Cardiomyopathy of Friedreich's Ataxia. Modern Methods of Diagnostic

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Friedreich's disease is a hereditary neurodegenerative multiple organ disease, primarily affecting the most energy-dependent tissues (cells of the nervous system, myocardium, pancreas), the lesion of which is characterized by progressive ataxia, dysarthria, dysphagia, oculomotor disorders, loss of deep tendon reflexes, pyramid signs, diabetes mellitus, visual impairment. Friedreich's ataxia is the most common of all hereditary ataxias; nevertheless, this disease is considered orphan. By its pathogenesis, Friedreich's disease is mitochondrial ataxia, caused by a deficiency in the transcription of the *FXN* gene, leading to a decrease in the synthesis of the frataxin protein. Frataxin is a protein associated with the inner mitochondrial membrane, which in turn is involved in the formation of iron-sulfur clusters, the lack of which leads to a decrease in the production of mitochondrial ATP, an increase in the level of mitochondrial iron and oxidative stress. The basis of the clinical picture of Friedreich's disease is ataxia of a mixed (sensitive and cerebellar) nature. The steady and gradual progression of neurological symptoms significantly affects the quality of life of patients and is most often the leading reason for seeking medical attention. However, the prognosis is primarily due to the involvement of cardiac tissue in the pathological process. The main causes of death in patients with Friedreich's ataxia are severe heart failure and sudden cardiac death due to cardiomyopathy. The overwhelming majority of foreign and domestic publications on Friedreich's ataxia are devoted to the neurological manifestations of this disease, and little attention is paid to this problem in the cardiological scientific and practical society. The purpose of this review is to provide up-to-date information on modern methods of diagnosing myocardial damage at various stages of Friedreich's disease.

Keywords: cardiomyopathy, Friedreich's ataxia, hypertrophy, echocardiography, heart failure.

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Introduction

Friedreich's ataxia (FA) is the most frequent inherited ataxia in the European population. The disease is characterized by the autosomal-recessive way of inheritance. The incidence rates are similar in men and women with the disease more often onset in the first two decades of life. The prevalence of FA ranges from 2 to 4 persons in 100,000 which allows to consider it an orphan disease. At that, the prevalence of heterozygous state of the disease mutation is about 1:60-1:100 persons [1].

In 1996, mutations in the FXN gene encoding the frataxin protein were demonstrated to be the cause of FA development [2]. The homozygous expansion of the guanine-adenine-adenine (GAA) trinucleotide repeat in the first intron of the FXN gene is revealed in almost 96% of the patients with this disease, while the rest 4% have the compound-heterozygous state of GAA-expansion in one allele combined with different pathogenic variant in another one [3]. The GAA-expansion in 34-65 repeats is regarded as unstable premutation while expansion of more than 66 GAA repeats is pathogenic. There are also a number of clinical-genetic relationships, in particular, the extent of the GAA-expansion in the

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smaller allele is inversely proportional to the age of FA neurological manifestation and determines the timing of the first symptoms onset by nearly 50% [4]. Besides, more extend expansion accounts for the more severe phenotype with early onset, rapid progression and more prominent cardiac and metabolic manifestations [5]. Frataxin is implicated in a range of cellular processes. One of its functions is the biosynthesis of iron-sulphur clusters (ISC) in the mitochondrial matrix. ISC are the cofactors for the Krebs cycle enzymes and also for the complexes I, II and III of the mitochondrial respiratory chain. Insufficient amount of frataxin leads to the secondary shortage of these proteins which in turn results in the decrease of mitochondrial ATP production. Mitochondrial dysfunction leads to the progressive lesion of the most energy-dependent tissues such as nervous system, myocardium, pancreas and skeletal muscles. This determines the multisystemic nature of the damage.

The mean age at the classical FA onset is 10-15 years (after age 25 years in the cases of later onset types). As a rule neurological lesions prevail in the FA clinical pattern. The earliest sign of the disease is the lack of deep reflexes which results in the total areflexia. In the course of the gradual damage of the deep sensibility conductors, peripheral nerves (sensory polyneuropathy) and, to a lesser degree, the cerebellum an ataxic gait and coordination disturbances augment, muscular hypotonia is also found out. The patients also develop pyramidal signs with the lower extremities involvement, dysphagia and pelvic disorders. Skeletal deformities (scoliosis and hollow foot), ophthalmic nerves atrophy and neurosensory deafness are as well specific. At the advanced stage of the illness patients cannot walk and take care of themselves [5].

Involvement of the cardiovascular system, more exactly myocardium, manifests as cardiomyopathy with heart failure and different rhythm disorders. Majority of FA patients develop cardiomyopathy. Being asymptomatic at the beginning cardiomyopathy is one of the principal causes of death in FA patients [6]. Absence of the heart lesion signs may be resulted not only from subclinical myocardial disorder but also from the significant limitation of physical activity due to the nervous system impairment which for a long time staves off heart failure manifestation. Nevertheless, laboratory and instrumental examination reveals specific pathological findings in the heart even in asymptomatic patients. The histological pattern of heart lesions consists of hypertrophy, diffuse fibrosis and focal myocardial necrosis [7-9].

Electrocardiogram (ECG) changes such as inversed T-wave, left axis deviation and repolarization abnormalities are reported in majority of the patients. Echocardiography reveals hypertrophic cardiomyopathy in about 65% of the patients. The parameters of global systolic and diastolic functions as well as heart chambers measurements remain for a long time unchanged, however more accurate imaging methods such as Doppler echocardiography and magnetic resonance imaging (MRI) find out changes resulted from intramyocardial fibrosis in almost all the patients [10,11].

Electrocardiography

Abnormalities of T-wave registered on an ECG recording, such as T-wave inversion or flattering in the left chest leads are the earliest signs of cardiomyopathy in majority of FA patients [12]. The trend to sinus tachycardia is revealed regardless of the degree of myocardial injury [13]. If severe left ventricular (LV) hypertrophy presents, typical electrocardiographic signs of hypertrophy are found out – high R-wave in V5 and V6 combined with deep S-wave in V1 and V2 leads [13]. It should be noted that even in the cases of significant left ventricular hypertrophy the QRS complex has no tendency to widening which points at the absence of bundle branch blocks; this is peculiar to hypertrophic cardiomyopathy [13]. It is suggested that patients with more severe cardiomyopathy more often develop supraventricular heart rhythm disorders such as atrial fibrillation (AF), atrial flutter and atrioventricular tachycardia [6]. The interval QT duration remains normal in majority of the patients which indicates the absence of predisposition to malignant ventricular heart rhythm disorders [14].

Echocardiography

Echocardiography is the most available and non-invasive method for the estimation of heart involvement in FA. Early studies of the echocardiographic features of the cardiomyopathy in FA placed greater focus on the estimation of systolic function and myocardial hypertrophy [15,16]. However, left ventricular remodeling, which is typical for the pathological process and associated with impairment of both systolic and diastolic functions, is more precisely characterized by such parameters of the LV geometry

as a sphericity index, left ventricular mass index (LVMI) and left ventricular relative wall thickness (RWT).

Examination of the large cohort of FA patients (n=173) revealed altered LV geometry due to the changes in LVMI and RWT in 82% of the patients [17]. 42% of the patients demonstrated concentric LV remodeling (elevated RWT with normal LVMI), 35% – concentric hypertrophy (elevated RWT and LVMI) and only 5% – eccentric hypertrophy (normal RWT with elevated LVMI) [17]. In the development of concentric hypertrophy the diastolic wall thickness as a rule amounts to less than 15 mm and does not lead to the left ventricular outflow tract obstruction [13,18].

In the Regner's study 30 of 173 patients revealed reduction in LV ejection fraction (EF) less than 50%, only 6 patients – less than 40%, while the majority of the examined patients had normal EF, i.e. more than 50% [17].

LV global systolic function remains normal during a long time. At the advanced stage of the illness it decreases in connection with diffuse hypokinesia and moderate LV enlargement [13,18]. It could be thus supposed that cardiomyopathy in FA is at first characterized by LV concentric remodeling with further progression towards concentric hypertrophy and then, along with fibrosis areas expansion, - to eccentric hypertrophy with LV dilation, which significantly alter its morphology and systolic function. Autopsy and myocardial biopsy findings in FA patients show the fibrosis areas presence [7,8,19,20]. Fibrosis leads to the LV wall thinning with further enlargement of the chamber, however EF does not change for a long time and only decreases in the final stage of the disease. Patients at the advanced stages of cardiomyopathy reveal thicker interventricular septum as compared to the LV posterior wall (LW PW) [13]. Influence of the disease duration on the LV myocardial wall thickness was also reported in a number of earlier works [19,21]. The prevalent localization of fibrosis in LV PW is not semeiotic to FA being also revealed in other inherited cardiomyopathies such as Fabri disease and Duchene muscular dystrophy [22,23].

The currently most large-scale study of the echocardiographic parameters in FA patients has reported LV diastolic dysfunction to be the principal finding, in particular 25% of the patients had normal diastolic function, 25% – impaired relaxation, 70% – pseudonormal filling pattern and 3% revealed restriction [17]. Evaluation of LV diastolic function was based on 4 types of the mitral flow pattern: normal function, impaired relaxation – type 1 (E/A velocities ratio=0.7-0.9, deceleration time (DT) is increased), pseudonormal filling pattern – type 2 (E/A=1.2-1.3, DT is short), restriction – type 3 (E/A>2, DT is short) [11,24]. Difficulties in the differentiation between normal and pseudonormal diastolic filling patterns did not possibly allow to pay more attention to its investigating in earlier conducted studies which predominantly concentrated on the assessment of the hypertrophy degree and systolic function [15,25,26]. In accordance with the international guidelines of 2016 the following parameters must be taken into account for the diastolic dysfunction diagnostics: left atrial volume index ˃34 ml/m2, peak tricuspid regurgitation velocity >2.8 m/sec, E/e'>14. LV diastolic function is defined as normal if more than a half of the available variables do not meet the cutoff values for identifying abnormal function. Diastolic dysfunction is present if more than a half of the available parameters meet these cutoff values [27].

Evaluation of the LV global systolic function may be not enough informative in some cases with poor correlation with the severity of clinical state in the early stages of heart failure [28,29]. Speckle-tracking echocardiography makes it possible to estimate parameters of myocardial deformation and reveal its subclinical dysfunction. The technique is based on the tracking of the motion patterns of acoustic myocardial markers (speckles) during the cardiac cycle in two-dimensional ultrasound image [30]. Every region of myocardial tissue is mapped by the individual tone of grey color which allows a special speckle pattern to be obtained peculiar to a certain myocardial region during the cardiac cycle [31]. Myocardium moves in three planes (longitudinal, circumferential and radial), this is dictated by the structure of the layers of myocardial fibers: during the cardiac cycle the subendocardial and the subepicardial layers move spirally in opposite directions while the mean layer moves circularly [32]. Interaction of the layers of myocardial fibers during the cardiac cycle results in a torsional movement (twist), forming the cardiac output [32]. Along with majority of hypertrophic cardiomyopathies the cardiomyopathy in FA patients is characterized by decreased global longitudinal strain [14,33,34]. Untwisting rate and the rate of longitudinal deformation (strain-rate) are more sen-

sitive parameters than LV EF for the detecting of myocardial dysfunction associated with hypertrophy; impairment of these parameters can precede LV EF reduction [35,36].

C. Dedobbeleer et al. in the study of 20 FA patients with normal both LV EF and myocardial mass revealed the decrease of global longitudinal and circumferential LV strains which possibly led to the reduction in the indexed LV stroke volume at normal ejection fraction [37]. Besides, the untwisting rate, which is an indicator of myocardial flexibility during the isovolumic relaxation and characterizes suction force for effective LV filling, was significantly reduced in FA patients, this is also an evidence of impaired LV early diastolic filling [38]. P.M. Mottram et al. in prospective follow up of 60 FA patients using the tissue Doppler imaging (TDI) had shown the decrease in the velocities of systolic and early diastolic peaks of the LV lateral wall in a greater degree than in those of the interventricular septum, which was associated with reduced LV measurements (end-diastolic and end systolic sizes) [10]. These changes are possibly explained by the more severe fibrosis of exactly the LV lateral wall. Increased LV relative wall thickness was another frequent abnormality in FA patients [10]. D.P. Dutka et al. have also revealed reduced systolic and early diastolic myocardial velocity gradients of the LV posterior wall in 29 FA patients [39].

Sometimes echocardiographic image in FA has a "grain" pattern such as in cardiac amyloidosis, but unlike the latter pericardial effusion is never occurred [33].

It should be noted that abnormal height and weight of FA patients is a difficult problem for the objectification of echocardiographic data which complicate calculations, especially involving indexation, thereby influencing the final conclusions.

Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) in FA patients have being used since recently for evaluation of myocardial edema [8] and replacement fibrosis spread [40-42] as the early signs of cardiomyopathy even in the absence of significant hypertrophy [43,44]. Due to high reproducibility and independence from operator cardiac MRI is ideal for the evaluation of heart chambers volumes, myocardial mass and ejection fraction. This is particularly true for the evaluation of the right ventricle which is often rather difficult using echocardiography [40].

B. Rajagopalan et al. have reported positive correlation between LV myocardial mass, a number of the GAA repeats and the age of FA onset. On the contrary at more than 15-year-duration of the disease myocardial mass revealed a tendency to reduction which may indicate heart chambers dilation in the long-term course of the disease [11]. Use of MRI with contrast enhancement allows a contrast agent delayed accumulation to be evaluated and therefore areas of fibrotic tissue can be visualized [41]. Both the presence and degree of late gadolinium enhancement (LGE) are of value in the evaluation of prognosis as even a small volume of fibrotic tissue (<2 % of LV myocardial mass) is associated with the 7-fold increase in the risk of adverse cardiac outcomes in patients with coronary heart disease [42]. Cardiac MRI with gadolinium in patients with non-ischemic cardiomyopathy also demonstrated LGE to be the predictor of malignant heart rhythm disturbances regardless of quantity and a mode of the contrast agent distribution [43].

Available data allow to consider myocardial fibrosis to be a specific finding in FA cardiomyopathy, it is the typical feature of the disease progression as in the late stages thinning of the LV myocardium is frequently observed, however presently we have no reliable data of the prevalent localization of the myocardial fibrosis in FA, this makes the differential diagnosis with other inherited hypertrophic cardiomyopathies more difficult [14,22,33,34].

Mitochondrial functions impairment leads to the muscular fibers necrosis and development of reactive myocarditis [45]. Myocardial inflammation, inclusive of subclinical one, can precede cardiomyopathy in FA with further gradual progression towards evident dilated cardiomyopathy, which is testified by the autopsy data of FA patients [44]. Myocarditis detection based on the MRI data using the Lake Louise criteria may be important for the early risk stratification in FA patients [46-48].

In accordance with the cardiac MRI data patients with FA and the intact coronary arteries have reduced myocardial perfusion reserve, which is one of the earliest manifestations of cardiomyopathy in this disease [49]. MRI with adenosine stress-test has also confirmed the significantly reduced index of the myocardial perfusion reserve, which was independent of the degree of LV myocardial hypertrophy and fibrosis presence, this allows to suppose that impaired perfusion is one of the

earliest component of pathogenic cascade in FA cardiomyopathy [8].

Such new MRI techniques as T1- and T2-mapping and detection of extracellular volume fraction (ECV) seem promising in studying cardiomyopathies including that one in FA as they allow to quantitatively evaluate diffuse changes in myocardial structure, visualize fibrosis, edema, amyloidosis and iron storage [50].

Evaluation of cardiomyopathy severity in Friedreich's disease

On the base of the available laboratory and instrumental research data of myocardial lesions in Friedreich's ataxia F. Weidemann et al. have proposed to allocate 4 stages in cardiomyopathy progression. The criteria for the staging were as follows: the LV EF (<55 %), the LV PW thickness (⩾11 mm), replacement fibrotic areas in accordance with MRI data (the LEG presence), elevated high-sensitivity troponin-T (⩾14 ng/ml), T-wave inversion. On the ground of these criteria the following stages were proposed: initial (T-wave inversion only), intermediate (T-wave inversion with myocardial hypertrophy – the LV PW thickness ⩾11 mm), severe (fibrosis with elevated high-sensitivity troponin T), terminal (decreased LV EF) [51].

So, abnormal ECG findings such as ST-T-wave changes are registered in almost all FA patients and may be considered the earliest signs of cardiomyopathy. Cardiomyopathy progression is characterized by the increased level of high-sensitivity troponin and formation of replacement fibrotic areas with further gradual reduction in myocardial hypertrophy and decreased LV ejection fraction.

Conclusion

Heart lesions are the main cause of death in patients with Friedreich's ataxia, however the manifestation of heart failure is often postponed from the onset of neurological lesions due to reduced physical activity because of neurological deficit. In this connection the complex diagnostics of the early signs of cardiomyopathy in FA, which could facilitate the predicting of heart failure progression in these patients, is of particular interest. Further investigation of this pathology with the search for early markers of heart lesions using the modern methods of visualization is necessary.

Relationships and Activities: none.

References / Литература

1. Bidichandani S.I., Delatycki M.B. Friedreich Ataxia. 1998 Dec 18 [Updated 2017 Jun 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1281/.
2. Campuzano V., Montermini L., Molto M., et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science. 1996;271:1423-7. DOI:10.1126/science.271.5254.1423.
3. Galea C.A., Huq A., Lockhart P.J., et al. Compound heterozygous FXN mutations and clinical outcome in Friedreich ataxia. Ann Neurol. 2016;79:485-95. DOI:10.1002/ana.24595.
4. Filla A., De Michele G., Cavalcanti F., et. al. The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. Am J Hum Genet. 1996;59:55460.
5. Fomicheva E.I., Myasnikov R.P., Selivyorstov Y.A., et al. Cardiomyopathy in the Fridreich's ataxia: clinical presentation and diagnostics of complications. Russian Journal of Cardiology. 2017;10(150):100-6 (In Russo) [Фомичева Е. И., Мясников Р.П., Селиверстов Ю.А., и др. Кардиомиопатия при атаксии Фридрейха: клинические проявления и диагностика осложнений. Российский Кардиологический Журнал. 2017;10(150):100-6]. DOI:10.15829/1560-4071-2017-10-100-106.
6. Tsou A.Y., Paulsen E.K., Lagedrost S.J., et al. Mortality in Friedreich ataxia. J Neurol Sci. 2011;307:46-9. DOI:10.1016/j.jns.2011.05.023.
7. Unverferth D.V., Schmidt W.R. II, Baker P.B., Wooley C.F. Morphologic and functional characteristics of the heart in Friedreich's ataxia. Am J Med. 1987;82:5-10. DOI:10.1016/0002-9343(87)90369-X.
8. Raman S.V., Phatak K., Hoyle J.C., et al. Impaired myocardial perfusion reserve and fibrosis in Friedreich ataxia: a mitochondrial cardiomyopathy with metabolic syndrome. Eur Heart J. 2010;32:561-7. DOI:10.1093/eurheartj/ehq443.
9. Koeppen A.H. Friedreich's ataxia: pathology, pathogenesisand molecular genetics. J Neurol Sci. 2011;303:1-12. DOI: 10.1016/j.jns.2011.01.010.
10. Mottram P.M., Delatycki M.B., Donelan L., et al. Early changes in left ventricular long-axis function in Friedreich ataxia: relation with the FXN gene mutation and cardiac structural change. J Am Soc Echocardiogr. 2011;24:782-9. DOI:10.1016/j.echo.2011.04.004.
11. Rajagopalan B., Francis J.M., Cooke F., et al. Analysis of the factors influencing the cardiac phenotype in Friedreich's ataxia. Mov Disord. 2010;25:846-52. DOI:10.1002/mds.22864.
12. Payne R.M., Peverill R.E. Cardiomyopathy of Friedreich's Ataxia (FRDA). Ir J Med Sci. 2012;181:569-70. DOI:10.1007/s11845-012-0808-7.
13. Weidemann F., Rummey C., Bijnens B., et al. The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. Circulation. 2012;125:1626-34. DOI:10.1161/CIRCULATIONAHA.111.059477.
14. Weidemann F., Niemann M., Ertl G., Stork S. The different faces of echocardiographic left ventricular hypertrophy: clues to the etiology. J Am Soc Echocardiogr. 2010;23:793-801. DOI:10.1016/j.echo.2010.05.020.
15. Giunta A., Maione S., Biagini R., et al. Noninvasive assessment of systolic and diastolic function in 50 patients with Friedreich's ataxia. Cardiology. 1988;75:321-7. DOI:10.1159/000174394.
16. Dutka D.P., Donnelly J.E., Palka P., et al. Echocardiographic characterization of cardiomyopathy in Friedreich's ataxia with tissue Doppler-echocardiographically derived myocardial velocity gradients. Circulation. 2000;102:1276-82. DOI:10.1161/01.cir.102.11.1276.
17. Regner S.R., Lagedrost S.J., Plappert T., et al. Analysis of echocardiograms in a large heterogeneous cohort of patients with Friedreich ataxia. Am J Cardiol. 2012;109:401-5. DOI:10.1016/j.amjcard.2011.09.025.
18. Payne R.M., Pride P..M, Babbey C.M. Cardiomyopathy of Friedreich's ataxia: use of mouse models to understand human disease and guide therapeutic development. Pediatr Cardiol. 2011;32:366-78. DOI:10.1007/s00246-011-9943-6.
19. Casazza F., Morpurgo M. The varying evolution of Friedreich's ataxia cardiomyopathy. Am J Cardiol. 1996;77:895-98. DOI:10.1016/s0002-9149(97)89194-1.
20. Quercia N., Somers G.R., Halliday W., et al. Friedreich ataxia presenting as sudden cardiac death in childhood: clinical, genetic and pathological correlation, with implications for genetic testing and counselling. Neuromuscul Disord. 2010;20:340-42. DOI:10.1016/j.nmd.2010.02.019.
21. Casazza F., Morpurgo M. Progression of hypertrophic into a dilated left ventricle in Friedreich's ataxia. G Ital Cardiol. 1988;18:615-8.
22. Silva M.C., Meira Z.M., Gurgel Giannetti J., et al. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. J Am Coll Cardiol. 2007;49:1874 -9. DOI:10.1016/j.jacc.2006.10.078.
23. Weidemann F., Strotmann J. Early detection of Fabry disease: cardiac cases. Clin Ther. 2008;30(suppl B):S46. DOI: 10.1016/s0149-2918(08)80039-2.
24. Roelandt J.R.T.C., Pozzoli M. Non-invasive assessment of left ventricular diastolic (dys)function and filling pressure. Heart. 2001;2:116-25. DOI:10.1002/ejhf.971.

25. Kipps A., Alexander M., Colan S.D., et al. The longitudinal course of cardiomyopathy in Friedreich's ataxia during childhood. Pediatr Cardiol. 2009;30:306-10. DOI:10.1007/s00246-008-9305-1.
26. Sutton M.G., Olukotun A.Y., Tajik A.J., et al. Left ventricular function in Friedreich's ataxia. An echocardiographic study. Br Heart J. 1980;44:309-16. DOI:10.1136/hrt.44.3.309.
27. Nagueh S.F., Smiseth O.A., Appleton C.P., et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular. Imaging. Eur Heart J Cardiovasc Imaging. 2016;17:1321-60. DOI:10.1016/j.echo.2016.01.011.
28. Nagueh S.F., McFalls J., Meyer D., et al. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. Circulation 2003;108:395-403. DOI:10.1161/01.CIR.0000084500.72232.8D.
29. Vinereanu D., Florescu N., Sculthorpe N., et al. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. Am J Cardiol 2001;88:53-60. DOI:10.1016/s0002-9149(01)01585-5.
30. Abduch M.C., Alencar A..M, Mathias W.Jr, Vieira M.L. Cardiac mechanics evaluated by speckle tracking echocardiography. Arq Bras Cardiol. 2014;102(4):403-14. DOI:10.5935/abc.20140041.
31. Nikiforov V.S., Marsalskaya O.A., Novikov V.I. Echocardiographic assessment of myocardial strain in clinical practice. Saint Petersburg: KultInform Press; 2015 (In Russ.) [Никифоров В.С., Марсальская О.А., Новиков В.И. Эхокардиографическая оценка деформации миокарда в клинической практике. СПб.: КультИнформПресс; 2015].
32. Mor-Avi V., Lang R.M., Badano L.P., et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr. 2011;12(3):167-205. DOI:10.1016/j.echo.2011.01.015.
33. Weidemann F., Breunig F., Beer M., et al. The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. Eur. Heart J. 2005;26:1221-7. DOI:10.1093/eurheartj/ehi143.
34. Weidemann F., Niemann M., Breunig F., et al. Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation. 2009;119:524-9. DOI:10.1161/CIRCULATIONAHA.108.794529.
35. Smiseth O.A., Torp H., Opdahl A., et al. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J. 2016;37(15):196-207. DOI:10.1093/eurheartj/ehv529.
36. He X.W., Song Z.Z. Evaluation of left ventricular function, rotation, twist and untwist in patients with hypertrophic cardiomyopathy. Exp Clin Cardiol. 2013;18(1):e47-55.
37. Dedobbeleer C., Rai M., Donal E., et al. Normal left ventricular ejection fraction and mass but subclinical myocardial dysfunction in patients with Friedreich's ataxia. Eur Heart J Cardiovasc Imaging. 2012;13:346-52. DOI: 10.1093/ejechocard/jer267.
38. Dong S.J., Hees P.S., Siu C.O., et al. MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. Am J Physiol Heart Circ Physiol. 2001;281:2002-11. DOI:10.1152/ajpheart.2001.281.5.H2002.
39. Dutka D.P., Donnelly J.E., Palka P., et al. Echocardiographic characterization of cardiomyopathy in Friedreich's ataxia with tissue Doppler echocardiographically derived myocardial velocity gradients. Circulation. 2000;102:1276-82. DOI:10.1161/01.CIR.102.11.1276.
40. Schalla S., Nagel E., Lehmkuhl H., et al. Comparison of magnetic resonance real-time imaging of LV function with conventional magnetic resonance imaging and echocardiography. Am J Cardiol. 2001;87:95-104. DOI:10.1016/s0002-9149(00)01279-0.
41. Kim R.J., Fieno D.S., Parrish T.B., et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100:1992-2002. DOI:10.1161/01.CIR.100.19.1992.
42. Kwong R.Y., Chan A.K., Brown K.A., et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation. 2006;113:2733-43. DOI:10.1161/CIRCULATIONAHA.105.570648.
43. Perazzolo Marra M., De Lazzari M., Zorzi A., et al. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. Heart Rhythm. 2014;11(5):856-63. DOI:10.1016/j.hrthm.2014.01.014.
44. Koeppen A.H., Ramirez R.L., Becker A.B., et al. The pathogenesis of cardiomyopathy in Friedreich ataxia. PLoS One. 2015;10(3):e0116396. DOI:10.1371/journal.pone.0116396.
45. Michael S., Petrocine S.V., Qian J., et al. Iron and iron-responsive proteins in the cardiomyopathy of Friedreich's ataxia. Cerebellum. 2006;5(4):257-67. DOI: 10.1080/14734220600913246.
46. Friedrich M.G., Sechtem U., Schulz-Menger J., et al. International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009;53(17):1475-87. DOI:10.1016/j.jacc.2009.02.007.
47. Lehrke S., Lossnitzer D., Schob M., et al. Use of cardiovascular magnetic resonance for risk stratification in chronic heart failure: Prognostic value of late gadolinium enhancement in patients with non-ischaemic dilated cardiomyopathy. Heart. 2011;97(9):727-32. DOI: 10.1136/hrt.2010.205542.
48. Frustaci A., Russo M.A., Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: The TIMIC study. Eur Heart J. 2009;30(16):1995-2002. DOI:10.1093/eurheartj/ehp249.
49. Raman S.V., Dickerson J.A., Al-Dahhak R. Myocardial ischemia in the absence of epicardial coronary artery disease in Friedreich's ataxia. J Cardiovasc Magn Reson. 2008;10:15. DOI:10.1186/1532-429X-10-15.
50. Mavrogeni S., Apostolou D., Argyriou P., et al. T1 and T2 mapping in cardiology: "Mapping the obscure object of desire". Cardiology. 2017;138(4):207-17. DOI:10.1159/000478901.
51. Weidemann F., Liu D., Hu K., et al. The cardiomyopathy in Friedreich's ataxia – New biomarker for staging cardiac involvement. Int J Cardiol. 2015;194:50-7. DOI: 10.1016/j.ijcard.2015.05.074.

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