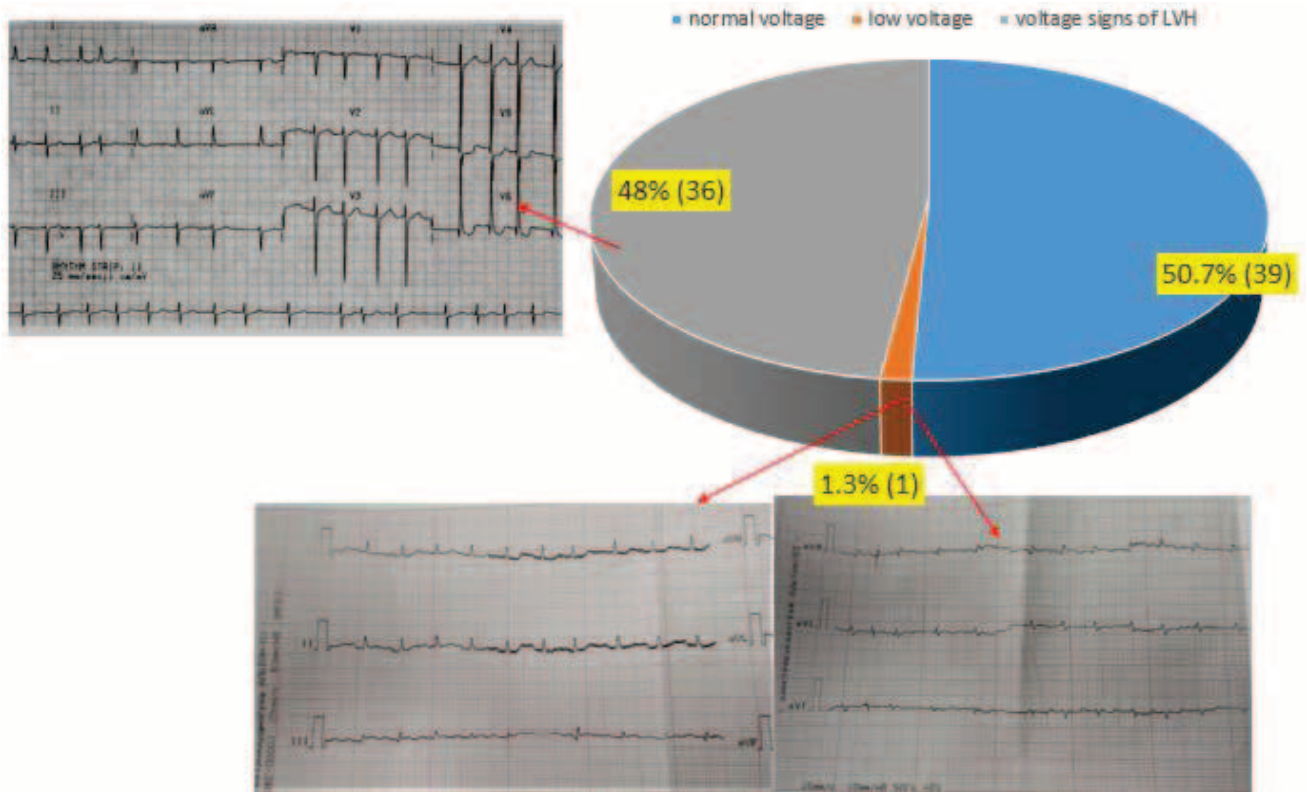

Figure 4. *ECG in patients with HCM*
Note: LVH — left ventricular hypertrophy

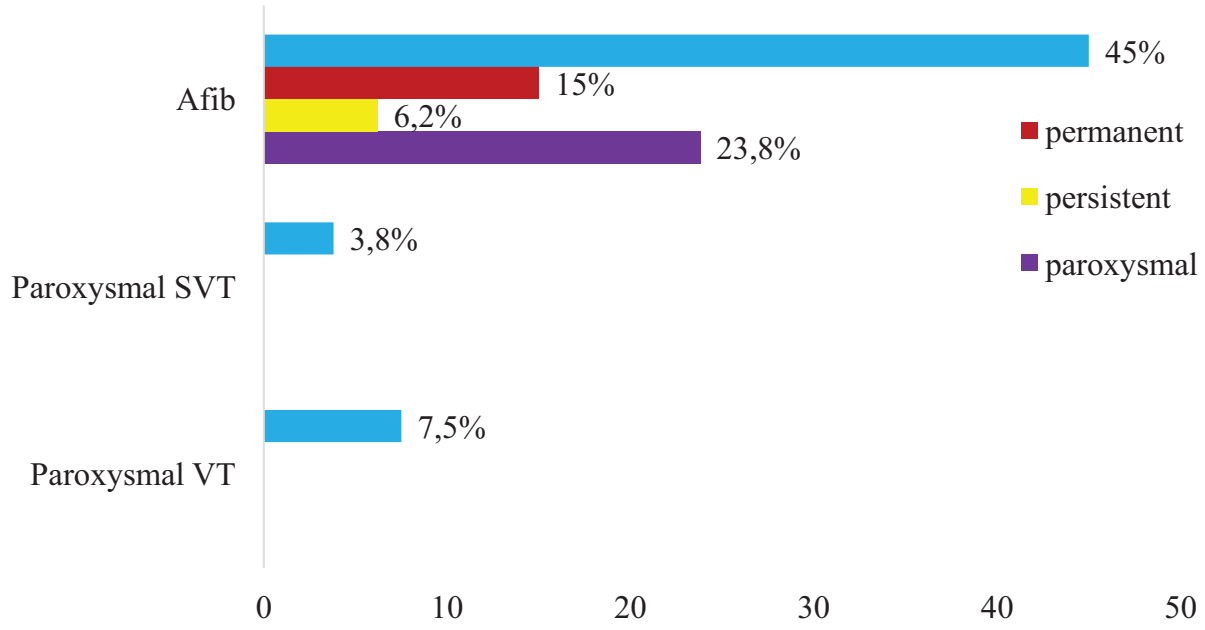

Figure 5. *Arrhythmias in patients with HCM*
Note: Afib — atrial fibrillation, SVT — supraventricular tachycardia, VT — ventricular tachycardia

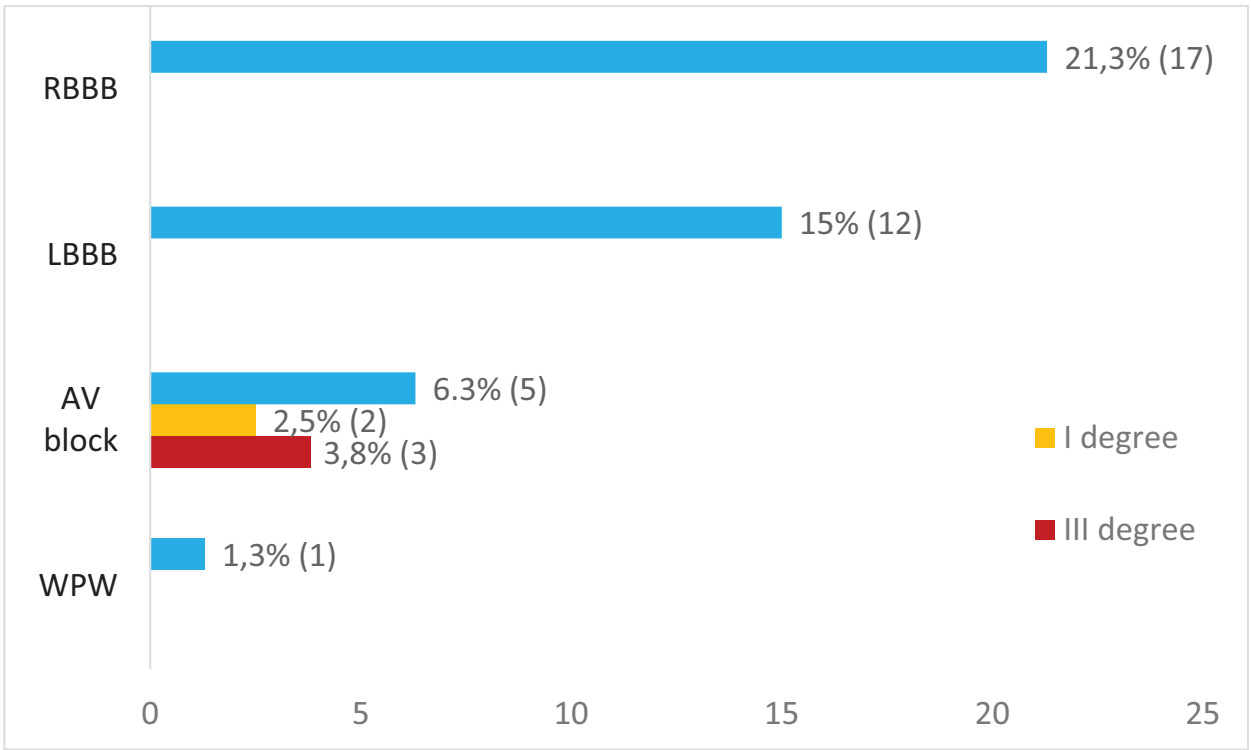

Figure 6. *Conduction disorders in patients with HCM*
Note: RBBB — right bundle branch block, LBBB — left bundle branch block, AV — atrioventricular, WPW — Wolff-Parkinson-White Syndrome

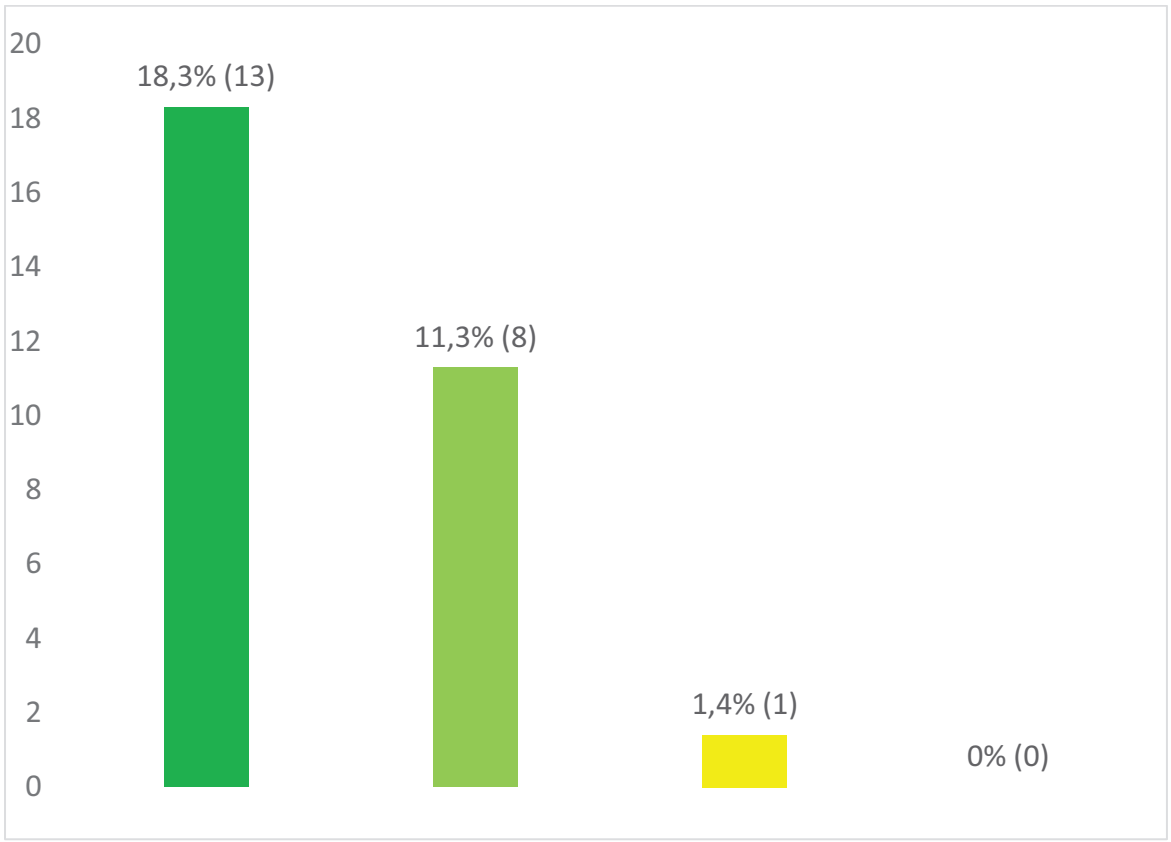

Figure 7. *CKD in patients with HCM*

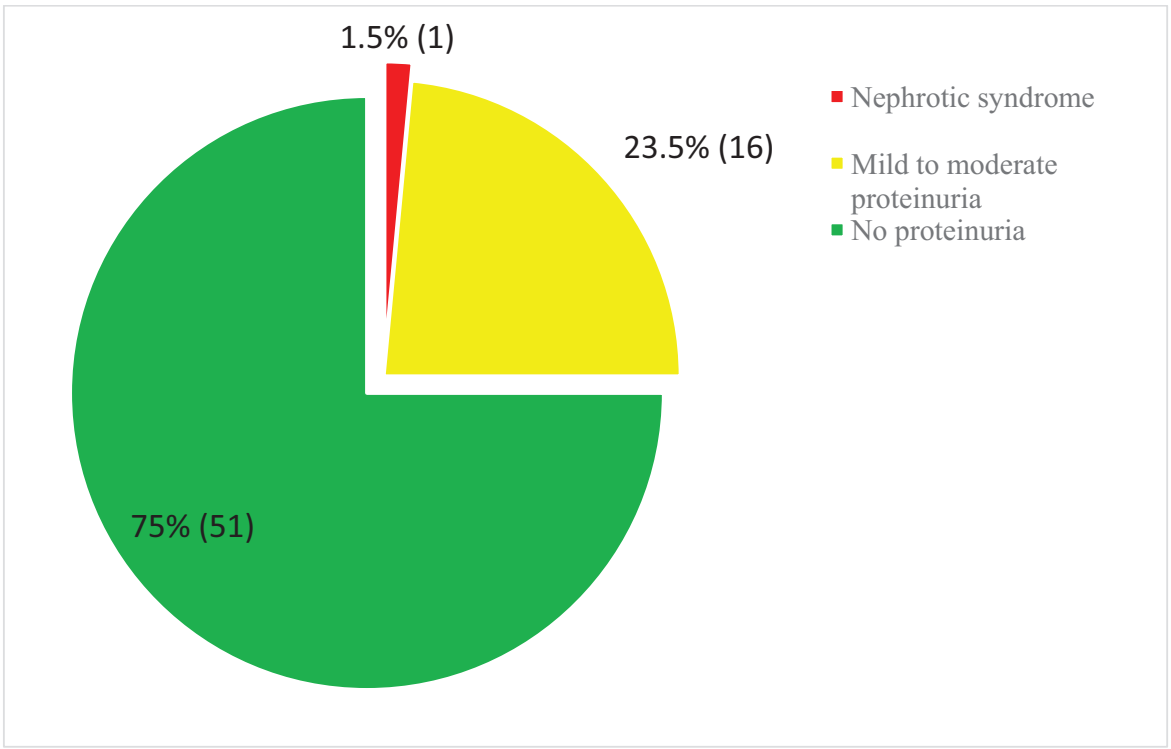

Figure 8. *Proteinuria in patients with HCM*

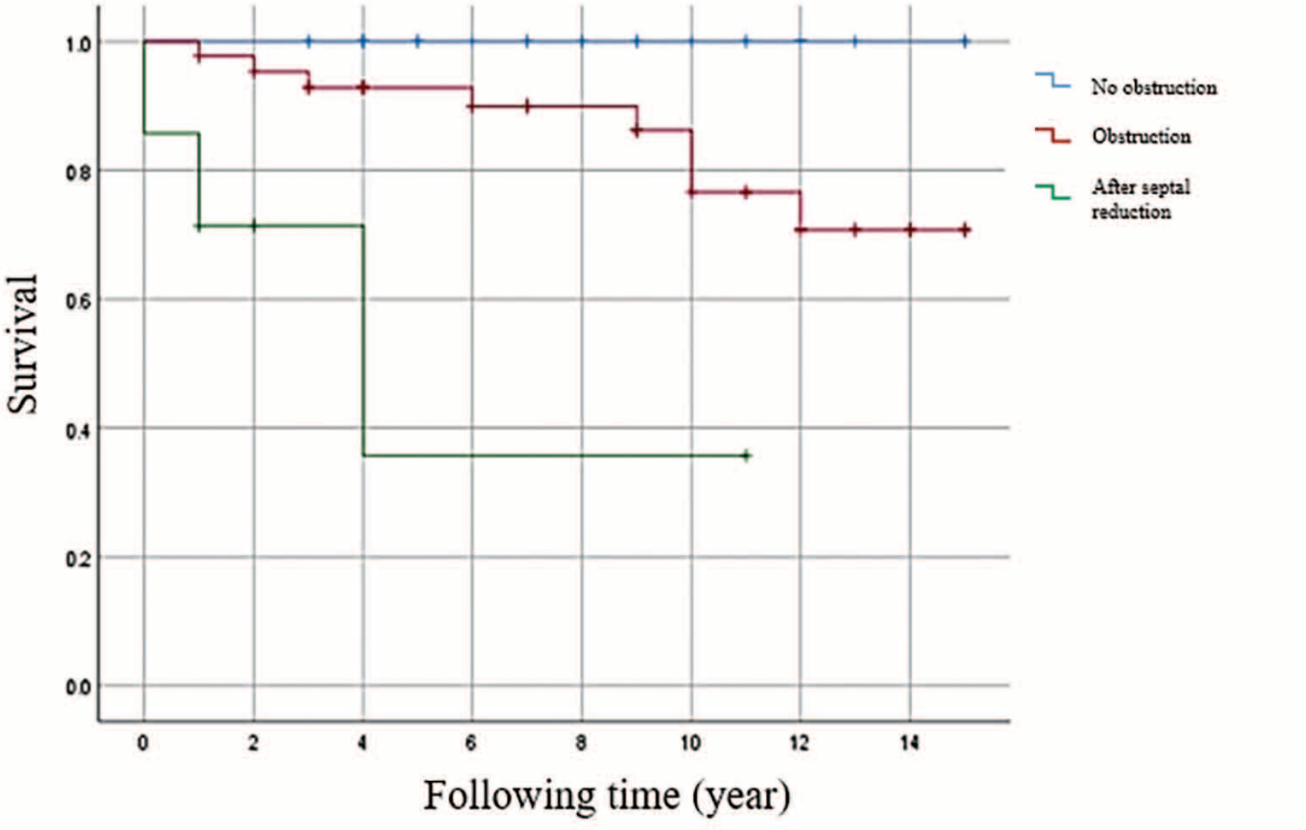

Figure 9. *Kaplan-Meier curve of the proportion of patients after septal reduction therapy, with or without left ventricular obstruction among 80 patients with hypertrophic cardiomyopathy (HCM).*

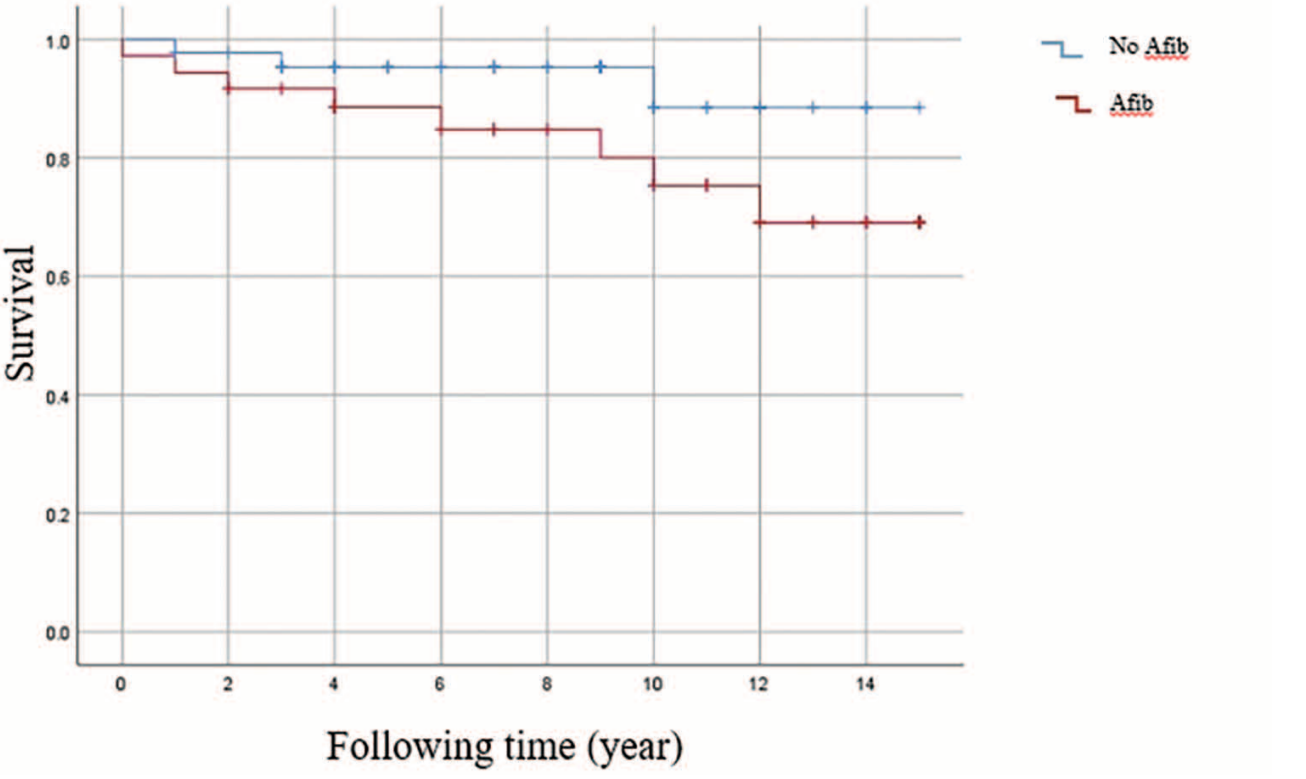

Figure 10. *Kaplan-Meier curve of the proportion of patients with or without Afib among 80 patients with hypertrophic cardiomyopathy (HCM).*

Note: Afib — atrial fibrillation

Table 2. Comparison of characteristics in deceased and surviving patients with HCM

Parameter	Deceased (n=11)	Alive (n=69)	p
Proteinuria, g/l	0.26 (0.00-2.00)	0.09 (0.00-3.0)	0.29
Presence of LVOT obstruction, %	**100**	**58.2**	**0.006**
LV wall thickness, mm	19.5 (17.8-24.3)	20.9 (18-23.7)	0.37
Presence of Afib, %	**72.7**	**40.6**	**0.047**
Presence of conduction disturbance, %	45.5	34.8	0.5
Arterial hypertension, %	36.4	56.5	0.22
GFR ml/min/1.73 m2	96(60-104)	64.5 (56-76)	0.087
Diabetes	36.4	58	0.39
LA diameter (mm)	49.4 (45-52)	45 (40-51.4)	0.23
LA volume (ml)	99 (81.5-202)	105 (60-140)	0.83
LV EDD (mm)	41 (39-51)	43.3 (40-47.6)	0.9
LV EDV (ml)	94.5 (80-126)	80 (68-97)	0.27

Note: LVOT — left ventricular outflow tract, LV — left ventricle, Afib — atrial fibrillation, GFR — glomerular filtration rate, LA — left atrium, EDD — end-diastolic diameter, EDV — end-diastolic volume

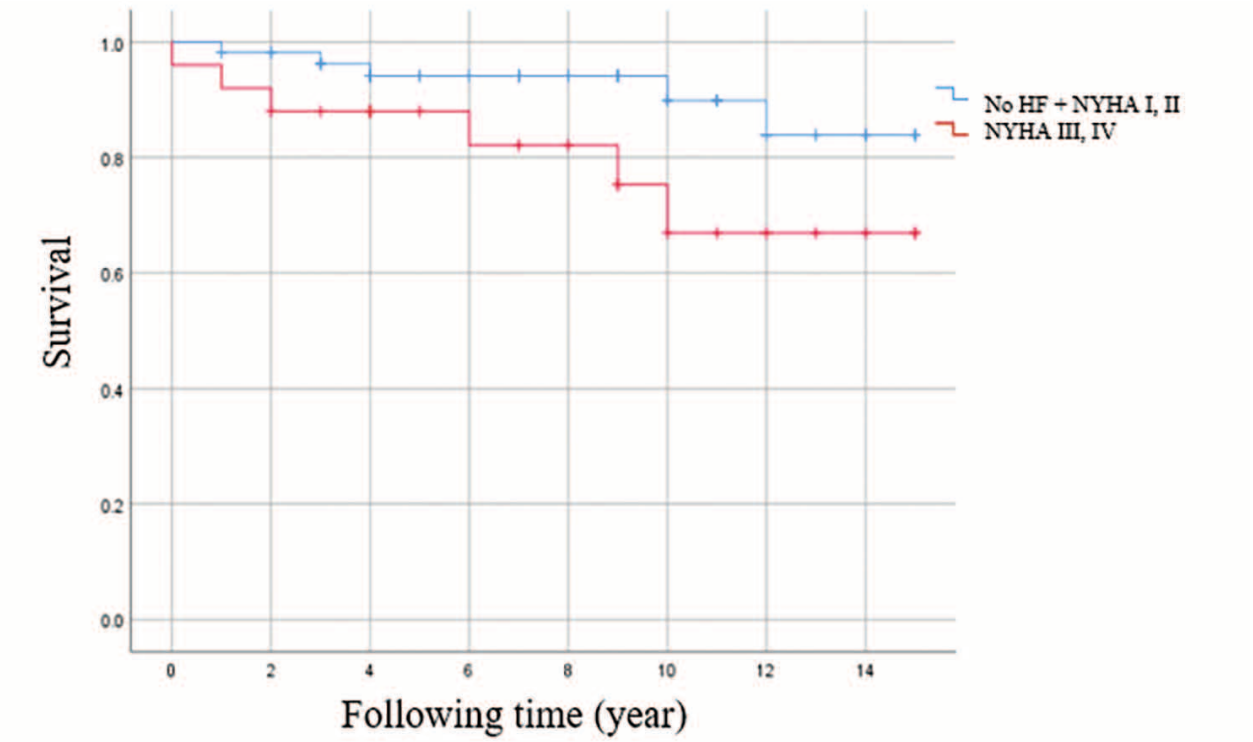

Figure 11. *Kaplan-Meier curve of the proportion of patients with different classes of CHF or without it among 80 patients with hypertrophic cardiomyopathy (HCM) (p=0.073)*

Note: HF — heart failure

Age, sex, severity, and form of LVH, LVEF, LV end-diastolic diameter and volume, LV diastolic function, left atrial dimension and volume, degree of proteinuria, GFR, NYHA functional class of CHF, CHF stage (according to the Vasilenko-Strazhesko classification), history of arterial hypertension, myocardial infarction, and diabetes mellitus in dead and alive patients were not significantly different (Table 2, Figure 11).

Fifty-five patients with LVH (5 (9.1 %) of the above-analyzed patients) underwent genetic testing to rule out HCM phenocopies. Of them, sarcomere protein gene mutations (true HCM) were found in 12 (21.8 %) patients, a transthyretin gene mutation (ATTR amyloidosis) was revealed in 1(1.8 %) patient.

Discussion

According to the published data, cases of HCM were diagnosed in 122 countries. Approximately 20 million people worldwide have this disorder, which is much greater than the previously estimated number of patients. HCM is not diagnosed in about 90 % of cases [1].

Over the period 2007 to 2021, in the multi-speciality hospital, the HCM detection rate was 14.26 per 100,000 patient-years. There is no similar statistical information on the website of the Federal State Statistics Service of the Russian Federation or in the available literature. In the period 1984 to 2016, the detection rate of HCM in the Rochester Epidemiology Project (Minnesota, USA) was 8.0/100,000person-years [6]. The differences may be due to the small sample size of the study and the inclusion of only hospitalized patients. Taking into account the HCM prevalence in the general population, which is 1 per 500 people, a lot of HCM cases are not diagnosed in real-life clinical practice [1].

A distinctive feature of HCM is heterogeneity of clinical manifestations, ranging from asymptomatic course to severe CHF and sudden cardiac death. Typical morphological signs of HCM include hypertrophy, cardiomyocyte damage, and cardiac fibrosis [1]. This disorder is characterized by disturbed myocardial calcium metabolism, inefficient energy use, and microvascular dysfunction. According to the data obtained in this study and published in literature, it is accompanied by impaired local and reduced global contractility, LV diastolic dysfunction, cardiac valve insufficiency, rhythm and contractility disorders, CHF (in 77.6 %, including CHFpEF in 68.8 % patients) [1,5].

In the guidelines of the European Society of Cardiology, the NT-proBNP, BNP assay is recommended as a mandatory criterion for the CHFpEF diagnosis (until 2021 and CHFpEF). This recommendation is not always followed in general clinical practice, and therefore this index was not evaluated in the patients with HCM in this study. According to the results of some authors, NT-proBNP, BNP level, high-sensitivity troponin can help differentiate HCM from its phenocopies and even distinguish phenocopies from each other. Liu H. et al. demonstrated that a significantly greater level of NT-proBNP [5,803.5 (2,533–13,969) vs. 1,513 (656–3,516), p=0.001)] and troponin T [91.9 (53.85–223.45) vs. 17.3 (11.9–45.3), p=0.001] in patients with cardiac amyloidosis compared to the patients with HCM. By contrast with HCM, the diagnosis of cardiac amyloidosis can be ruled out at normal values of NT-proBNP. None of the patients with cardiac AL amyloidosis had NT-proBNP <55 pmol/L. Hu K. et al. found that the levels of high sensitive troponin (hsTn) and NT-proBNP were much greater in the cardiac amyloidosis group [median: hsTn 98 pg/mL, NT-proBNP 4,110 pg/mL] than in the group of Friedrich's ataxia [hsTn 14 pg/mL, NT- proBNP 40 pg/mL] and in the Fabry disease group [hsTn 18 pg/mL, NT-proBNP 131 pg/mL, P<0.001 in both groups]. hsTn >60 pg/mL (sensitivity 0.79, specificity 0.93) and NT-proBNP >1,000 pg/mL (sensitivity 0.91, specificity 0.93) allowed differentiating cardiac amyloidosis from Friedrich's ataxia and Fabry disease [7,8]. For this reason, a large-scale implementation of the test for these biomarkers in patients with left ventricular hypertrophy and especially with HCM.

In HCM, AF is the most frequent persistent arrhythmia. Its prevalence depends on the disease severity and makes up from 22 % in patients with HCM to 32 % in patients with HCM waiting for implantation of cardioverter defibrillator and electric cardiac pacemaker [9]. In this study, a greater incidence of AF was found in patients with HCM: in 45 % of cases. Cardiac conduction disorders were detected in every third patient; in 9 % of patients, cardiac conduction disorders occurred after IVS resection. Such frequency is comparable with the frequency of AF and cardiac conduction disorders in patients with amyloidosis found in one of the studies [2]. It is likely that the group of patients with HCM was heterogeneous, the diagnosis was generally established based on EchoCG data, and its phenocopies (e.g., cardiac amyloidosis) were not ruled out. According to the results of previous studies, the frequency of hereditary ATTR amyloidosis in patients with diagnosed HCM is 5 % and reach 7.6 % at the age of 55 years and older [3]. In the recent study in the cohort of Afro-Caribbean patients with unexplained LV hypertrophy, cardiac amyloidosis was found in 33.9 % of patients [10].

A meta-analysis by Liu Q. et al. demonstrated that in patients with HCM, NYHA functional class, AF, and LVOT obstruction were significant prognostic factors of cardiovascular death [11]. Moreover, NYHA class III/IV was the most important risk factor for cardiovascular mortality and the strongest prognostic factor for overall

mortality. In this study, dead patients with HCM were significantly more likely to have LVOTO (p=0.006) and AF (p=0.047); there were differences in NYHA functional class between dead and alive patients; however, they were not statistically significant (p=0.073). This may be due to a small sample size and heterogeneity of the patient cohort in the study, possible presence of hypertensive patients in patients with established HCM diagnosis, as well as specificity of CHFpEF diagnosis in the absence of biomarker detection (BNP, NT-proBNP).

The survival rate of patients after the surgery aimed at reducing the pressure gradient in LVOT (myectomy, alcohol septal ablation) is lower than in patients without surgery and without obstruction. This may be explained by the greater severity of clinical symptoms and presence of higher CHF FC in patients requiring myectomy [11] This is consistent with the results of this study.

The frequency of patients with a history of myocardial infarction in the study was much greater than in the Taiwan study (15 % and 3 %), [12]and the frequency of patients with myocardial infarction without significant coronary stenoses was similar to the results of Puwanant S. et al. study (7.5 % and 9 %, respectively) [13]. In addition to coronary atherosclerosis, microvascular dysfunction, intramural coronary stenosis and endothelial dysfunction may contribute to the development of ischemia and/or myocardial infarction in HCM. In HCM phenocopies, especially in cardiac amyloidosis, ECG changes or local contractility abnormalities on echoCG may mimic the clinical presentation of MI and be due to amyloid deposition in the LV wall or coronary arteries [2,3].

In the study, half of the patients with HCM had a history of arterial hypertension (AH), 35 % had a history of grade 3 AH. The result obtained in the study does not differ from those in the previous studies [14]. Although these two disease areas can be comorbid, genetic testing is required in patients with AH to confirm HCM in order to rule out hypertensive heart disease as the cause of LVH.

Low (even normal) voltage of QRS complexes observed in some patients with HCM are a manifestation of mass-voltage dissociation. This may be one of signs of HCM phenocopies and require screening to reveal the causes of HCM (genetic test, biopsy, etc.).

In this study, 30 % of patients with HCM had a carbohydrate metabolism disorder (17.5 % had DM). This is twice as high as in the general population and similar to the DM frequency in the cohort of patients with HCM in Taiwan [12]. DM may be a cause of microvascular dysfunction and MI without significant coronary stenosis in the patients with HCM. Patients with HCM and DM have a higher cardiovascular risk. They have higher FC and more pronounced heart failure due to LV diastolic dysfunction. It is interesting that the clinical presentation of diabetic cardiomyopathy can develop in the patients with DM, manifesting as LVH, diastolic dysfunction, left atrial dilation [15]. LVH caused by DM is aggravated by AH and renal dysfunction [15]. In patients with LVH and DM, especially in the presence of AH, renal dysfunction, genetic testing is required to confirm HCM and perform differential diagnosis with diabetic cardiomyopathy.

In this study, kidney disease was found in every third patient with HCM; however, it was not pronounced in most patients. Proteinuria detected in the urinalysis was mainly mild; no tests for albuminuria or daily proteinuria/albuminuria were conducted. It is generally acknowledged that in patients with such cardiovascular diseases (CVD) as coronary heart disease (CHD) and chronic heart failure (CHF) CKD is a significant risk factor associated with adverse outcomes. However, the significance of CKD in HCM is still unclear [16]. On the one hand, CKD is closely related to the progression of LVH and cardiac fibrosis. On the other hand, LV hypertrophy and diastolic dysfunction may promote a decrease in GFR and development of renal dysfunction in patients with HCM [16]. Screening of urinary albumin excretion, including daily albuminuria, is required for timely diagnosis of renal disorders in patients with HCM. It is notable that pronounced LVH in combination with renal disorders can be considered as “a red flag” of systemic amyloidosis and other infiltrative heart diseases [2,3], requiring screening for HCM phenocopies.

According to the genetic testing in patients with HCM, sarcomere protein gene mutations were detected in 21.8 % of patients, while a transthyretin gene mutation (hereditary ATTR amyloidosis was diagnosed) was revealed in 1.8 %. Clinicians should be suspicious of this disease and perform screening to rule it out in patients with HCM who have the mentioned “red flag” symptoms [16].

Study restrictions

Due to the retrospective design of the study, different causes and timing of hospitalization, different clinical manifestations and applied medical and economic standards of patient management, not all of the tests required for patients with HCM according to the current guidelines were conducted; genetic testing and exclusion of HCM phenocopies were not performed either.

Conclusion

In real-life clinical practice, HCM is probably diagnosed less frequently than it occurs. Moreover, overdiagnosis of HCM in patients with arterial hypertension

and diabetes mellitus, as well as underdiagnosis of HCM phenocopies cannot be excluded. All patients with HCM require EchoCG according to up-to-date protocols, including the assessment of diastolic function, mass index, cardiac strain, pulmonary hypertension, etc., evaluation of troponin and NTproBNP levels, genetic testing, as well as other tests to exclude phenocopies. Considerable achievements and wide availability of genetic testing facilitate the detection of sarcomere mutations that cause HCM, as well as the diagnosis of other genetic diseases that can mimic HCM. Visualization techniques are not always reliable when it comes to differentiation of these conditions. Although HCM phenocopies are relatively rare, it is extremely important to distinguish these conditions at an early stage, since their natural course, treatment and prognosis are significantly different from those in HCM with sarcomere mutations. In this study, sarcomere protein gene mutations were found in each fifth patient, while a transthyretin gene mutation (ATTR amyloidosis) was revealed in 2% of patients with pronounced LVH. This confirms the need for wide implementation of genetic testing, screening for HCM phenocopies and their inclusion in the Program on State Guarantees in the Russian Federation for timely use of specific pathogenetic therapy and improvement of patients' prognosis.

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DOI: 10.20514/2226-6704-2023-13-3-196-202
УДК 616.36-003.826-073.43:616.13-004.6
EDN: IMJZGU

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ИСПОЛЬЗОВАНИЕ УЛЬТРАЗВУКОВОЙ ШКАЛЫ ВЫРАЖЕННОСТИ СТЕАТОЗА ПЕЧЕНИ В ДИАГНОСТИКЕ АТЕРОСКЛЕРОЗА ПЕРИФЕРИЧЕСКИХ АРТЕРИЙ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Ultrasound Score of Liver Steatosis Severity in the Diagnosis of Peripheral Arterial Atherosclerosis in Patients with Nonalcoholic Fatty Liver Disease

Резюме

Неалкогольная жировая болезнь печени (НАЖБП) является широко распространенным заболеванием, тесно ассоциированным с ожирением и метаболическими нарушениями. В диагностике неалкогольной жировой болезни печени большое внимание уделяется неинвазивным инструментальным маркерам. **Целью** настоящего исследования было изучение взаимосвязи значений ультразвуковой шкалы стеатоза Hamaguchi с распространенностью атеросклероза периферических артерий, а также оценка диагностической ценности Hamaguchi score в отношении наличия стенозов сонных артерий и артерий нижних конечностей. **Материалы и методы**. Всем участникам проводили дуплексное сканирование артерий каротидного бассейна и артерий нижних конечностей, абдоминальное ультразвуковое исследование. **Результаты.** В исследовании приняло участие 175 пациентов, среди них 72 мужчины и 103 женщины. Медиана возраста пациентов составила 50 лет. Сочетанный атеросклероз сонных артерий и артерий нижних конечностей выявлен у 76 (43,4 %) пациентов. Медиана выраженности стеатоза печени по шкале Hamaguchi составила 2 балла. В группе пациентов с сочетанным атеросклерозом сонных артерий и артерий нижних конечностей были отмечены достоверно более высокие значения Hamaguchi score (p=0,026). По данным логистического регрессионного анализа увеличение балла по шкале Hamaguchi на одну единицу ассоциировалось с увеличением относительного риска выявления сочетанного атеросклероза двух бассейнов (сонные артерии и артерии нижних конечностей) в 1,192 раза (95 % ДИ 1,023-1,387). По данным ROC-анализа увеличение значений шкалы Hamaguchi более 2 баллов позволяло диагностировать сочетанные стенозы каротидных артерий и артерий нижних конечностей с чувствительностью 52,6 % и специфичностью 63,6 % (AUC=0,596; p=0,024). **Заключение.** У пациентов с неалкогольной жировой болезнью печени значения шкалы Hamaguchi более 2 баллов позволяет диагностировать сочетанные стенозы каротидных артерий и артерий нижних конечностей с чувствительностью 52,6 % и специфичностью 63,6 %.

Ключевые слова: *неалкогольная жировая болезнь печени; атеросклероз периферических артерий; шкала Hamaguchi*

Конфликт интересов

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

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Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 22.11.2022 г.
Принята к публикации 14.04.2023 г.

Для цитирования: Кузнецова А.С., Долгушина А.И., Поспелов В.Н. и др. ИСПОЛЬЗОВАНИЕ УЛЬТРАЗВУКОВОЙ ШКАЛЫ ВЫРАЖЕННОСТИ СТЕАТОЗА ПЕЧЕНИ В ДИАГНОСТИКЕ АТЕРОСКЛЕРОЗА ПЕРИФЕРИЧЕСКИХ АРТЕРИЙ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ. Архивъ внутренней медицины. 2023; 13(3): 196-202. DOI: 10.20514/2226-6704-2023-13-3-196-202. EDN: IMJZGU

Abstract
Non-alcoholic fatty liver disease (NAFLD) is a widespread disease closely associated with obesity and metabolic disorders. Noninvasive instrumental markers are of great importance in the diagnosis of NAFLD. **The aim** of the present investigation was to study the correlation of Hamaguchi score with the prevalence of peripheral arterial atherosclerosis and to evaluate the diagnostic value of Hamaguchi score in relation to the presence of carotid and lower limb arterial stenoses. **Materials and Methods.** All the participants underwent duplex scanning of the arteries of the carotid basin and the arteries of the lower extremities, and abdominal ultrasound examination. **Results**. The study involved 175 patients, including 72 men and 103 women. Median age of the patients was 50 years. Combined atherosclerosis of carotid arteries and the arteries of the lower extremities was detected in 76 (43,4 %) patients. Median severity of hepatic steatosis according to Hamaguchi score was 2 points. Significantly higher Hamaguchi score values (p=0,026) were observed in the group of patients with combined atherosclerosis of carotid arteries and lower limb arteries. According to logistic regression analysis, a one unit increase in Hamaguchi score was associated with a 1,192-fold (95 % CI 1,023-1,387) increase in the relative risk of finding combined atherosclerosis of two basins (carotid and lower extremity arteries). According to ROC-analysis, increasing Hamaguchi score>2 points allowed to diagnose combined stenoses of carotid and lower limb arteries with sensitivity of 52,6 % and specificity of 63,6 % (AUC=0,596; p=0,024). **Conclusion**. In patients with NAFLD the Hamaguchi score>2 made it possible to diagnose combined stenoses of the carotid and lower extremity arteries with a sensitivity of 52,6 % and specificity of 63,6 %.

Key words: *nonalcoholic fatty liver disease; peripheral arterial atherosclerosis; Hamaguchi score*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 22.11.2022
Accepted for publication on 14.04.2023

For citation: Kuznetsova A.S., Dolgushina A.I., Pospelov V.V. et al. Ultrasound Score of Liver Steatosis Severity in The Diagnosis of Peripheral Arterial Atherosclerosis in Patients with Nonalcoholic Fatty Liver Disease. The Russian Archives of Internal Medicine. 2023; 13(3): 196-202. DOI: 10.20514/2226-6704-2023-13-3-196-202. EDN: IMJZGU

AUC — area under the curve, FLI — fatty liver index, LFS — Liver Fat Score, ROC — receiver operating characteristic, CI — confidence interval, CHD — coronary heart disease, II — interquartile interval, Me — median, NAFLD — non-alcoholic fatty liver disease, TCS — total cholesterol, GFR — glomerular filtration rate, TGs — triglycerides, HDL cholesterol — high density lipoprotein cholesterol, LDL cholesterol — low density lipoprotein cholesterol

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common disease which is closely associated with obesity and metabolic disorders [1-3]. However, this condition can be observed also in persons with normal body weight: in general, approximately 40 % of NAFLD patients have normal body mass index [4]. This fact is important to understand the significance of this disease. Results of recent metaanlyses show a high risk of fatal and non-fatal cardiovascular events (myocardial infarction, stroke, revascularisation) in groups of NAFLD patients, irrespective of the presence or absence of metabolic syndrome and obesity [5, 6]. It is important to note that cardiovascular diseases were the main cause of deaths in NAFLD patients (38 % of all causes) in the studies conducted in the USA, Europe and Asia [7, 8].

In NAFLD diagnosis, a greater emphasis is put on noninvasive laboratory and instrumental markers (in particular, on fatty liver index (FLI), hepatic steatosis index (HSI), Hamaguchi score). Often these parameters are used as a means to search for correlations between NAFLD and cardiovascular diseases. Biyao Zou et al. (2021) noted a higher incidence of atrial fibrillation, coronary heart disease (CHD), stroke, cardiac failure, and also statistically higher cardiovascular death rates (10.42 per 1000 person years, 95 % CI 10.15–10.70 vs. 5.18 per 1000 person years, 95 % CI 5.04–5.32) in patients with FLI > 60 vs. patients with FLI < 60 [8]. A study by Chenxi Wang et al. (2021) demonstrated that an increase in HSI by one quartile was associated with 1.16-fold increase in the odd ratio (OR) to diagnose carotid atherosclerosis (95 % CI 1.114–1.207) [9]. A number of researchers noted a close correlation between endothelial dysfunction markers, in particular vascular endothelial growth factor, and HSI values [10]. Also a correlation between impaired lipid metabolism and ultrasound steatometry indices was established: Daniele Pastori et al. (2018) found that Hamaguchi score (semi-quantitative ultrasound hepatic steatosis

scale) statistically correlated with the remnant cholesterol concentration [11].

Literature data analysis demonstrates that noninvasive steatosis markers can be an efficient tool for cardiovascular risk stratification and search for associations with cardiovascular complications. The objective of this study was to analyse the correlation between Hamaguchi ultrasound steatosis score and the incidence of peripheral arterial atherosclerosis; and to evaluate the diagnostic value of Hamaguchi score in relation to carotid steatosis and arterial steatosis of lower limbs.

Materials and methods

The study enrolled 175 patients (72 male subjects and 103 female subjects) with ultrasound verified NAFLD. Median age was 50 (44.0; 56.0) years old.

All subjects signed a voluntary informed consent form. Subjects with the following conditions were excluded from the study: acute cardiovascular event (acute coronary syndrome, acute cerebrovascular event, transient ischaemic attack), stage C4–C5 chronic kidney disease (CKD), malignancies, hepatic cirrhosis, viral hepatitis. The study protocol was approved by the Local Ethics Committee (Meeting Minutes No. 10 dated 27 October 2018).

NAFLD was diagnosed using the generally accepted criteria: excessive fatty deposits in the liver found during ultrasound examination; no history of chronic consumption of toxic doses of alcohol [12].

All subjects underwent a duplex ultrasonography screening of carotid system arteries and lower limb arteries. For a full report on peripheral artery ultrasound examination, please see our previous articles [13]. Percentage of artery stenosis was measured planimetrically in B mode using the vessel cross section diameter and haemodynamic criteria. Stenosis was measured under the ECST (The European Carotid Surgery Trial) method. ≥ 50 % carotid stenosis was diagnosed if the following criteria were met: peak systolic velocity (PSV) > 125 cm/s; the ratio of internal carotid artery (ICA) PSV and the common carotid artery PSV > 4; ICA end-diastolic velocity > 40 cm/s [14,15]. ≥ 50 % lower limb artery stenosis was diagnosed if the following criteria were met: an increase in PSV up to 200–400 cm/s; spectral dilatation in the stenotic area; biphasic blood flow [16].

Abdominal ultrasound was performed using Canon Aplio 400 (Japan); a 2.5–5 MHz curved transducer was used. The standard ultrasound signs of hepatic steatosis were evaluated: increased hepatic tissue echogenicity; intrahepatic vessel blurring; and echo signal fading. Hepatic steatosis intensity was evaluated with a semi-quantitative method developed by Hamaguchi M. (2007), according to which each of the above steatosis parameters was scored as follows: liver brightness — 0 to 3 points; echo signal fading — 0 to 2 points; vessel blurring — 0 to 1 point [17]. The highest score was six points.

All subjects underwent laboratory tests for total cholesterol, high density and low density lipoprotein cholesterol, triglycerides, creatinine level, and glomerular filtration rate was calculated using the CKD-EPI formula (2011).

All subjects were interviewed; their standard anthropometric parameters (height, wight, body mass index (BMI), and waist circumference) were measured. The obesity type (metabolically healthy/unhealthy phenotype) was determined separately [18,19].

The characteristics of subjects is presented in Table 1.

The data were analysed using MedCalc (version 20.110) and IBM SPSS Statistics (version 18). Qualitative variables were described with absolute and relative frequency (percents). Quantitative variables were described with the median (Me), and the interquartile interval [25th percentile; 75th percentile] was stated. Spearman analysis was used in order to identify correlations bewteen parameters; and a the coefficient of rank correlation was calculated. The value of the coefficient of correlation was interpreted as follows: $r \geq 0.7$ — strong correlation between parameters; $0.3 < r < 0.7$ — moderate correlation between parameters; $r \leq 0.3$ — weak correlation between parameters [20]. The relevance of differences between the groups was evaluated using Mann-Whitney test. Differences were statistically significant if the relevance threshold was 0.05. Variables interdependence was evaluated using logistic regression. ROC-analysis was performed in order to identify the thresholds of test parameters and to determine sensitivity and specificity.

Results

A majority of patients had various cardiovascular risks. Over a half of all patients had abdominal obesity; one out of five patients (21.7 %) was a smoker. A combination of carotid atherosclerosis and arterial atherosclerosis of lower limbs was observed in 76 (43.4 %) patients. The median Hamaguchi score for hepatic steatosis intensity was 2 points (refere to Table 1).

The correlation analysis demonstrated a positive correlation between Hamaguchi score and triglycerides concentration (r=0.317; p=0,0001) and weak negative correlation with high density lipoprotein concentration (r=-0.191; p=0.012).

The group of patients with a combination of carotid atherosclerosis and arterial atherosclerosis of lower limbs

demonstrated a higher Hamaguchi score vs. patients without peripherial atherosclerosis (median Hamaguchi score is 3.0 (0,0; 4.0) points and 1.0 (0.0; 4.0) point, respectively, p=0.026).

In order to identify the potential diagnostic value and optimal Hamaguchi score thresholds for forecasting a combination of carotid stenosis and arterial stenosis of lower limbs, logistic regression analysis and ROC analysis were performed (Table 2, Figure 1).

The logistic regression analysis showed that an increase in Hamaguchi score by one point was associated with 1.192-fold increase in the relative risk of a combined atherosclerosis of both areas (carotid arteries and lower limb arteries) (95 % CI 1.023–1.387).

According to ROC-analysis, an increase in Hamaguchi score by > 2 points made it possible to diagnose a combination of carotid stenosis and arterial stenosis of lower limbs with the sensitivity of 52.6 % and specificity of 63.6 % (AUC=0.596; p=0.024).

In the comparative analysis of Hamaguchi score for men and women, men had statistically higher score vs. women (median score value: 3.0 (1.0; 4.0) points and

Table 1. *Characteristics of patients included in the study*

Показатель/ Indicator	Пациенты / Patients (n=175)	Мужчины/ Men (n=72)	Женщины/ Women (n=103)
Age, years, Me (IQR)	50,0 (44,0; 56,0)	47,5 (44,0; 55,0)	51,0 (45,0; 56,0)
BMI, kg/m^2, Me (IQR)	26,8 (23,4; 30,5)	28,1 (25,7; 31,2)	25,5 (22,3; 29,4)
Obesity: Metabolically healthy phenotype Metabolically unhealthy phenotype	48 (27,4 %) 8 (4,57 %) 40 (22,9 %)	25 (34,7 %) 3 (4,17 %) 22 (31,4 %)	23 (22,3 %) 5 (4,85 %) 18 (17,5 %)
Waist circumference, cm, Me (IQR)	84 (77; 98)	96,0 (85,0; 104)	81,0 (76,0; 91,0)
Abdominal obesity, n (%)	98 (56 %)	49 (68,1 %)	49 (47,6 %)
Smoking, n (%)	38 (21,7 %)	23 (31,9 %)	15 (14,6 %)
Coronary artery disease, n (%)	4 (2,28 %)	4 (5,55 %)	0
Arterial hypertension, n (%)	62 (35,4 %)	36 (50,0 %)	26 (25,2 %)
Type 2 diabetes mellitus, n (%)	3 (1,71 %)	2 (2,78 %)	1 (0,97 %)
Carotid atherosclerosis, n (%)/	121 (69,1 %)	57 (79,2 %)	64 (62,1 %)
Maximum stenosis of the carotid arteries, %, Me (IQR)	24,0 (0,0; 30,0)	26,0 (20,0; 33,8)	20,0 (0,0; 25,0)
Carotid artery stenoses ≥50 %, n (%)	5 (2,86 %)	3 (4,16 %)	2 (1,94 %)
Atherosclerosis of lower limb arteries, n (%)	96 (54,8 %)	54 (75,0 %)	42 (40,8 %)
Lower limb arterial stenoses ≥50 %, n (%)	1 (0,57 %)	1 (1,39 %)	0
Combination of atherosclerosis of carotid arteries and lower extremity arteries, n (%)	76 (43,4 %)	46 (63,9 %)	30 (29,1 %)
Total cholesterol, mmol/l, Me (IQR)	5,91 (5,03; 6,58)	5,74 (4,70; 6,50)	6,06 (5,23; 6,62)
LDL cholesterol, mmol/l, Me (IQR)	3,71 (2,94; 4,55)	3,48 (2,89; 4,36)	3,94 (3,14; 4,59)
HDL cholesterol, mmol/l, Me (IQR)	1,40 (1,16; 1,63)	1,19 (1,01; 1,40)	1,53 (1,35; 1,72)
Triglycerides, mmol/l, Me (IQR)	1,16 (0,80; 1,70)	1,30 (0,90; 2,10)	1,1 (0,80; 1,50)
Creatinine, μmol/l	89,7 (73,5;103;6)	95,8 (81,7; 110)	85,1 (68,9; 100)
pGFR, ml/min/1,73 m^2 to CKD-EPI (2011)	76,0 (63; 91)	78,0 (67,2; 95,3)	70,0 (60,0; 89,0)
Hamaguchi score, Me (IQR)	2,0 (0,0; 4,0)	3,0 (1,0; 4,0)	1,0 (0,0; 4,0)

Note: Me — median; IQR — interquartile range; TCH — total cholesterol; TG — triglycerides; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol; cGFR — calculated glomerular filtration rate

Table 2. *Data from the logistic regression analysis*

	B	RMSE	Wald	DF	Significance level	Exp (B)	95 % CI EXP(B)	
							Lower	Upper
HamaScore	0,175	0,077568	5,104	1	0,024	1,192	1,023	1,387
Constant	-0,652	0,232698	7,841	1	0,005	0,521		

Примечание: RMSE — среднеквадратичная ошибка; DF — degrees of freedom
Note: RMSE — Root Mean Square Error; CI — confidence interval

1.0 (0.0; 4.0) points, respectively, p=0.003). However, ROC-analysis results for the assessment of diagnostic value of Hamaguchi score in forecasting a combination of carotid stenosis and arterial atherosclerosis of lower limbs performed separately for men and women did not reveal any statistical significance (Figure 2A–B).

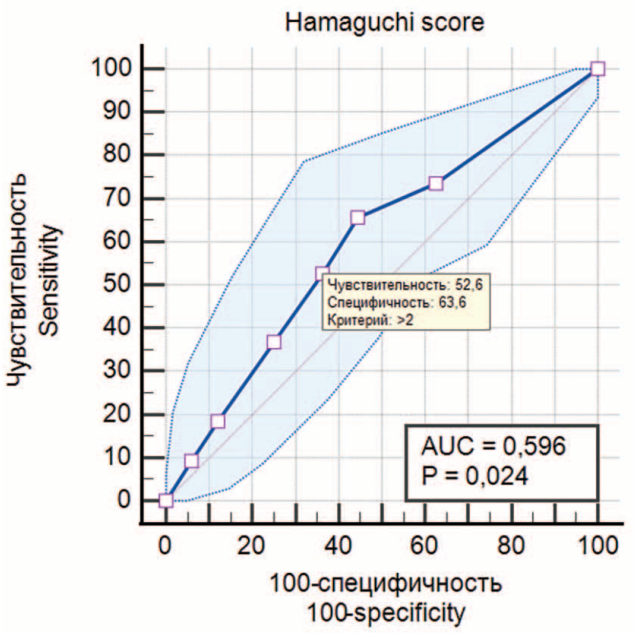

Figure 1. *Results of the ROC analysis for the Hamaguchi scale*

Discussion

Correlation between NAFLD and cardiovascular diseases is one of the most actively studied areas of medicine [21]. NAFLD deaths are caused mostly by cardiovascular events rather than by hepatic outcomes. Also, NAFLD and CVD share a lot of pathogenic mechanisms: system inflammation, insulin resistance, endothelial dysfunction, intestinal dysbiosis [22, 23].

In our study, steatometry Hamaguchi score demonstrated diagnostic value in relation to carotid atherosclerosis and arterial atherosclerosis of lower limbs in patients with NAFLD. Despite the low sensitivity and specificity, we managed to demonstrate for the first time that this ultrasound scale can be a useful tool for the assessment of hepatic steatosis severity and a predictor of a combination of carotid atherosclerosis and arterial atherosclerosis of lower limbs.

In this article, we noted the correlation between Hamaguchi score and lipid metabolism parameters. The available data correlate with the results of previous studies. Sookoian S et al. (2008) demonstrated that carotid atherosclerosis is observed statistically more frequent in patients with NAFLD and noted the correlation between the carotid Intima-media thickness and alanine aminotransferase and gamma-glutamyl transpeptidase levels [24]. The results of a metaanalysis by Tang ASP et al. (2022) showed that the presence of NAFLD increases the chances of carotid atherosclerosis by 3.2 times (95 % CI 2.37–4.32; p<0.0001), while the risk of stroke increases 1.88-fold (95 % CI 1.23–2.88; p=0.02) [25].

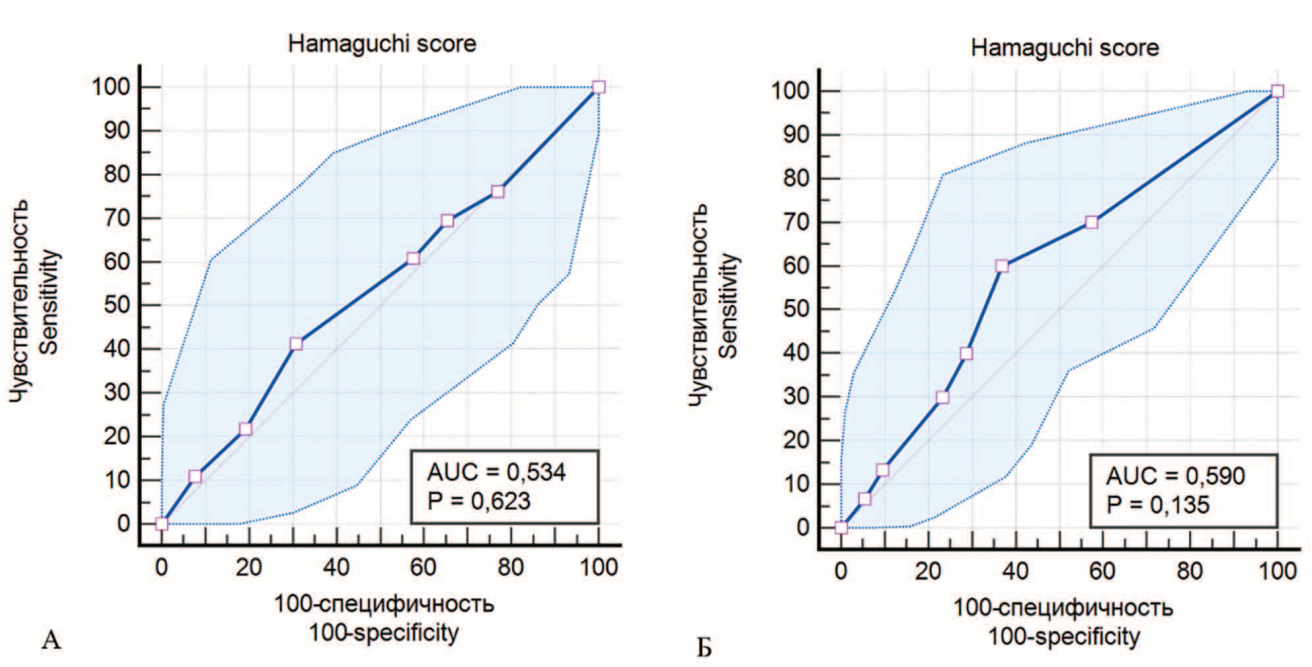

Figure 2. *ROC analysis results for the Hamaguchi scale in men (A) and women (Б)*

A number of studies discuss the correlation between noninvasive markers of hepatic steatosis (in particular, Liver Fat Score (LFS)) and carotid atherosclerosis prevalence, correlations between steatometry indices (Hamaguchi score) and insuline resistance biomarkers (HOMA index) [26, 27].

Conclusion

For NAFLD patients, Hamaguchi score of > 2 points allows diagnosing a combination of carotid stenosis and arterial stenosis of lower limbs with the sensitivity of 52.6 % and specificity of 63.6 %. Evaluation of hepatic steatosis using Hamaguchi method can be used as a screening for peripheral atherosclerosis in high-risk patients.

Вклад авторов

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2023-13-3-203-212
УДК 616.36-004-06:616.24-008.4-07-085
EDN: NZBGNM

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ГЕПАТОПУЛЬМОНАЛЬНЫЙ СИНДРОМ ПРИ ЦИРРОЗЕ ПЕЧЕНИ: РАСПРОСТРАНЕННОСТЬ, КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ, ОСОБЕННОСТИ ДИАГНОСТИКИ, ПОДХОДЫ К ТЕРАПИИ

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Hepatopulmonary Syndrome in Patients with Liver Cirrhosis: Prevalence, Clinical Significance, Clinical Features, Therapeutic Approaches

Резюме

Гепатопульмональный синдром является тяжёлым осложнением хронических заболеваний печени, значительно снижающим качество и продолжительность жизни пациентов, патогенетическим проявлением которого является гипоксемия и внутрилёгочные вазодилатации. По данным некоторых авторов он выявляется у 35 % пациентов с терминальной стадией поражения печени. Основное клиническое проявление гепато-пульмонального синдрома — прогрессирующая одышка с возможным возникновением платипноэ и ортодексии. Однако, его диагностика вызывает трудности, так как «золотой стандарт» — трансторакальная эхокардиография с внутривенным введением контрастного препарата — инвазивная процедура, требующая специфического оснащения и не получившая широкого распространения в лечебных учреждениях Российской Федерации. В качестве дополнительного метода используется физикальный осмотр, при котором могут выявляться телеангиоэктазии, цианоз, изменение пальцев рук по типу «барабанных палочек», а ногтей по типу «часовых стекол», однако эти проявления не обладают высокой специфичностью. В связи с этим необходимо продолжать дальнейший поиск малоинвазивных, применимых в рутинной практике диагностических методов и лабораторных маркёров. В этом обзоре представлены данные о распространённости, патогенезе, клинической картине, диагностике и лечении этого синдрома. Его целью является структурирование

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современных данных и накопленного опыта для более ранней верификации диагноза и, соответственно, применения оптимальной тактики ведения пациентов с данной патологией. Основным эффективным методом лечения гепатопульмонального синдрома в настоящий момент является пересадка печени, поэтому его раннее выявление позволяет своевременно направить пациента в центр трансплантологии для включения в лист ожидания, назначив при необходимости длительную кислородотерапию, что значимо продлевает жизнь пациентов и улучшает ее качество.

Ключевые слова: *гепатопульмональный синдром, цирроз печени, гипоксемия, вазодилатации, одышка, ортодексия, платипноэ*

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

Статья получена 13.01.2023 г.
Принята к публикации 09.03.2023 г.

Для цитирования: Цымбал А.С., Карнаушкина М.А., Аришева О.С. и др. ГЕПАТОПУЛЬМОНАЛЬНЫЙ СИНДРОМ ПРИ ЦИРРОЗЕ ПЕЧЕНИ: РАСПРОСТРАНЕННОСТЬ, КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ, ОСОБЕННОСТИ ДИАГНОСТИКИ, ПОДХОДЫ К ТЕРАПИИ. Архивъ внутренней медицины. 2023; 13(3): 203-212. DOI: EDN: 10.20514/2226-6704-2023-13-3-203-212. NZBGNM

Abstract

Hepatopulmonary syndrome is a severe complication of chronic liver diseases, significantly reducing the quality and duration of patient's lives, the pathogenetic manifestation of which is hypoxemia and intrapulmonary vasodilation. The disease is widespread enough: according to some authors, up to 35 % of patients with the terminal stage of liver damage suffer from this syndrome. The main clinical manifestation is progressive dyspnea with possible occurrence of platypnea and orthodexia. Diagnosis is difficult, since the "gold standard" — transthoracic echocardiography with intravenous injection of contrast agent — is an invasive procedure requiring specific equipment, that's why it is poorly used in medical institutions of the Russian Federation. Physical examination is used as an additional method, in which we see dyspnea, cyanosis, spider nevi, digital clubbing, but these manifestations are not highly specific. Therefore, there is an urgent need for minimally invasive, widespread diagnostic methods and clinical markers that can provide early verification of the diagnosis. This review presents data on the prevalence, pathogenesis, clinical presentation, diagnosis and treatment of this syndrome. The aim of this review is to structure the current data and the accumulated experience for an earlier verification of the diagnosis and accordingly, to apply the optimal management tactics for patients with this pathology. Liver transplantation is currently the main effective method of treatment. Patients with hepatopulmonary syndrome who underwent liver transplantation have been proven to have better survival rate.

Key words: *hepatopulmonary syndrome, cirrhosis, hypoxemia, vasodilatations, dyspnea, orthodeoxia, platypnea*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 13.01.2023
Accepted for publication on 09.03.2023

For citation: Tsymbal A.S., Karnaushkina M.A., Arisheva O.S. et al. Hepatopulmonary Syndrome in Patients with Liver Cirrhosis: Prevalence, Clinical Significance, Clinical Features, Therapeutic Approaches. The Russian Archives of Internal Medicine. 2023; 13(3): 203-212. DOI: 10.20514/2226-6704-2023-13-3-203-212. EDN: NZBGNM

A-a gradient — alveolar–arterial gradient, CO — carbon monoxide, DL_{CO} — diffusing capacity of the lungs for carbon monoxide, eNOS — endothelial nitric oxide synthase, ET-1 — endothelin 1, ETB — endothelin receptor type B, NO — nitrogen oxide, PaO_2 — partial pressure of arterial oxygen, Sat O_2 — oxygen saturation, TIPS — transjugular intrahepatic portosystemic shunt, VEGF — vascular endothelial growth factor, HPS — hepatopulmonary syndrome, chest CT — chest computed tomography, LT — liver transplantation, TNF-α — tumor necrosis factor alpha, EchoCG — echocardiography

Introduction

Hepatopulmonary syndrome (HPS) is a serious complication of liver disease, which is characterized by a triad of signs: cirrhosis and/or portal hypertension, arterial deoxygenation and intrapulmonary vascular dilatation. According to the published studies, this syndrome can worsen prognosis in patients with chronic liver disease in the presence of hepatic impairment. In a multivariate analysis with a statistical correction for the influence of such factors as severity of liver cirrhosis, age, gender, it was found that HPS is an independent factor of increased mortality [1–3].

In 1884, Fluckiger first published a clinical case report, describing a woman with liver cirrhosis, cyanosis, and drumstick fingers. Later, in 1977, the term "hepatopulmonary syndrome" was introduced by Kennedy and Knudson to describe these clinical symptoms of this condition. The postmortem morphological studies in these patients revealed dilation of pulmonary vessels and significant peripheral dilatation of pulmonary arteries at precapillary and capillary levels, without any other changes in the pulmonary parenchyma [4]. Prior to 1988, HPS was treated only with non-surgical methods, the efficacy of which was quite low [5]. For a long time, hepatopulmonary syndrome had been considered a contraindication for liver transplantation (LT); however, after numerous studies the situation changed radically: it was noted that transplantation could reverse hypoxemia and

contribute to a significant increase in survival. In combination with the absence of effective medical treatment, this discovery made LT the main method of HPS treatment [5].

This article describes a systematic analysis of studies on the relationship of clinical, laboratory, and instrumental markers with the clinical presentation, severity, and prognosis of HPS, and discussed possible directions for further work in this area.

The study was aimed at developing a list of the most significant clinical markers for early diagnosis verification and treatment initiation in real-life clinical practice based on the published data on prevalence, pathogenesis, clinical, laboratory and instrumental data on HPS in patients with liver cirrhosis.

Materials and methods

During the study, the search and analysis of articles published over the period: January 2017 to August 2022 was performed in the database PubMed (https://pubmed.ncbi.nlm.nih.gov/). The search query included the words "hepatopulmonary" and derivatives, "syndrome" and derivatives, "cirrhosis" and derivatives, "hypoxemia" and derivatives, "vasodilatation" and derivatives, "orthodeoxia" and derivatives, "platypnea" and derivatives, "treatment" and derivatives, "liver transplantation" and derivatives, "diffusing capacity" and derivatives, "cardiac involvement" and derivatives. To narrow the search, articles containing the word "children" and its variations were excluded. Therefore, the search algorithm was as follows: "liver cirrhosis" OR "prevalence" OR "diagnosis" OR "vasodilation" OR "clinical features" OR "orthodeoxia" OR "platypnea" OR "treatment" OR "liver transplantation" OR "pulmonary dysfunction" OR "diffusing capacity" OR "cardiac involvement" OR "myocardial function" AND "hepatopulmonary syndrome."

When using the described search algorithm, 255 articles were initially selected. Further, 47 articles including studies in patients under 18 years of age were excluded. Then, another 130 publications were excluded as they did not fully meet the purpose of this study (articles dwelt on the surgical treatment of HPS rather than its diagnosis; moreover, they mainly studied portal hypertension, not HPS). The reduced list included 78 articles.

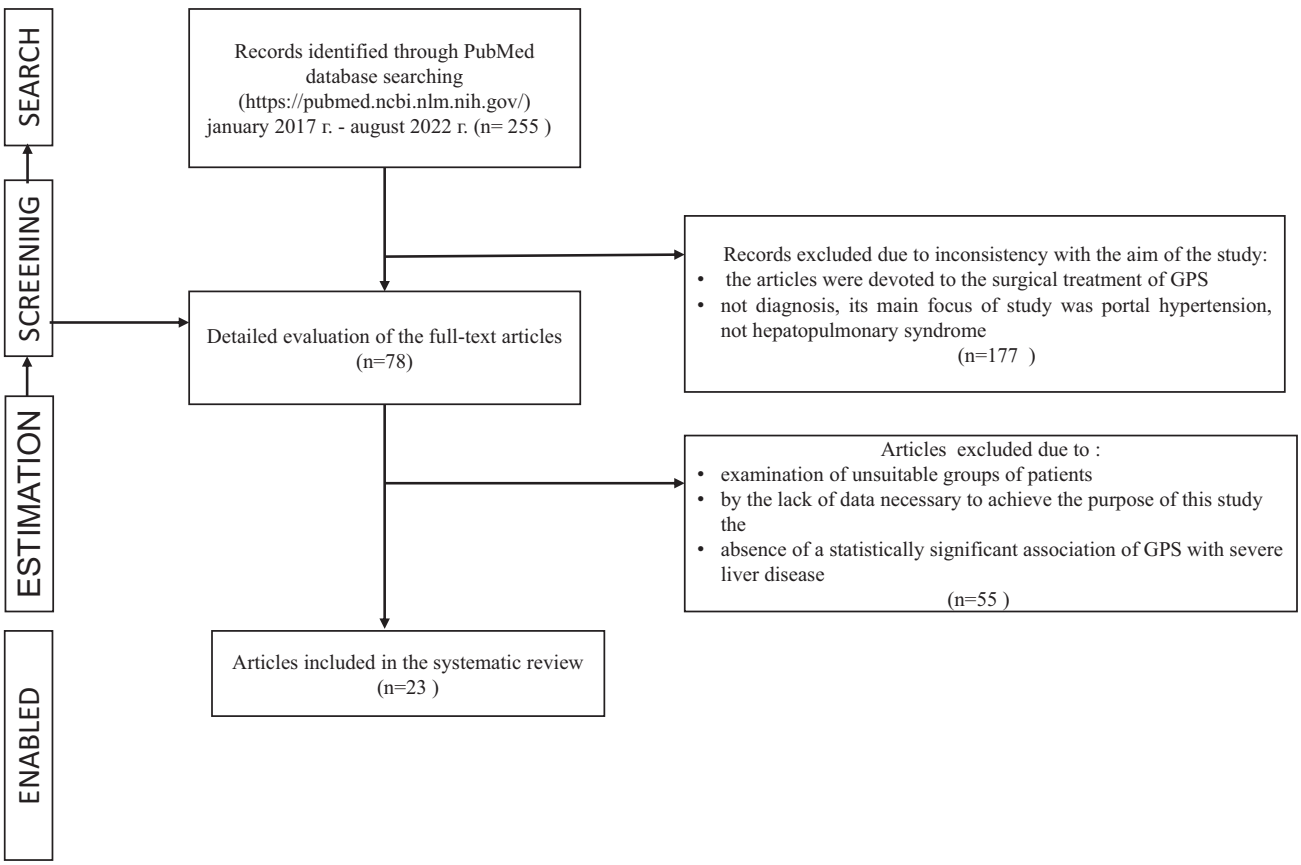

Figure 1. *Schematic representation of the selection process for publications on hepatopulmonary syndrome in patients with liver cirrhosis*

After a careful analysis of publications, the articles that either referred to the examination of patients with liver disease without cirrhosis or did not contain patient examination data essential for the purpose of this study were additionally excluded. Single clinical case reports were also excluded, since the patient data contained therein were sparse. The studies where the relationship between HPS and severe liver disease was statistically insignificant (p>0.05) were also excluded. Therefore, at the last stage of the literature analysis, another 55 publications were excluded from the 78 articles. After the search, a list of 23 publications was formed, which demonstrated a clear association between HPS with worsened quality of life and increased mortality, the importance of early screening and search for new study methods to improve survival and prognosis of patients with HPS (Figure 1).

Diagnosis and criteria

Hepatopulmonary syndrome is defined as hypoxemia caused by dilation of pulmonary vessels and formation of vascular shunts in patients with liver disease with or without portal hypertension [6]. Table 1 shows the criteria for HPS diagnosis.

The conducted studies revealed a correlation between HPS severity and severity of liver disease, assessed by the MELD (Model for End-Stage Liver Disease) scale [4], which is used to calculate the survival prognosis for patients with end-stage liver failure.

Table 2 shows the HPS classification, based on the evaluation of the severity of pulmonary gas exchange disorder, characterized by a decrease in arterial blood oxygen levels [6].

The given table shows that the HPS severity depends on the level of partial oxygen pressure in arterial blood, with alveolar-arterial gradient exceeding 15 mm Hg, which is one of the most sensitive markers for early arterial hypoxia detection.

Prevalence

According to the study data, HPS is found in 5 %–35 % of patients with end-stage liver disease. This data variation is likely due to the use of different diagnostic criteria for diagnosis [8,9]. For example, according to American scientists, HPS was revealed on contrast Echo-CG in 38 % of patients with chronic liver disease, but only 17.5 % of these patients were diagnosed with hypoxemia [30]. The frequency of HPS detection was the highest when using the alveolar–arterial gradient (A-a gradient) as a more sensitive marker of hypoxemia, as well as screening of asymptomatic patients with liver cirrhosis [10].

Pathogenesis

The HPS pathogenesis is not fully understood, since the literature contains contradictory data. This syndrome is most often associated with severe liver cirrhosis which is accompanied by portal hypertension syndrome; However, it can also occur in patients with other disease areas: non-cirrhotic portal fibrosis (idiopathic portal hypertension) and extrahepatic portal vein obstruction [11, 12].

Table 1. *Diagnostic criteria for hepatopulmonary syndrome (with changes) [6, 7]*

Parameter	Definition
Oxygenation	PaO_2 <80 mmHg or PA–a,O_2 > 15 mmHg; > 20 mmHg for patients aged > 64 years old
Pulmonary vasodilation	Positive CEE or 99mTcMAA, showing the presence of a shunt >6 %
Liver disease	Cirrhosis and/or liver failure

Note: CEE — contrast-enhanced echocardiography, PaO_2 — arterial oxygen tension, PA-a,O_2 — alveolar-arterial oxygen tension difference, 99mTcMAA — perfusion lung scanningusing technetium-99m-labelled macroaggregated albumin

Table 2. *Grading of severity of hepatopulmonary syndrome [6]*

Stage	PA–a,O_2, mmHg	PaO_2, mmHg
Mild	≥15	≥ 80
Moderate	≥15	≥ 60 <80
Severe	≥15	≥ 50 <60
Very severe	≥15	<300 on 100 % O_2

Note: PaO_2 — arterial oxygen tension, PA-a,O_2 — alveolar-arterial oxygen tension difference

The general information on HPS pathogenesis can be obtained in animal experiments. The most frequently used method was ligation of the common bile duct in rats, which caused secondary biliary cirrhosis in these rats and resulted in decreased blood oxygenation and intrapulmonary vasodilation [13]. The studies on experimental models demonstrated that the key cause of HPS formation is capillary dilation and formation of intrapulmonary shunts, leading to decreased blood oxygenation due to violation of ventilation/perfusion relationship and increased alveolar-arterial gradient. The study authors stated predominant dilation of pulmonary pre-capillary and capillary vessels up to 15–100 μm (normal diameter of these vessels varies from 8 to 15 μm), increase in their number and dilation of pleural capillaries [14].

The studies revealed a decrease in the lung diffusion capacity (DL_{CO}) in patients with HPS and normal ventilatory lung capacity. This decrease can be explained by the development of a pulmonary shunt and thickening of alveolar-capillary membrane against endotheliitis [7, 15-16]. Occurrence of the latter is related to activation of endothelin synthesis produced by cholangiocytes in the liver. These findings are confirmed on experimental rat models. Zhang J et al. have found that proliferating cholangiocytes produce endothelin-1 (ET-1), activating the pulmonary endothelin receptor-B (ETB), which, in its turn, mediates activation of endothelial NO synthase (eNOS), a NO precursor that leads to vascular endothelial inflammation [17–20]. In clinical studies in patients with HPS conducted in 1997–1998, Rolla G et al. noted an increased content of NO in the exhaled air, attributing it to the increased NO production by the pulmonary vascular endothelium. After liver transplantation, the level of exhaled NO level normalized [21, 22], which also confirms the role of endotheliitis in the HPS formation.

In HPS, the loss of pulmonary capillary tone and inhibition of pulmonary vasoconstrictors such as endothelin-1, serotonin, angiotensin II, histamine, prostaglandin and increased nitric oxide (NO) production are considered to be the main cause of pre-capillary and capillary vasodilation [16]. Moreover, according to the studies, carbon monoxide (CO) and tumor necrosis factor alpha (TNF-α) are among the mediators that cause pulmonary vasodilation [17, 18]. Rabiller A. (2002), Sztrymf B. (2005), Zhang H.Y. (2007) et al. considered the theory of bacterial translocation of intestinal flora from patients with portal hypertension, which leads to macrophage infiltration of lung parenchyma as another mechanism of pulmonary vasodilation. This hypothesis is supported by the positive effect of norfloxacin treatment in the experimental rat model of cirrhosis [23–25].

There is another hypothesis that hypoxemia in patients with HPS may be related to thickening of the alveolar-capillary membrane due to collagen accumulation during chronic inflammatory process caused by endotheliitis and against the background of bacterial translocation of intestinal flora [26–28].

Clinical presentation

The main clinical sign of HPS is progressing dyspnea. This was supported by the data from a multicenter study conducted by Michael B. Fallon and Michael J. Krowka in the USA in 2008. The researchers found that the incidence of dyspnea in patients with HPS is 1.65 greater than in patients without this syndrome [2]. A specific feature of dyspnea in HPS is the occurrence of platypnea and orthodexia, which are highly specific, but not pathognomonic signs. Platypnea is dyspnea that increases when moving the patient to an upright position, while orthodexia is a decrease in partial oxygen pressure by more than 4 mm Hg and/or a decrease in oxygen saturation by more than 5 % when the patient is upright [29]. It is considered that the cause of their development is intensification of ventilation-perfusion mismatch following a change in the body position due to an increase in the pulmonary shunt effect [30].

It should be noted that HPS can have an asymptomatic course, especially in patients with mild hypoxia. Observations show that dyspnea is more frequent in patients with a decrease in PaO_2 of less than 70 mm Hg, which can explain late detection of this syndrome [31].

Physical examination of a patient with HPS may reveal telangiectasia, cyanosis, drumstick fingers and watch-glass nails [32]. In patients with chronic liver disease and telangiectasia, the prevalence of HPS is greater than in the patients without this symptom [33].

Therefore, all patients with chronic liver disease complaining of dyspnea should be screened for HPS.

Methods of intrapulmonary vasodilation diagnosis

Contrast-enhanced transthoracic echocardiography with foamed saline is considered as the gold standard of intrapulmonary vasodilation diagnosis. The advantage of this method is low invasiveness and sufficient sensitivity. Common normal saline is shaken to form microbubbles >10 μm; after that it is injected into a peripheral vein of the arm during a four-chamber transthoracic Echo-CG to assess whether the foamy liquid enters the left heart. The size of pulmonary capillaries normally varies in the range 8 to 15 μm, therefore microbubbles cannot pass. However, in the presence of a dilated vascular bed and/or arteriovenous shunting, microbubbles are not captured by the lungs and reach the left heart within 3–6 cardiac cycles after their first appearance in the right atrium [34].

Although contrast-enhanced transesophageal Echo-CG is a more sensitive method of intrapulmonary vasodilation determination, it is not recommended for patients with cirrhosis because of a potential risk of damage to varicose esophageal veins [35, 36].

Another instrumental method for hepatopulmonary syndrome diagnosis is radioisotope scanning with macroaggregated albumin. In the presence of intrapulmonary vasodilation, technetium-labeled albumin particles can reach extrapulmonary sites and are found in the brain, kidneys, and other organs. Cerebral tissue absorption is considered abnormal if it is ≥6 % [3]. The advantage of this method is the quantitative assessment of intrapulmonary vasodilation, as well as its high specificity. Its main disadvantage is the impossibility of differential diagnosis of intracardiac and intrapulmonary shunting, as well as its lower sensitivity [37].

Additional study methods

The most common methods that are used to rule out concomitant pulmonary diseases are chest X-ray and chest computed tomography (chest CT). There are no convincing data on the use of these methods directly for diagnosis of HPS [6,38]. According to the retrospective study conducted by Yingming Amy Chen et al. in Canada in 2016, chest CT cannot be used for HPS diagnosis, since it can only find systemic vasodilation. The authors believe that bilateral nodular or reticular changes in the basal areas of the lungs caused by dilation of the peripheral pulmonary arteries in the lower lobes can still be detected on chest X-ray in patients with chronic liver disease. These data can be confirmed by chest CT: patients with chronic liver disease show an increase in the ratio of segmental arterial diameter to segmental bronchial diameter >2 with normal size of the central pulmonary arteries. However, this sign may be seen in patients with and without HPS, for example in case of pulmonary artery thromboembolia development. The conducted study shows that signs of systemic vasodilation in liver disease can be revealed by chest CT; however, these radiological signs do not have a significant role in the HPS diagnosis [39]. Only two small-scale studies have been found, according to which dilation of the basilar pulmonary arteries is more frequently detected in patients with HPS compared to the patients with cirrhosis but without this syndrome [40–41].

Angiopulmonography is also rarely used for HPS diagnosis. This is due to the invasiveness of this method and its low sensitivity for intrapulmonary dilation detection. It is indicated in patients with severe hypoxemia and a low response to 100 % oxygen inhalation, as well as to make a decision on embolization of arteriovenous shunt [42].

In patients with HPS, impairment of external respiratory function can be manifested as a decrease in vital capacity and forced expiratory volume in 1 second (FEV_1) [2, 43].

The test for diffusing capacity of the lungs for carbon monoxide (DL_{CO}), which is often decreased in patients with HPS, is a more sensitive functional method of pulmonary function testing in such patients [2,43]. Based on the data from the study conducted by Moon-Seung Park and Min-Ho Lee in South Korea in 2012, diffusion defects are more common in patients with progressive liver disease and correlate with liver severity. The authors clearly demonstrated that minimal changes in spirometry parameters in the form of a mild decrease in total lung capacity in patients with HPS was associated with is a decrease in pulmonary diffusion capacity. Therefore, changes in DL_{CO} may be an important diagnostic marker to predict hepatopulmonary syndrome development in patients with chronic liver disease [44].

The data from the study conducted by Z. Alipour et al. in 2020 to compare lung scintigraphy with technetium-99m human serum albumin and contrast-enhanced Echo-CG can be interesting. The obtained data showed that following lung scintigraphy findings, HPS was detected in 13 patients (48.1 %), compared to 5 (18.51 %) patients who were diagnosed using contrast-enhanced Echo-CG [45].

In 2022, A. Singhai et al. proposed the use of the 6-minute walk test as the screening method to reveal the risk of HPS development in patients with chronic liver diseases. The patients were asked to walk at their own tempo; the pulse oximetry was conducted at the beginning and at the end of the test. The test was positive at SpO2 <94 % or a decrease in SpO2 by ≥3 % of baseline. The study included 100 patients: 21 (21 %) patients were diagnosed with HPS based on the detected intrapulmonary shunts by contrast-enhanced transthoracic Echo-CG and arterial hypoxemia by arterial blood gas test. The 6-minute walk test was positive in 20 (95.23 %) patients with hepatopulmonary syndrome. The authors have demonstrated that the 6-minute walk test is an important instrument of this syndrome screening, having sensitivity of 95.24 % and specificity of 92.41 % [46].

Treatment

According to the published data, liver transplantation is the only effective method of HPS treatment that is available nowadays. In patients with HPS after liver transplantation, the five-year survival rate is 76 %–88 %, the ten-year survival rate is 64 % [47,48]. In patients without liver transplantation, the five-year survival rate is 5 %–12 %. There is evidence of improved blood gas

parameters (an increase in PaO2, a decrease in A-a gradient) 6–12 months after liver transplantation in patients with HPS [49,50]. Moreover, in patients who were on continuous oxygen therapy, the need for it often significantly decreases or disappears completely after liver transplantation [51].

Another method of surgical treatment for HPS can be transjugular intrahepatic portosystemic shunt (TIPS), which reduces hypoxemia due to reduced severity of portal hypertension. However, currently there are not enough studies, meeting the requirements of evidence-based medicine to form a final opinion on the effectiveness of this method in patients with HPS [52, 53]. The same could be said about embolization of arteriovenous shunts [42], which is associated with better oxygenation after embolization of arteriovenous malformation by placing the spiral into the feeding artery proximal to the malformation [54].

In patients with HPS, long-term oxygen therapy is recommended for severe hypoxemia; however, but no sufficient data on the effect of oxygen therapy on survival rate and disease prognosis could be found. There are two clinical case reports published in 2007 by Japanese researches describing liver function improvement following long-term oxygen therapy [45].

Currently available non-surgical methods of treatment for HPS are also low effective or poorly studied. The majority of these studies were conducted on animals [55–60].

During the literature search, 13 articles on non-surgical methods of HPS treatment in humans have been found. In these studies, the main purposes of treatment were NO-mediated pulmonary vasodilation and angiogenesis induction by proinflammatory cytokines. The most well-studied substance is pentoxifylline, a TNF-α inhibitor that reduces NO production by inhibiting eNOS. However, the results of its use in patients with HPS are contradictory [61]. Gupta LB et al. (2008) have found that pentoxifylline 400 mg three times daily improved oxygenation and reduced the level of TNF-α in 9 patients with HPS [62]. However, the results of another group of researchers demonstrated the absence of a significant therapeutic effect in patients with the studied syndrome and significant gastrointestinal side effects [63].

Garlic in the treatment of HPS has been shown to have unexpected efficacy (although it has not been tested on animals, and its true mechanism of action is not understood). A comparative study to assess garlic oil capsules versus placebo with a total sample size of 41 patients with HPS, and another non-controlled study involving 15 patients demonstrated favorable results with improved oxygenation and other symptoms [64, 65].

When injected intravenously, methylene blue, which is an oxidant limiting NO-mediated vasodilation by blocking stimulation of soluble guanylate cyclase by NO, reduced intrapulmonary shunting and improved oxygenation in experimental models and in a few patients with HPS [55, 56].

Indometacin (a cyclooxygenase inhibitor) was found to have a positive effect, which was considered to be due to a decrease in the synthesis of vasodilator eicosanoids that can impair gas exchange [66]. According to H. Silva et al., mycophenolate mofetil (an immunosuppressant) was also demonstrated to be effective in HPS treatment. However, neither indometacin nor mycophenolate have been studied in large randomized clinical trials [67].

There have been no data obtained on the efficacy of octreotide (somatostatin analog) in patients with liver cirrhosis [68], norfloxacin (antibiotic) [57], N-nitro-L-arginine methyl ester (NO synthesis inhibitor) [69], almitrine bismesylate (analeptic) [70], paroxetine (antidepressant) [71] in patients with HPS.

It should be noted that experimental studies have demonstrated the efficacy of norfloxacin in the treatment of HPS in rats [25]. This may be explained by the fact that the HPS rate model is significantly different from HPS with liver cirrhosis in humans. In the experimental model, the liver damage was caused by ligation of the bile ducts, whereas in the patient with HPS, the causes of liver cirrhosis are multiple [57].

Sorafenib (an antitumor agent) can become a promising option: in experimental models it improved oxygenation by reducing VEGH-mediated angiogenesis (VEGH, vascular endothelial growth factor) and suppressing eNOS activation by inhibiting tyrosine kinase receptor [58,59].

Another medicinal product that requires further study may be rosuvastatin. In 2015, Ching-Chih Chang et al. came to the view that it reduces A-a gradient, hypoxemia, intrapulmonary shunts, and VEGF and TNF-α plasma levels in experimental rat models, which may allow its use in the treatment of HPS [60]. However, it should be noted that there are currently insufficient data on the complete safety of this medicinal product in patients with liver cirrhosis.

Conclusion

Based on the analysis of the data published from January 2017 to August 2022, the following conclusions may be made.

Hepatopulmonary syndrome is a common and severe complication of chronic liver disease, which can worsen patients' quality of life and increase mortality rates.

Currently, there are clear criteria for HPS diagnosis; however, their use in routine practice is still difficult due to its invasiveness, inaccessibility, and high cost.

According to the published data, if hepatopulmonary syndrome is suspected in a patient with liver cirrhosis, hypoxemia assessment may be recommended, starting with oxygen saturation evaluation by pulseoximetry in a sitting or lying position [10, 72]. However, the evidence base of these recommendations was insufficient, and the patient should undergo further examination in the specialized center.

The available data on the role of respiratory function, diffusing capacity of the lungs, lung scintigraphy, Echo-CG with targeted examination of right heart function, 6-minute walk test in the diagnosis of HPS are scattered and insufficiently systematize.

It is necessary to continue the search for new methods of HPS diagnosis and to develop doctor-support programs (algorithms) for its early detection. This approach will improve the prognosis in patients with chronic liver disease and allow general practitioners to carry out their screening in order to identify and timely refer such patients to a liver transplantation center.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2023-13-3-213-223
УДК [616.24-002-036.12-06:616.13-004.6]-07
EDN: PKZRCJ

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АНАЛИЗ БИОМАРКЕРОВ ВОСПАЛЕНИЯ В КОНДЕНСАТЕ ВЫДЫХАЕМОГО ВОЗДУХА У ПАЦИЕНТОВ С ХОБЛ В СОЧЕТАНИИ С ОБЛИТЕРИРУЮЩИМ АТЕРОСКЛЕРОЗОМ АРТЕРИЙ НИЖНИХ КОНЕЧНОСТЕЙ

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Analysis of Inflammation Biomarkers in Exhaled Breath Condensate in Patients with COPD Combined with Peripheral Arterial Disease

Резюме

Актуальность. Хроническая обструктивная болезнь легких (ХОБЛ) является одной из наиболее значимых респираторных патологий, что связано с ее высокой распространенностью и влиянием на прогноз. Частота обострений и коморбидность — важные факторы, влияющие на течение ХОБЛ. Считается, что локальное и системное воспаление могут лежать в основе гетерогенного течения ХОБЛ. В этой связи оценка активности локального воспаления в дыхательных путях может быть полезна для оценки течения ХОБЛ. **Цель.** Изучить молекулярные механизмы ХОБЛ и оценить биомаркеры воспаления в конденсате выдыхаемого воздуха у пациентов с ХОБЛ с частыми обострениями в сочетании с периферическим атеросклерозом. **Материалы и методы.** Проведен биоинформационный анализ данных из Gene Expression Omnibus (GEO) с целью изучения генной онтологии дифференциально экспрессируемых генов при ХОБЛ. Далее проведено исследование провоспалительных цитокинов интерлейкина — 1 бета (interleukin (IL)-1β) и фактора некроза опухоли альфа (tumor necrosis factor alpha (TNFα)) в конденсате выдыхаемого воздуха (КВВ) у пациентов с ХОБЛ с частыми обострениями без сопутствующих атеросклеротических сердечно-сосудистых заболеваний (АССЗ) и у пациентов с ХОБЛ с частыми обострениями и облитерирующим атеросклерозом артерий нижних конечностей (ОААНК) в сравнении со здоровым контролем. **Результаты.** Дифференциально экспрессируемые гены вовлечены в биологические процессы и сигнальные пути по Киотской энциклопедии генов и геномов (Kyoto Encyclopedia of Genes and Genomes, KEGG пути), связанные с иммунным ответом, которые могут связывать развитие и прогрессирование ХОБЛ и атеросклероза. У пациентов с ХОБЛ в сочетании с атеросклерозом наблюдались более высокие значения IL-1β и TNFα в КВВ, по сравнению с контролем ($p < 0,001$). У пациентов с ХОБЛ с частыми обострениями и ОААНК были обнаружены наиболее высокие уровни IL-1β и TNFα в КВВ в сравнении с пациентами без АССЗ ($p=0,0038$ и $p=0,0005$ соответственно). **Вывод.** У пациентов с ХОБЛ с частыми обострениями и ОААНК повышены уровни TNFα и IL1β в КВВ, что может свидетельствовать о наличии локального воспаления в дыхательных путях, выраженность которого связана с клиническим течением ХОБЛ.

Ключевые слова: *ХОБЛ, воспаление, конденсат выдыхаемого воздуха, иммунная система, цитокины*

Конфликт интересов

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

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Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 06.03.2023 г.
Принята к публикации 17.05.2023 г.

Для цитирования: Котляров С.Н., Сучков И.А., Урясьев О.М. и др. АНАЛИЗ БИОМАРКЕРОВ ВОСПАЛЕНИЯ В КОНДЕНСАТЕ ВЫДЫХАЕМОГО ВОЗДУХА У ПАЦИЕНТОВ С ХОБЛ В СОЧЕТАНИИ С ОБЛИТЕРИРУЮЩИМ АТЕРОСКЛЕРОЗОМ АРТЕРИЙ НИЖНИХ КОНЕЧНОСТЕЙ. Архивъ внутренней медицины. 2023; 13(3): 213-223. DOI: 10.20514/2226-6704-2023-13-3-213-223. EDN: PKZRCJ

Abstract

Background. Chronic obstructive pulmonary disease (COPD) is one of the most significant diseases due to its high prevalence and impact on prognosis. The frequency of exacerbations and comorbidity are important factors influencing the course of COPD. It is believed that local and systemic inflammation may underlie this heterogeneous course of COPD. In this regard, assessment of local inflammation activity in the respiratory tract may be useful to assess the course of COPD. **Aim.** To study molecular mechanisms of COPD and assess inflammation biomarkers in the exhaled breath condensate (EBC) in patients with COPD with the phenotype of frequent exacerbations combined with peripheral atherosclerosis. **Materials and Methods.** Bioinformatic analysis of data from Gene Expression Omnibus (GEO) was performed to examine gene ontology of differentially expressed genes in COPD. Proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNFα) in EBC in COPD patients without concomitant atherosclerotic cardiovascular disease (ASCVD) in the stable course phase, in patients with COPD with the phenotype of frequent exacerbations and peripheral artery disease (PAD) compared with healthy controls were examined. **Results.** Differentially expressed genes are involved in biological processes and signaling pathways according to the Kyoto Encyclopedia of Genes and Genomes (KEGG pathway) associated with the immune response that may link the development and progression of COPD and atherosclerosis. Patients with COPD combined with atherosclerosis had higher values of IL-1β and TNFα in EBC compared with controls (p <0.001). COPD patients with frequent exacerbations and PAD had the highest levels of IL-1β and TNFα in EBC compared with patients without ASCVD (p=0.0038 and p=0.0005, respectively). **Conclusion.** TNFα and IL1-β levels in EBC are elevated in COPD patients with frequent exacerbations and PAD, which may indicate the presence of local inflammation in the airways, the severity of which is associated with the clinical course of COPD.

Key words: *COPD, inflammation, exhaled breath condensate, immune system, cytokines*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 06.03.2023
Accepted for publication on 17.05.2023

For citation: Kotlyarov S.N., Suchkov I.A., Uryasev O.M. et al. Analysis of Inflammation Biomarkers in Exhaled Breath Condensate in Patients with COPD Combined with Peripheral Arterial Disease. The Russian Archives of Internal Medicine. 2023; 13(3): 213-223. DOI: 10.20514/2226-6704-2023-13-3-213-223. EDN: PKZRCJ

BODE — B — body mass index, O — obstruction, D — dyspnea (одышка), E — exercise tolerance, BP — Biological Processes, CC — Cellular Components, FDR — false discovery rate, GEO — The Gene Expression Omnibus, GO — GENE ONTOLOGY, GOLD — Global Initiative for Chronic Obstructive Lung Disease, IL-1β — Interleukin1β, KEGG — Kyoto Encyclopedia of Genes and Genomes, MCODE — Molecular Complex Detection, MF — Molecular Functions, mMRC –Modified Medical Research Council Dyspnea Scale, NCBI –The National Center for Biotechnology Information, PAD — peripheral artery disease, PPI — Protein-Protein Interaction, STRING — Search Tool for the Retrieval of Interacting Genes database, TLR– Toll-like receptor, TNFα — Tumor necrosis factor alpha, ACVD — atherosclerotic cardiovascular diseases, CI– confidence interval, CHD — coronary heart disease, EBC — expired breath condensate, LDLPs — low-density lipoproteins.; LLAOA — obliterating atherosclerosis of lower limb arteries, FEV_1 — forced expiratory volume per 1 second, COPD — chronic obstructive pulmonary disease

Introduction

The topicality of the problem of a combination of chronic obstructive pulmonary disease (COPD) and atherosclerotic cardiovascular diseases (ACVD) is caused by their high medical and social significance and economic burden both for patients and their families and for the healthcare in general. These diseases have high incidence and are among main causes of permanent disability and death [1]. Both conditions have several common risk factors, e.g., smoking and ageing, and are associated with a higher risk of unfavourable outcome. Therefore, it is essential to search for new diagnostic tools which will increase the efficiency of early diagnosis and management of such patients. Recently, the clinical significance of COPD and obliterating atherosclerosis of lower limb arteries (LLAOA) is of interest, since the patients with these diseases can have a higher mortality and morbidity risks. Studies show that patients with COPD and LLAOA are at a considerably higher risk of death compared to patients with any one of these conditions. It is assumed that a higher mortality risk is caused by general factors and the impact of these conditions on the cardiovascular system. Patients with COPD and LLAOA are also at a higher risk of hospitalisation and have lower quality of life. Understanding the clinical significance of both these conditions and their common risk factors is essential for development of an efficient management strategy and improved treatment [2]. It is worth mentioning that very

often GPs downplay the problem of COPD and LLAOA comorbidity and rather target other atherosclerosis locations, such as coronary heart disease.

The pathogenesis of atherosclerosis and COPD includes an array of various mechanisms with sophisticated regulation paths [3–5]. In the pathogenesis of both COPD and atherosclerosis, an important role is played by inflammation, the analysis of biomarkers of which is described in numerous papers [6]. COPD is known to affect smokers and is characterised by progressive disease caused by chronic airways inflammation. Various immune cells, such as macrophages and neutrophils, contribute to inflammation. They express an aray of chemokines and inflammatory cytokines that facilitate recruitment of new cells and make inflammation even worse [6]. In addition to a local bronchial inflammation, inflammation in COPD has also a system component underlying comorbid associations with other diseases, such as atherosclerosis [7]. The growing number of evidences contribute to the understanding that vascular wall inflammation is significant for atherogenesis. Endothelial cells, a monolayer of arterial walls, have a number of functions; they ensure a barrier and regulate vascular hemodynamics and other cells behaviour in vascular wall and blood flow [8,9]. Endothelial dysfunction is believed to be a key early event in atherogenesis [10]. Systemic inflammation commonly observed in COPD facilitates endothelial dysfunction, cell recruitment from the blood flow to the vascular wall, and atherosclerosis progression. Smoking-associated oxidative stress is another significant factor contributing to atherosclerosis in COPD [11]. Macrophages which differentiate in the vascular walls from recruited monocytes and macrophage progenitor cells in tissues participate in the intake of low-density lipoproteins (LDLPs), thus giving rise to in foam cells[12]. Macrophages in an atherosclerosis plaque have different polarisation, they are also of pro-inflammatory phenotype which is known to produce pro-inflammatory cytokines that facilitate inflammation [13].

Taking into account the role of airways inflammation in COPD, the information on the evaluation of inflammation markers in expired breath condensate (EBC) [14]can be of interest. Expired air is known to be saturated with evaporated water, which can condensate when cooled. Despite the fact that condensate consists primarily of evaporated water, it also contains aerosols of various particles from the lower respiratory tract. Thus, a local bronchial inflammation in COPD is a source of inflammatory agents in EBC. Inflammation biomarkers found in EBC can be clinically significant as they reflect local processes in bronchi and are a valuable source of diagnostic information [15].

EBC is a biological material obtained with the use of non-invasive methods, which contains a lot of various biomolecules, including cytokines, that can give an idea of the pathophysiology of airways inflammation [16]. EBC biomarkers were proposed as sensitive and specific indicators of pulmonary inflammation and oxidative stress and they can provide important information on the pathogenesis and clinical course of COPD. Also, such pro-inflammatory cytokines as tumour necrosis factor-α (TNFα) and interleukin (IL)-1β, were found in EBC of patients with COPD and can be associated with the nature of COPD [14]. It is assumed that the local inflammation intensity can be associated with systemic inflammation and development of comorbidities [6]. COPD exacerbations are caused by inflammation intensification and are an important COPD-affecting factor.

Thus, molecular mechanisms underlying COPD development and progression, as well as mechanisms that bind COPD and LLAOA are of huge research and clinical interest.

The objective of this study is to evaluate inflammation biomarkers in EBC of patients with frequent COPD and LLAOA.

Materials and Methods

Identification of molecular mechanisms of COPD pathogenesis

We analysed the GSE5058 data set, which includes the data on the gene expression levels in bronchial epithelium samples of patients with COPD received from The Gene Expression Omnibus (GEO), The National Center for Biotechnology Information (NCBI), by fiberoptic bronchoscopy from 12 healthy non-smokers and 6 smokers with COPD [17]. The data were obtained using GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. The data were normalised using Mas5 normalisation. GEO is an international open repository archiving and circulating data on microchips, next generation sequencing and other forms of high-performance functional genomics data provided by the research community [18].

Differentially expressed genes were evaluated with the help of a bioinformatic analysis in experimental groups using limma package in Bioconductor, R (v. 4.0.2) [19]. For analysis, data were normalised including log2 transformation and quantile normalisation. In order to adjust the level of statistical significance for multiple comparisons, the algorithm by Benjamini & Hochberg (false discovery rate, FDR) was used. The conditions for the screening of differentially expressed genes were the absolute value of logFC >1 and p value of FDR ≤ 5 %.

Protein-protein interactions (PPIs) of protein products of common differentially expressed genes were evaluated using an online tool, Search Tool for the Retrieval

of Interacting Genes database (STRING) [20]. Correlations bewteen differentially expressed genes were analysed using Cytoscape Network Analyzer plug-in module [21]. Also, gene clusters in the PPI network were searched for using Molecular Complex Detection, MCODE v. 2.0.2 [22].

The most important genes in the network were identified using cytoHubba app in Cytoscape (v. 3.9.1) [23]. Cytoscape cytoHubba plug-in was used for node ranking in the network by their network properties. Main proteins were analysed, predicted, and visualised in molecular PPI networks using Maximal Clique Centrality (MCC) algorithm. Biological processes Gene Ontology (GO) and KEGG paths for the key genes in teh network were identified with the help of GEO2Enrichr [24], ShinyGO v0.741 [25] and g:Profiler; [26] gene ontology (GO) was analysed in accordance with their biological processes obtained from THE GENE ONTOLOGY RESOURCE [27]; signal paths were identified according to KEGG (Kyoto Encyclopedia of Genes and Genomes) [28,29] and Reactome database [30]; and their functional enrichment and visualisation were performed in Weishengxin. The p value of < 0.05 adjusted using the algorithm by Benjamini & Hochberg was set as a threshold for identification of biological processes and paths.

Clinical characteristics of study subjects

The following groups wer formed in accordance with the study objective: 20 patients with frequent COPD without ACVD (males, mean age: 60.55 (95 % CI 57.21; 63.89) ears); 20 patients with frequent COPD and LLAOA (males, mean age: 63.9 (95 % CI 61.54; 66.26) years; and controls: 20 healthy subjects (males, mean age: 62.85 (95 % CI 61.6; 64.1) years).

All subjects provided their informed consent for participation and met inclusion criteria (no exclusion criteria).

Inclusion criteria for group 1 (patients with COPD without ACVD):

1. Inactive COPD
2. No clinical manifestations of ACVD

Inclusion criteria for group 2 (patients with COPD and LLAOA):

1. Inactive COPD
2. Clinical manifestations of LLAOA

Inclusion criteria for controls (healthy subjects):

1. Absence of broncho-obstructive diseases
2. No clinical manifestations of ACVD

Exclusion criteria:

1. Acute infectious diseases
2. Acute coronary heart disease (CHD)
3. Renal and hepatic insufficiency
4. Tumours
5. Mental disorders
6. Constant administration of anti-inflammatory agents, system glucocorticosteroids
7. Bronchial asthma

COPD was diagnosed on the basis of clinical data, medical history, and spirometery results using Global Initiative for Chronic Obstructive Lung Disease (GOLD) [31] criteria. Disease exacerbation was assessed using the criteria developed by N. R. Anthonisen.[32] In accordance with the clinical recommendations for the management of chronic obstructive pulmonary disease approved by the Scientific and Practical Board at the Ministry of Health of the Russian Federation, frequent exacerbations occur at least twice a year. Patients enrolled in this study had 3 and more exacerbation a year. LLAOA was stage IIB according to the classification developed by A. V. Pokrovskiy–Fontaine and was diagnosed on the basis of clinical and ultrasound results in accordance with the National Recommendations for the Diagnosis and Management of Lower Limb Arterial Diseases [33].

Dyspnea was evaluated using mMRC scale (modified Medical Research Council Dyspnea Scale); comorbidities were evaluated with Charlson comorbidity index [34]. Also, the BODE index was calculated which is a multiple index comprising the following parameters: B — body mass index; O — obstruction; D — dyspnea; E — exercise tolerance [35].

Clinical characteristics of patients enrolled in the study are presented in Table 1.

EBC sampling

EBC was sampled using a portable R-Tube device (Respiratory Research, USA) in accordance with the manufacturer's method. Examination was perform before noon after a thorough mouth rinse with distilled water. EBC was sampled for 10 minutes using an RTube colled to -20˚C. Collected samples were placed into polypropylene tubes, frozen, and stored in a freezer at -80ºC until analysis.

Enzyme-linked immunosorbent assay

TNFα and IL-1β levels in EBC were measured using appropriate ELISA kits. Cytokine concentrations were used with Cloud-Clone Corp. kits (USA). High Sensitive ELISA Kit for TNFa and ELISA Kit for IL-1β had sensitivity of 0.52 pg/mL and 0.49 pg/mL, respectively.

Statistical data processing

Statistical data processing was performed using MedCalc (v. 20.1.4) and R packages (v. 4.2.2). Categorical data were compared between subgroups using chi square and continuous variables with the help of Student t-test or Mann–Whitney–Wilcoxon test, ANOVA or ANOVA

Table 1. *Characteristics of comparison groups*

Parameter	Control group (n=20)	Patients with COPD without ASCVD (n=20)	Patients with COPD and PAD (n=20)	p
Age, years	62,85 (95 % ДИ 61,6; 64,1)	60,55 (95 % ДИ 57,21; 63,89)	63,9 (95 % ДИ 61,54; 66,26)	$p^{1,2}$= 0,1877 $p^{1,3}$= 0,4344 $p^{2,3}$ =0,1033
Smokers	0	100 %	100 %	-
Pack-years index	0	35,8 (95 % ДИ 31,09; 40,51)	39,2 (95 % ДИ 35,4; 43)	p= 0,0861
FEV_1, % predicted	98,58 (95 % ДИ 97,82; 99,34)	44,96 (95 % ДИ 36,97; 52,96)	44,21 (95 % ДИ 38,28; 50,15)	$p^{1,2}$ <0,001 $p^{1,3}$ <0,001 $p^{2,3}$ =0,4516
Стадия ХОБЛ/ COPD stage	-	2,85 (95 % ДИ 2,54; 3,16)	3,0 (95 % ДИ 2,66; 3,34)	p= 0,4528
Dyspnea, MRC	0,65 (95 % ДИ 0,27; 1,03)	2,85 (95 % ДИ 2,47; 3,23)	3,15 (95 % ДИ 2,77; 3,53)	$p^{1,2}$ <0,001 $p^{1,3}$ <0,001 $p^{2,3}$ = 0,1339
Body mass index, kg/m^2	26,04 (95 % ДИ 25,04; 27,05)	28,15 (95 % ДИ 26,32; 29,98)	26,93 (95 % ДИ 25,44; 28,42)	$p^{1,2}$ =0,0231 $p^{1,3}$= 0,2706 $p^{2,3}$ =0,2706
Charlson Comorbidity Index	1,45 (95 % ДИ 0,8; 2,1)	4,6 (95 % ДИ 3,87; 5,33)	7,4 (95 % ДИ 6,37; 8,43)	$p^{1,2}$ <0,001 $p^{1,3}$ <0,001 $p^{2,3}$ <0,001
Arterial hypertension	9 (45 %)	11 (55 %)	19 (95 %)	$p^{1,2}$ =0,593 $p^{1,3}$ <0,001 $p^{2,3}$ =0,0027
Coronary artery disease	0	0	20 (100 %)	-
Chronic heart failure	0	3 (15 %)	10 (50 %)	$p^{2,3}$ <0,001
Total cholesterol, mmol/l	4,68 (95 % ДИ 4,47; 4,89)	4,83 (95 % ДИ 4,27; 5,39)	6,27 (95 % ДИ 5,81; 6,72)	$p^{1,2}$= 0,6142 $p^{1,3}$ <0,001 $p^{2,3}$ <0,001
LDL, mmol/l	2,7 (95 % ДИ 2,47; 2,93)	2,85 (95 % ДИ 2,49; 3,21)	3,96 (95 % ДИ 3,61; 4,31)	$p^{1,2}$ =0,5054 $p^{1,3}$ <0,001 $p^{2,3}$ <0,001
Blood glucose, mmol/l	4,43 (95 % ДИ 4,16; 4,7)	5,02 (95 % ДИ 4,59; 5,45)	6,14 (95 % ДИ 5,38; 6,9)	$p^{1,2}$= 0,0427 $p^{1,3}$ <0,001 $p^{2,3}$= 0,0093

Kruskal-Wallis test after evaluation of criteria for teh use of parametric tests. Differences were statistically significant at $p < 0.05$. Data were presented with 95 % confidence interval (CI) of the mean.

Ethical approval

The clinical part of the study was conducted in accordance with the ethical principles of the Good Clinical Practice, Declaration of Helsinki, medical regulations of the Russian Federation and was approved by the Local Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Ryazan State Medical University of the Ministry of Health of Russia. All patients received detailed information on participation in the study and consented to take part in the study.

Results

Identification of differentially expressed genes and analysis of their gene ontology

The biological information analysis made it possible to identify 1355 differentially expressed genes with higher expression and 370 differentially expressed genes with lower expression (Fig. 1).

The obtained differentially expressed genes with up-regulation were used to plot a protein-protein interactions network where MCODE plug-in was used to identify 35 clusters. Further analysis was performed using the most significant cluster from the common subnetwork with MCODE value of 16.857 and 36 nodes (**Fig. 2**). cytoHubba plug-in was used to identify the following gene concentrators (**рис. 3**) in the selected cluster.

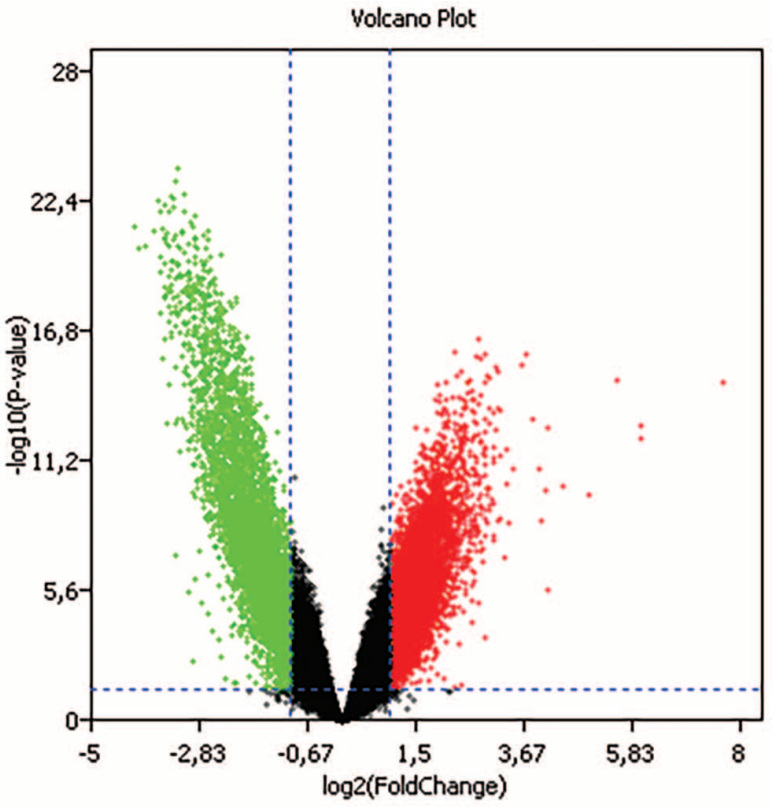

Figure 1. *Volcano plot characterizing differentially expressed genes*

Note: The colored dots in the graph indicate genes that show differential expression with | log2 FC |> 1 and p <0.05, while the black dots do not meet these criteria. Red dots indicate differentially expressed genes with up-regulation and are displayed on the right side of the graph, and green dots indicate differentially expressed genes with down-regulation (they are displayed on the opposite side)

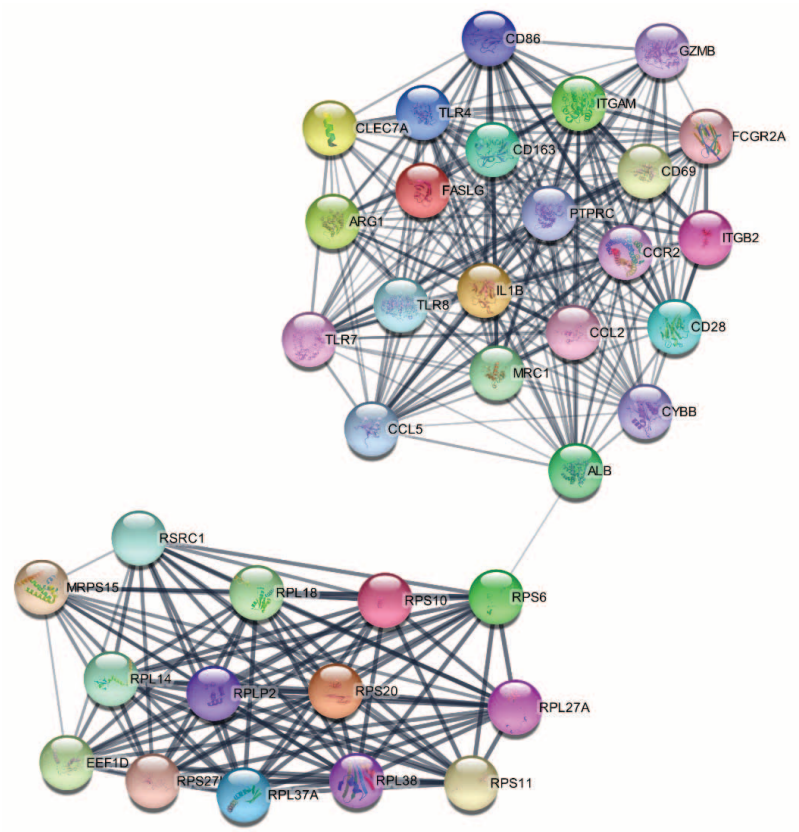

Figure 2. *Cluster 1 identified in a network of protein-protein interactions derived from differentially expressed genes in COPD*

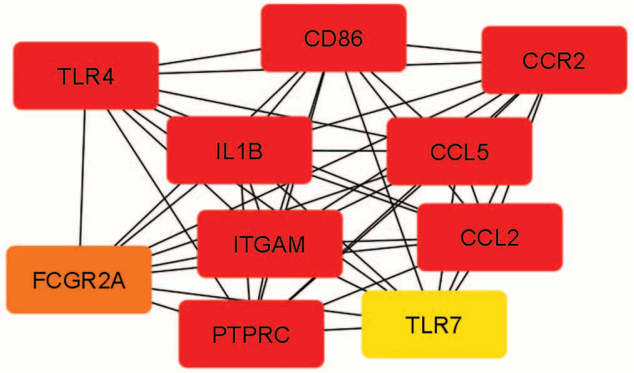

Figure 3. *The most important genes identified in the PPI network using the MCC algorithm in CytoHubba*
Note: The hub genes are ranked as follows: the most important genes are highlighted in red, the least important genes are highlighted in orange, and the least important genes are highlighted in yellow

The analysis of the functional enrichment in biological processes of identified gene concentrators in the modules was related primarily with the immune system (**Fig. 4**).

The analysis of the functional enrichment of these gene concentrators in KEGG paths was related primarily to the following: TLR receptor signal paths (hsa04620); TNF (hsa04668) signal path; interaction between cytokines and receptors (hsa04060) and between lipid signal path and atherosclerosis (hsa05417), characterising the presence of common molecular links of COPD with comorbidities (**Fig. 4**). Molecular functions of gene concentrators were related to cytokine activity, whereas functional gene enrichment in cell components was associated with cell plasma membrane.

Thus, the obtained data allowed identifying objectives for further experimental studies. It was found out that airway inflammation in COPD is characterised by innate immune system involvement with the help of cytokines, e.g., IL-1β and TNFα.

Results of EBC cytokine analysis

Study results demonstrated that COPD patients had higher IL-1β and TNFα levels in EBC vs. controls ($p < 0.001$). At the same time, the group of COPD patients with frequent exacerbations and LLAOA demonstrated higher TNFα levels vs. both controls and teh group of COPD patients without ACVD (**Fig. 5**).

EBC IL-1β levels demonstrated moderate correlation with the rate of exacerbations (r=0.612 (95 % CI 0.453; 0.733), $p < 0.0001$) and FEV1 values vs. expected values (r=-0.650 (95 % CI -0.761; -0.503), $p <0.0001$) and high correlation with BODE index (r=0.711 (95 % CI 0.582; 0.805), $p < 0.0001$). EBC TNFα levels had moderate correlation with the rate of exacerbations (r=0.557 (95 % CI 0.384; 0.692, $p < 0.0001$), FEV1 values vs. expected values (r=-0.646 (95 % CI -0.758; -0.497), $p < 0.0001$) and high correlation with BODE index (r=0.757 (95 % CI 0.645; 0.838), $p <0.0001$).

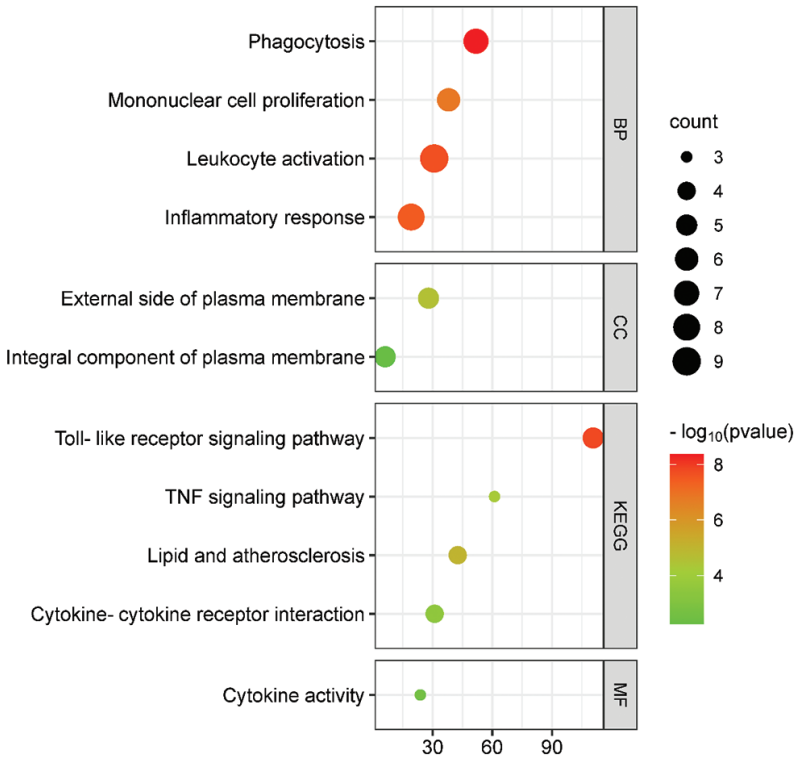

Figure 4. *Biological Processes (BP), KEGG Pathways (KEGG), Cellular Components (CC), and Molecular Functions (MF) in which Hub genes are involved. The data are ranked by Fold Enrichment values*

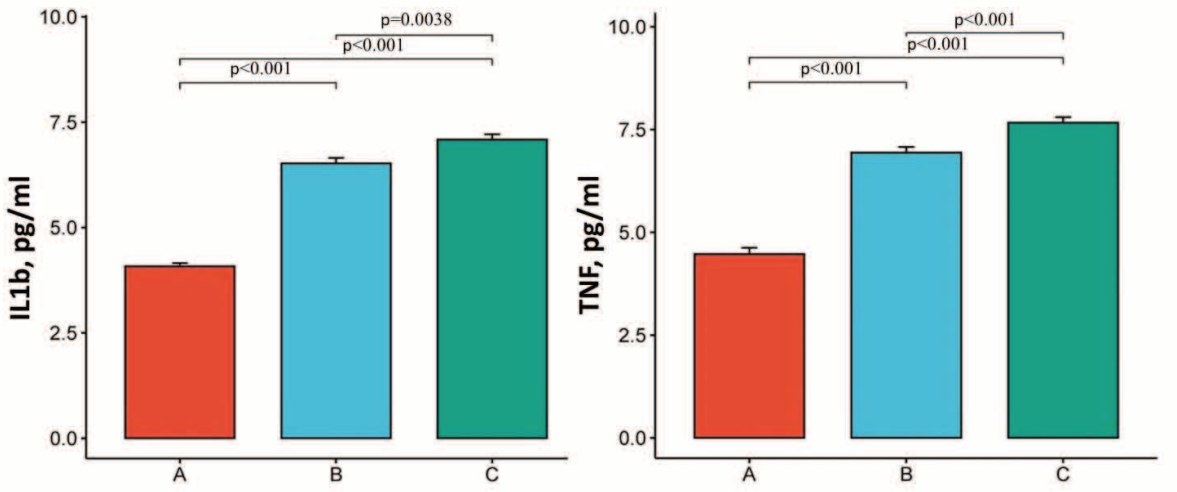

Figure 5. *Plot of changes in TNFα and IL-1β levels in the EBC in the comparison groups.*
Note: A — cytokine levels in the control group; B — cytokine levels in the group of COPD patients with frequent exacerbations without ASCVD; C -cytokine levels in the group of COPD patients with frequent exacerbations and PAD

Therefore, analysis of inflammation biomarkers in EBC showed that COPD is characterised with a marked local inflammation; COPD patients with LLAOA have higher inflammation biomarker levels, which can be related to the intensity of a system inflammation and more severe disease.

Discussion

In this study, we performed a biological information analysis of the data obtained from GEO, which allowed identifying signal paths involving differentially expressed genes with higher expression to airway epithelium in COPD patients vs. controls (non-smokers). Taking into account these data, we evaluated proinflammatory biomarkers in EBC of patients with heterogeneous COPD. The study enrolled patients with COPD without any clinically manifested ACVDs. Controls were subjects without COPD and LLAOA. The data for both groups were compared to the data on healthy volunteers without COPD and clinically manifested ACVDs, who did not smoke and were of a similar age to that of the study patients. COPD patients and controls had an expired breath condensate sample taken using RTube in accordance with the manufacturer's protocol for proinflammatory cytokine evaluation using ELISA.

It was found out that differentially expressed genes from bronchi endothelium in COPD were related to the innate immune system, namely to TLR, TNF signal paths, interaction with cytokines, such as IL-1β. COPD patients demonstrated higher TNFα and IL-1β levels in EBC vs. controls, potentially showing a local inflammation in COPD. At the same time, COPD patients with LLAOA had higher TNFα and IL-1β levels vs. both controls and COPD patients without ACVD. These data demonstrate that a local bronchial inflammation is involved in COPD pathogenesis and its clinically heterogeneous progression.

The data in this study improve the understanding of the role of inflammation in comorbid COPD progression. Previous studies demonstrated that COPD is associated with a higher risk of peripheral arterial diseases and mortality [36,37]. At the same time, immune biological processes and signal paths can connect the development and progression of COPD and atherosclerosis [38].

COPD is known to be a disease underlied by a chronic inflammation in airways associated with long-term exposure to tobacco smoke components. This inflammation involves numerous cells which express various cytokines. Inflammation in COPD has local and systemic components characterised by an increase in cytokine levels, including TNFα and IL-1β, which are associated with the disease severity [39, 40]. Inflammation intensity and cytokine production are higher in COPD exacerbations that are a significant clinical characteristic of the disease. It was demonstrated that COPD exacerbations caused a significant rise in IL-1β and TNFα levels in EBC vs. stable COPD [41]. A systemic inflammation and circulating cytokines are an important link between COPD and atherosclerosis, including LLAOA. At the same time, high cytokine levels can be potential biomarkers for forecasting atherosclerosis progression [42]. Recent studies demonstrated an association between COPD exacerbations and a higher risk of cardiovascular events. Prevention of exacerbations can reduce the risk of cardiovascular catastrophes at a later stage [43, 44]. Of note, even one moderate exacerbation in a COPD patient with a number of symptoms increases the riks of exacerbations and death within next three years [45].

IL-1β is an important cytokine of the innate immune system and is an important inflammation biomarker.

A growing number of proofs improves the understanding of the importance of this cytokine in COPD [46]. Besides, IL-1β is involved in atherosclerosis pathogenesis, as demonstrated in clinical studies of Canakinumab CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) [47]. IL-1β is produced by various cell types, including monocytes, macrophages and endothelial cells, in response to various stimuli, such as bacterial and viral infections, oxidative lipoproteins, and local hemodynamics disorders. It was demonstrated that IL-1β facilitates atherogenesis via a number of mechanisms, including pro-inflammatory gene induction, stimulation of reactive forms of oxygen and endothelial cell activation. IL-1β can activate and recruit immune cells in the inflammation site, including monocytes and T-cells, which contribute to atherosclerosis plaques [48]. There are evidences that IL-1β stimulates production of other pro-inflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), which can boost the inflammatory response. In addition to its pro-inflammatory effect, IL-1β can directly facilitate atherosclerosis plaque development. Studies demonstrated that IL-1β can stimulate expression of adhesion molecules on endothelial cells, facilitating adhesion and migration of monocytes to the subendothelial space [49, 50].

TNFα is another pro-inflammatory cytokine with an array of functions and it demonstrates involvement in pathogenesis of various diseases. TNFα levels can be associated with muscle weakness caused by sarcopenia and cachexia in COPD patients [51]. TNFα is a cytokine which plays an important role in atherogenesis [52].

Therefore, a systemic inflammation is a significant factor contributing to atherosclerosis in COPD patients. At the same time, a high rate of exacerbations can be associated with an increase in the local and systemic inflammation in COPD, a mechanism of disease progression and a cardiovascular comorbidity [6].

A clinical assessment of inflammation biomarkers, such as IL-1β and TNFα, in COPD is possible with the use of available methods, including measurements of serum, induced sputum and EBC levels. Recently EBC has been of interest as a non-invasive tool for measuring biomarkers reflecting the course of chronic respiratory diseases [14]. Literature data show that EBC, which is mostly water from the expired air, contains a large number of dissolved substances, including numerous biologically active organic substances [16]. It was demonstrated that EBC can be used to diagnose and monitor the course of bronchial asthma and COPD [53, 54]. Our data demonstrated that EBC tests can be used to monitor COPD progression. A high frequency of COPD exacerbations is associated with a more severe local inflammation, biomarkers of which can be found in EBC. Overall, these studies show that EBC cytokine levels can be a useful biomarker of COPD severity; they can be used to monitor therapeutic interventions and manage patients with severe disease.

It is worth mentioning that this study has a number of limitations associated with a small sample size and participation of male patients only. Besides, this study did not include an analysis of other factors facilitating production of pro-inflammatory cytokines. On the other hand, this study emphasises the significance of inflammation in COPD and LLAOA comorbidity. For better understanding of comorbid relations, further studies are required which will include a more detailed multivariate analysis of clinical data making it possible to take into account the multifactor nature of pro-inflammatory cytokines. Perspective areas of future studies are analysis of inflammation biomarkers taking into account clinical heterogeneity of COPD, identification of comorbid relations between various inflammation endotypes in COPD.

Therefore, our results add to the data obtained during previous studies which demonstrated the role of a COPD-associated system inflammation in comorbid atherosclerosis. Our study provides an insight into the diagnostic value of biomarkers in expired breath condensate in order to assess COPD comorbidity. These results have high clinical value since they allow suggesting that system inflammation diagnosis and correction can be an important strategy for prevention and management of LLAOA progression in COPD patients. A comprehensive clinical and immunological assessment of COPD with an early identification of inflammation biomarkers and the use of adequate therapeutic strategies can be a perspective objective for disease improvement and forecast.

Conclusions

Therefore, IL-1β and TNFα levels were elevated in EBC of COPD patients; COPD with LLAOA was associated with a higher level of pro-inflammatory cytokines, thus evidencing the intensity of a local bronchial inflammation in COPD and comorbidity. The obtained data demonstrate the significant role of an inflammation in COPD and LLAOA comorbidity. It necessitates an increase in the quality of COPD exacerbation diagnostics and analysis of their clinical and immunological characteristics in COPD monitoring. Identification of immune biomarkers in expired breath condensate is an efficient non-invasive clinical tool for COPD monitoring.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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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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DOI: 10.20514/2226-6704-2023-13-3-224-231
УДК 616.329-002-06:616-009.12
EDN: RUAQMV

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ГАСТРОЭЗОФАГЕАЛЬНАЯ РЕФЛЮКСНАЯ БОЛЕЗНЬ С РАЗВИТИЕМ ВТОРИЧНОГО ДИФФУЗНОГО ЭЗОФАГОСПАЗМА

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Case of Gastroesophageal Reflux Disease Resulted in Secondary Esophageal Spasm

Резюме

Гастроэзофагеальная рефлюксная болезнь — это широко распространённое хроническое заболевание, характеризующееся забросом в пищевод желудочного или дуоденального содержимого. Эзофагоспазм и ахалазия кардии являются недостаточно изученными заболеваниями, связанными с нарушением нервно-мышечной передачи импульса и дискоординацией моторики пищевода, проявляющимися загрудинной болью и дисфагией. В статье представлен клинический случай молодого пациента с гастроэзофагеальной рефлюксной болезнью и анамнезом нетипичных загрудинных болей, требующих дифференциального диагноза между вариантами нарушенной моторики пищевода.

Ключевые слова: *гастроэзофагеальный рефлюкс, эзофагит, эзофагоспазм, ахалазия кардии*

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

Статья получена 23.07.2022 г.
Принята к публикации 14.02.2023 г.

Для цитирования: Ищенко А.Ю., Галушко М.Ю. ГАСТРОЭЗОФАГЕАЛЬНАЯ РЕФЛЮКСНАЯ БОЛЕЗНЬ С РАЗВИТИЕМ ВТОРИЧНОГО ДИФФУЗНОГО ЭЗОФАГОСПАЗМА. Архивъ внутренней медицины. 2023; 13(3): 224-231. DOI: 10.20514/2226-6704-2023-13-3-224-231. EDN: RUAQMV

Abstract

Gastroesophageal reflux disease is a widespread chronic disease in which stomach or duodenal contents rise up into the esophagus. Esophageal spasm and achalasia cardia are poorly studied disorders associated with impaired neuromuscular impulse transmission and motor discoordination of the esophagus, manifested by chest pain and dysphagia. The article presents a clinical case of a young patient with gastroesophageal reflux disease and a history of atypical chest pain requiring differential diagnosis between variants of impaired esophageal motility.

Key words: *gastroesophageal reflux, esophagitis, esophageal spasm, achalasia cardia*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 23.07.2022
Accepted for publication on 14.02.2023

For citation: Ishchenko A.Yu., Galushko M.Yu. Case of Gastroesophageal Reflux Disease Resulted in Secondary Esophageal Spasm. The Russian Archives of Internal Medicine. 2023; 13(3): 224-231. DOI: 10.20514/2226-6704-2023-13-3-224-231. EDN: RUAQMV

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GERD — gastroesophageal reflux disease, DES — diffusive esophagism, PPIs — proton pump inhibitors, MAFLD — matabolism-associated fatty liver disease, NAFLD — non-alcoholic fatty liver disease, LES — lower esophageal sphincter, RS — radiographic contrast study, UDCA — ursodeoxycholic acid, EGDS — esophagogastroduodenoscopy, DCI — distal contractile integral, IRP — integrated relaxation pressure

Gastroesophageal reflux disease (GERD) is a chronic recurrent disease caused by impaired motor-evacuation function of gastroesophageal organs and characterised by recurrent reflux of gastric and sometimes duodenal contents into the esophagus. In Russia, the incidence of GERD in adults varies from 11.3 to 23.6% [1]. GERD-associated factors are the age of over 50 years and smoking, and the main comorbidity is obesity. A typical set of symptoms includes hearburn, belch, regurgitation, odynophagia. Symptoms worsen in prone position and when by bending over.

Esophagism is a gastric disease caused by spastic contraction of the gastric wall without cardia opening disorders following a gulp [2]. Esophagism pathogenesis in unknown; it is assumed that the disorder is caused by defective neurotransmission. Russian and foreign literature sources have no references to any clinical, laboratory, and instrumental signs of esophagism which can reliably confirm or invalidate the diagnosis. Depending on the causes, esophagism can be primary (caused by organic changes in the nervous system) and secondary (caused by GERD, gastroesophageal hernia, esophagitis); in terms of the involvement pattern — segmental or diffusive (DES) [2].

Esophageal achalasia (idiopathic esophageal dilatation, cardiospasm) is an idiopathic neuromuscular disease, manifestations of which include functional disorders of cardia patency due to incoordination between gulping, reflex opening of the lower esophageal sphincter (LES), and motor and tonic activity of smooth gastric muscles [3]. The main symptoms of the disease are progressive dysphagia, regurgitation and retrosternal pain caused by incomplete esophagus evacuation and chronic esophagitis.

Case Study

Patient D., 33 years old at first visit in October 2019.

Complaints: Pain in xiphoid appendix area, especially in prone position and when the patient eats crude vegetable fibers (hard apples, cabbage, beetroot) and drinks water. The pain worsens during speaking.

Medical history:

- According to the patient, the onset of the disease was in 2013 (when he was 27 years old), when the above complaints appeared for the first time. At that time the patient had his first esophagogastroduodenoscopy (EGDS), and reflux esophagitis was diagnosed. He had several courses of proton pump inhibitor (PPI) therapy (various doses and regimens of omeprazole, rabeprazole, esomeprazole) and promotility agents (domperidone, itoprid, trimebutine, various duration) without any marked effect. At the same time, the patient followed all non-drug recommendations for GERD patients.
- In 2016, the patient underwent a 24-hour pH monitoring and gastric manometry; all results were normal. Also, he had cardia dilatation without any clinical effect. The patient denied dysphagia and regurgitation both before and after dilatation.
- Over the period from 2016 to 2018, several examinations recommended by cardiologist and neurologist did not resolve the pain the patient suffered from.
- In 2018, when there was no effect from conservative therapy, the patient was recommended to undergo gullet bougienage, but he refused because of possible complications.
- Before visiting MedElite Medical Center (MedElite-Pro LLC) in October 2019, the patient took PPIs and promotility agents from time to time without prescription and without any clinical effect; he underwent several esophagogastroduodenoscopy (EGDS) procedures, that revealed cardia insufficiency; peptic esophagitis; esophagus erosions and superficial gastritis (twice); duodenogastric reflux (from time to time).
- In February 2019, the patient underwent first-line eradicative anti-helicobacter therapy without any clinical changes during and after therapy.

Life history: Occasional smoking up to 2009 (4 years before complaints appeared), alcohol consumption — non-toxic doses no more than three times a year. No allergic background. In 2012, the patient had antiviral therapy for chronic hepatitis C with direct-acting antiviral drugs, and sustained virological response was achieved; hepatic fibrosis stage F0 as demonstrated by transient elastometry (2017). Familial history: his mother has type 2 diabetes mellitus, chronic thyroid gland disorder.

Physical examination: Satisfactory condition. The patient is emotionally stable, cooperative, has regular normosthenic constitution with moderately developed subcutaneous fat and muscles; BMI: 25.2 kg/m^2, abdominal circumference: 90 cm. The skin has physiological shade and is moderately moist; hand skin is dry.

The oral cavity is restored to health; the tongue is moist, with white coat Respiratory system: the chest is symmetric and is evenly engaged in respiration; no abnormalities by palpation; clear pulmonary tones by percussion; auscultatory vesicular respiration in all chest sections; without stridor. Cardiovascular system: regular cardiac rhythm; clear heart tones without any murmur or diastolic shock; heart rate (HR) is 72 bpm, blood pressure (BP) is 122/77 mm HG on both arms. Abdomen: evenly engaged in respiration; soft, painless. The liver is within the costal arch and is not enlarged by percussion. Cholecystic symptoms are negative. Peritoneal signs are negative. Kidney punch is negative on both sides. Peripheral oedema is not observed. Bowel and bladder habits are normal.

Preliminary diagnosis: gastroesophageal reflux disease — endoesophagitis, a history of erosive esophagitis. A history of duodenogastric reflux. H.pylori-associated chronic superficial gastritis, condition after first-line eradicative therapy (February 2019). Esophageal achalasia?

Examination results:

- Complete blood count and blood chemistry: unremarkable.
- EGDS revealed cardia insufficiency, peptic esophagitis (biopsy was performed in order to exclude Barrett's esophagus, and the histology report demonstrated the presence of esophagitis without any signs of metaplasia), superficial gastritis, duodenitis, duodenogastric bile reflux; rapid urease test for H.pylori came positive, pH 7 (Fig. 1).
- Abdomen US examination revealed focal masses in right lobe of liver with signs of haemangiomas and regular echo structure in remaining liver parenchymatous tissue with even contours. Also, the examination revealed deformed gall bladder without signs of cholestasis and biliary hypertension, with signs of pancreatic lipomatosis. No sonographic signs of portal hypertension and changes in spleen.
- High-resolution gastric manometry showed resting pressure in lower esophageal sphincter (LES) of 10–12 mm Hg (normal value: 10–45 mm Hg). No hiatal hernia was found. Diagnosis according to The Chicago Classification of Esophageal Motility Disorders, v. 3 (2015): Inefficient esophageal motility: esophagogastric junction is unobstructed; IRP (integrated relaxation pressure) is < 15 mm Hg; over 50 % of contractions are inefficient; DCI (distal contractile integral) is < 450 mm Hg x cm (Fig. 2).
- Barium esophagography revealed signs of gastroesophageal reflux, cardia insufficiency, peptic esophagitis, duodenogastric reflux.
- 24-hour esophagus pH-impedancemetry at the level of 5 cm above LES revealed 7 acidic refluxes (normal value: < 50) with the total duration of 8 min (normal value: < 60). Acidic refluxes, vertical position (daytime): 7, horizontal position (during sleep): 0. Chemical clearance lasted for 1 minute (normal value: < 3 minutes). Duration of pH < 4.0 episodes during the day was 0.6 % (normal value: < 4.5 %). De Meester score was 2.19 (normal value: < 14.72). Impedancemetry signal analysis results: low acidity refluxes during the day was 20 (normal value: < 21), alkaline refluxes during the day was 32 (normally, they should be absent). At the same time, over 60 % of the time, gastric pH was over 4.0, therefore, hypoacidic gastritis was suspected; signs of duodenogastric reflux were recorded from 6.00 am to 8.00 am (Fig. 3).

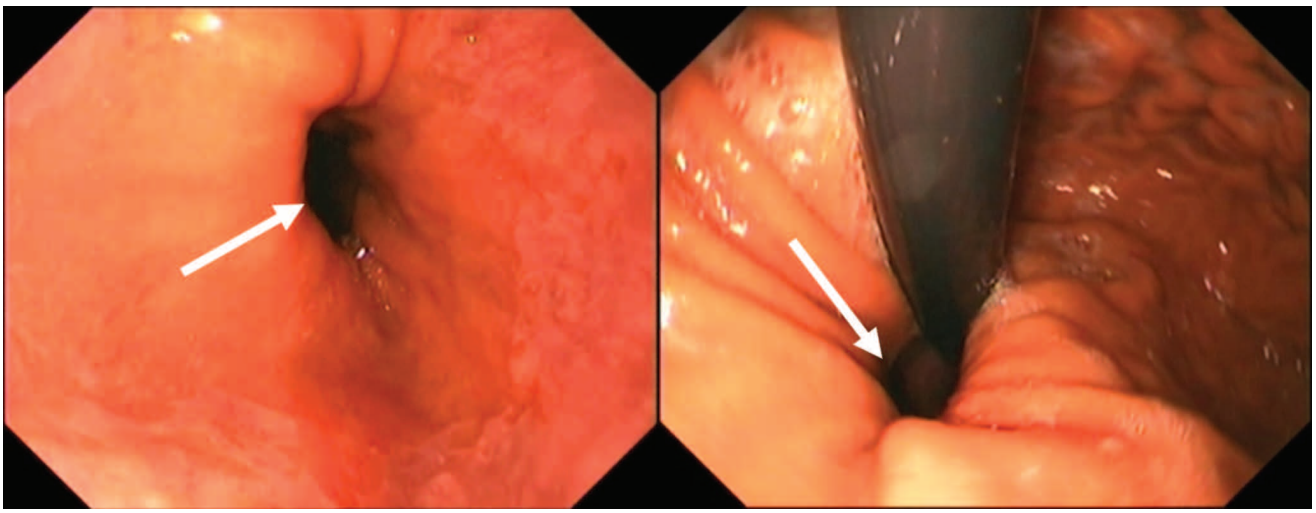

Figure 1. *Cardiac sphincter on endoscopy: insufficiency on direct and retroversion examination (marked with white arrows).*

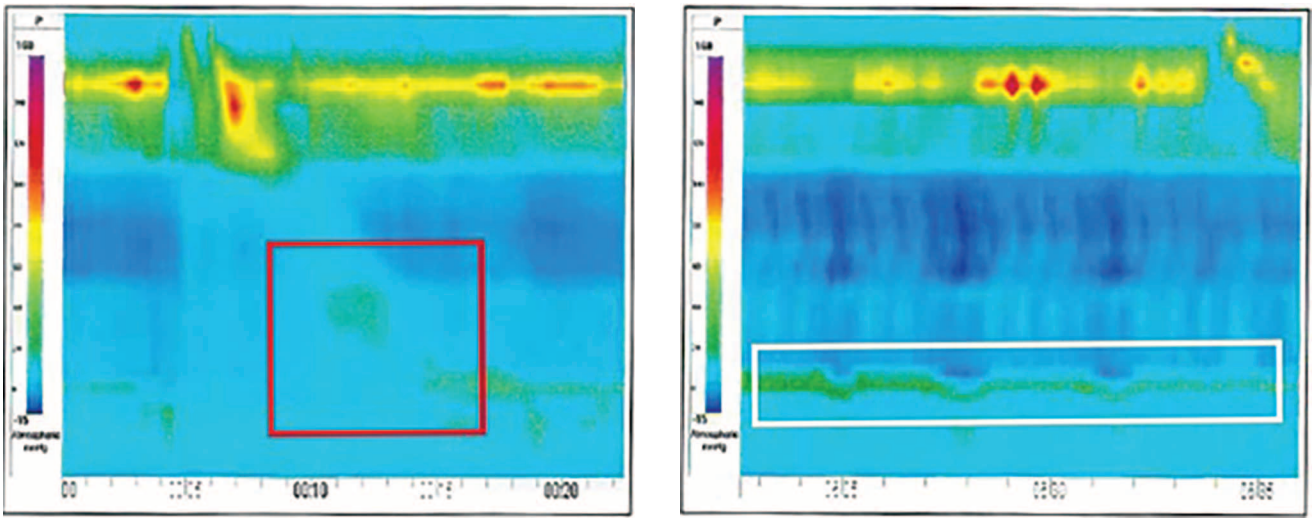

Figure 2. *Esophageal manometry. The red frame highlights the absence of esophageal contraction in swallow phase; DCI is 31 mm Hg, with the normal range of 450-8000 mm Hg. The white frame highlights the LES pressure at rest, equal to 12 mm Hg with the normal range of 10-45 mm Hg.*

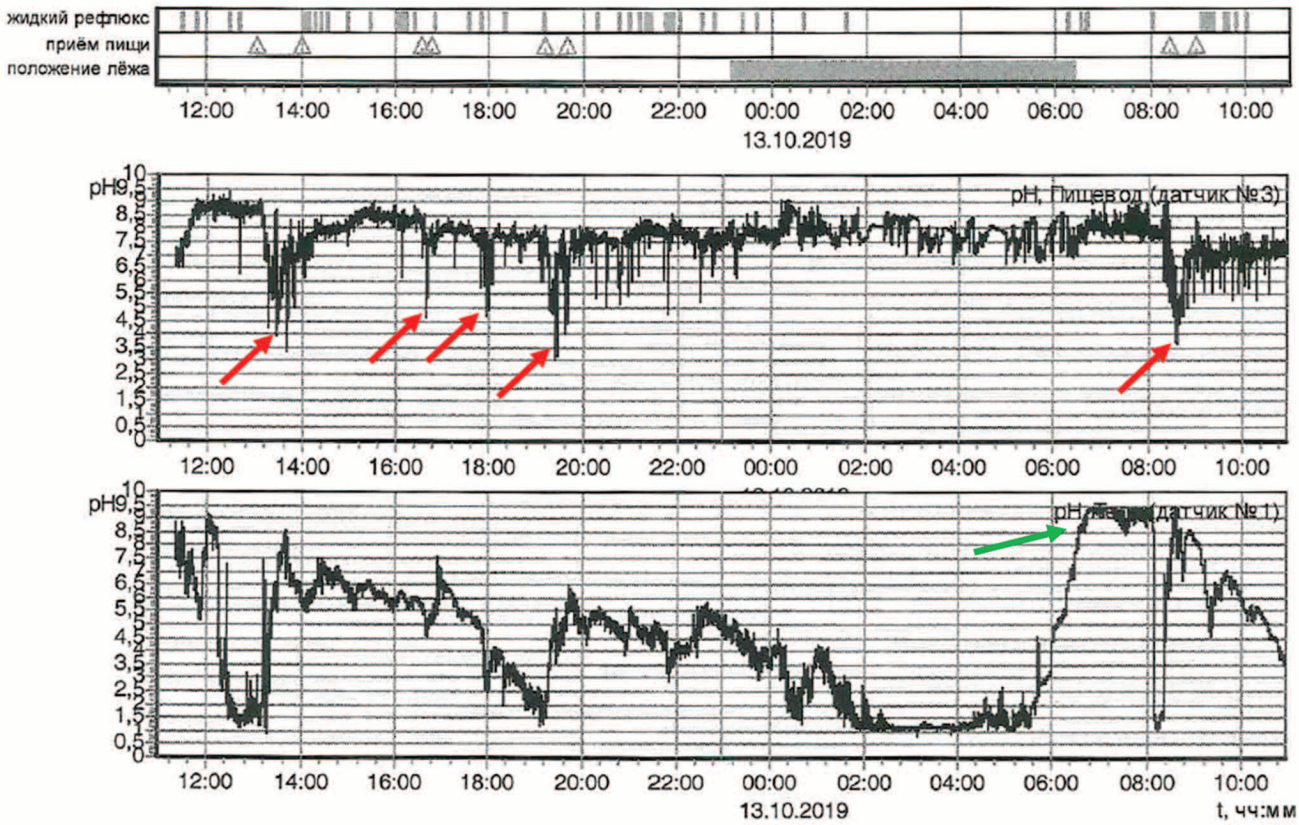

Figure 3. *The result of 24-hours pH-impedancemetry. The red arrows indicate acid refluxes into the esophagus. The green arrow indicates alkaline duodeno-gastric reflux*

Based on the results, the following diagnosis was made: gastroesophageal reflux disease — endoesophagitis, a history of erosive esophagitis. Duodenogastric reflux. Secondary diffusive esophagism. H.pylori-associated chronic superficial gastritis. Condition after eradicative therapy — first-line A and first-line B, both were ineffective. Hepatic haemangiomas.

Recommended therapy: Calcium channel blockers nifedipine with gradual dose titration to 10 mg 3 times per day — continuously; esophagus protective agent (sodium hyaluronate + chondroitin sodium sulfate), 1 sachet 3 times per day; PPI and ursodeoxycholic acid (UDCA), standard regimen — 1 month.

One and a half month after nifedipine therapy initiation, the patient noted reduction in pain intensity. With regular drug administration his condition remained stable; from time to time the patient had dull pain which did not affect the quality of his life. Five months later, the patient discontinued nifedipine (since the drug was not available on the market), and his condition deteriorated significantly in just two weeks: intense pain resumed and the patient started coughing. The patient was examined by a GP and underwent chest X-ray, the results of which excluded respiratory disorders. Nifedipine therapy resumption with titration to previous doses (30 mg daily) resulted in gradual improvement in the patient's condition over a month: cough resolved quickly, pain became less frequent and less intense. As of March 2022, the patient has been taking nifedipine regularly, 1 sachet of esophagus protective agent 1–3 times per day (in courses), PPI — standard regime (Rabeprazole 10 mg or Dexlansoprazole 30 mg once daily for 2–4 weeks). The patient undergoes annual follow-up endoscopy and histological examination, that demonstrate endoesophagitis without any negative trend. In March 2022, overweight was diagnosed: the patient gained 5 kg over 3 years (BMI: 26.9 kg/m2), his abdominal circumference reached 95 cm. According to the patient, it was a result of reduced physical activity during the COVID-19 pandemic and restrictions. In March 2022, an ultrasound follow-up examination of hepatic haemangiomas revealed newly diagnosed hepatic steatosis. The patient underwent transient elastometry and steatometry using FibroScan: METAVIR fibrosis stage F0 and NAS steatosis stage S3. Matabolism-associated (non-alcoholic) fatty liver disease (MAFLD/NAFLD) was diagnosed. The patient was recommended to do more physical exercises; UDCA 14.6 mg/kg and vitamin E were added to the therapy.

Discussion

Epidemiological data cannot provide deep insight into the actual incidence of esophageal dyskinesia because of under-diagnosis due to unclear oligosymptomatic course of disease and resulting late diagnosis with low body weight and malnutrition. Besides, quite often dyskinesias are confused with GERD. The incidence rises with age; middle-aged and elderly women are more susceptible to the disease. The incidence of a combination of GERD and esophageal dyskinesia is unknown due to a limited studies. It is known that in patients with confirmed GERD with resistance to PPI therapy, the incidence of impaired esophageal motility is up to 75 % [4].

In our case study, at the onset of disease in a 27-year-old patient, retrosternal pain was thought to be a symptom of peptic esophagitis revealed during EGRS. It is worth mentioning that the patient denies heartburn, dysphagia; however, the character of pain, i.e., worsening with meals, drinks, in prone position, are typical of esophagus pathologies. Standard GERD therapy regimen did not have any effect, and diagnostic search continued; cardiac and neurological disorders were excluded. Esophageal achalasia was suspected despite the absence of dysphagia observed in 99 % of patients with esophageal achalasia [3]. Gastric manometry did not reveal any signs of esophageal achalasia: the integrated LES relaxation pressure was not increased (IRP > 15 mm Hg) and there were no contraction disorders present. According to clinical recommendations on esophageal achalasia, conservative therapy with calcium channel blockers or nitrates can have some effect in this pathology; however, it is just a temporary measure, while the primary management of esophageal achalasia is cardia dilatation, which is effective in 60-85 % [3]. Nevertheless, instead of further diagnostic search and selection of alternative conservative therapy, the patient underwent cardia dilatation which did not have any positive effect. It is worth noting that at this stage the therapy with calcium channel blockers or nitrates was not considered.

During his first visit to the clinic in 2019, the patient underwent a comprehensive examination of esophagus (including EGDS, esophagography, pH-impedancemetry, manometry), and the results came controversial.

EGDS, which is not a method of choice for esophageal dyskinesia diagnosis, is important to exclude organic disorders. In this case study, EGDS did not reveal any abnormalities which could be a sign of esophageal dyskinesia (dilated esophageal lumen, constrained endoscope passage, cardia obstruction, etc.). Cardia insufficiency, peptic esophagitis, superficial gastritis, duodenitis, and duodenogastric bile reflux were observed.

Esophagography confirmed gastroesophageal reflux, peptic esophagitis, and duodenogastric reflux. There were no typical signs of DES, however, this diagnosis cannot be ruled out: according to literature, abnormalities are observed only in 60 % of patients, while pathognomonic changes ("corkscrew" or "string of beads" esophagus) is

reported in less than 5 % of cases [5]. Radiographic evidences of esophageal achalasia (cardia spasm and dilated esophagus) were not observed.

Manometry revealed inefficient esophageal motility: hypokinetic dyskinesia with clinical signs of regurgitation, dysphagia, feeling of weight in epigastrium. The patient denied these symptoms, his only complaint (retrosternal pain) was typical of hyperkinetic forms, since it is caused by spastic muscle contractions. It is worth mentioning that gastric manometry is a golden standard in esophageal dyskinesia diagnosis; however, The Chicago Classification of Esophageal Motility Disorders (v. 3, 2015) used at that time is useful to diagnose primary motility disorders, whereas secondary changes have no clear validated criteria. The report on The Chicago Classification of Esophageal Motility Disorders (v. 4, 2021) emphasises the role of manometry in differentiation between disorders which allow making a final diagnosis (for instance, achalasia) and other phenomena that are insignificant for the diagnosis and that require clinical interpretation [6]. In this case study, manometry allowed ruling out achalasia, a mandatory criteria of which is increased integrated LES relaxation pressure (IRP) of over 15 mm Hg.

24-hour esophagus pH-impedancemetry demonstrated normal acidic refluxes and time when pH was below 4; however, there were 32 alkaline refluxes, which correlated with EGDS results of duodenogastric bile reflux.

It is worth mentioning that during EGDS procedures the patient did not have any pain, and it can be an indirect evidence of neuroreflex nature of esophageal spasm and can explain the absence of typical abnormalities observed during manometry. The same situation was observed during the initial examination in 2016: the patient did not have any pain during pH-impedancemetry and manometry.

To sum up the instrumental assessment results, it is worth noting that, despite their specificity, the existing diagnostic methods are not always useful for correct diagnosis, since there are no validated diagnostic criteria for any type of esophageal dyskinesia [6]. These methods are auxiliary; diagnosis requires comparative analysis of results of the mentioned instrumental assessments with clinical manifestations [6].

Table 1 presents primary clinical and instrumental characteristics of the patient as well as DES and esophageal achalasia criteria which were used in differential diagnosis [2, 3].

It seems to be possible to develop a practical algorithm for diagnostic search in patients with non-cardiac retrosternal pain. The primary method should be EGDS (if there are no contraindications) as it is highly informative and can help in ruling out organic disorders: esophageal cancer and cardiac cancer, gastroesophageal hernia, esophagitis, esophageal strictures. If the diagnosis is clear, therapy should follow the current recommendations; if no effect is observed or if information is limited, barium esophagography should be performed. The diagnostic search algorithm in case of non-cardiac retrosternal pain proposed by the authors is presented in Figure 4.

Table 1. *Differential diagnosis of the patient based on the criteria for diffuse esophagospasm and achalasia cardia*

Feature	Case	Diffuse esophagospasm	Achalasia cardia
Pain	++	++	+ (60 %)
Dysphagia	-	+	++ (99 %)
Regurgitation	-	+- (seldom)	+
Weight loss	-	+ (Late stages)	+ (Late stages)
Uncoordinated peristalsis, rosary symptom (X-ray)	-	+	-
Normal patency of the lower esophageal sphincter (X-ray)	+	+	-
Spasm of the cardia, expansion of the esophagus (X-ray)	-	-	+
Expansion of the esophagus, tightly closed cardia (endoscopy)	-	-	+
An increase in the total relaxation pressure of the lower esophageal sphincter >15 mm Hg. (high-resolution manometry)	-	-	++
Spasmodic contractions (high-resolution manometry)	-	+-	+
Number of acid refluxes above normal (pH monitoring)	-	+-	-
The effect of a calcium channel blocker	++	++	+
The effect of PPI	-	+	-

Note: X-ray — X-ray with barium contrast; PPI — proton pump inhibitors

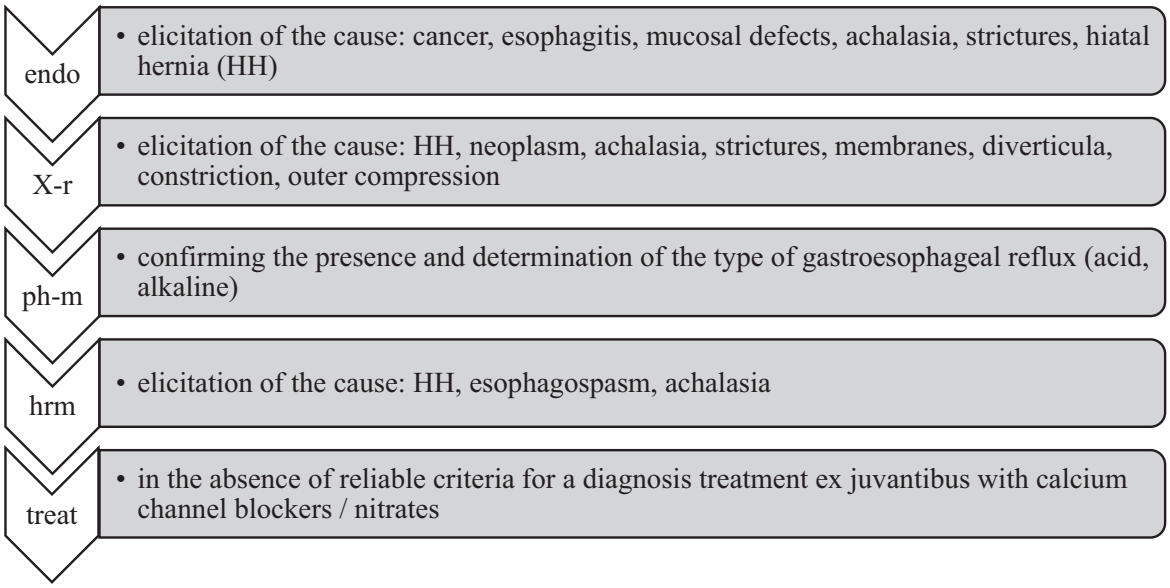

Figure 4. *Diagnostic search algorithm in the presence of non-cardiac retrosternal pain.*
Note: Endo — endoscopy; X-r — X-ray with barium contrast; pH-m — pH-monitoring; hrm — high-resolution manometry; treat — treatment

In this case study, this is efficient calcium channel blocker therapy that allowed confirming hyperkinetic esophageal dyskinesia — diffusive esophagism with GERD.

It is worth mentioning that at the onset of disease in 2013 and when the patient came to the clinic in 2019, he did not have any metabolic disorders; however, in March 2022 overweight and NAFLD were observed; these are frequent comorbidities of GERD with understudied relations [7, 8]. A number of studies are dedicated to the correlation between these disorders; in a majority of cases, the question is an increased risk of GERD in patients with fatty liver disease [7, 8], the pathologic relation between which is caused by overweight. In this case study, GERD developed well before, when the patient was a young man, while metabolic disorders appeared later and might have been triggered by forced limitation of physical activity.

Conclusion

Esophageal achalasia and diffusive esophagism are diagnosed relatively rarely and are understudied conditions. Retrosternal pain requires differential diagnosis to rule out myocardial or musculoskeletal disorders; however, a correct diagnosis is not an easy task even when extra-oesophageal pathology has been ruled out. Highly specific modern methods for esophagus pathology diagnosis can return controversial results that do not correlate with one another nor match clinical manifestations. This case study of a young patient with a long-lasting history of resistant retrosternal pain emphasises the need in a comprehensive examination and assessment of clinical and instrumental results for practical purposes, as well as development of more clear criteria for scientific confirmation or exclusion of these diagnoses. Also, the relationship between esophagus involvement and metabolic disorders, specifically NAFLD, is of practical and scientific significance.

Вклад авторов

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Author Contribution

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

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DOI: 10.20514/2226-6704-2023-13-3-232-240
УДК 616.89-008-085-06:616.995.428-07-084
EDN: XBNAPQ

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ДИАГНОСТИКА И ПРОФИЛАКТИКА ЧЕСОТКИ У МАЛОМОБИЛЬНЫХ ПАЦИЕНТОВ С КОГНИТИВНЫМИ НАРУШЕНИЯМИ

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Diagnosis and Prevention of Scabies in Low Mobility Patients with Cognitive Impairment

Резюме

Чесотка представляет собой инфекционное кожное заболевание, вызываемое специфичным для человека эктопаразитом Sarcoptes scabiei var. hominis. Несмотря на всестороннюю изученность чесотки, проблема ее своевременной диагностики у маломобильных пациентов с определенными неврологическими и когнитивными нарушениями остается актуальной во всем мире. Одновременное назначение большого количества лекарственных препаратов маломобильным пациентам может маскировать клинические проявления чесотки и ошибочно относить зуд к проявлениям кожных аллергических реакций или иных дерматозов. Авторы наблюдали пациента К., который находился в ФГБУ «ФЦМН» ФМБА России с 14.11.2022 по 15.11.2022. Клинический диагноз при поступлении: I69.3. Последствия инфаркта мозга. Основное заболевание: ранний восстановительный период ишемического инсульта в бассейне левой средней мозговой артерии от 09.08.2022, атеротромботический подтип по критериям TOAST. Правосторонний гемипарез. Грубая афазия. Нарушение функции тазовых органов. Шкала реабилитационной маршрутизации 5 баллов. Фоновые заболевания: гипертоническая болезнь III стадии 3 степени, контролируемая, риск сердечно-сосудистых осложнений — 4 (очень высокий). Целевое значение артериального давления менее 135/85 мм рт. ст. Окклюзия левой передней мозговой артерии, средней мозговой артерии. Токсико-аллергический дерматит (лекарственный) в фазе обострения. На основании комплекса клинических данных и лабораторного обнаружения возбудителя пациенту К. был поставлен диагноз: B86 — чесотка. Несмотря на то, что пациент находился под медицинским наблюдением на догоспитальном этапе, чесотка не была своевременно диагностирована. Поздняя диагностика чесотки ведет к распространению заболевания и поддержанию неблагоприятной эпидемиологической ситуации.

Ключевые слова: *чесотка, маломобильные пациенты, когнитивные нарушения, зуд, диагностика чесотки*

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

Статья получена 10.01.2023 г.
Принята к публикации 07.03.2023 г.

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Для цитирования: Гайдина Т.А., Дворников А.С., Милушкина О.Ю. и др. ДИАГНОСТИКА И ПРОФИЛАКТИКА ЧЕСОТКИ У МАЛОМОБИЛЬНЫХ ПАЦИЕНТОВ С КОГНИТИВНЫМИ НАРУШЕНИЯМИ. Архивъ внутренней медицины. 2023; 13(3): 232-240. DOI: 10.20514/2226-6704-2023-13-3-232-240. EDN: XBNAPQ

Abstract

Scabies is an infectious skin disease caused by the human-specific ectoparasite Sarcoptes scabiei var. hominis. Despite the comprehensive study of scabies, the problem of its timely diagnosis in low-mobility patients with neurological and cognitive impairments remains relevant all over the world. Simultaneous administration of a large number of medications to patients with limited mobility may mask the clinical manifestations of scabies and mistakenly attribute itching to manifestations of skin allergic reactions or other dermatoses. The authors observed patient K., who was admitted in FCBRN of FMBA of Russia from 14.11.2022 to 15.11.2022. Clinical diagnosis upon admission: I69.3. The consequences of a stroke. Early recovery period of ischemic stroke in the basin of the left middle cerebral artery from 09.08.2022, atherothrombotic subtype according to TOAST criteria. Right-sided hemiparesis. Gross aphasia. Violation of the pelvic organs function. RMS 5. Comorbid diseases: arterial hypertension, controlled, the risk of CVE 4 (very high). The target blood pressure is less than 135/85 mmHg. Occlusion of the left anterior cerebral artery, middle cerebral artery. Toxic-allergic dermatitis (medicinal) in the acute phase. Based on a set of clinical data and laboratory detection of the pathogen, patient K. was diagnosed with B86 — scabies. Even though the patient was under medical supervision at the ambulatory step, scabies was not diagnosed timely. Late diagnosis of scabies leads to the spread of the disease and an unfavorable epidemiological situation.

Key words: *scabies, patients with limited mobility, cognitive impairment, itching, diagnosis of scabies*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 10.01.2023

Accepted for publication on 07.03.2023

For citation: Gaydina T.A., Dvornikov A.S., Milushkina O.Yu. et al. Diagnosis and Prevention of Scabies in Low Mobility Patients with Cognitive Impairment. The Russian Archives of Internal Medicine. 2023; 13(3): 232-240. DOI: 10.20514/2226-6704-2023-13-3-232-240. EDN: XBNAPQ

BP — blood pressure; ALT — alanine aminotransferase; AST — aspartate amino transferase; HMF — higher mental functions; DS BCA — duplex ultrasonography screening of brachiocephalic arteries; CHD– coronary heart disease; BMI — body mass index; chest CT — chest computer tomography; CPK — creatine phosphokinase; LV — left ventricle; HDLPs — high-density lipoproteins; LDLPs — low-density lipoproteins; ARU — anaesthesiology and reanimation unit, AMI — acute myocardial infarction; ACE — acute cerebrovascular event; PTPS — postthrombophlebitic syndrome; EMS– emergency medical service; CVCs — cardiovascular complications; LVEF — left ventricular ejection fraction; CCCH — Central City Clinical hospital; RR — respiratory rate; HR — heart rate; RRS — rehabilitation routing scale

Relevance

Scabies is a contagious skin disease caused by human-specific ectoparasite Sarcoptes scabiei var. hominis. According to the World Health Organisation (WHO), over 200 million of people all over the globe have scabies at the same time [1]. Outbreaks often occur in closed, mostly overcrowded closed institutions [2]. Despite the extensive studies of scabies, the issue of its timely diagnosis in handicapped patients with certain neurological and cognitive disorders is still a burning problem globally [3]. There are several causes for this. On the one hand, clinical manifestations of scabies in this group of patients can be unrepresentative; on the other hand, they can be interpreted as symptoms of other skin diseases. In some neurological disorders, collection of complaints and history is practically impossible, especially if the patient does not have any close relatives who care for them constantly. Prescription of a number of drugs to handicapped patients can obscure clinical signs of scabies, and intense itching can be interpreted as a sign of skin allergies or other dermatoses. Delayed diagnosis of scabies causes spread of the disease and contributes to an unfavourable epidemiological situation.

CASE STUDY

Patient K., 47 years old, was hospitalised to the inpatient unit for the rehabilitation of patients with CNS dysfunctions of the Federal State Budgetary Institution Federal Centre for Brain and Neurotechnology at the Federal Medical and Biological Agency of Russia from 14 November 2022 to 15 November 2022. Clinical diagnosis upon admission: I69.3. Cerebrovascular accident complications. Primary disease: early period of recovery after ishemic stroke in the left medial cerebral artery area dated 09 August 2022, atherothrombotic subtype (TOAST categories). Right-sided hemiparesis. Severe aphasia. Pelvic organs dysfunction. Rehabilitation routing scale (RRS): 5 points. Background diseases: controlled stage III hypertensive disease, 3rd degree; risk of cardiovascular complications (CVCs): 4 (very high). Target blood pressure (BP) is below 135/85 mm Hg. Occlusive disease of the left anterior cerebral artery, medial cerebral artery. Comorbidities: coronary heart disease (CHD), postinfarction cardiosclerosis. Chronic cardiac failure with interim left ventricular ejection fraction (LVEF 42 %), stage IIA, functional class III. Thrombosed postinfarction aneurysm of the left ventricular apex. 50 % stenosis of the right carotid artery. Acute toxic

allergic dermatitis (drug-induced). Suprapubic urinary catheter user from 12 August 2022. Postthrombophlebitic syndrome (PTPS).

Complaints upon admission: collection of complaints and history is challenging due to speech disorders. According to the relatives, the patient has speech disorders, weak right limbs, especially the arm, impaired pelvic organ functions, itching, and skin rash all over the body.

Medical History

According to the medical records and relatives, on 10 August 2022, the patient was found lying on the floor. The emergency medical service (EMS) team transported him to the Reutovo Central City Clinical Hospital (CCCH); brain CT confirmed ishemic stroke in the left medial cerebral artery (MCA) area. The patient was transferred to the Federal Centre for Brain and Neurotechnology on 10 August 2022 for the treatment in the anaesthesiology and reanimation unit (ARU). Examinations: chest computer tomography (chest CT) — bilateral minor hydrothorax; lower limb vein duplex ultrasonography screening — superficial vein thrombosis of the right shank; duplex ultrasonography screening of brachiocephalic arteries (DS BCA) — obliterating atherosclerosis; echocardiography — delated left heart chambers; LVEF 47 %; thrombosed postinfarction aneurysm of the left ventricular (LV) apex. The patient underwent a rehabilitation course at the same institution. Discharged on 14 September 2022 with positive changes.

While in the inpatient unit, in September 2022 the patient developed an unspecified toxic allergic reaction; according to the relatives, the patient was consulted by a dermatologist, who recommended skin care; however, the condition did not improve.

Since the patient had rehabilitation potential, the Clinical Screening Committee at the Federal State Budgetary Institution Federal Centre for Brain and Neurotechnology at the Federal Medical and Biological Agency of Russia decided to hospitalise the patient for rehabilitation on the account of the Federal Compulsory Medical Insurance Fund (FCMIF).

Life History

According to the relatives, the patient had the following conditions: acute myocardial infarction (AMI) — March 2020 (no document were presented), previous acute cerebrovascular accidents (ACE) — denied. History of surgeries: coronary stenting in March–April 2020 (according to the relatives); trocar cystostomy dated 12 August 2022. History of hypertensive disease. Constantly taken medications: apixaban 2.5 mg twice daily; enalapril 10 mg twice daily; cetirizine 10 mg/day; for outward application: clobetasol, emulsion with vitamin E, urea, vitamin A, ceramides. Disability: no; changes in the place of residence: no; bad habits: no.

Epidemiological history. Prior contagious diseases (including TB and TB contacts, infectious hepatitis, STDs — gonorrhea, syphilis, HIV infection) — denied (according to the relatives). The patient did not travel abroad during the past 6 months. The patient did not contact infectious persons and persons with fever, or persons who came from areas with high rates of COVID-19 morbidity.

History of allergies: unspecified toxic allergic reaction, possibly drug-induced (statins, rivaroxaban).

Pre-hospitalisation instrumental examinations are presented in Table 1.

Physical Examination Results upon Admission

Visual examination: overall condition is satisfactory. Height: 186 cm. Weight: 70 kg. Body mass index (BMI): 20.23 mg/m^2.Body temperature: 36.6˚C. Visible mucosa and skin are of normal colour. Widespread rash on limbs, body. Head lice, scabies: absent.

Respiratory organs. The patient breathes naturally.

The chest is hypersthenic.

Respiratory rate (RR) is 17/min. SpO_2 = 99 %. By auscultation, the lung respiration is harsh, even in all sections, without wheeze.

Blood circulation organs. Muffled heart tones, regular rhythm. No heart murmurs. Heart rate (HR) = Ps = 78 bpm. BP: 130/80 mm Hg.

Digestive system. Oral feeding. Th tongue is pink, no plaques. Abdomen is soft, painless. Peritoneal signs are negative. Vermicular movements: observed. No physical signs of liver enlargement; spleen is not palpable. Bowel movements are controlled, regular.

Urinary system. Kidney punch is negative on both sides. Cytostome-assisted urination (according to the relatives, cytostome was replaced on 08 November 2022). By percussion, the fundus of bladder does not protrude over the lap. Diuresis is adequate.

Neurologic State

Cerebral symptoms. Clear consciousness. Contact is challenging due to speech and cognitive disorders. No cerebral symptoms (no complaints of headache, nausea, vomiting).

Higher mental functions. Mixed aphasia with dominating severe motor component. A detailed examination of the higher mental functions (HMFs) is challenging due to speech disorders.

Table 1. *Instrumental studies at the prehospital stage*

Laboratory and instrumental studies	Results
Computed tomography of the chest organs 10.08.2022	without focal or infiltrative pathology
Ultrasound of the veins of the lower extremities 09.11.2022	no signs of thrombosis
Electrocardiography 08.11.2022	sinus rhythm, heart rate 100 per minute, horizontal position of the electrical axis of the heart. Hypertrophy of the left ventricle (LV) QS V1-M3, cicatricial changes of the myocardium without acute focal pathology
Echocardiography 10.08.2022	LV cavity expansion, HLV, EF 42 %, LV apical akinesis with transition to the septum, apical aneurysm with thinning of the walls and the presence of a blood clot in the cavity 19*16 mm, insignificant hydropericardium
General blood test 08.11.2022	hemoglobin 145 g/l hematocrit 44.2 % erythrocytes 4.9×10^{12}/l platelets 303×10^{9}/l leukocytes 8.9×10^{9}/l ESR 16 mm/hour
Biochemical blood analysis 24.11.2022	ALT 20.0 E/L AST 24.0 E/l total bilirubin 13.6 mmol/l glucose 5.01 mmol/l creatinine 68.0 mmol/l urea 6.1 mmol/l potassium 4.3 mmol/l
Lipid profile 24.10.2022	cholesterol 6.03 mmol/l
General urine analysis 02.11.2022	relative density 1011 reaction pH 7.0 protein is absent glucose is absent leukocytes are absent erythrocytes are absent bacteria are detected in the field of vision
Infectious serology 10.08.2022	antibodies to Treponema pallidum (*Treponema pallidum*) total (screening) — negative antibodies to hepatitis C virus (*Hepatitis C virus*) — negative antibodies to human immunodeficiency virus (HIV types 1/2) and antigen p24 — negative HBs-hepatitis B virus antigen (qualitative) — negative
PCR examination 11.11.2022	coronavirus, RNA (SARS-CoV-2, PCR) quality. — not detected coronaviruses similar to SARS-CoV RNA (SARS-CoV, PCR) quality. — not detected

Note: PCR — polymerase chain reaction, ESR — erythrocyte sedimentation rate, RNA — ribonucleic acid, HLV — hypertrophy of the left ventricle, EF — ejection fraction, LV — left ventricle, HIV — human immunodeficiency virus

The meningeal syndrome is not observed. Small meningeal signs, neck stiffness, Kernig's symptom and Brudzinski's reflex are not observed. Photophobia: no.

Sensory system. A detailed assessment of sensory disorders is challenging due to aphasia. Peripheral nerve stretch symptoms (Lasegue's sign, Neri's sign, Wassermann's test, Mazkewitch's test) are negative.

Coordination system. Static ataxia is not observed. Not observed in Romberg's position. Coordination tests (finger-to-nose test, heel-shin test, pointing test, diadochocinesia test) with the right arm are not possible due to paresis; the patient does not do the tests with his leg as he does not understand the instructions. The gait is paretic; the patient can walk on his own with a cane. The patient's walking pace is decreased.

Vegetative system. Dermographism is red. Pilomotor reflex is preserved. Claude Bernard-Horner syndrome is negative.

Examinations in inpatient settings. Taking into account that patient K. had unspecified toxic allergic reaction (according to his relatives), upon admission the attending physician scheduled a consultation by a STD and skin specialist.

Consultation by STD and skin specialist dated 14 November 2022. Status localis: the pathologic process of the skin is widespread; the rash presents as follicular papules on the interdigital spaces of the hands, on the skin of radiocarpal and elbow joints, armpits, outer abdomen, chest, outer and posterior thigh surface, in pubic region (Figure 1).

On hands, papules are paired (Figure 2). The patient presents with multiple excoriations, haemorrhagic scabs (Figures 3, 4). Hair and nails are normal. Skin scraping for itch mite: itch mite confirmed by laboratory tests (Figure 5). A set of clinical and laboratory data on the causative agent helped make a diagnosis: B86 — scabies.

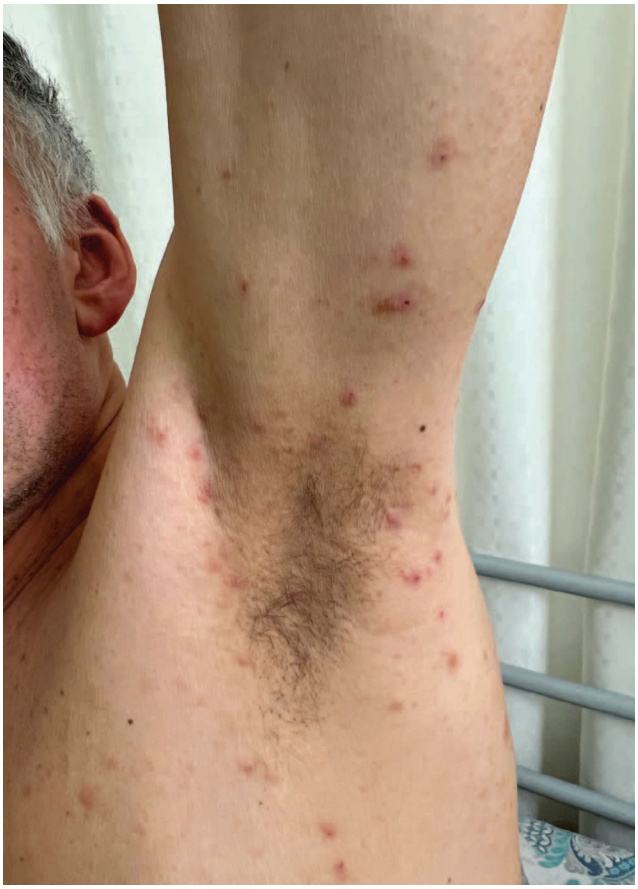

Figure 1. *Follicular papules on the skin in the left armpit*

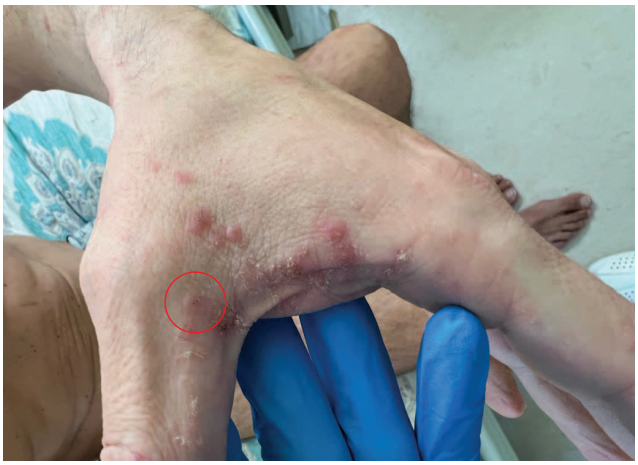

Figure 2. *Paired follicular papules on the skin in the interdigital spaces of the left hand. The red circle indicates the place from which the scraping on Sarcoptes scabiei var was taken. hominis*

Rehabilitation-limiting factors: suprapubic urinary catheter, scabies. Rehabilitation potential: moderate. The rehabilitation target was not achieved due to an early discharge of the patient for outpatient management.

Pursuant to SanPiN (Sanitary Regulations and Norms) 3.3686-21, Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases, in order to prevent an outbreak and spread of infectious diseases in Moscow region, sanitary and antiepidemic (preventive) measures were taken in accordance with the sanitary regulations.

The infectious case of the patient K. was notified by phone within 2 hours; the territorial body in charge of the federal state sanitary and epidemiological monitoring at the patient's place of residence was urgently notified in writing within 12 hours. The infectious case was recorded in the infectious disease log.

Pursuant to the Industry Standard "Patient Management Protocol. Scabies" approved by Order of the Ministry of Health of the Russian Federation No. 162 dated 24 April 2003, all contacts were examined. Contacts of the patient were subject to epidemiological follow-up.

Disinfection was conducted to ensure the break of the infection mechanism and to stop the epidemiological process: current and final disinfection, disinvasion, disinfestation.

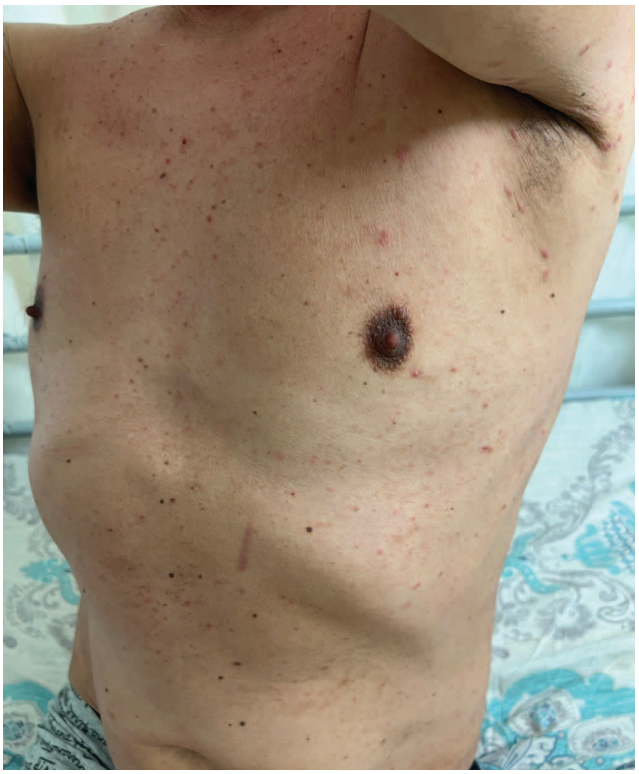

Figure 3. *The skin pathological process on the outer surface of the abdomen is widespread, rashes are represented by follicular papules, excoriation, hemorrhagic crusts*

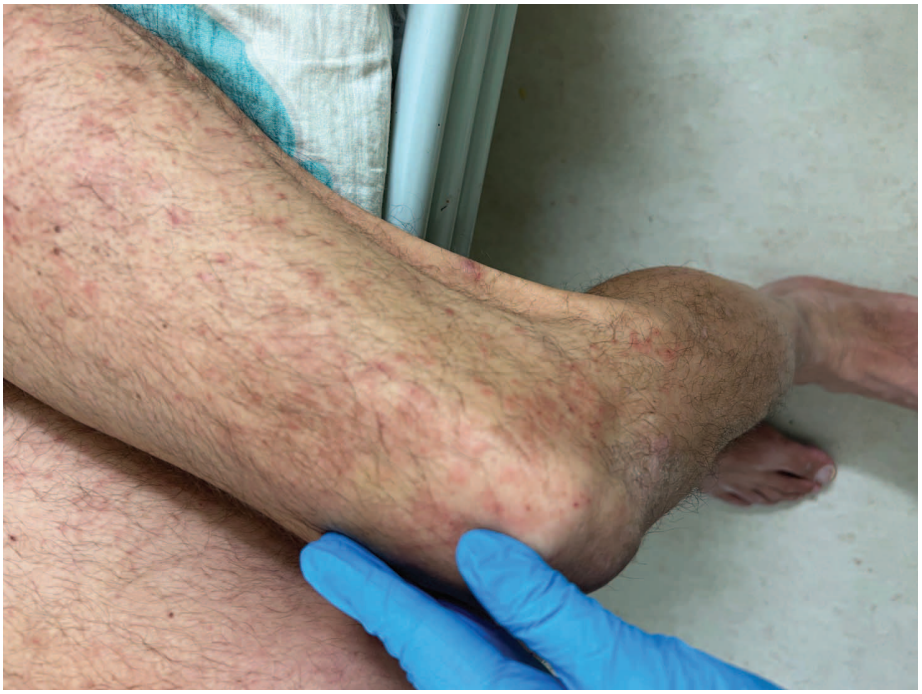

Figure 4. *The skin pathological process on the lower extremities is widespread, rashes are represented by follicular papules, excoriation*

Current disinfection was performed in the presence of the patient K. as soon as his disease was confirmed. Current desinfection was performed by the patient's carers once they had been briefed by a medical professional. Current desinfection of the environment was performed over the period from the patient K.'s admission and up to his discharge by the staff of Federal State Budgetary Institution Federal Centre for Brain and Neurotechnology at the Federal Medical and Biological Agency of Russia. Final disinfection was performed after the patient had been isolated at home in accordance with the legislation of the Russian Federation.

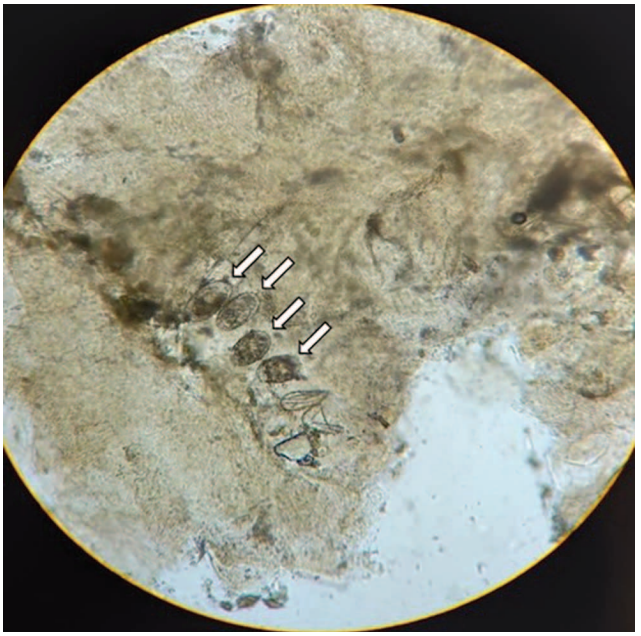

Figure 5. *Scabies mite eggs at various stages of development (white arrows) scraped from the skin in the interdigital space between the thumb and forefinger of the left hand. The location of the scraping is indicated in Figure 2*

Recommendations upon discharge:

1. A diet limiting the intake of easily digested carbohydrates, animal fats. Water intake schedule. Reduction of daily salt intake to 3 g. Reduction carbohydrate intake. Low-cholesterol diet. Nutritious diet (increased intake of seasonal fruits and vegetables).
2. BP, HR monitoring, self-assessment diary (morning, evening), diuresis monitoring. Antihypertensive therapy: Enalapril 5 mg twice daily (morning/evening). Bisoprolol 2.5 mg in the morning. Spironolactone 25 mg in the morning. Follow-up by cardiologist at the place of residence.
3. Anticoagulant therapy: Apixaban 2.5 mg twice daily.
4. Lipid-lowering therapy: Atorvastatin 40 mg once daily in the evening. Blood biochemistry (alanine aminotransferase (ALT), aspartate amino transferase (AST), creatine phosphokinase (CPK), cholesterol, high-density lipoproteins (HDLPs), low-density lipoproteins (LDLPs), triglycerides) in a month; once every 3–6 months.
5. Recommendations by the STD and skin specialist: prior to treatment initiation, the patient should take a warm shower using soap, trying to steam out the skin as much as possible in order to enhance medication penetration, and dry the skin with a towel.

Day 1: 200 mL of benzyl benzoate emulsion 20 % should be thoroughly rubbed in the skin of arms/hands, then of the body and legs, including feet, toes, and external sex organs. Do not wash hands for 3 hours after the procedure; rub in the medication on hands every time you wash your hands. Put on clean underwear and change your bedding.

Days 2 and 3: do not apply ointment, do not wash youself, do not change underwear and bedding.

Day 4: take a shower in the morning using soap, dry yourself with a towel, then thoroughly rub 200 mL of benzyl benzoate emulsion 20 % in the skin of arms/hands, then of the body and legs, including feet, toes, and external sex organs. Put on clean underwear and change your bedding.

Day 5: wash the remaining medication away with warm water and soap; do not rub your skin. Change underwear and bedding.

The healing (repeated scraping) should be checked by the STD and skin specialist at the patient's place of residence on day 3 and 10 after therapy completion.

Discussion

The presented case study demonstrates the peculiarities of the somatic and mental health of the patient that resulted in delayed diagnosis of scabies. It is obvious that primary healthcare professionals should be made aware of possible skin conditions in handicapped persons in order to improve the routing of patients and provide for timely preventive measures.

The intensive scabies morbidity in the Russian Federation in 2011 was 45.9 cases per 100,000 people [4]. In 2017, scabies morbidity was 15.5 cases per 100,000 people; while in 2018 it was 15.0 cases [5]. The actual scabies morbidity might be higher, since diagnosis errors alter the statistics, and late diagnosis causes delays in antiepidemic measures in the focal areas.

In 2011–2014 in the Russian Federation, the scabies morbidity in the age group of 40+ years old demonstrated an almost 2-fold increase [6]. There is no information on scabies morbidity in handicapped patients with cognitive disorders in the Russian Federation. Both Russian [7] and foreign authors [8, 9] point out delayed scabies diagnosis in elderly patients with cognitive disorders. One of the main reasons for long-term immobilisation of patients is cerebrovascular disorders; also, patients have comorbidities which interfere with timely diagnosis of other pathologies. Impaired social functioning aggravates the course of scabies, contributes to its late diagnosis, especially in multiple comorbidities and abnormal clinical progression. Delayed scabies diagnosis in handicapped patients with cognitive disorders is caused by a number of factors: challenging collection of complaints and history, atypical clinical progression, diagnosis errors and inattention by medical professionals, impaired social functioning, social factors, including lower material welfare and poor personal hygiene to a number of reasons, e.g., handicapped status. Despite the fact that the patient K. was followed up at the pre-hospital stage, scabies was not timely diagnosed. According to current observations, a visiting GP (general practitioner) follows up 350–400 handicapped patients, while a nurse follows up 150–200 such patients. On the average, a GP visits a handicapped patient four times a year, while nursing staff — 12 times a year. It is recommended to visit post-ACE patients more frequently. On the average, a GP examines a handicapped patient twice a quarter [10]. A retrospective analysis of 2803 medical records of patients who died in a multidisciplinary inpatient clinic in Moscow in 2011–2012, including 10 % of long-term handicapped patients, demonstrates that every fifth handicapped patient is examined by a GP once every 2–4 months, 27 % of patients are examined more rarely. 33 % patients were examined by a GP once every month; and the example of the patient [11] shows that this is not enough.

We can assume that the patient got infected in September 2022, when first itching rash appeared; however, scabies was diagnosed as late as on 14 November 2022. Cassell J.A. et al. conducted a prospective study to identify scabies in ten care homes accomodating 430 persons. Median age was 86.9 (interquartile range: 81.5–92.3) years; 76 % were women; 68 % of patients had dementia. All patients had various comorbidities: cancer, diabetes mellitus, impaired nutrition, use of corticosteroids. Confirmed, possible or potential scabies was diagnosed in 27 % of examined patients. The highest morbidity was recorded in the age group of 90–94 years old (30 %). 31 patients with confirmed scabies did not complain of itching, rash or scratching; 24 of them had dementia. Researchers concluded that dementa (odd ratio 2.37, 95 % confidence interval 1.38–4.07) is a risk factor for scabies in care homes. The staff failed to see skin manifestations in 12 patients who were later diagnosed with scabies. Median time from infection to confirmed diagnosis was 22 (interquartile range, 7.5–186) days [12]. In order to standartise the diagnostics of scabies, in 2020 the Alliance for the Control of Scabies (IACS) suggested scabies diagnosis criteria which inclide three levels of diagnostic accuracy: confirmed scabies with visualisation of itch mite or its products (level A), clinical scabies (level B), and suspected scabies (level C) [13]. However, these criteria are not designed for the diagnosis of atypical scabies, crusted scabies, scabies in persons with compromised immunity, scabies in elderly persons, scabies in persons with cognitive disorders, and scabies in bed-bound patients. New, more accurate and simple

diagnostic methods and criteria for Sarcoptes scabiei var. hominis are required. Prevention of scabies in handicapped persons with cognitive disorders has huge social significance; the primary task is to break path of infection transmission from contagious patients to healthy individual. This problem can be resolved easier with the participation of patient's relatives and coordination of medical and non-medical efforts. A contagious person can spread the disease even in the absence of any symptoms. The probability of disease transmission is the highest in direct and close skin-to-skin contact, i.e., among family members. Contacts are recommended to undergo preventive therapy simultaneously with the patient in order to minimise the risk of re-infection [4, 14]. In some endemic heavily populated islands (Fiji), positive experience with the use of Ivermectin for mass therapy and prevention of scabies was described [15, 16]. Literature sources describe development of scabies vaccines [17]. In the Russian Federation, prevention of scabies is performed in accordance with SanPiN 3.3686-21, Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases: contacts are treated in their households and organised groups with a 2-week follow up and two examinations (when the disease is diagnosed and in two weeks).

Conclusion

Challenges with collection of complaints and history, abnormal clinical progression, multiple comorbidities, and slow augmentation of symptoms in handicapped persons with cognitive disorders hinder early scabies diagnosis and facilitate the spread of this contagious skin disease. In order to prevent outbreaks of scabies, rigorous observation of all sanitary rules and regulations of the Russian Federation is essential. Medical professionals should be more vigilant about patients with impaired social functioning in order to prevent diagnostic errors. Special attention should be paid to the hygiene of skin and cutaneous appendages, a set of additional measures for improvement of the quality of life and prevention of complications.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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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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