



Neurological Manifestations of Fabry Disease: Literature Review

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Abstract

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BACKGROUND: Fabry disease (FD) or Anderson FD is a hereditary disease belonging to the group of lysosomal storage diseases caused by decreased or absent activity of the enzyme α -galactosidase A. Enzyme deficiency leads to accumulation of glycospholipids in the lysosomes of cells of various organs, including the heart, kidneys, nervous system, and vascular endothelium. The complexity of the diagnosis of FD is due to the variety of its symptoms, the simultaneous involvement of many organs and systems. At present, possible pathogenetic treatment of the disease is enzyme replacement therapy, but its effectiveness is reduced in the later stages of the disease, when there are irreversible abnormal changes in vital organs and systems. In this regard, an urgent task is the early diagnosis of FD.

AIM: Determination of neurological manifestations of FD as well as clinical criteria for screening for FD.

MATERIALS AND METHODS: We analyzed cohort studies, randomized controlled trials, systematic reviews and meta-analyses, case-control studies, and case series from scientific medical databases: PubMed, Web of Science, Google Scholar in Russian, and English languages.

CONCLUSION: The authors found that lesions of the nervous system in FD are detected in more than 80% of patients and can manifest as isolated or combined lesions of both the central and peripheral and autonomic nervous systems.

Introduction

Fabry disease (FD) or Anderson FD is a hereditary disease belonging to the group of lysosomal storage diseases caused by decreased or absent activity of the enzyme α -galactosidase A. Enzyme deficiency leads to accumulation of glycospholipids in the lysosomes of cells of various organs, including the heart, kidneys, nervous system, and vascular endothelium. FD is the second most common genetic metabolic disease in the world. The prevalence of classical FD in the general population ranges from 1: 845 to 1: 117000. To date, more than 800 mutations associated with the disease have been described. FD affects people all over the world regardless of race [1]. According to the data of the Ministry of Health of the Republic of Kazakhstan (the "RK") for 2020, 16 people with FD have been identified in the RK and are subject to regular medical check-up. FD is an X-linked disease, but despite this, the clinical symptoms of the disease develop not only in men, but are also present in most

female carriers. In men, reduced α -galactosidase activity is a sufficiently informative sign of FD and can be used as a screening test. However, in women with FD the activity of this enzyme may be within normal limits, so only a genetic test (GLA gene sequencing) can reliably rule out or confirm the diagnosis [2]. Symptom severity is less in heterozygous women than in men, but when a healthy X chromosome is inactivated, FD is just as severe in women. Severe clinical manifestations were reported in 43% of female carriers [3]. Regarding the onset of the disease, the average age of the first clinical symptoms of Fabry disease is 12 years [4]. The time from the appearance of the first symptoms to diagnosis is 15 years [5], because of the lack of suspicion to this disease, as well as the diversity and lack of specificity of its symptoms. The Mainz Severity Score Index, MSSi (2004); fabry disease severity scoring system-fabry DS3 (2010); fabry-specific pediatric health and pain questionnaire, (2012), are used to assess the severity and monitor the progression of FD. In each of them, neurological manifestations play a major role, which makes it

necessary to widely inform primarily neurologists about possible symptoms of FD [6].

lesions of varying degrees of myelination of myelinated and unmyelinated fibers, while larger fibers are virtually unaffected [7], [8].

Relevance

The complexity of the diagnosis of FD is due to the variety of its symptoms, the simultaneous involvement of many organs and systems. Currently possible pathogenetic treatment of the disease is enzyme replacement therapy (ERT), but its effectiveness is reduced in the later stages of the disease, when there are irreversible abnormal changes in vital organs and systems. In this regard, an urgent task is the early diagnosis of FD.

Goals and objectives

The study was aimed to determine the neurological manifestations of FD; the objective of the study was to raise the awareness of neurologists about this disease and to determine the clinical criteria for screening for FD.

Results

Nervous system involvement in FD is detected in more than 80% of patients, and can manifest as isolated or combined lesions of both the central, peripheral, and autonomic nervous systems (Table 1).

Discussion

Peripheral nervous system

Peripheral neuropathy affects more than a quarter of patients with FD and is characterized by

Neuropathic pain

Pain is one of the earliest symptoms of FD, the onset of the pain syndrome most often occurs at the age of 3 to 16 years, but pain can also appear before the age of 1 year and in older people [7]. According to data from the FD registry of 1,765, neuropathic pain was present in 62% of men and 41% of women, with an average age of onset of 9 and 10 years, respectively [9], [10].

Pain in FD can vary in intensity and duration: episodic pain, hypersensitivity to mechanical stimuli, heat and cold intolerance, chronic pain [5]. There are four types of pain that occur in FD: "Caused" pain, episodic pain, chronic pain, and pain crises [7].

The most common type of pain is "caused" pain. According to some studies, 31% to 45% of patients with FD report pain triggered by touch, pressure, or cold. The frequency of this type of pain varies from once a month to 4 times a week [7], [11]. Most studies show that between 12% and 40% of patients report chronic pain lasting more than 3 months. This type of pain is mostly localized in the upper and lower extremities, but in some patients it may present as dental, abdominal, or joint pain [7], [11].

Pain crises begin in the extremities and spread to the proximal parts of the body. Crises occur spontaneously or are provoked by physical exertion, fever, or a change in ambient temperature [7], [12]. Studies show that pain crises occur in 10–30% of patients, with a higher prevalence in men than in women [5], [11], [12]. The frequency of pain crises varies from 4 times a month to once a year, lasting from several hours to several weeks, with some patients having several crises a week [5].

In addition, many patients with FD experience abdominal pain, which can manifest as unprovoked chronic pain between meals or episodic pain after meals [7], [13], [14], [15]. Neuropathic pain affects the daily life of patients with FD, significantly reducing quality of life [16]. In some patients, the intensity of

Table 1: Neurological manifestations of FD

Clinical manifestation	Characteristics	Prevalence
Neuropathic pain	Onset at the age of 3 to 16 years. Neuropathic pain is triggered by touch, pressure or cold, or occurs spontaneously. This type of pain is mostly localized in the upper and lower extremities, but in some patients it may present as dentalgia, gastralgia, or arthralgia	"Caused" pain- 31–45%; chronic pain- 12–40%; pain crises- 10–30%
Acroparesthesias, paresthesias/dysesthesias	Onset in childhood, older than 3 years, is manifested by a tingling sensation, running goosebumps, cold, accompanied by pale skin of the hands and feet	60–80%
Hypohidrosis/Anhidrosis	Onset in childhood or adolescence. This symptom often accompanies neuropathic pain; it causes poor tolerance of hot weather, stuffy rooms and physical exertion up to the development of fainting	33.3%
Headache	Predominantly migraine	26.6–41.7%
Hearing loss	Predominantly episodes of sudden asymmetric hearing loss	30–35%
Dizziness	Vestibular vertigo	50–54.4%
TIA and ACVA	Onset under the age of 55. Predominantly lacunar infarction with vertebrobasilar lesions	Men- 4.9–6.9% Female 2.4–4.3%
Parkinsonism	Onset after the age of 60. Predominantly late onset, with more pronounced clinical severity of FD, accompanied by moderate cognitive deficiency and cortical-subcortical white matter/small cerebral vascular lesions	1.3% of the total cohort, among them Men-55.1% Women-44.9%

the pain syndrome decreases in adulthood, but the majority continues to live with debilitating pain for many years [17].

Autonomic nervous system

In addition to chronic and acute pain, patients with FD may have impaired tolerance to heat or cold. While for a healthy person temperature fluctuations of 1°C are perceptible, for patients with Fabry's disease they are 2–5°C [7], [18]. Both heat and cold can provoke an attack of pain [5], [8], [14]. However, heat is a more common trigger: One study states that heat caused an attack of pain in 62% of the subjects [7], [8]. Some patients report a paradoxical sensation of cold, that is, they perceive a cold stimulus as warm or hot [7]. Patients often have changes on the part of the autonomic nervous system, which appear in the form of sweating disorders. The most common manifestations are anhidrosis or hypohidrosis [11].

Central nervous system

Headache/migraine

Headache, predominantly migraine headache, is a frequent neurological symptom that develops in patients with FD. The prevalence of migraine was 26.6% in a study of patients with FD in Europe, North and South America [19]. In contrast, the prevalence of FD in the migraine patient cohort was 1.37% [20]. In a study conducted in Japan in 2021, 5 of 12 (41.7%) patients had headache, and 4 (33.36%) of those patients were diagnosed with migraine [21]. Because of this prevalence, we believe that caution should be exercised for FD in patients with migraine. Another cause of headache episodes in FD may be Chiari type I abnormality (identified in 4 of 45 patients with confirmed FD) [22].

Dizziness

Due to the fact that the cochleovestibular nerve is involved in the pathological process in 70% of cases, approximately 30% of patients actively complain of hearing loss, 50% complain of vestibular vertigo, and 40% complain of tinnitus [21]. In a single-center study involving 57 patients with FD, 20 patients (35.1%) complained of hearing loss, with 18 patients (90%) reporting one or more episodes of sudden hearing loss that was asymmetrical and two patients (10%) reporting slowly progressive hearing loss. 54.4% had complaints of dizziness, with 17 patients having intermittent vestibular dizziness, two patients having persistent dizziness, and 12 patients having dizziness that could be provoked, 28.1% having both symptoms. Tinnitus was described by 43.9% (15 men and 10 women). Nystagmus in patients with FD is predominantly caused

by peripheral vestibular lesions, but the central nature of the lesion is detected in 30% of cases [23].

Cerebrovascular disorders

Involvement in the pathological process of the central nervous system in patients with FD is represented primarily by changes in white matter, ischemic stroke (IS) and transient ischemic attacks (TIA). Some patients develop intracerebral and subarachnoid hemorrhages. In an analysis of a cohort of 2446 patients from the Fabry Registry, strokes were found in 6.9% of men and 4.3% of women. In 77% of these women, stroke was the first clinically significant manifestation of FD. Among all patients, ischemic stroke was registered in 87%, and hemorrhagic stroke in 13% [24]. The development of stroke in FD is more often observed at the age of 18–55 [25]. Ischemic strokes in FD are most often lacunar infarcts, which are localized in the vertebrobasilar system. Hemorrhagic strokes in FD are localized in the subcortical nuclei. The visualizing features of stroke in patients with FD do not differ from those present in similar cases of stroke of other etiology [26]. In a 2005 selective screening of patients with cryptogenic stroke, FD was detected in 4.9% of men and 2.4% of women [27]. However, a multicenter study conducted by A. Rolfsetal in 2012, which included more than 47 clinics from 15 European countries, assessed the incidence of FD among all patients with acute cerebrovascular events under the age of 55 years. "Definite" FD was found in 0.5% of patients and "probable" FD in 0.4% [28]. Likewise, a prospective study performed in 2020 based on the Australian Clinical Stroke Registry, where 1 case of FD was identified among 326 young adults (average age-53 years [48–56 years]), indicating FD in 0.3% of cryptogenic stroke cases [29]. A similar study was conducted at Ohio State University in 2021, in which 986 patients with cerebrovascular events were screened for FD, resulting in 16 (1.6%) patients (13 patients with IS, 2 with TIA and 1 with intracerebral hemorrhage) being found positive. Two (0.2%) patients with lacunar ischemic stroke had a pathogenic variant associated with classical FD. Both patients in whom a pathogenic variant of the GLA gene was detected were younger than 50 years of age; 14 patients (1.4%), had a variant of the GLA gene considered to be benign [30]. Based on these data, we consider it necessary and appropriate to suspect FD in patients with ischemic cryptogenic stroke at the age of 19 to 55 years.

Rare neurological manifestations

Parkinsonism

When screening for Parkinson's disease (PD) among 229 patients with FD, 3 patients (1.3% of all subjects and 3.0% of the ≥50 year subgroup) were found to have extrapyramidal symptoms [31], [32]. In a similar

study that included 90 patients with FD, 2 patients were diagnosed with PD (2.2% of all subjects) [31]. All patients had the akinetic-rigid form of PD. In a study conducted in 2018 to 2020 in which 126 of 236 patients diagnosed with PD (20 men and 106 women with low FD biochemical markers) had their GLA gene sequenced. As a result, 4 patients (3.2%) with a significant genetic mutation were identified, all four were women, without other clinical manifestations of FD [33]. The authors state that the results of these studies suggest that individuals with GLA mutations may have an increased risk of developing PD, but these results should be interpreted with caution, given the limitations of the study design [31], [32], [33].

FD and multiple sclerosis (MS)

In some cases, FD may be misdiagnosed as other neurological diseases. In particular, FD has been described as one of the possible mimics of MS [34], [35], [36]. The reason for misdiagnosis is that patients with any disease can have pain and white matter lesions from brain magnetic resonance imaging (MRI) scans. The study, which examined 86 patients (58 women and 28 men; average age-42 years, range 18–66 years) who had previously been diagnosed with MS. All patients had lesions of the nervous system, and MRI revealed white matter lesions. However, four women in the cohort (4.7%) were found to have mutations in GLA, which argues in favor of Fabry disease [37].

For differential diagnosis of MS and FD, the following criteria can be distinguished:

1. A complete family history can help make the right diagnosis
2. Multiple organ failure (damage to the kidneys, heart, eyes), especially in male patients argues in favor of FD [37]
3. FD should be suspected in all cases of suspected MS with atypical clinical picture, atypical MRI data, and in the absence of oligoclonal bands in the cerebrospinal fluid [37]. In some cases, the correct diagnosis may be more difficult, and the search for additional neuroradiological features, such as the relative preservation of medial [38] and infratentorial [39] structures, may help differentiate FD from MS.

The ability to distinguish FD from MS is crucial to choosing the appropriate treatment, which ultimately leads to improved quality of life for patients.

Epilepsy

In FD, due to vascular and metabolic disorders, patients can have epileptic seizures [40]. However, the detailed characterization, prevalence rate, and severity of clinical manifestations have not been described in any study.

Diagnosis of FD

MRI signs of FD

Neuroimaging is an important diagnostic measure for patients with FD, both to confirm the diagnosis and to make a differential diagnosis. It is necessary to examine the brain with MRI and magnetic resonance angiography, on 1.5–3 T high-field tomographs.

A characteristic neuroradiological sign of FD is hyperintensity of white matter (observed in 80% of patients) [26]. These changes are associated with damage to the microvascular bed as a result of endothelial damage by glycosphingolipids. Symmetric hyperintensity in the subcortical area and periventricularly is diagnosed [41].

The next neuroimaging sign of FD is the pulvinaric symptom, which is detected mainly in men with a frequency of 3% [42] and 13.9% [43]. On MRI, it shows bilateral hyperintensity on T1-weighted images of the posterior thalamic region. However, this phenomenon has now been identified in other conditions (CNS infections, consequences of chemotherapy and radiation therapy, and phacomatoses) [41].

Dilation arteriopathy of the vertebrobasilar system is a frequent, although inconstant neuroradiological sign of FD. Vascular changes include lengthening, tortuosity, ectasia, and focal aneurysmatic dilation of the vertebral and basilar arteries. Lengthening and dilation of the basilar artery appears to be an age-related phenomenon, more pronounced in patients with FD [44].

Laboratory diagnosis of FD

Laboratory diagnosis of FD includes determination of the activity of the lysosomal enzyme alpha-galactosidase A (α -Gal A), accumulation levels of the metabolites globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb3), and molecular genetic analysis to detect mutations in the GLA gene.

A method of diagnosing FD by determining the activity of the lysosomal enzyme α -Gal A in plasma, lacrimal fluid, leukocytes, and any biopsy or cell culture of skin fibroblasts is available worldwide. In men, reduced α -galactosidase A activity is a sufficiently informative sign of FD and can be used as a screening test. However, in women with FD, the activity of this enzyme may be within normal limits [2]. Determining the concentration of the biomarker lyso-Gb3 in dried blood spots significantly improved the diagnosis of FD in women compared with enzyme activity alone. Elevated levels of lyso-GL-3 are a much more important indicator than low enzyme activity [45], suggesting that this biomarker can be used for the primary diagnosis of women with FD [46]. Only a genetic test (GLA gene sequencing) can definitively rule out or confirm the diagnosis. "The gold standard

for figuring out whether a new mutation is pathogenic or probably benign involves *in-vitro* GLA mutation expression analysis. If a proband has the mutation, all its relatives should be examined [2].

Treatment of FD

Today, pathogenetic treatment of the disease - ERT - is possible. Two different forms of ERT are available: Agalsidase-alpha (Replagal, Takeda) and agalsidase-beta (Fabrazyme, Sanofi Genzyme) [30], [47]. Long-term treatment can slow the progression of the disease, but most patients still develop cardiac, renal, and cerebral complications, and the effectiveness of treatment is also reduced in the later stages of the disease when there are irreversible abnormal changes in vital organs and systems [16]. In addition, life-long intravenous treatment is burdensome. Therefore, several new treatment approaches have been explored over the past decade.

Chaperone therapy (migalastat; 1-deoxygalactonoglyrimycin) is the only currently approved treatment for FD. This small molecule for oral administration aims to improve the enzymatic activity of mutated α -galactosidase A and can only be used in patients with specific mutations [16], [47]. Drugs currently in preclinical trials are second-generation enzyme replacement therapies (pegunigalsidase-alpha, Moss-aGal), substrate-reducing therapies (venglustat and lucerastat), mRNA and gene therapy [47].

Conclusions

FD is another “chameleon” in neurology, a rare, hard-to-diagnose disease that affects all parts of the nervous system. That is why it is very important for the neurologist to know and remember about this pathology. Timely diagnosis of FD, will allow to prescribe early pathogenetic treatment, qualitatively changing the life of patients with FD.

Thus, the following individuals should be screened for FD

1. With a family history of FD within the third degree of consanguinity
2. With at least one neurological risk factor:
 - Cryptogenic ischemic stroke at the age of 19–55 years
 - Idiopathic neuropathic pain and/or acroparesthesia and/or hypohidrosis, anhidrosis at the age of 3–16 years.
3. Additional factors may include:
 - Cardiac manifestations: Left ventricular hypertrophy, hypertrophic cardiomyopathy, conduction disorders requiring fitting of a pacemaker;

- Nephrological manifestations: terminal stage of renal failure, with the need for dialysis and/or kidney transplantation;
- Skin manifestations - angiokeratomas;
- Ophthalmological manifestations-corneal clouding, lens opacity, retinal vascular pathology.

Biochemical laboratory methods are used to confirm the diagnosis of FD: measuring the activity of the lysosomal enzyme α -galactosidase A, GL-3 levels in urine or blood and/or globotriaosylsingosine levels in blood, then sequencing of the GLA gene is necessary in patients with low enzyme levels.

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