Russian Journal of Cardiology 2023;28(S1):5259
doi:10.15829/1560-4071-2023-5259
https://russjcardiol.elpub.ru

OPINION ON A PROBLEM
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)
ISSN 2782-2257 (online)

Red flags to diagnose infiltrative cardiomyopathies

Reznik E. V.[1,2], Nguyen T. L.[1], Ustyuzhanin D. V.[3], Semyachkina A. N.[1], Shkolnikova M. A.[1]

Infiltrative cardiomyopathies are a group of diseases characterized by the deposition of abnormal substances in heart tissues, which leads to thickening of the walls or dilation of chambers with a secondary decrease in wall thickness and the development of diastolic, less often systolic, ventricular dysfunction. Most often, these are progressive diseases that, in the absence of adequate therapy, have an unfavorable prognosis. Clinical manifestations of infiltrative cardiac diseases are variable, which often leads to diagnostic difficulties and errors. In most cases, specific laboratory and morphological tests are required to confirm or clarify the diagnosis. Early diagnosis is critical to initiating therapy and improving patient prognosis. This article provides characteristic signs and symptoms, the so-called "red flags", making it possible to suspect infiltrative cardiomyopathies, diagnose them at an early stage and start life-saving therapy.

Keywords: infiltrative heart diseases, infiltrative cardiomyopathies, red flags, diagnostic keys, amyloidosis, sarcoidosis, hemochromatosis, Fabry disease, mucopolysaccharidosis, Danon disease, Pompe disease, heart failure, arrhythmia.

Relationships and Activities: none.

[1]Pirogov Russian National Research Medical University, Moscow; [2]City Clinical Hospital № 31, Moscow; [3]E. I. Chazov National Medical Research Center of Cardiology, Moscow, Russia.

Reznik E. V.* ORCID: 0000-0001-7479-418X, Nguyen T. L. ORCID: 0000-0002-8856-4542, Ustyuzhanin D. V. ORCID: 0000-0002-0402-3977, Semyachkina A. N. ORCID: 0000-0002-4026-3791, Shkolnikova M. A. ORCID: 0000-0001-7115-0186.

*Corresponding author:
elenaresnik@gmail.com

Received: 16.10.2022
Revision Received: 09.11.2022
Accepted: 29.01.2023

For citation: Reznik E. V., Nguyen T. L., Ustyuzhanin D. V., Semyachkina A. N., Shkolnikova M. A. Red flags to diagnose infiltrative cardiomyopathies. *Russian Journal of Cardiology*. 2023;28(1S):5259. doi:10.15829/1560-4071-2023-5259. EDN ZGFWNJ

Infiltrative cardiomyopathy (ICM) is a group of diseases characterized by the deposition of abnormal substances in the heart tissue, causing diastolic, less often systolic, dysfunction of the ventricle(s). Physiological and morphological characteristics of ICM are variable, which quite often leads to diagnostic and therapeutic errors.

The aim of this review was to analyze current studies on the clinical course of ICM, to identify symptoms and signs characteristic of ICM for the timely diagnosis of the disease — their "red flags" and "diagnostic keys".

Material and methods

We systematically searched the PubMed database for the following keywords: "infiltrative heart diseases", "infiltrative cardiomyopathies", "red flags", "keys for diagnosis", "amyloidosis", "sarcoidosis", "hemochromatosis", "Fabry disease", "mucopolysaccharidosis", "Danon's disease", "Pompe's disease", "oxalosis" and in the eLIBRARY.RU database for the corresponding Russian keywords for the period from January 1, 2012 to June 1, 2022. Based on the results of the search, 242 following literature sources were analyzed: consensus docu-

ments, meta-analyses, literature reviews, articles, case reports.

The review provides information on the definition, classification of ICM, their clinical manifestations, diagnostic methods, "diagnostic keys" and the examination algorithm.

Classification

The term ICMappeared in connection with modern ideas about the etiology, pathophysiology of diastolic dysfunction and restrictive cardiomyopathy (RCM) — the development of myocardial fibrosis or infiltration by certain substances or cellular elements. In 1997, Kushwaha SS, et al. proposed a classification of RCM, where ICM includes 5 diseases: amyloidosis, sarcoidosis, Gaucher disease, Hurler disease, fatty infiltration [1]. Subsequently, Moiseev VS, Braunwald E, Sewald JB, Madan N suggested some definitions and expanded the list of diseases in the ICM group [2-5] (Table 1). Currently, ICM includes cardiac amyloidosis, cardiac sarcoidosis, hemochromatosis, Fabry disease (FD), ANCA-associated vasculitis, Danon disease, Friedreich ataxia, mucopolysaccharidosis, cardiac oxalosis, etc.

Over the past decades, several revisions to ICM definitions have been proposed, but a single classification still does not exist. The MOGE(S) classification system, published in 2013, reflecting information about morphofunctional features, affected organs and tissues, genetic mutations, acquired causes, inspired us to the idea of ICM classification, which was named after the first letters of the parameters underlying the classification, MORAL-STAGE (Table 2).

As a simpler tool for clinical practice, we a staging system for ICM from 3 stages can be proposed (Figure 1):

Stage 1 — the stage of infiltration, the accumulation of foreign substances in the heart begins, which can be detected microscopically. Patients are mostly asymptomatic, and the standard clinical and imaging evaluation does not reveal any pathology. There may be an increase in specific biomarkers.

Stage 2 — the stage of structural and functional cardiac changes. Changes are revealed during echocardiography, magnetic resonance imaging (MRI), DPD-scintigraphy. In addition, the infiltrative process can be indirectly detected by pathologically elevated levels of high-sensitivity troponin T (hs-TnT). Clinically, this can be manifested by unexplained chronic fatigue, decreased physical activity. Symptoms and signs of heart failure (HF), as a rule, are not yet present.

Stage 3 — HF. It is characterized by pronounced structural changes, including fibrosis from local to diffuse. With echocardiography, structural and functional cardiac anomalies are more pronounced.

Table 1

Different classifications of ICM

Authors	Year	Diseases classified as ICM											
		Amyloidosis	Sarcoidosis	Hemochromatosis	Fabry disease	Gaucher disease	Mucopolysaccharidosis	Glycogen storage diseases	Cardiac oxalosis	Friedreich's ataxia	ANCA-associated vasculitis	Endomyocardial diseases, radiation injury	Radiation injury	Metastasis	Fat infiltration
Kushwala SS, et al. [1]	1997	+	+	-	-	+	+ (Hurler syndrome)	-	-	-	-	-	-	-	+
Моисеев В.С. [5]	2011	+	+	+	-	-	-	+	-	-	-	-	-	-	-
Braunwald E, et al. [4]	2001	+	+	+	+	+	-	+	-	-	-	-	-	-	-
Sewald JB, et al. [2]	2010	+	+	+	+	-	+	+ (Danon disease)	+	+	+ (Wegener's granulomatosis)	-	-	-	-
Madan N, et al. [3]	2020	+	+	+	+	-	+	+ (Danon disease)	+	+	+ (Wegener's granulomatosis)	+	+	+	-

Abbreviation: ICM — infiltrative cardiomyopathy.

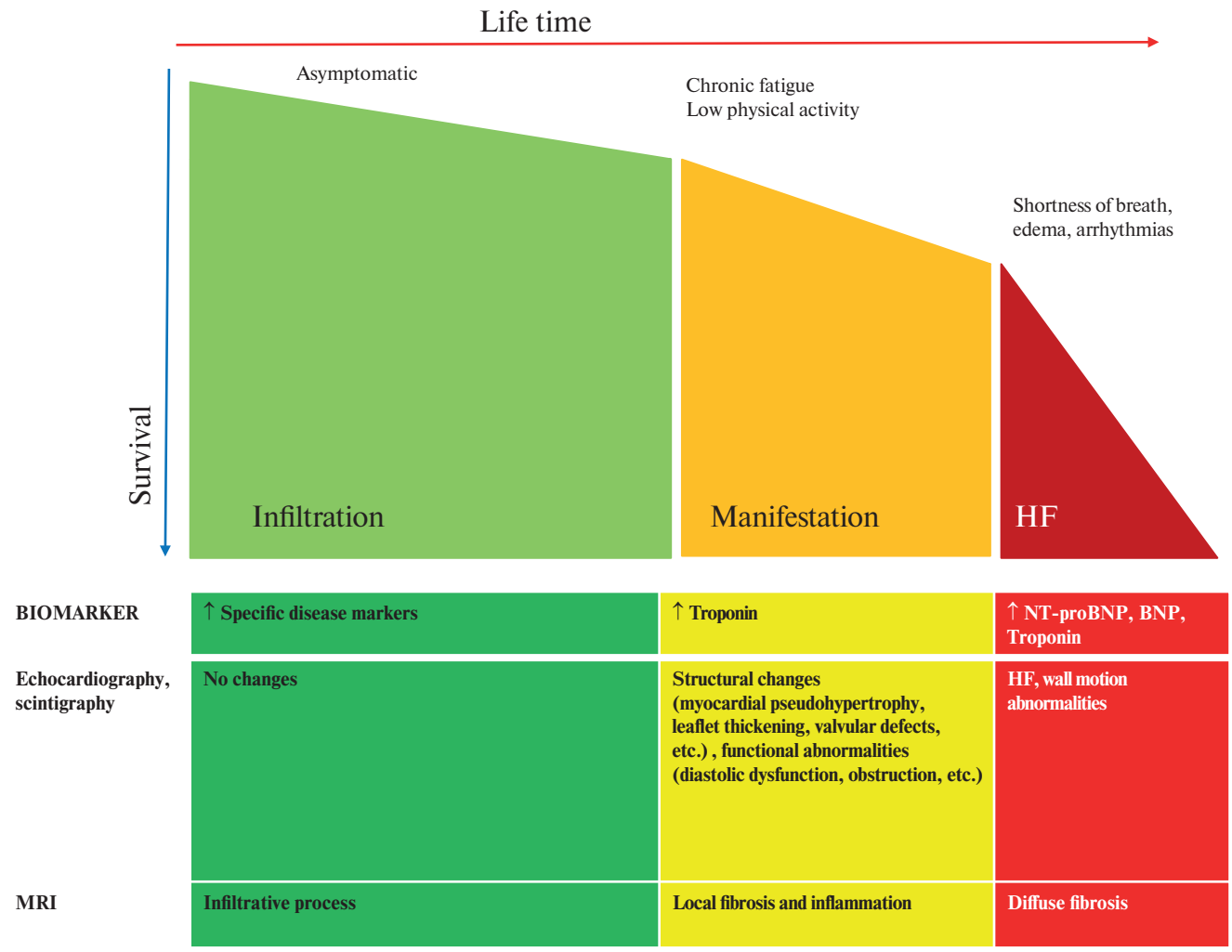

Figure 1. Staging of ICM.
Abbreviations: MRI — magnetic resonance imaging, HF — heart failure, BNP — brain natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide.

Increased levels of hs-TnT, the N-terminal pro-brain natriuretic peptide (NT-proBNP), brain natriuretic peptide. Clinically, shortness of breath, edema, weakness, fatigue, and arrhythmias are detected.

Understanding and identifying the 3 stages of cardiac involvement in ICM patients is important for treatment, the effectiveness of which is related to the stage of therapy initiation.

Clinical signs

ICM in young people (<30 years) is largely due to genetic abnormalities, while in the elderly (>65 years), amyloidosis, iron overload, and sarcoidosis are more common causes [2].

ICM in general are part of a systemic pathology whose phenotypic expression in other organs usually precedes cardiac manifestations. The role of the cardiologist is to look for heart disease in a patient who already has a diagnosis. In some cases, heart damage is a characteristic sign (Friedreich's ataxia, transthyretin amyloidosis (ATTR-amyloidosis), mucopolysaccharidosis), while the probability of correct diagnosis depends on the qualification and clinical alertness of the cardiologist in relation to ICM (Figure 2).

Carpal tunnel syndrome, especially bilateral, occurs in about half of patients with amyloidosis and often precedes cardiac manifestations by several years. It and proximal biceps tendon rupture, leading to Popeye sign, are "red flags" of amyloidosis [6]. Carpal tunnel syndrome can occur not only in amyloidosis, but also in mucopolysaccharidosis. Such signs of amyloidosis, as well as macroglossia or periorbital purpura, are highly specific but poorly sensitive and should not be used to exclude the disease (Figure 3).

Ocular impairments are not uncommon in patients with ICM. In FD, *cornea verticillata*, lens

Table 2

MORAL-STAGE classification

Designation	Characteristics	Letter code
M (Morpho-functional phenotype)	Morphofunctional signs or external clinical manifestations	D — dilated cardiomyopathy, H — hypertrophic cardiomyopathy, R — restrictive cardiomyopathy, E — early stage without clear phenotype, E(D) — early diagnosis of dilated cardiomyopathy, E(H) — early diagnosis of hypertrophic cardiomyopathy, NS — non-specific variant, 0 — without cardiac involvement, NA — not available.
O (Organ/system invovement)	What organs/systems are affected	H — heart (LV — left ventricle, RV — right ventricle, RLV — right and left ventricles), A — hearing organs, C — cutaneum, E — eyes, G — gastrointestinal tract, K — kidneys, Li — liver, Lu — lungs, M — skeletal muscles, N — nervous system, S — skeleton, 0 — without organ and system damage.
R (RIsk of cardiac death)	Cardiovascular risk	SCD — 5-year risk of sudden cardiac death according to the HCM risk SCD score (%), HF — 3-year risk of mortality for HF patients according to the MAGGIC score (%).
A (Age of onset, time on treatment)	Onset age and duration of pathogenetic therapy	2 digits: first — onset age (years), second — duration of pathogenetic therapy (years).
L (localization of pathological process)	Location of the pathological process outside or inside the cell	O — pathological process outside cells, I — pathological process inside cells, OI — pathological process outside and inside cells.
S (Stage)	ICM and heart failure stages with NYHA functional class	ICM stage (1-3). Heart failure stage (I-III). NYHA functional class (I-IV).
T (Treatment)	Treatment	0 — not treated, S — symptomatic therapy (treatment of HF, arrhythmias), P — pathogenetic therapy.
A (Type of arrhthmias, conduction disturbance	Arrhythmias, conduction disorders	0 — no arrhythmia, AF — atrial fibrillation, VT — ventricular tachycardia, AF+VT — atrial fibrillation and ventricular tachycardia, VF — ventricular fibrillation, AVRT — atrioventricular reciprocating tachycardia, LBBB — left bundle branch block.
G (Genetic)	Inheritance type	AD — autosomal dominant, AR — autosomal recessive, XL–X-linked, M — maternal line, 0 — no data, S — sporadic, N — non-hereditary, U — unknown.
E (Etiology)	Etiology	G — genetic, A — amyloidosis (AA — AA-amyloidosis, AL — AL-amyloidosis), S — sarcoidosis, H — hemochromatosis, U — unknown etiology, non-hereditary amyloidosis, H-T — secondary hemochromatosis in thalassemia, O — oxalosis, W — Wilson-Konovalov disease.

Abbreviations: ICM — infiltrative cardiomyopathy, HF — heart failure, NYHA — New York Heart Association.

opacity (Fabry cataract), increased tortuosity of the vessels of the conjunctiva and retina are observed [7]. Such signs usually do not impair vision, but correlate well with disease severity and genotype [8]. In contrast to FD, ocular lesions in mucopolysaccharidosis, including retinal pigment degeneration, retinal angiospasm, corneal clouding, edema, optic nerve atrophy, and glaucoma, can lead to significant visual impairment [9].

Skeletal muscle weakness indicative of a primary neuromuscular disorder (Friedreich ataxia, storage disease) usually precedes cardiac involvement and dominates the clinical picture, but sometimes skeletal myopathy is subtle and early symptoms or signs of disease may be due to cardiomyopathy (for example, in Danon disease) [10, 11].

If patients have symptoms such as fatigue, pain in the right hypochondrium, arthralgia, chondrocalcinosis, skin pigmentation, liver enlargement, especially the presence of cirrhosis, HF events, or diabetes, hemochromatosis should be suspected [12].

Electrocardiography

Electrocardiography (ECG) in ICM car reveal low QRS voltage, which is associated with the accumulation of non-conductive substances in the myocardium (glycosaminoglycans, amyloid, iron) and, possibly, also with myocardial edema [9, 13]. Low QRS voltage is a warning sign of the disease, often preceded by significant left ventricular (LV) hypertrophy; however, in hemochromatosis and amyloidosis, it manifests itself in late stages [14, 15]. There is usually a characteristic discrepancy between the limb leads and the precordial leads, with low voltage in the limb leads and normal or high voltage in the precordial leads. This discrepancy is not seen in low voltage QRS conditions such as pericardial or pleural effusion, obesity, emphysema, pneumothorax, or myxedema. The prevalence of low QRS

Figure 2. Red flags for ICM diagnosis.
Note: cardiac and systemic red flags with an increasing likelihood of ICM from internal (cardiac symptoms) to external circles (specific symptoms). Popeye sign: prominence above the elbow, with simultaneous concavity near the shoulder due to proximal biceps tendon rupture. Cherry-on-top or apical sparing: intact apical regions with high strain values, located in the central part and colored red against the background of low strain of the middle and basal regions in cardiac amyloidosis. Limb- precordial voltage dissociation: voltage mismatch between the limb leads and precordial leads, with low voltage in the limb leads while normal or sometimes high voltage in the precordial leads.
Abbreviations: AV block — atrioventricular block, LBBB — left bundle branch block, RBBB — right bundle branch block, HCM — hypertrophic cardiomyopathy, LVH — left ventricular hypertrophy, DCM — dilated cardiomyopathy, VT — ventricular tachycardia, ICM — infiltrative cardiomyopathy, MRI — magnetic resonance imaging, SVT — supraventricular tachycardia, GFR — glomerular filtration rate, TIA — transient ischemic attack, AF — atrial fibrillation, CHF — chronic heart failure, ECG — electrocardiography, BNP — brain natriuretic peptide, GAA — acid alpha-glucosidase, GAG — glycosaminoglycan, Glc4 — glucose tetrasaccharide, LGE — late gadolinium enhancement, Lyso-Gb3 — globotriaosylsphingosine, NT-proBNP — N-terminal pro-brain natriuretic peptide.

voltage in AL amyloidosis ranged from 27% to 84% depending on its criterion. Notably, the absence of a low-voltage ECG pattern does not rule out ICM. The discrepancy between QRS voltage and LV mass measured on echocardiography may be even greater than QRS voltage alone [16].

In ICM, in addition to myocardial pseudohypertrophy, true hypertrophy also occurs (FD, Danon

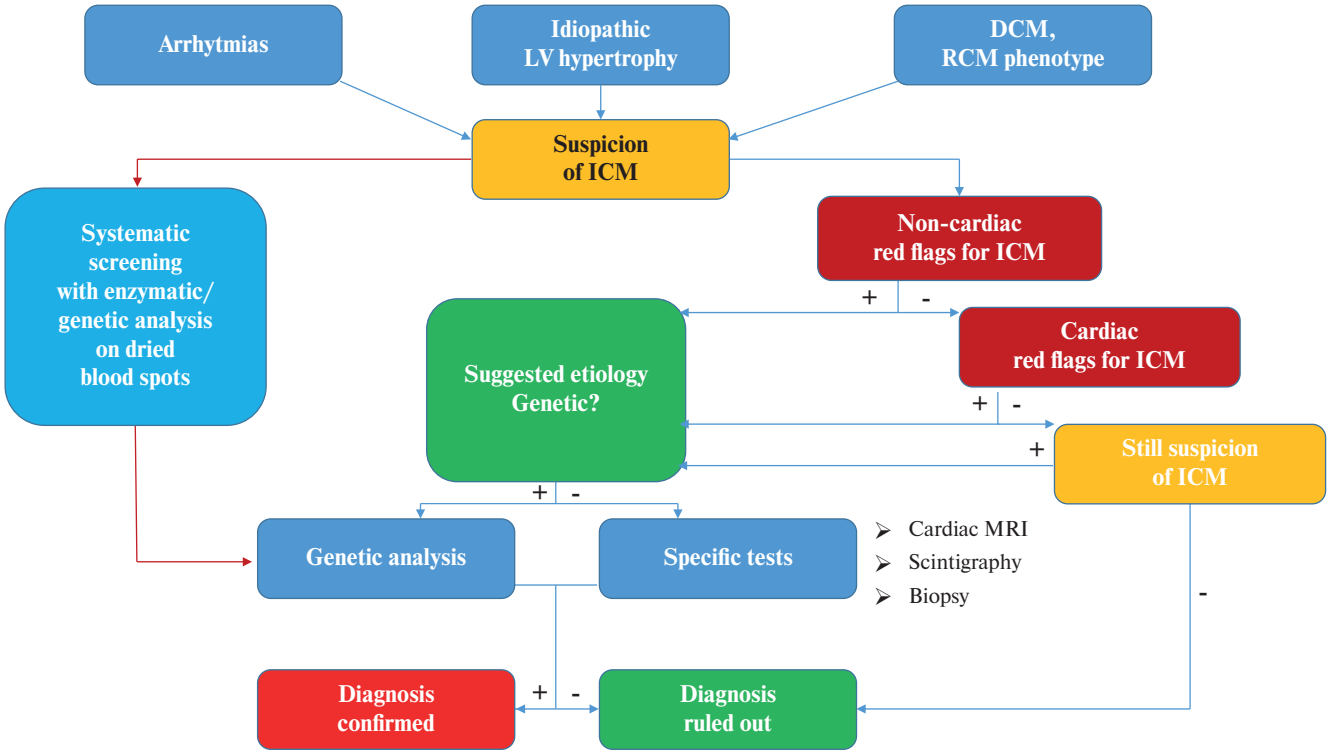

Figure 3. Proposed scheme-algorithm for ICM diagnosis.
Abbreviations: DCM — dilated cardiomyopathy, ICM — infiltrative cardiomyopathy, LV — left ventricle, MRI — magnetic resonance imaging, RCM — restrictive cardiomyopathy.

disease, partially ATTR-amyloidosis). In the second group, there is a sharp increase in the QRS amplitude with impaired repolarization (usually at a young age, even in childhood) [17].

For FD, short PR interval is often the first (and sometimes the only) sign of heart damage due to a decrease in P wave duration [18]. Wolff-Parkinson-White syndrome in the presence of LV hypertrophy is a screening criterion for Danon disease [10] and Pompe disease [19] diagnosis, while it is rare in hypertrophic cardiomyopathy (HCM).

Conduction disorders are common in patients with coronary artery disease [16]. In patients with LV hypertrophy, a QTc prolongation >440 ms with a simultaneous Sokolow-Lyon index <1,5 mV has a sensitivity of 85% and a specificity of 100% for the detection of cardiac amyloidosis, and a QTc <440 ms in combination with a PQ interval minus P-wave duration in lead II <40 ms had 100% sensitivity and 99% specificity for FD [17]. Patients with cardiac oxalosis usually develop complete atrioventricular block and ventricular conduction disorders [20]. In cardiac sarcoidosis, conduction disturbances were detected in 75% of patients [21].

Other ECG features reported in patients with ICM include abnormal P wave morphology and duration, a pseudoinfarct pattern with QS complexes in the anterior leads, and an unusual QRS axis [6]. Atrial fibrillation is also quite common in patients with ICM: in our retrospective study, 44% of patients with amyloidosis had some form of atrial fibrillation [14].

Holter ECG monitoring

Patients with ICM often have symptoms such as dizziness, fainting, and palpitations, for which Holter ECG monitoring (HM ECG) is indicated. In addition, HM ECG can be a useful tool for the differential diagnosis of LV hypertrophy etiology. In a study by Yamada S, et al. severe disorders of heart rate variability and turbulence have been shown in cardiac AL-amyloidosis. The standard deviation of all R-R intervals, the standard deviation of the 5-minute mean R-R intervals, and the turbulence slope were significantly lower in cardiac amyloidosis compared with HCM (P<0,001, respectively) [22].

According to Azevedo O, et al., myocardial hypertrophy with the presence of bifascicular block and areas of contrast enhancement in the delayed phase on MRI in the basal segment of LV inferolateral wall are characteristic signs of FD, and their absence makes it possible to exclude this diagnosis in a patient with an accuracy of 95,8% [23].

Presence of ventricular ectopic beats of 100 or more in HM ECG with a sensitivity of 67% and

Table 3

Revised 2012 Mayo staging system of AL-amyloidosis

Thresholds for risk factors	Stage		Death hazard ratio (95% CI)*
Troponin: Cardiac troponin T ⩾0,025 μg/l *or* High-sensitivity cardiac troponin T ⩾40 ng/l BNP: NT-proBNP ⩾1800 ng/l *or* BNP ⩾400 ng/l dFLC ⩾18 mg/dl	I stage	No risk factors	Reference
	II stage	1 risk factor	1,7 (1,2-2,3)
	III stage	2 risk factors	4,1 (3,1-5,5)
	IV stage	3 risk factors	6,3 (4,8-8,3)

Note: * — hazard ratios presented reflect the use of cardiac troponin T and NT-proBNP.

Abbreviations: BNP — brain natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide, dFLC — difference between involved and uninvolved free light chains.

a specificity of 80% identifies cardiac involvement in patients with systemic sarcoidosis [24].

Laboratory data

Cardiac biomarkers

Troponin T and NT-proBNP are included in the diagnostic criteria for heart damage in ICM [2, 25]. The normal range of their values almost excludes cardiac involvement, while an elevated level may indicate involvement of the heart, but is not specific for ICM, and should be interpreted in accordance with cardiac imaging data [25].

NT-proBNP and troponins are elevated in ICM patients due to an infiltrative process in the myocardium or direct toxic effects of abnormal substances on cardiomyocytes. In one study among patients with cardiac AL amyloidosis, NT-proBNP levels were never below the 97,5 percentile for normal individuals, indicating 100% sensitivity; moreover, the NT-proBNP threshold of 1285 ng/L was 92% accurate for detecting cardiac involvement [26]. NT-proBNP can serve as an early indicator of LV diastolic dysfunction in patients with iron overload and FD [15, 23]. Since an increase in NT-proBNP predicts the development of HF in amyloidosis, hemochromatosis, FD, and other ICM, routine determination of NT-proBNP during the observation of patients at high risk of ICM is recommended [15].

An increase in plasma level of hs-TnT is observed in most patients with ICM [27], including in patients without overt cardiac involvement, and represents a "red flag" for the disease. Moreover, hs-TnT is associated with HF severity, LV systolic dysfunction, and wall thickness in patients with ICM [27]. Hs-TnT is a useful marker for assessing the activity of cardiac sarcoidosis: sensitivity and specificity were 87,5% and 75,0%, respectively [28]. Interestingly, troponin is elevated in patients with ATTR cardiomyopathy, usually to a lesser extent than in AL cardiomyopathy, despite a greater increase in wall thickness and deterioration in LV systolic function [29].

In addition to NT-proBNP and troponin, several measures of myocardial injury and cardiac function have been proposed as biomarkers, but they lack sensitivity and specificity for detecting ICM, or there is insufficient evidence for their diagnostic value.

To assess the severity of heart damage in AL-amyloidosis, the already mentioned Mayo classification based on troponin T, NT-proBNP and the difference between free kappa and lambda light chains is of primary importance (Table 3) [6]. The most recent proposed system for staging cardiac ATTR amyloidosis uses NT-proBNP (>3000 pg/ml) and glomerular filtration rate (<45 ml/min) [30]. Staging in both systems is defined such that stage 1 has none of the criteria, stage 2 has 1 of the 2 criteria, and stage 3 has both criteria.

Amyloidosis

There are 36 types of amyloidosis, of which special attention will be paid to those in which heart involvement is frequently observed.

Unlike AL amyloidosis, no plasma or urine biomarkers are currently available to diagnose ATTR amyloidosis. There are newer serological assays for the endogenous transthyretin-retinol-binding protein ligand, which may serve as a tested biomarker in the future [31]. Separate studies have shown the predictive value of transthyretin as a serum marker for wild-type ATTR amyloidosis. A low serum transthyretin level at the time of diagnosis is prognostically unfavorable [6].

If AL-amyloidosis is suspected, additional laboratory tests are needed. First, electrophoresis is performed with the determination of the M-gradient and immunofixation electrophoresis of blood serum and urine, followed by a quantitative determination of free kappa and lambda light chains in blood serum, as well as the calculation of their ratio and

difference. A kappa-lambda ratio <0,26 indicates monoclonal lambda gammopathy, and a kappa-lambda ratio >1,65 indicates monoclonal kappa gammopathy [32]. In addition, 24-hour urine should be quantified for albumin and protein excretion. Proteinuria >500 mg per day indicates severe kidney damage.

Fabry disease

Detection of insufficient activity of α-galactosidase in blood plasma or leukocytes is the method of choice for laboratory diagnosis of FD in men [8]. On the contrary, in girls and adult women, enzyme activity may be within the normal range, so they need genotyping (detection of a *GLA* gene mutation) [8]. According to recent results, plasma globotriaosylsphingosine with a cut-off value of 2,7 ng/mL can serve as a useful and reliable biomarker to improve the diagnosis of FD in heterozygous women, as well as for therapeutic evaluation and monitoring [8].

Hemochromatosis

If the transferrin saturation is ⩾45% and/or the serum ferritin level is >200 μg/l in women or 300 μg/l in men, then a genetic study is necessary to determine the HFE genotype [2]. In homozygotes (C288Y/C288Y), the diagnosis of hereditary hemochromatosis was confirmed. In C288Y/H63D heterozygotes, other C288Y heterozygotes, or non-C288Y heterozygotes, careful exclusion of other hepatic or hematologic diseases should be considered [2]. Serum ferritin and its iron saturation ratio is also an easy way to monitor therapy.

Danon disease

Laboratory diagnostic tools include detection of normal acid maltase activity, vacuolization in skeletal and/or endomyocardial biopsy, LAMP-2 deficiency in various tissues, including leukocytes, and detection of a *LAMP-2* gene mutation. In Danon disease, there is an increase in following cardiomyocyte damage indicators: troponin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase [33]. *LAMP-2* is commonly included in genetic panels used to test unclassified cardiomyopathies, and gene testing is currently the most common and least invasive method used to diagnose Danon disease.

Oxalosis

Oxaluria must be confirmed by two urine samples. Primary hyperoxaluria is characterized by urinary oxalate excretion in most cases >0,7 mmol/1,73 m^2 per day, and in some cases may exceed 2,0 mmol/1,73 m^2 per day in contrast to normal urinary excretion, which is usually <0,45 mmol/1,73 m^2 per day [34].

As the glomerular filtration rate decreases, urinary oxalate excretion decreases and its estimate may be inaccurate. Plasma oxalate levels should be measured. The final diagnosis of primary hyperoxaluria is established using genetic studies [34].

Mucopolysaccharidosis

Mucopolysaccharidoses include 13 different conditions caused by a deficiency of specific enzymes in the glycosaminoglycan degradation pathway. Enzyme tests are usually performed on the blood. Identification of variants in the specific genes that encode each enzyme associated with mucopolysaccharidosis is useful for diagnosis confirmation, carrier detection, prenatal diagnosis, and phenotype prediction [9]. There is a growing trend to conduct genotype-based studies at the start of the survey, with the pathogenicity of identified genetic variants to be confirmed by measurement of enzyme activity and/or identification and/or quantification of glycosaminoglycan classes [9].

Echocardiography

The most common echocardiographic features seen in ICM are biatrial enlargement, symmetrical ventricular hypertrophy with small or normal LV size, pericardial effusion. Although asymmetric interventricular septal (IVS) hypertrophy, normal wall thickness, and ventricular dilatation may also occur. AL-amyloidosis is characterized by a rapid increase in heart wall thickness over several months, while the indexed stroke volume is usually greatly reduced against the background of HF with preserved ejection fraction (EF) [13].

The endocardial "binary" sign, first discovered and described by Pieroni, et al., in the form of a hyperechoic endocardium and a hypoechoic subendocardial space, can be a "red flag" of FD, although its specificity and sensitivity are not high [35]. Absolute papillary muscle area and the ratio of papillary muscle size to LV circumference have been proposed as an echocardiographic marker for FD [23].

In sarcoidosis, cardiac dilatation, LV systolic dysfunction, impaired local myocardial contractility without coronary artery involvement, focal intracardiac inclusions caused by granulomas, and pericardial effusion can be detected [36]. Wall aneurysm may develop with retraction of an area of fibrosis, especially in patients treated with corticosteroids.

The myocardium in ICM usually has a heterogeneous structure, may acquire a granular shiny pattern in cardiac amyloidosis, or contain inclusions of high echo intensity indicating granulomatous inflammation in cardiac sarcoidosis, as well as an inhomogeneous echo-dense signal, most noticeable in papillary muscles, in primary hyperoxaluria [2, 3]. The deposition of non-conductive substances in the myocardium explains the discrepancy between QRS voltage and LV hypertrophy severity, as described above.

Doppler ultrasound usually reveals mild valvular dysfunction, leaflet thickening, while more often the mitral and aortic valves are affected with the appearance of insufficiency and/or stenosis [13, 37]. Diastolic function is often significantly impaired. At the initial stages, there is an impaired relaxation, possibly progression to a restrictive pattern. With cardiac oxalosis, there is a rapid deterioration in diastolic function with an increase in filling pressure and a restrictive pattern [20]. In cardiac amyloidosis, the peak early diastolic velocity (e') decreases in the earliest stages of the disease and further decreases as the disease progresses [6].

The technique for assessing myocardial strain makes it possible to detect impaired ventricular longitudinal contraction before a decrease in EF and HF development. A LVEF strain coefficient was proposed with a threshold value of 4,1, which makes it possible to distinguish cardiac amyloidosis from HCM or normal with an accuracy of 91% [38]. Usually there is a severe impairment of the basal longitudinal strain with a relative preservation of apical strain [39]. This apical preservation has both high sensitivity and specificity for diagnosing cardiac amyloidosis [6]. Studies by Serra W, et al. proved that visualization of the strain rate makes it possible to differentiate sarcomeric HCM from cardiomyopathy in FD and cardiac amyloidosis [18]. Değirmenci H, et al., using strain assessment, showed that the detection of left atrial and ventricular myocardial strain may indicate subclinical LV dysfunction and subclinical electrophysiological cardiac changes in patients with respiratory sarcoidosis [40].

Left atrial function is very often impaired in ICM [40]. In cardiac amyloidosis, the prevalence of left atrial thrombosis is very high, even among patients with sinus rhythm [13].

Cardiac MRI

Cardiac MRI is the gold standard method for quantifying the cardiac size and volume, myocardial thickness, and determining ventricular EF. In delayed contrast-enhanced cardiac MRI, myocardial contrasting occurs both due to fibrosis, and due to impaired kinetics of the contrast agent and its delay in the intercellular space, where the accumulation of pathological proteins or other substances occurs in most ICMs. Amyloidosis is characterized by diffuse subendocardial accumulation with damage to all LV walls, which can be combined with early darkening of the blood pool due to rapid washout of contrast from the blood into the interstitial space, which is enlarged due to amyloid deposition. A typical contrast pattern is a red flag for the diagnosis of amyloidosis, which appears before a significant increase in myocardial mass develops [13]. Notably, atypical patterns of contrast agent accumulation (focal, diffuse transmural, or patchy) do not completely rule out cardiac amyloidosis.

In hemochromatosis, MRI can quantify the iron content in the heart, liver, and spleen by reducing the signal in T2 and T2* modes [41]. In sarcoidosis, it is possible to visualize sarcoid granulomas and assess the activity of inflammation by edema on T2-weighted images [42].

The absence of areas of delayed enhancement in IVS in male patients with suspected HCM is an indication for genetic screening for Danon disease [43]. In female patients with HCM, Danon disease should be suspected if inhomogeneous subendocardial enhancement without coronary involvement is detected [43]. The classical location of contrast enhancement in FD is the inferolateral wall in the basal segment, where fibrosis is detected in 50% of patients at a late disease stage [23].

T1 mapping without contrast agent injection can potentially distinguish HCM from ICM. Myocardial T1 values gradually increase in various pathological conditions from diffuse fibrosis, scar tissue to abnormal substances [6]. An increase in T1 values is observed before LV myocardial thickening or an increase in blood biomarkers and is a red flag for cardiac amyloidosis. For MRI machines with a field strength of 1,5 T, threshold values of native T1-mapping were determined (T1 <1036 ms to exclude cardiac amyloidosis with a negative predictive value of 98%; T1 >1164 ms to confirm cardiac amyloidosis with a positive predictive value of 98%), which allowed develop a diagnostic algorithm that involves the administration of a contrast agent only to patients with intermediate T1 values [44].

Areas with low T1 values represent sphingolipid deposition in FD associated with an increase in extracellular volume, but are not seen in cardiac amyloidosis. Karur GR, et al. confirmed that the IVS T1 value of 1220 ms can be used as a cutoff point for differentiating FD from HCM with a sensitivity of 97% and a specificity of 93% [45].

The T2-mapping technique can detect edema (an important element of AL-cardiomyopathy), inflammation, and can be used to detect active cardiac sarcoidosis [42], identify an increased risk of ventricular arrhythmias, and assess the adequacy of therapy [46].

Scintigraphy and positron emission tomography

Myocardial scintigraphy with phosphate-labeled complexes is the method of choice for diagnosing cardiac ATTR amyloidosis, among which ^{99m}Tc-pyrophosphate (PYP) is the most widely used in Russia. Intense retention of phosphate-labeled complexes is mostly pathognomonic for ATTR amyloidosis, and the absence of uptake usually excludes this diagnosis [47].

To determine the severity of cardiac damage, the Perugini scale was proposed: degree 0 — no cardiac uptake; grade 1 — cardiac uptake which is less intense than the bone signal; grade 2 — cardiac uptake with intensity similar or greater than bone signal; grade 3 — cardiac uptake with much attenuated or absent bone signal [47]. This system was included in the algorithm for non-biopsy diagnosis of cardiac ATTP amyloidosis in suspected cardiac amyloidosis based on a combination of clinical signs, biohumoral and/or imaging data. When the Perugini grade is 2 or 3 and no monoclonal protein is found, the diagnosis of cardiac ATTR amyloidosis is confirmed. When a monoclonal protein or Perugini grade 1 is detected, histological confirmation and amyloid typing are suggested. Finally, when the Perugini degree is 0, ATTR-cardiomyopathy is unlikely [47]. There is a quantitative scale for differentiating cardiac AL and ATTR amyloidosis, based on the calculation of the ratio of cardiac uptake to that in the contralateral side. The value of this indicator >1,5 showed a sensitivity of 97% and a specificity of 100% for the detection of cardiac ATTR amyloidosis [48].

For other ICMs, more advanced nuclear imaging techniques, including combined positron emission tomography and MRI, can examine the role of inflammation along with assessment of angina and coronary blood flow and identify early signs of cardiac involvement. Numerous studies have demonstrated the presence of abnormal perfusion on both single photon emission computed tomography and positron emission tomography in the absence of epicardial coronary artery disease, suggesting microvascular dysfunction [49].

Conclusion

The diagnosis of ICM is challenging due to phenotypic heterogeneity, multiple organ involvement, lack of a single non-invasive diagnostic tool, and limited awareness in the medical community. Interaction between experts from different fields is often required. Recent studies have challenged the dogma of ICM as a rare, incurable disease and have redefined the epidemiology and therapeutic possibilities of these conditions. Absence or delay in diagnosis of ICM can have a major impact on outcome, as potentially life-saving treatment may not be initiated or recommended at the stage of irreversible change. For timely identification, physicians potentially facing ICM should pay attention to its "red flags" that require specific diagnosis.

Relationships and Activities: none.

References

1. Kushwaha SS, Fallon JT, Fuster V. Restrictive Cardiomyopathy. New England Journal of Medicine. 1997;336:267-76. doi:10.1056/NEJM199701233360407.
2. Seward J, Verzosa G. Infiltrative Cardiovascular Diseases. Cardiomyopathies That Look Alike. Journal of the American College of Cardiology. 2010;55:1769-79. doi:10.1016/j.jacc.2009.12.040.
3. Madan N, Kalra D. Clinical evaluation of infiltrative cardiomyopathies resulting in heart failure with preserved ejection fraction. Rev Cardiovasc Med. 2020;21:181-90. doi:10.31083/j.rcm.2020.02.65.
4. Braunwald E, Zipes DP, Libby P. Heart Disease: A Textbook of Cardiovascular Medicine. Saunders 2001. 2297 p. ISBN: 0721685617.
5. Moiseev VS. Cardiomyopathy and myocarditis. GEOTAR-Media, 2020. 512 p. (In Russ.) ISBN: 978-5-9704-5429-9.
6. Vergaro G, Aimo A, Barison A, et al. Keys to early diagnosis of cardiac amyloidosis: red flags from clinical, laboratory and imaging findings. European Journal of Preventive Cardiology. 2020;27:1806-15. doi:10.1177/2047487319877708.
7. Moiseev AS, Moiseev SV, Tao EA, et al. Clinical manifestations and outcomes of Fabry disease in 150 adult patients. Clinical pharmacology and therapy. 2021;30:43-51. (In Russ.) doi:10.32756/0869-5490-2021-3-43-51.
8. Weidemann F, Reiser M. Fabry Disease. JACC: Cardiovascular Imaging. 2019;12:1684-5. doi:10.1016/j.jcmg.2018.05.029.
9. Kubaski F, de Oliveira Poswar F, Michelin-Tirelli K, et al. Diagnosis of Mucopolysaccharidoses. Diagnostics (Basel). 2020;10:172. doi:10.3390/diagnostics10030172.
10. Cenacchi G, Papa V, Pegoraro V, et al. Review: Danon disease: Review of natural history and recent advances. Neuropathol Appl Neurobiol. 2020;46:303-22. doi:10.1111/nan.12587.
11. Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. British Medical Bulletin. 2017;124:19-30. doi:10.1093/bmb/ldx034.
12. Díez-López C, Comín-Colet J, González-Costello J. Iron overload cardiomyopathy: from diagnosis to management. Current Opinion in Cardiology. 2018;33:334-40. doi:10.1097/HCO.0000000000000511.
13. Reznik EV, Nguyen TL, Stepanova EA, et al. Amyloidosis of the heart: the view of the therapist and cardiologist. Archives of Internal Medicine. 2020;10:430-57. (In Russ.) doi:10.20514/2226-6704-2020-10-6-430-457.
14. Reznik EV, Stepanova EA, Nguyen TL, et al. Retrospective analysis of damage to the cardiovascular system in patients with systemic amyloidosis. Cardiovascular Therapy and Prevention. 2021;20(1):2496. (In Russ.) doi:10.15829/1728-8800-2021-2496.
15. Singh MM, Kumar R, Tewari S, et al. Determining Nt-proBNP Levels with Diastolic Dysfunction in Thalassemia Major Patients. J Pediatr Genet. 2017;6:222-6. doi:10.1055/s-0037-1603193.
16. Child JS, Perloff JK, Bach PM, et al. Cardiac involvement in Friedreich's ataxia: A clinical study of 75 patients. Journal of the American College of Cardiology. 1986;7:1370-8. doi:10.1016/S0735-1097(86)80159-0.
17. Namdar M, Steffel J, Jetzer S, et al. Value of Electrocardiogram in the Differentiation of Hypertensive Heart Disease, Hypertrophic Cardiomyopathy, Aortic Stenosis, Amyloidosis, and Fabry Disease. The American Journal of Cardiology. 2012;109:587-93. doi:10.1016/j.amjcard.2011.09.052.
18. Serra W, Marziliano N. Role of cardiac imaging in Anderson-Fabry cardiomyopathy. Cardiovasc Ultrasound 2019;17:1. doi:10.1186/s12947-019-0151-5.
19. Fatehi F, Ashrafi MR, Babaee M, et al. Recommendations for Infantile-Onset and Late-Onset Pompe Disease: An Iranian Consensus. Frontiers in Neurology. 2021;12. doi:10.3389/fneur.2021.739931.
20. Albakri A. Deposition diseases cardiomyopathy: A review and pooled analysis of pathophysiology, diagnosis and clinical management. Trends in Research. 2019;2. doi:10.15761/TR.1000147.
21. Rosenfeld LE, Chung MK, Harding CV, et al. Arrhythmias in Cardiac Sarcoidosis Bench to Bedside. Circulation: Arrhythmia

and Electrophysiology. 2021;14:e009203. doi:10.1161/CIRCEP.120.009203.
22. Yamada S, Yoshihisa A, Hijioka N, et al. Autonomic dysfunction in cardiac amyloidosis assessed by heart rate variability and heart rate turbulence. Ann Noninvasive Electrocardiol. 2020;25:e12749. doi:10.1111/anec.12749.
23. Azevedo O, Marques N, Reis L, et al. Predictors of Fabry disease in patients with hypertrophic cardiomyopathy: How to guide the diagnostic strategy? American Heart Journal. 2020;226:114-26. doi:10.1016/j.ahj.2020.04.006.
24. Suzuki T, Kanda T, Kubota S, et al. Holter Monitoring as a Noninvasive Indicator of Cardiac Involvement in Sarcoidosis. CHEST. 1994;106:1021-4. doi:10.1378/chest.106.4.1021.
25. Hu K, Liu D, Salinger T, et al. Value of cardiac biomarker measurement in the differential diagnosis of infiltrative cardiomyopathy patients with preserved left ventricular systolic function. J Thorac Dis. 2018;10:4966-75. doi:10.21037/jtd.2018.07.56.
26. Perfetto F, Zampieri M, Fumagalli C, et al. Circulating biomarkers in diagnosis and management of cardiac amyloidosis: a review for internist. Intern Emerg Med. 2022;17:957-69. doi:10.1007/s11739-022-02958-2.
27. Seydelmann N, Liu D, Krämer J, et al. High-Sensitivity Troponin: A Clinical Blood Biomarker for Staging Cardiomyopathy in Fabry Disease. Journal of the American Heart Association. 2016;5:e002839. doi:10.1161/JAHA.115.002839.
28. Baba Y, Kubo T, Kawaguchi J, et al. High sensitivity cardiac troponin T is a useful biomarker for predicting prognosis of the patients with sarcoidosis. European Heart Journal. 2020;41:ehaa946.2121. doi:10.1093/ehjci/ehaa946.2121.
29. Takashio S, Yamamuro M, Izumiya Y, et al. Diagnostic utility of cardiac troponin T level in patients with cardiac amyloidosis. ESC Heart Fail. 2017;5:27-35. doi:10.1002/ehf2.12203.
30. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. European Heart Journal. 2018;39:2799-806. doi:10.1093/eurheartj/ehx589.
31. Arvanitis M, Simon S, Chan G, et al. Utility of Retinol Binding Protein 4 (RBP4) concentration for screening of V122I transthyretin cardiac amyloidosis. Amyloid. 2017;24:120-1. doi:10.1080/13506129.2017.1295371.
32. Heaney JLJ, Richter A, Bowcock S, et al. Excluding myeloma diagnosis using revised thresholds for serum free light chain ratios and M-protein levels. Haematologica. 2020;105:e169-71. doi:10.3324/haematol.2019.224360.
33. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. NEJM. 2005;352. doi:10.1056/NEJMoa033349.
34. Demoulin N, Aydin S, Gillion V, et al. Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review. American Journal of Kidney Diseases. 2022;79:717-27. doi:10.1053/j.ajkd.2021.07.018.
35. Azevedo O, Cordeiro F, Gago MF, et al. Fabry Disease and the Heart: A Comprehensive Review. International Journal of Molecular Sciences. 2021;22:4434. doi:10.3390/ijms22094434.
36. Houston BA, Mukherjee M. Cardiac sarcoidosis: clinical manifestations, imaging characteristics, and therapeutic approach. Clin Med Insights Cardiol. 2014;8:31-7. doi:10.4137/CMC.S15713.
37. Gurinova EE, Sukhomyasova AL, Semyachkina AN, et al. Treating a teenager with Morquio A syndrome (mucopolysaccharidosis IV A) with Vimizim. Russian Bulletin of Perinatology and Pediatrics. 2021;66(4):109-17. (In Russ.) doi:10.21508/1027-4065-2021-66-4-109-117.
38. Pagourelias ED, Duchenne J, Mirea O, et al. The Relation of Ejection Fraction and Global Longitudinal Strain in Amyloidosis: Implications for Differential Diagnosis. JACC: Cardiovascular Imaging. 2016;9:1358-9. doi:10.1016/j.jcmg.2015.11.013.
39. Rameeva AS, Rameev VV, Bobkova IN, et al. Leading factors in the progression of cardiac amyloidosis. Rational Pharmacotherapy in Cardiology. 2022;18:143-52. (In Russ.) doi:10.20996/1819-6446-2022-04-02.
40. Değirmenci H, Demirelli S, Arısoy A, et al. Myocardial deformation and total atrial conduction time in the prediction of cardiac involvement in patients with pulmonary sarcoidosis. Clin Respir J. 2017;11:68-77. doi:10.1111/crj.12307.
41. Titova AM, Trufanov GE, Fokin VA. T2* Magnetic resonance relaxometry in the quantitative non-invasive evaluation of iron overload in the liver and heart. Translational Medicine 2017;4:37-45. (In Russ.) doi:10.18705/2311-4495-2017-4-5-37-45.
42. Poponina YuS, Poponina TM, Mochula OV, et al. Cardiac sarcoidosis: Difficulties and possibilities of differential diagnosis for acute coronary syndrome without ST segment elevation in real clinical practice. The Siberian Journal of Clinical and Experimental Medicine. 2022;37(1):142-8. (In Russ.) doi:10.29001/2073-8552-2022-37-1-142-148.
43. Fang T, Wang J, Kang Y, et al. The Value of Cardiac Magnetic Resonance Imaging in Identification of Rare Diseases Mimicking Hypertrophic Cardiomyopathy. Journal of Clinical Medicine. 2021;10:3339. doi:10.3390/jcm10153339.
44. Mongeon F-P, Jerosch-Herold M, Coelho-Filho OR, et al. Quantification of Extracellular Matrix Expansion by CMR in Infiltrative Heart Disease. JACC: Cardiovascular Imaging 2012;5:897-907. doi:10.1016/j.jcmg.2012.04.006.
45. Karur GR, Robison S, Iwanochko RM, et al. Use of Myocardial T1 Mapping at 3.0 T to Differentiate Anderson-Fabry Disease from Hypertrophic Cardiomyopathy. Radiology. 2018;288:398-406. doi:10.1148/radiol.2018172613.
46. Crouser ED, Ruden E, Julian MW, et al. Resolution of abnormal cardiac MRI T2 signal following immune suppression for cardiac sarcoidosis. J Investig Med. 2016;64:1148-50. doi:10.1136/jim-2016-000144.
47. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using 99mTc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy. Journal of the American College of Cardiology. 2005;46:1076-84. doi:10.1016/j.jacc.2005.05.073.
48. Bokhari S, Castaño A, Pozniakoff T, et al. 99mTc-Pyrophosphate Scintigraphy for Differentiating Light-Chain Cardiac Amyloidosis From the Transthyretin-Related Familial and Senile Cardiac Amyloidoses. Circulation: Cardiovascular Imaging. 2013;6:195-201. doi:10.1161/CIRCIMAGING.112.000132.
49. Tower-Rader A, Jaber WA. Multimodality Imaging Assessment of Fabry Disease. Circulation: Cardiovascular Imaging. 2019;12:e009013. doi:10.1161/CIRCIMAGING.119.009013.