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Neurological manifestations in Fabry disease

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ABSTRACT

Fabry disease (FD) is a rare, progressive, multisystem and highly debilitating disease. FD is an X-linked lysosome storage disorder that results in α-galactosidase A deficiency. The subsequent accumulation of glycosphingolipids is more evident in vascular endothelium and smooth-muscle cells. The resulting effect of the deposition is generalized inflammation and vasculopathy, which can also affect the central and peripheral nervous system. FD progresses with kidney dysfunction, angiokeratoma of the skin, cardiomyopathy, cerebrovascular events and neurological disorders. In the present review, the neurological manifestations of FD are summarized with emphasis on cerebral vasculopathy, cochlear nerve dysfunction, psychiatric and cognitive symptoms, autonomic dysfunction and peripheral neuropathy. Enzyme replacement therapy is also discussed in the light of its more prominent effects when administered early in life, which make it essential to diagnose FD as soon as possible.

INTRODUCTION

Fabry disease (FD; Online mendelian inheritance in man #301500) is a rare, progressive, multisystem and highly debilitating lysosome storage disorder, resulting in α-galactosidase A (α-Gal A) (*300644) deficiency. FD birth prevalence is approximately 1:40,000 and more than 600 mutations in the α-Gal have been described. The disease is X-linked inherited,[1,2] and X-inactivation in women may render them vulnerable to severe manifestations of FD.[3,4] Even with the same gene mutation there is an intrafamilial variability of phenotypical presentation of FD, leading to variable signs, symptoms and severity of the disease.[5]

α-Gal A deficiency leads to progressive accumulation of glycosphingolipids such as globotriaosylceramide (GL-3) in various tissues and organs. The accumulation is predominantly in vascular endothelial and smooth-muscle cells. In the 19th century, William Anderson and Johannes Fabry described angiokeratoma of the skin as the first clinical sign of the disease. Subsequently, identification of kidney dysfunction,[6] cardiomyopathy,[7] gastrointestinal disorders,[8] cerebrovascular events[9] and other neurological disabilities was reported. These conditions are the most severe clinical manifestation of

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FD and may lead to increased morbidity and mortality, with concomitant reduction in life expectancy.[10] While the literature on the skin, kidney and cardiovascular manifestations of FD has been consistent, there have been very few reports on the neurological aspects of the disease.

The aim of this article was to describe the neurological manifestations in FD. They may occur at any stage of the disease, including its onset. Therefore, although relatively rare, FD is a differential diagnosis for young individuals with unexplained neurological manifestations.

CEREBRAL VASCULOPATHY

The prevalence of cerebrovascular diseases such as stroke events in FD patients is 4-6%. These events may be the first clinical manifestation of the disease and are more often observed between the ages of 18 and 55 years, affecting both genders equally.[11]

Cerebral endothelial vasculopathy in FD is not fully understood, but it is accepted that GL-3 accumulation and polymorphisms of pro-thrombotic genes can modify Virchow's triad and create a pro-thrombotic state.[12,13] These alterations include changes to interleukin-6-G-174C, G894T of endothelial nitric oxide synthase, factor V G1691A mutation and protein Z A-13G or G79A.[13] Few studies have concentraded on intravenous thrombolytic therapy for acute ischemic stroke in FD patients and the outcomes are not fully understood.[14]

Although ischemic stroke and transient ischemic attacks are the main types of cerebrovascular events in FD, cerebral hemorrhage, microbleeding, cerebral venous thrombosis and cervical carotid dissection have also been reported. The main etiology of stroke comes from the effect of the disease on the small arteries. The posterior circulation (vertebrobasilar system) is often more involved than the carotid system.[15-18]

White matter lesions are a reflection of secondary microangiopathy involvement of the central nervous system. As many as 80% of these patients present these abnormalities on magnetic resonance imaging (MRI), even without clinical symptoms of focal neurological involvement. Increased cerebral blood flow, vascular hyper-reactivity and GL-3 deposition ultimately induce cell dysfunction and increase interstitial pressure, thus generating vulnerability of elongated perforating arteries and leading to reduction of cerebral blood flow.[19]

Brain microangiopathy in FD can be misdiagnosed as multiple sclerosis due to intermittent disseminated sensory deficits and white matter lesions fulfilling the McDonald criteria.[20-22] However, T2-FLAIR MRI of the white matter usually produces asymmetric and confluent images, with little involvement of the corpus callosum and no enhancement of the lesion through gadolinium. There are no lesions in the spinal cord. These characteristics help differentiating FD images from multiple sclerosis.[23] Vertebrobasilar system ectasia, proteinuria, cardiac hypertrophy and histories of death among young relatives (renal, cardiac or cerebrovascular causes) are other frequently found elements in these patients' medical history.[24,25]

Calcification of cerebrovascular dolichoectasia in cerebral white matter and thalamus (pulvinar region) is due to dysfunction of the cerebrovascular circulation and to GL-3 accumulation. Cerebrovascular hyperperfusion reflects the increased vascular reactivity and the effect on the nitric oxide pathway, while increased oxidative stress and formation of peroxynitrite can create persistent vasodilation and increased risk of atherosclerosis.[26]

COCHLEAR NERVE DYSFUNCTION

The data in the literature on the pathogenesis of cochlear dysfunction in FD are limited. It has been hypothesized that GL-3 accumulation in the cochlear nerve can progress to hearing loss, especially at 2-3 kHz.[27]

PSYCHIATRIC AND COGNITIVE SYMPTOMS

High prevalence of neuropsychiatric symptoms, such as depression and neuropsychological deficits, reduces quality of life among FD patients. Although the pathophysiological mechanisms have not been fully elucidated, cerebral vasculopathy is involved. Furthermore, FD patients may be chronically distressed by pain and psychosocial impairment.[28-30]

AUTONOMIC DYSFUNCTION

Hypohidrosis, reduced saliva flow and impaired tear production may be present and have mechanisms that are not fully understood. GL-3 accumulation in autonomic ganglia and dysfunction of eccrine glands are found in patients with FD. Gastrointestinal symptoms (which may be associated with autonomic dysfunction) are the second most common clinical manifestation among children and young adults with FD.[8] During unexplained attacks of abdominal pain, the patients may also suffer from postprandial flatulence and bouts of diarrhea.[31,32]

PERIPHERAL NEUROPATHY

Peripheral neuropathy has an important negative impact on quality of life among FD patients. It has been described as being present since the beginning of GL-3 deposition, i.e. from these patients' first years of life. It affects both genders equally, and is often associated with fever and pain during exercise. The pain may last for periods ranging from minutes up to several days, and may be incapacitating.[31-35]

As mentioned above regarding other neurological manifestations of FD, the pathophysiological mechanisms of neuropathy are not fully understood either. It has been proposed that inhibition of central nociceptors would occur as a result of constant activation of nociceptive afferents, in association with neuronal dysfunction, Wallerian degeneration, activation of the inflammatory cascade, vasa nervorum ischemia and molecular changes in the peripheral nociceptor, similar to dying-back neuropathies.[36-40] In addition, disproportion and dysfunction of axonal sodium channels would increase the frequency of nociceptive discharge. This last topic has practical importance, since pain treatment in these patients must be carried out using sodium channel-blocking drugs such as carbamazepine. Involvement of distal, small Aδ- myelinated fibers and C-unmyelinated fibers is prevalent among patients with symptoms relating to temperature. It is important to establish a uniform quantitative assessment battery for sensitive symptoms.[41-45]

ENZYME REPLACEMENT TREATMENT

Enzyme replacement therapy with humanized recombinant α-Gal A (agalsidade beta, or more recently, agalsidase alpha) reduces the secondary clinical events relating to FD by 60% to 80%. The effect of this enzyme replacement is seen in prevention of cerebral, renal and cardiological life-threatening events, which, in untreated patients, are responsible for more than 90% of deaths.[46,47] There is evidence that early treatment with enzyme replacement therapy can stabilize vascular disease progression and decrease the risk of stroke.[48] Patients may have different response to treatment with agalsidade alpha or beta.[49-51]

CONCLUSION

Neurological manifestations of FD are often related to significant morbidity and mortality. Early detection and specific treatment of neurological involvement in cases of α-Gal A deficiency may result in improved quality of life for patients with FD.

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Conflict of interest

There are no conflicts of interest.

Patient consent

No patient involved.

Ethics approval

This article does not contain any studies with human participants or animals.

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