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Fabry Disease - literature review

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Fabry Disease - literature review

Summary

Fabry disease (FD) is a rare lysosomal storage disorder that can manifest in classical and atypical forms, with the latter being more common. It results from deficient alpha-galactosidase activity, leading to the accumulation of globotriaosylceramide (Gb3), causing inflammation, cellular damage, and mitochondrial dysfunction. Symptoms include proteinuria, kidney failure, hypertrophic cardiomyopathy, valve defects, peripheral neuropathy, and gastrointestinal issues. The disease affects life expectancy, primarily due to cardiovascular complications. Early diagnosis is often delayed due to non-specific symptoms, and prognosis tends to be worse in males. Current treatments include enzyme replacement therapy (ERT), chaperone therapy with migalastat, and second-generation ERT.

Introduction and purpose: The aim of this publication is to discuss various aspects of Fabry disease based on the latest literature.

Material and methods: The PubMed database was searched to find scientific articles in which the term "Fabry disease" or the abbreviation "FD" appears in the title, abstract, or keywords.

Conclusions

Given the rarity of Fabry disease, research is limited, and there is a need for more studies to explore novel therapeutic options that could improve patient quality of life and mitigate the disease's complications.

Keywords: Fabry disease; Alpha-galactosidase A; GLA; lyso-Gb3

Introduction

Fabry disease (FD) is a rare disorder belonging to the group of lysosomal storage diseases [1]. FD is inherited in an X-linked manner and results from mutations in the alpha-Gal A gene, leading to reduced activity of alpha-galactosidase A [2]. Impaired activity of this enzyme disrupts the metabolism of neutral glycosphingolipids and globotriaosylceramide (Gb3), causing these compounds to accumulate in lysosomes, impairing their function [1,2]. Since lysosomes are found in nearly all human cells, the symptoms of the disease are diverse and affect various organs and systems [3]. FD is generally classified into classical and atypical forms, which differ in the timing of symptom onset and their severity [1].

Initial symptoms are often nonspecific, making early diagnosis challenging [4]. Currently, FD is an incurable disease; however, in recent years, several treatments have emerged that can delay the onset of life-threatening complications [5].

Objective

The aim of this publication is to discuss various aspects of Fabry disease based on the latest literature.

Methodology

The PubMed database was searched for scientific articles where the terms "Fabry disease" or "FD" appear in the title, abstract, or keywords. The focus was on articles published between 2017 and 2024, although in some cases, older sources were consulted when more recent data was lacking. Articles were selected that addressed the etiology, epidemiology, symptomatology, diagnostics, and treatment of the disease.

Etiology and pathophysiology

Unlike pathophysiology, the etiology of Fabry disease (FD) is relatively well understood. The disease results from mutations in the alpha-Gal A gene, located on the X chromosome [1,2]. To date, at least 900 mutations have been identified (about 69% of which are missense mutations, 17% deletions, 5% splicing mutations, and 5% insertions or duplications), which are responsible for the disease, though this list is expected to grow over time [2,6]. Mutations in the alpha-Gal A gene lead to a complete or partial loss of activity of the lysosomal enzyme alpha-galactosidase A, which disrupts the metabolism of certain glycosphingolipids and causes the accumulation of their metabolites (primarily globotriaosylceramide (Gb3)) in lysosomes and various tissues. However, the mechanism behind this phenomenon has not yet been fully understood [1,7]. Clinically significant FD develops only when the activity of alpha-galactosidase A drops below a critical level, approximately 30-50% of the normal value [1].

Gb3 primarily accumulates in the vascular endothelium, vascular smooth muscle cells, pericytes, autonomic ganglia, dorsal root ganglia, renal glomeruli, renal tubules, interstitial cells, cardiac muscle cells, corneal endothelial cells, valvular fibrocytes, and cardiac conduction cells, resulting in a highly varied clinical presentation [1]. Cell damage occurs both mechanically and as a result of inflammation induced by Gb3 and other mechanisms not yet identified [8]. The functional defect of alpha-galactosidase A impairs the degradation of lipid antigens, and their accumulation activates NK cells, leading to chronic inflammation and autoimmunity [8]. Some researchers also suggest that Gb3 accumulation negatively impacts endocytosis and autophagy, disrupting mitochondrial function and promoting premature apoptosis [9]. A key role in FD pathogenesis is also played by water-soluble deacylated Gb3 (lyso-Gb3), which significantly increases in the blood and urine of affected individuals [1,10]. Lyso-Gb3 stimulates the proliferation of smooth muscle cells, thereby increasing vascular wall stiffness [1,2,11]. Additionally, it impairs endothelial nitric oxide synthase (eNOS) activity, damages podocytes, and leads to glomerular fibrosis [11]. It has also been observed that the concentration of lyso-Gb3 in the blood correlates with the severity of the disease [10].

Some researchers also highlight low levels of thrombomodulin (TM) and elevated levels of plasminogen activator inhibitor (PAI) in FD patients, suggesting that, through an as-yet-unknown mechanism, the disease promotes thromboembolic complications [2].

Epidemiology

Data regarding the prevalence of Fabry disease (FD) is highly variable. According to some authors, the disease occurs with a frequency between 1:40,000 and 1:117,000 live male births [6], with the atypical form of the disease being much more common than the classical form [2]. In recent years, newborn screening studies have been conducted in several countries, including Italy [12], where dried blood spots (DBS) from 173,342 newborns were analyzed, estimating the prevalence of FD to be between 1:1,145 and 1:18,436. A slightly larger number of samples, 200,643, were analyzed by researchers in the UK, who estimated the prevalence of FD to be 1:5,573 live births [13].

Given that FD leads to kidney failure, it is important to note studies regarding the prevalence of the disease in dialysis patients. These studies suggest the occurrence of FD in 0-1.6% of males and 0-0.54% of females [14,15,16,17]. A recent meta-analysis on this topic suggests that these percentages are lower, with values of 0.21% for males and 0.15% for females [18].

Symptomatology

As mentioned earlier, Fabry disease (FD) is essentially divided into classical and atypical types [1]. In the classical form of the disease, alpha-galactosidase A activity is undetectable or less than 3% of normal levels, which leads to earlier onset of symptoms and a more severe course of the disease [1,19]. In the atypical form, enzyme activity remains at a varied, higher level, causing symptoms to appear later and be more diverse [1,19].

Among the symptoms related to the urinary system, the most notable are proteinuria and progressive kidney failure [1]. Albuminuria is typically observed in the first or second decade of life, while total renal failure usually develops in the fourth decade [7]. The pathological changes are primarily due to podocyte damage resulting from the accumulation of Gb3 within them, leading to albuminuria and gradual sclerosis of the renal glomeruli (further driven by progressing proteinuria) [1,7,20]. This pathophysiological sequence has been confirmed in a study by Tøndel et al. [21]. Some researchers also point out that Gb3 and lyso-Gb3 stimulate the synthesis of TGF-beta (transforming growth factor-beta) in renal tubular epithelial cells, leading to increased extracellular matrix synthesis [22].

The accumulation of Gb3 and lyso-Gb3 also negatively affects all types of cells in the heart and blood vessels, resulting in interstitial fibrosis, hypertrophy, and excessive proliferation of myocytes [8,23]. A typical symptom of FD is hypertrophic cardiomyopathy, primarily affecting the left ventricle [1,7]. Valve abnormalities also appear to be common in FD, occurring in at least half of the patients, but are rarely advanced [1]. Other cardiovascular symptoms include: fainting, reduced exercise tolerance, hypertension (resulting from, among other things, aortic stiffening), arrhythmias, and heart failure, which usually peaks in the 4th-5th decade of life [7].

Neurological symptoms of FD arise both from the direct impact of Gb3 and lyso-Gb3 on nerve cells and the vascular complications described earlier [1]. In terms of the peripheral nervous system, peripheral neuropathy is typical for FD, while cerebrovascular diseases are common in the central nervous system [1,7].

FD leads to damage to myelinated and unmyelinated nerve fibers and degeneration of axons, resulting in neuropathic pain, intolerance to heat and/or cold, and hypohidrosis—symptoms that typically appear early, in the first decade of life [1,7,24]. Individuals with FD are significantly more likely to experience transient ischemic attacks (TIAs) and ischemic strokes, due both to the direct effect of Gb3 on cerebral vessels and the arrhythmogenic impact of the disease on the heart muscle [1,25].

At least half of those with FD experience gastrointestinal symptoms, including nausea, vomiting, diarrhea, and constipation [1,7]. These symptoms result from both autonomic neuropathy and mesenteric vessel narrowing [7,26].

Ophthalmic symptoms of FD include cornea verticillata, conjunctival or retinal vessel alterations, and posterior cataracts [1,27]. These are often present early in life (even from birth) and result from the accumulation of glycosphingolipids in eye tissues [1,7]. Some researchers suggest that the presence of cornea verticillata correlates with a more severe disease course [1].

The vast majority of individuals with FD (at least 70%) show skin symptoms early in life, with angiokeratomas being the most common, especially in the pelvic region [28]. These lesions result from weakened capillary vessel walls and dermal ectasia due to Gb3 accumulation [7].

FD also affects the respiratory system, causing obstructive disturbances, and later, restrictive ones, attributed to the accumulation of glycosphingolipids in cells of small and medium-sized airways [29]. Some patients also experience lymphatic edema in the limbs, osteopenia, osteoporosis, and mild facial dysmorphia [7].

It is also worth noting that FD affects the neuropsychological state of affected individuals, leading to depression, anxiety disorders, and social adaptation difficulties [30]. The development of these symptoms is most likely due to living with a chronic illness, but the destructive effect of the disease on brain structures, including the hippocampus, is also considered [30].

So far, no clear genotype-phenotype correlation has been established, but some studies have shown that, for example, the IVS4 919G > A mutation is associated with a higher incidence of cardiomyopathy and valve defects and fewer extra-cardiac symptoms, while the N215S mutation results in a moderate decrease in alpha-galactosidase A activity, limiting symptoms mainly to the heart muscle [1,31].

Diagnostics

The primary test used in the diagnosis of Fabry disease (FD) is the measurement of α-Gal activity in plasma, leukocytes, or dried blood spots (DBS) [1,7]. This test is sufficient in the case of males; however, genetic testing is still recommended to detect pathogenic mutations [7]. In females, these tests are necessary to confirm the diagnosis, as biochemical tests, especially from plasma, do not provide clear results [7,32].

If variants of unclear significance (VUS) are detected during genetic testing, it is essential to correlate clinical, biochemical, and family history data of the patient [7,32]. In some cases, a kidney or heart biopsy may help with the diagnosis [7,33]. Many researchers also emphasize that cornea verticillata is a rather characteristic symptom that can lead to the diagnosis of FD, although this symptom can also appear when using certain medications, such as amiodarone [7].

Many researchers highlight the importance of newborn screening and testing family members of individuals diagnosed with FD, as family history analysis often leads to the identification of several other affected individuals [7]. Programs based on measuring α-Gal activity in newborn screening (NBS) are being conducted in several countries, although ethical concerns have been raised about such practices. Nevertheless, according to some researchers, most patients report that they would prefer to be aware of their diagnosis [7,34,35].

In the past, some researchers suggested that the pattern of X chromosome inactivation (XCI) in leukocytes correlates with FD symptoms and heart involvement; however, a meta-analysis of data on this topic did not confirm this correlation [6,36,37,38].

Recent studies [39] suggest that the concentration of neurofilament light chains (NfL) in plasma seems to be a good marker for neuroaxonal and cerebrovascular damage in FD. Furthermore, it has been suggested that this parameter correlates with kidney function, although further research is needed [39].

Treatment

Currently, three main treatment options for Fabry Disease (FD) can be distinguished: enzyme replacement therapy (ERT), chaperone therapy, and second-generation enzyme replacement therapy [5].

ERT involves the intravenous administration of exogenous alpha-galactosidase A, which includes Replagal and Fabrazyme [40]. Both compounds have confirmed efficacy in reducing lyso-Gb3 levels in plasma and are relatively safe [41]. In males with classic FD, it is recommended to start ERT as soon as possible (regardless of the presence of clinical symptoms). In males with atypical FD and in females, treatment is initiated upon the appearance of clinical symptoms or in asymptomatic patients when organ damage is confirmed (e.g., a decrease in GFR or albuminuria) [1,7]. Limitations of ERT include poor penetration through the blood-brain barrier, the inability to reverse some already existing organ complications, undesirable infusion reactions, and the formation of antibodies that inhibit the action of the drugs (ADA) [42]. ADA are most commonly of the IgG1 and IgG4 classes, and they reduce drug uptake by target cells, leading to worse therapeutic outcomes [43]. To counteract the effects of ADA, two therapeutic strategies are currently used. The first involves gradually increasing the drug dose, as it has been shown that while this leads to an increase in ADA titers, therapeutic efficacy also improves [44]. The second strategy involves the concurrent use of immunosuppressive drugs, as they lower ADA levels [45]. So far, it has not been determined which of these strategies is superior, as both have advantages and disadvantages [1].

Chaperone therapy involves the use of migalastat, which is a competitive inhibitor of the α-GalA enzyme [1]. This drug stabilizes the enzyme, making its transport into the lysosome easier, and the conditions inside the organelle lead to the dissociation of the enzyme, which can then perform its biological function [1]. Migalastat has several advantages over ERT: it is administered orally, has better tissue distribution, and is not immunogenic [1,41]. However, due to its mechanism of action, this drug can only be used in certain patients in whom the α-GalA enzyme shows sufficiently high activity [1]. In such patients, migalastat has shown relatively high efficacy in reducing symptoms from the cardiovascular and renal systems [46].

Second-generation enzyme replacement therapy is a relatively new treatment method that involves the use of PEGylated, chemically modified α-GalA enzyme [47].

Pegylation significantly extends the drug's duration of action from about 2 hours in the case of classic ERT to about 80 hours [5]. Due to the small number of studies comparing the efficacy of this drug to existing therapies, it is difficult to definitively assess its superiority over any of them [5].
It is worth noting that a meta-analysis conducted by Veldman et al. [5], aimed at evaluating the effectiveness of different FD therapies, found that definitively establishing the efficacy of each treatment is relatively difficult due to methodological issues in the studies conducted so far.

Prognosis

Fabry disease has a varied course and clinical presentation in different patients, so the prognosis depends on the specific form of the disease [1]. Life expectancy is primarily influenced by the impact of FD on the renal system (complications from this system account for about 10% of FD-related deaths) and the cardiovascular system (complications from this system account for about 40% of FD-related deaths), while the impact on other systems mainly affects the quality of life of affected individuals [1,48]. It should also be noted that due to the nonspecific course of the disease, its diagnosis is often delayed (according to some authors, it often takes around 10 years from the onset of the first symptoms), which negatively impacts the prognosis due to the progressive damage to internal organs over time [1].
Before the introduction of effective renal replacement therapies, FD patients primarily died from renal complications [49], and later, the causes of death became closer to the current ones [1]. FD patients typically died before the age of 50-60, but after the introduction of enzyme replacement therapy (ERT), their life expectancy significantly increased – the current median is 77.5 years [1,28].
Past studies [50] have shown that early initiation of nephroprotective treatment with ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) significantly improves the prognosis of FD by delaying the need for renal replacement therapy.
It is also worth mentioning the tool developed by Mignani et al. [3], called FASTEX, which allows for a quantitative assessment of FD stability by evaluating seven clinical parameters indicative of disease activity.
Additionally, it should be noted that, according to many researchers, the prognosis for FD is worse in males – their average life expectancy is shorter, and severe disease complications occur earlier and more frequently [28].

Summary

Fabry disease (FD) is a rare lysosomal storage disorder that can present in both classical and atypical forms. The disorder is caused by a deficiency of alpha-galactosidase, leading to the accumulation of glycosphingolipids, particularly globotriaosylceramide (Gb3). This accumulation disrupts cellular functions, triggers inflammation, induces autoimmunity, and impairs mitochondrial function. Additionally, deacylated Gb3 contributes to glomerular fibrosis. Clinical manifestations of FD include proteinuria, progressive renal failure, hypertrophic cardiomyopathy, valve defects, peripheral neuropathy, cerebrovascular disease, gastrointestinal issues, cornea verticillata, retinal changes, posterior cataracts, angiokeratomas, and both obstructive and restrictive pulmonary disorders.

The disease significantly impacts life expectancy, with cardiovascular issues responsible for around 40%. Due to its non-specific symptoms, the diagnosis of FD is often delayed, and prognosis is generally poorer in males.
Diagnosis primarily relies on measuring alpha-galactosidase activity in plasma, leukocytes, or dried blood spots. Current treatment strategies for FD include enzyme replacement therapy (ERT), chaperone therapy, and second-generation ERT. However, ERT is limited by the formation of anti-drug antibodies (ADA), which reduce therapeutic efficacy. Chaperone therapy using migalastat is effective in some patients, while second-generation ERT offers extended drug action. Due to the rarity of FD, research is limited, and further studies are needed to identify new therapeutic approaches to improve quality of life and address the disease's complications.

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