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CARDIOVASCULAR DISORDERS IN FABRY DISEASE

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REZUMAT

AFECTĂRILE CARDIOVASCULARE ÎN BOALA FABRY

Boala Fabry (BF) este o tulburare de depozitare lizozomică rară a metabolismului glicozigigolipidic cauzată de deficienţa totală sau parţială a enzimei lizozomice alfa-galactosidaza A. Acumularea progresivă intracelulară multisistemică explică diversitatea manifestărilor clinice, inclusiv la nivelul sistemului cardiovascular. Afectarea cardiacă a fost raportată la 40-60% pacienți. dintre care cardiomiopatia Fabry este adesea responsabilă pentru moartea prematură a unor bolnavi. La copii cu BF implicarea cardiacă include iniţial tulburări de conductibilitate sau hipertrofie ventriculară stângă (LVH) inexplicabilă. Evaluarea copilului cu BF implică investigaţii cardiovasculare standard complexe și investigaţii genetice. Pacienţii cu BF necesită o abordare multidisciplinară, inclusiv evaluare sistematică cardiacă. Aprecierea concentraţiilor enzimelor serice este suficientă pentru confirmarea diagnosticului la băieți, dar testele genetice sunt indispensabil la fete. Obiectivul principal în conduita copiilor cu BF şi afectare cardiacă este prevenirea morţii cardiace subite. Tratamentul farmacologic cardiac în BF rămâne un subiect controversat. Beneficiul tratamentului enzimatic este evident în variantele cu HVS. În prezența fibrozei și aritmiilor, riscul de moarte subită cardiacă este crescut, ceea ce demonstrează importanța inițierii tratamentului specific la etapele preclinice, inclusiv la pacienții pediatrici.

Cuvinte-cheie: Boala Fabry, hipertrofie ventriculară stângă, cardiomiopatie, aritmii

РЕЗЮМЕ

ПОРАЖЕНИЯ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ ПРИ БОЛЕЗНИ ФАБРИ

Болезнь Фабри (БФ) представляет собой редкое лизосомальное нарушение накопления гликозигиголипидного метаболизма, вызванное полным или частичным дефицитом лизосомального фермента альфа-галактозидазы А. Многосистемное внутриклеточное прогрессирующее накопление объясняет разнообразие клинических проявлений, включая сердечно-сосудистую систему. Болезнь сердца отмечается у 40-60% пациентов. из которых кардиомиопатия Фабри часто ответственна за преждевременную смерть пациентов. У детей с БФ поражение сердца изначально включает нарушения проводимости или необъяснимую гипертрофию левого желудочка (ГЛЖ). Оценка ребенка с БФ включает стандартные исследования сердечно-сосудистой системы и генетические тесты. Пациенты с БФ требуют междисциплинарного подхода, в том числе систематической оценки состояния сердца. Оценка концентрации фермента в сыворотке достаточна для подтверждения диагноза у мальчиков, но генетические тесты необходимы для девочек. Основной целью при ведении детей с БФ и поражением сердечной мышцы является предотвращение внезапной сердечной смерти. Медикаментозное лечение сердечных изменений у больных с БФ остается спорным. Преимущество ферментативного лечения очевидно в вариантах с ГЛЖ. При наличии фиброза и аритмий риск внезапной сердечной смерти повышается, что доказывает важность начала специфического лечения на доклинических стадиях, включая педиатрических больных.

Ключевые слова: болезнь Фабри, гипертрофия левого желудочка, кардиомиопатия, аритмии.

Introduction

Fabry disease (FD) is a rare X-linked genetic disease in which the gene mutation (GLA) disrupts the structure and function of the α-galactosidase enzyme A. To date, more than 240 mutations have been identified for FD at the chromosome Xq22.1. Private X recessive transmission explains why all children of a FD mother, both boys and girls, have a 50% risk of inheriting the disease. The classical form is found in males, incidence is 1/40,000-1/60,000 [13].

Clinical variability of different mutations, variable disease severity and symptom onset explain why the disease very difficult to diagnose. All organ complications can however occur in classical and late-onset phenotype (table 1).

Cardiovascular disorders are present in 40-60% of adult patients and involve all cardiac structures. Fabry cardiomyopathy and arrhythmias are responsible for premature cardiac death of patients [31]. Current guidelines show the importance of administering substitution treatment at preclinical stages. The beneficial effects of early-onset treatment on LVH regression have been proven to help prevent premature death.

Based on the actuality of the problem, we have proposed in this paper to estimate the clinical-evolutionary impact of cardiac disorders in children with FD. In achieving the proposed goals, we used the Cochrane library, PubMed medical databases, analyzing the publications up to December 2019.

Table 1. Typical organ involvement in Fabry disease [4,20]

Organ system	Complications
Ophthalmological	Cornea verticillata, tortuous vessels, cataracts
Dermatological	Angiokeratoma, hipo/anhidrosis, telangiectasia, lymphedema
Neurological	Neuropathic pain, transient ischemic attack, stroke, neuropsychiatric complications (depression)
Cardiac	Conduction abnormalities, left ventricular hypertrophy, sudden cardiac death
Renal	Proteinuria, reduced glomerular filtration rate
Gastrointestinal	Diarrhea, constipation, early satiety, nausea
Auditory	Hearing loss, tinnitus, vertigo
Respiratory	Cough, wheezing, airflow limitation

Gold standard diagnosis of Fabry disease is genetic analysis, but distinguishing non-pathogenic variants can still be a challenge. Multidisciplinary work is key to comprehensive management of this pathology. To confirm the definitive diagnosis, it is necessary to know the meaning of the following diagnostic methods:

1) Specific enzyme assays include determining the level of α-galactosidase activity in leukocytes or fibroblast cultures. *Interpretation:* A low level of enzymatic activity or even its absence confirms the disease;

2) Molecular biology tests by DNA analysis allow the identification of mutations.

In addition, in the carriers (heterozygous) of the mutant gene, where the activity level of the enzyme is at the lower limit of normal, DNA analysis is required from the first evaluation to identify mutations to indicate the carrier state [15].

Disease begins in childhood and has a slowly progression with multisystemic, age-dependent and sex-dependent impairment. Symptomatology may occur in boys at the age of 9 and in girls around the age of 13 [3]. Preclinical manifestations are important in suspecting the disease. Proteinuria and unexplained left ventricular hypertrophy (LVH) may be rise suspicion of early diagnosis [26].

Current strategies for patients affected by FD include screening of newborns, genetic testing for any suspicion of illness, examination of probands in the patients' families, and differential diagnosis in children with hypertrophic cardiomyopathy [29].

Cardiac disorders

Cardiac involvement is frequent in FD. Patients develop hypertrophic cardiomyopathy (HCM), arrhythmias, conduction abnormalities and valvular abnormalities. The isolated cardiac variant of FD seems to be more common than previously thought: around 3-6% of male patients with left ventricular hypertrophy seem to suffer from this disease variant [25].

FD in adults have various cardiac manifestations, of which the most common are LVH, Fabry cardiomyopathy, hypertension, heart failure, valvulopathy, coronary heart disease, arrhythmias, dilatation of the aorta. Cardiac symptomatology becomes evident in men at 32 years of age and in women at 40 years [16]. At the same time, major cardiac events are responsible for 5% of patients' deaths, which is why the detection and evaluation of LVH and hypertension are crucial in evaluating of patients with FD [24].

Cardiovascular complications of the disease are very frequent and contribute substantially to disease-related morbidity and mortality in men and leading cause of premature death in heterozygous female patients with FD. Men with classic or lather-onset FD caused by GLA missense mutations developed prominent and similar cardiovascular disease at similar ages, despite markedly different α-galactosidase A activities [2].

The classic cardiac model in FD is HCM or Fabry cardiomyopathy. In turn, HCM is the most common genetic disorder (1/500 general population), mainly

caused by mutations in genes encoding the heart sarcomeric proteins. In 25-30% of cases, the mutant gene is not identified [17]. Recent epidemiological studies have estimated that the 0.5-1% of the patients with HCM suffer from FD [7,14]. Furthermore, FD should be included in the differential diagnosis algorithm of idiopathic hypertrophy [3]. Although it is an X-linked infection, evidence is if heterozygous women can often have a severe HCM associated with heart failure, which can lead to premature cardiac death [36].

Significant cardiomyocyte substrate accumulation led to severe and irreversible cardiac fibrosis before development of LVH or other significant cardiac manifestation. The pathophysiological changes in Fabry's cardiomyopathy are LVH and/or fibrosis. These histological findings allowed the hypothesis that Fabry cardiomyopathy is presented by hypertrophy and vacuolization [28]. Deposits contribute to the initiation of hypertrophic processes, but the progression of hypertrophy does not correlate with pathological accumulations. Histological studies have found only 1-3% of patients with pathological inclusions typical of FD in the hypertrophied myocardial infarction, a finding that does not explain the severity of cardiomyopathy [6]. In patients with classical FD, the left hypertrophy is concentric, rarely asymmetric, or mimic other primary cardiomyopathies [19]. It is possible that these forms of cardiomyopathy are mixed genetic etiology (metabolic and sarcomeric), a hypothesis that presents an additional clinical challenge in determining the diagnosis. Cohort studies shows that women and young men initially present fibrosis with the evidence of LVH, the mechanism of this phenomena is not yet elucidated. In any case, the occurrence of fibrosis is an advanced, irreversible cardiomyopathy with an unfavorable prognosis [9,10].

The most common rhythm and conduction disorders in FD are supraventricular and ventricular arrhythmias. Nevertheless, these symptoms specified for cardiomyopathy, but they can also be present at pre-clinical stages [32]. Another leading disorder, predominantly encountered in adults, is the short PR interval, present in 15% of patients [11]. The authors approved that electrophysiological changes are progressing with disease evolution. Thus, myocardial fibrosis is responsible for fatal ventricular arrhythmias. However, the incidence and predictive factors of the occurrence of arrhythmias requires implantation of cardiac devices are not well-defined [31].

In additional to genetic criteria, the diagnosis of cardiac damage is based on the instrumental methods. Standard electrocardiography (ECG) is an easy and inexpensive test. It is only in examining the children that the accuracy of the age-based criteria for LVH is necessary, including the use of percentile options. The method's readability is doubled by detecting asymptomatic rhythm or driving disturbances. In arrhythmias, additional Holter monitoring is recommended to evaluate arrhythmic events over 24-48 hours. The results of this monitoring are important in detecting fatal arrhythmias, so the risk of sudden death and the need for therapeutic regimens will be appreciated. Cardiodefibrillator implantation was assessed, to prevent sudden cardiac death. [8]. Exciting ECG methods may also highlight other electrolyte disturbances, such as disturbances in repolarization processes. The latter, as well as effortlessness, may be suggestive of the presence of myocardial fibrosis or heart failure [22].

The LVH is a pathognomonic in diagnosis of FD. The LVH detection allows clinicians to suspect a FD form and argues the need for specific genetic testing. Smid et al. have developed the criteria for a definitive diagnosis, where genetic confirmation is mandatory. The uncertain diagnosis includes nonspecific signs, especially the LVH and stroke at young age. The authors said that in any non-classical FD form, the detection of specific lysosomal deposits in organs or tissues (heart, kidneys, skin, etc.) by microscopy techniques by a trained specialist constitutes a diagnostic confirmation [34]. The recommendations of the European Fabry Working Group have developed a consensus document, formulating a series of recommendations for the initiation and termination of substitution treatment in patients with FD, based on the results of several randomized trials. The choice of treatment criteria will take into account the type of disease (classical/non-classical) and gender apathy. According to these recommendations, substitution treatment (Class I recommendation) is initiated in any type of illness, in the presence of LVH and/or arrhythmia [5].

Echocardiography is the reference test in confirming the presence of LVH or other specific changes, provided pediatric anthropometric criteria are taken into account [23]. In addition to assessing structural parameters, patients with FD are evaluated for ventricular dysfunction. Early detection of left ventricular diastolic dysfunction is important for the treatment of patients with beta-blockers. Beta-blockers are also indicated in asymptomatic patients with diastolic dysfunction in the absence of LVH [25]. At the advanced stages of the disease, with the progression of heart remodeling, systolic dysfunction of the left ventricle is associated. Pathological remodeling of the heart, by definition, associated with the occurrence of fatal arrhythmias requiring specific therapy. In the advanced stages, implantation of devices will be performed to prevent sudden cardiac death. Adult patients benefit from all clinical and non-pharmacological treatment methods according to current recommendations [1].

Fibrosis is an advanced, irreversible cardiomyopathy indicator. Nuclear Magnetic Resonance (MRI) is a method of choice in the detection of fibrosis, pathophysiological modification characteristic of the late stage of cardiomyopathy. Descriptive signs and localizations for FD are described in the primary diagnosis (posterolateral, median and subepicardiac). A long-term study has demonstrated the utility of MRI in guiding substitution

treatment, with appreciation of effects on the regression of histomorphological modifications of myocardial structures [12]. In this context, MRI performance is recommended for close relatives of patients for an early diagnosis of HCM. Clinical importance of serial MRI is confirmed by the improvement of cardiac changes on the background of treatment in localized fibrosis or without fibrosis, but in the presence of LVH in the spouse to improve cardiac function. Concomitantly, no improvement in left ventricular function was observed in patients with diffuse fibrosis, in whom the last treatment option remains transplantation [35]. A particular feature seen in young female patients is the initial development of fibrosis in the absence of LVH. The asymptomatic patient, but with MRI confirmed cardiac fibrosis, will be treated as early as possible [21,30]. Invasive diagnostic methods, especially endomyocardial biopsy, are rarely performed, preferentially in unclear cases, to differentiate the type of cardiomyopathy.

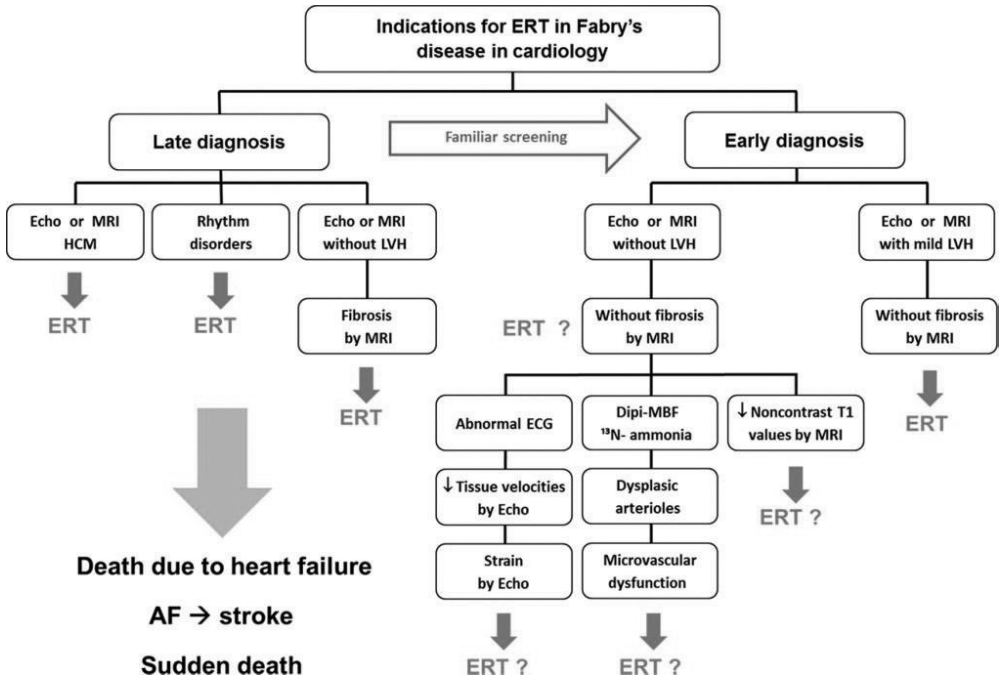
Fabry cardiomyopathy is an important and potentially reversible cause of heart failure that involves LVH, increased susceptibility to arrhythmias and valvular regurgitation. Genetic testing and cardiac MRI are important diagnostic tools, and Fabry cardiomyopathy is treatable if the therapy is early-introduced [27].

Children with classical FD, cardiac involvement includes unexplained, slower and more evolutionary LVH, HCM, rhythm and conduction disorders, but casuistic valvulopathy or dilatation of the aorta. The advantage of pediatric age is that the diagnosis can be early established in the preclinical stages and the chances of reversibility of the morphological changes are greater. Assessing a child with FD involves complex cardiovascular investigations similar to adults. In the same time, children with HCM require genetic investigations to complete the diagnosis. The major objective in the management of children with FD and heart disease is the prevention of sudden cardiac death. Conventional anti-congestion medications have shown a significant rate of adverse effects in children with FD, although current recommendations do not exclude the use of ACEI (anti-conversion enzyme inhibitors, diuretics and beta-blockers. Propranolol or atenolol is indicated in obstructive forms of HCM, and carvedilol, due to its additional properties, can be administered as an additional anti-congestion treatment [33]. Amiodarone, due to the pharmacological properties of interference with lysosomal metabolism, is contraindicated in the treatment of arrhythmias in FD [1]. Selecting effective and harmless pharmacological treatment in this patient group remains an unresolved topic and requires controlled clinical trials.

Prenatal diagnosis is indicated in high-risk groups with FD. Enzymatic activity of α-galactosidase can be detected in the first trimester by villous cord biopsy or in the second trimester of pregnancy with the help of amniocenteses [12].

Recent observations support consideration for routine prospective screening for FD in all patients without a definitive etiology for LVH. This strategy would likely result, through cascade family testing, in the earlier identification of new FD-affected males and female heterozygotes who my benefit from monitoring and/or enzyme replacement therapy (ERT) [18].

Figure 1. Indications for ERT in Fabry disease in cardiology. AF indicates atrial fibrillation; Dip-MBF, myocardial blood flow following dipyridamole infusion with 13N-labeled ammonia by positron-emission tomography; ECG, electrocardiogram; Echo, echocardiogram; ERT, enzyme replacement therapy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging.



Conclusions.
Patients with FD require a multidisciplinary approach, including systematic cardiac evaluation. Enzyme measurements are sufficient in boys, but genetic testing is needed in girls. Cardiac pharmacological treatment in FD remains a challenging topic. The benefit of enzymatic treatment is evident in LVH variants. In the presence of fibrosis and arrhythmias, the risk of sudden cardiac death is increased, indicating the importance of initiating substitution treatment at preclinical stages, including pediatric patients [37] (figure 1).

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