

# Neurological Findings in Anderson-Fabry Disease

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## Abstract

Anderson-Fabry disease (AFD) is an X-linked lysosomal storage disorder caused by mutations in the  $\alpha$ -galactosidase A gene on chromosome Xq22, resulting in  $\alpha$ -galactosidase A enzyme deficiency. It is characterized by progressive accumulation of lipids (e.g., globotriaosylceramide) in the lysosomes of a variety of cell types, including neural cells. Neurological manifestations, other than cerebrovascular accidents, include small fiber neuropathy and dysautonomic disorders. Small fiber peripheral neuropathy often is clinically manifested at young ages. Peripheral pain can be chronic and/or can occur as provoked attacks of excruciating pain. Manifestations of dysfunction of small autonomic fibers may include impaired sweating, gastrointestinal dysmotility, and abnormal pain perception. Patients with AFD often remain undiagnosed until the emergence of a more typical clinical manifestation, characterized by chronic renal and cardiac failure. Early clinical benefits of enzyme replacement therapy include reduction of neuropathic pain, and adequate management of residual pain to a tolerable and functional level, which can substantially improve the quality of these patients. Thus, it is important that physicians consider AFD in the differential diagnosis of neurological manifestations to provide an appropriate diagnostic and therapeutic workup.

## Keywords

- Fabry disease
- neurological
- $\alpha$ -galactosidase A
- enzyme replacement therapy

## Introduction

Anderson-Fabry disease (AFD) is a rare X-linked inherited lysosomal storage disorder caused by the deficiency of the enzyme  $\alpha$ -galactosidase A ( $\alpha$ -gal A) due to a defect in the  $\alpha$ -galactosidase (*GLA*) gene. The deficiency of  $\alpha$ -gal A (► Fig. 1) causes progressive accumulation of globotriaosylceramide (Gb3) in a variety of cell types, preferentially within the vascular endothelium and smooth muscle cells, leading to progressive vessel occlusion, ischemia, and ultimately, multi-

organ dysfunction (► Fig. 2).<sup>1</sup> The *GLA* gene maps on chromosome Xq22.1 and more than 400 mutations, mainly of the missense and nonsense types, but also small and large deletions, have been identified so far, according to the Human Gene Mutation Database.<sup>2</sup> Although, AFD is transmitted in an X-linked way, females commonly manifest symptoms, presumably as a result of skewed X-chromosome inactivation.<sup>3</sup>

The severity of AFD is related to the residual  $\alpha$ -gal A enzymatic activity. Phenotypically, AFD can be distinguished into the: (1) more severe classical form; and (2) nonclassical

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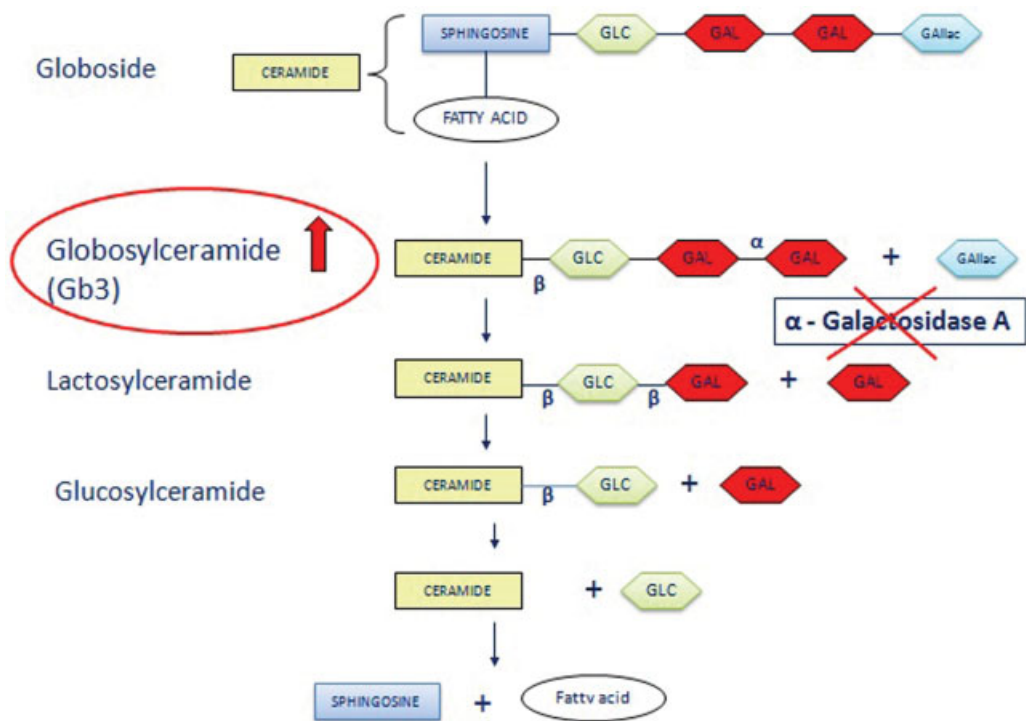


Fig. 1 Globoside metabolism.

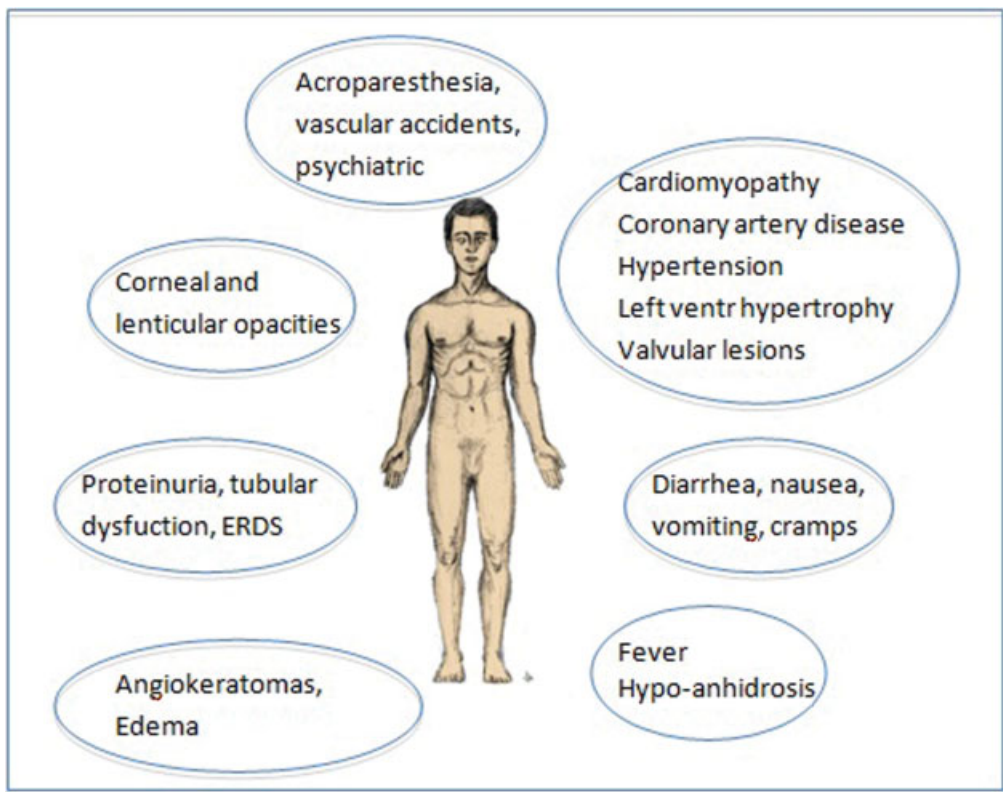


Fig. 2 Multisystemic involvement in Fabry disease.

form, the latter typical of patients with residual enzyme activity. Even in the absence of a clear genotype–phenotype correlation, mutations leading to a complete loss of function generally result in the classical phenotype. A wide inter- and intrafamilial variability in terms of age at onset, clinical features, and disease course is well known.<sup>4</sup>

The prevalence of AFD is estimated at 1:40,000–1:170,000 live births,<sup>5</sup> although recent screening studies in newborns and high-risk groups suggested that the prevalence of non-classical AFD may be much higher than previously thought.<sup>6</sup>

First symptoms typically arise in childhood or adolescence and include peripheral pain, gastrointestinal disorders, hypohidrosis, angiokeratoma, and cornea verticillata.<sup>7</sup> Serious complications, developing in adulthood, include progressive renal insufficiency, cardiac complications (arrhythmia, hypertrophic cardiomyopathy), and/or cerebrovascular complications (e.g., early stroke).

The diagnosis of AFD is often delayed in the pediatric population, because signs and/or symptoms may appear in a nonspecific way in this young age group. Usually, AFD is suspected on the basis of strong clinical signs and recognition of the peculiarity of clinical findings and then confirmed by enzyme/genetic analysis. Measuring  $\alpha$ -Gal A enzyme activity in leukocytes is the gold standard assay for diagnosis of AFD in males.<sup>8</sup> Many females with AFD, however, may have enzyme activity levels within the normal range, therefore, diagnosis requires genetic studies to detect or confirm the pathogenetic mutation.

## Clinical Features

The classic form of AFD is generally observed in male patients in the pediatric age.<sup>9</sup> Painful neuropathy and angiokeratoma are observed in the majority of patients.<sup>10</sup> The onset of painful neuropathy is observed at an average age of 11 years, but it has also been reported at earlier ages. Gastrointestinal disturbances, including diarrhea, constipation, abdominal pain, nausea, and vomiting in young patients, are frequent early symptoms of the disease.<sup>11</sup> Cornea verticillata without alterations of vision is a very frequent finding. Neurosensory hearing loss and paroxysmal vertigo can also be observed; the latter may be an expression of labyrinth damage. Clinical manifestations are sometimes not recognized until the youth or adult age, when organ lesions are already established.

The most frequent clinical signs of AFD recorded in childhood are reported in ►Table 1. Later, in adulthood, between 30 and 40 years of age, complications usually develop involving kidney, heart, and central nervous system (CNS).<sup>12</sup> Kidney dysfunction occurs in nearly all patients with AFD and usually presents with mild proteinuria followed by progressive reduction of glomerular filtration rate and, by the age of 40 years, end-stage renal disease usually occurs.<sup>13</sup> Cardiac disease, including progressive development of concentric left ventricular hypertrophy, severe loss of left ventricular systolic function, mitral, and aortic valvulopathy, and conduction abnormalities leading to dysfunction, are common.<sup>12</sup> Stroke, with a prevalence of up to 7.0% in familial Alzheimer disease registries is a common finding and often occurs before the

onset of other manifestations.<sup>14</sup> Organ involvement is progressive and is the principal cause of morbidity and premature mortality in patients with AFD.<sup>15</sup>

In women, the clinical course is less aggressive, with onset later in adult life. So as in men with atypical clinical phenotypes, manifestations involving only one organ are paramount in females (e.g., CNS or heart, while angiokeratoma has only limited extension or it is not referred to the physician by patients, and proteinuria is mild or absent), and painful neuropathy seems to have a lower incidence than in men. The average onset of painful neuropathy in women is around 17 years of age, but it may also be observed earlier in life.<sup>16</sup>

Life expectancy for male patients was approximately 41 to 50 years before enzyme replacement therapy (ERT), while for female patients, is 55 to 70 years, lower than the average life expectancy in women in the general population.<sup>16</sup>

## Neurological Involvement

Neurological manifestations of AFD are due to both central and peripheral nervous system involvement. Given their relative late onset and the clinician's unawareness, neurological signs and/or symptoms may be attributed to other disorders or causes, leading AFD to be overlooked. The abnormal neuronal accumulation of glycosphingolipid appears to have little clinical effect on the natural history of AFD, except for mild cognitive abnormalities. The most important pathogenic role is related to the accumulation of Gb3 in other cells as described below.

### Neuropathy

The incidence of neuropathic involvement, which can be the first clinical manifestation of the disease, can be as high as 80% in AFD.<sup>17</sup> The primary neuropathic insult in AFD is presumably due to a combination of factors that are linked with accumulation of Gb3, and possibly with deposition of its deacylated form.<sup>18</sup> Accumulated Gb3 in dermal vascular endothelial and smooth muscle cells, endothelial and perithelial cells of epineural and endoneural small blood vessels, perineural cells, myelinated and unmyelinated axons and in the dorsal root ganglia can interfere with the function of critical proteins, for example, ion channels, thereby causing nerve injury and dysfunction.<sup>19</sup> The neuropathy in AFD is typically associated with a marked reduction of thinly myelinated A $\delta$  fibers (mediating sharp pain, cold perception), unmyelinated C fibers (pain, warmth perception), and loss of unmyelinated autonomic fibers.<sup>20</sup> Female patients, even when asymptomatic, may also be affected by loss of small fiber function. With progression of the disease, however, large fiber involvement with associated nerve conduction abnormalities may develop. The mechanism is yet unclear: it has been suggested that Schwann cell pathology due to Gb3 accumulation might account for slowing of conduction velocities.<sup>20</sup> Manifestations related to autonomic nervous system dysfunction may include hypo or anhidrosis, reduced salivation and lacrimation, gastrointestinal dysmotility (abdominal cramping pain, bloating, diarrhea, nausea), Raynaud phenomena, tinnitus and sensory losses, reduced heart rate acceleration upon exercise and, in advanced stages, orthostatic hypotension.<sup>21</sup> Hyperhidrosis can

**Table 1** Early signs and symptoms of classic Fabry disease

Early signs and symptoms of classic Fabry disease
• Acroparesthesias
• Fabry crisis
• Gastrointestinal symptoms, including diarrhea, abdominal pain, vomiting, nausea, postprandial bloating.
• Angiokeratomas
• Whorled corneal opacity, retinal vascular tortuosity
• Heat, cold, and/or exercise intolerance
• Hypohidrosis or anhidrosis.
• Microalbuminuria, mild proteinuria and urinary sediment containing globotriaosylceramide
• Urinary hyperfiltration
• Impaired heart rate variability
• Arrhythmias
• Mild valvular insufficiency

also be recognized in patients with AFD, mainly in females. If present, it often manifests in childhood or adolescence.<sup>9</sup> Tinnitus is a frequent symptom and is reported by 27 to 38% of hemizygous males and 25% of female carriers.<sup>22</sup> Neuropathic pain was reported in approximately 60 and 80% of affected boys and approximately 40 to 60% of affected girls—often a few years later versus boys.<sup>7</sup> Peripheral neuropathic pain in young patients with AFD can manifest as chronic, burning pain, and superimposed attacks of acute excruciating pain, dysesthesias, thermal sensation deficits, and paresthesias.<sup>22,23</sup> Recurrent attacks of pain (pain crises), described as “excruciating,” “agonizing,” “lightning,” or “stabbing” pain, often begin in the distal parts of the extremities and may radiate proximally. They can be so intense that the patient can be confined to bed with daily episodes of pain. These episodes, may be triggered by a rapidly changing core body temperature (e.g., for fever, stress, physical activity), presumably due to a decreased ability to sweat.<sup>20</sup> Additional triggering factors include sudden exposure to cold, rapid changes in humidity, and fatigue. Pain crises can be accompanied by deep ache, joint pain, bouts of unexplained fever, and elevated erythrocyte sedimentation rate.<sup>24,25</sup> Over time, neuropathic pain appears to diminish, perhaps due to progressive loss of nerve fibers, but can also become more severe.<sup>26</sup> The symptoms lead to increasing neurological disability and impairment of quality of life in both males and females.<sup>27</sup>

As in other conditions with chronic neuropathic pain, pain medication dependence and substance abuse can occur.<sup>28</sup> Patients may develop social-adaptive or psychological functioning deficits and many become depressed.<sup>29</sup>

**Cerebrovascular Disease**

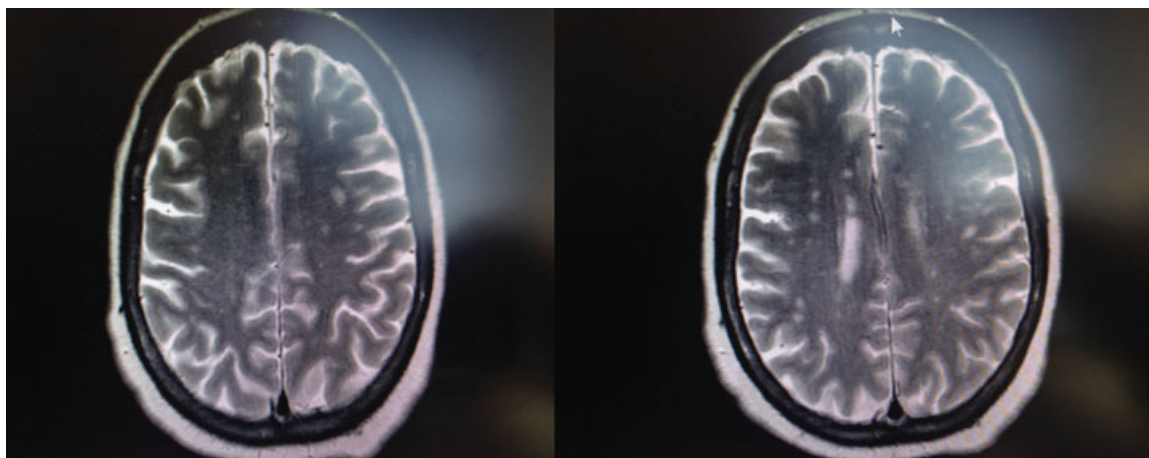
CNS involvement in AFD is mainly due to cerebral vasculopathy, affecting the vertebrobasilar system and the carotid circulation.<sup>30</sup> Cerebral vasculopathy affects both large and small cerebral vessels. Macroangiopathic alterations lead to an increased incidence of ischemic stroke, while micro-

angiopathic alterations lead to the so-called “white matter lesions (WML)” visible at magnetic resonance imaging (MRI). Cerebrovascular involvement in AFD is not uncommon, with a reported frequency ranging from 7 to 48% in males and from 4 to 32%<sup>31</sup> in symptomatic females. The mean age at onset of cerebrovascular manifestations is 33 to 46 years in males and 40 to 52 years in females.<sup>32</sup> The disease has a progressive clinical course, characterized by recurrent cerebrovascular episodes increasing with age and detectable on neuroimaging. Consequently, several neurological manifestations may occur: hemiparesis, vertigo/dizziness, diplopia, dysarthria, nystagmus, nausea/vomiting, headaches, hemiataxia and dysmetria, cerebellar gait ataxia, and rarely, cerebral hemorrhage, psychiatric behavior, and dementia.<sup>33</sup> The pathophysiology of the extensive cerebral vasculopathy in AFD is still poorly understood; probably it derives from a complex multifactorial systemic vascular dysfunction that involves changes in the vessel wall architecture, dysfunctional endothelium, and abnormalities in blood constituents.<sup>34</sup> Pathological examination reveals: glycosphingolipid accumulation both in blood vessel walls and in specific neuronal populations, especially in the brainstem, hypothalamus, amygdala, hippocampus, and entorhinal cortex. Obstructive vasculopathy, either primarily due to accumulation of glycolipid in endothelial and vascular smooth muscle cells or secondary to consequent inflammation and confounding vascular risk factors, may develop in response to abnormal endothelial and vessel wall function, similar in some respects to that observed with accumulation of cholesterol in atherosclerosis. Smooth muscle cell proliferation, caused by toxic effect of lyso-compound of Gb3, has also been suggested to be involved in AFD-related vasculopathy.<sup>35</sup> Cerebral small vessel disease with juvenile-onset and progressive course, often preceding the appearance of neurological symptoms, is the most common neuroradiological manifestation of AFD. Cerebral angiography is the “gold standard” technique for demonstrating vessel obstruction. Magnetic resonance angiography, a noninvasive technique, has also been utilized. MRI shows numerous silent lesions increasing with age, mainly in small perforant arteries (periventricular white matter, brainstem, cerebellum, basal ganglia). Pulvinar calcifications, due to an increase in cerebral hyperperfusion, could be specific of AFD. T2- and fluid-attenuated inversion recovery-weighted brain MRI typically shows multiple hyperintensities (WML) in the deep hemispheric white matter and brainstem (→Fig. 3), indicating perforating artery occlusion.<sup>36</sup> Another radiological finding consists of tortuosity and abnormal ectasia of large vessels (dolichoectasia). However, as radiological features of small vessel disease associated with AFD are not specific, and not distinguishable from hypertensive encephalopathy, they cannot be specific AFD markers.

**Treatment Strategies**

The management of AFD requires a multidisciplinary approach, involving specialist physicians in the disease itself,





**Fig. 3** MRI images of multiple hyperintensities (WML) in the deep hemispheric white matter. MRI, magnetic resonance imaging; WML, white matter lesions.

but also professional nurses, pediatricians, ophthalmologist, nephrologists, cardiologists, neurologists, gastroenterologists, dermatologists, and geneticists.

Until the introduction of ERT, in 2001, treatment of AFD was based only on symptomatic therapies. Two distinct recombinant protein replacement drugs are used: agalsidase alfa (Replagal; Shire Human Genetic Therapies, Dublin, Ireland) and agalsidase  $\beta$  (Fabrazyme; Genzyme Corporation, Cambridge, Massachusetts).<sup>37</sup> Both agalsidase  $\alpha$  and agalsidase  $\beta$  are recombinant forms of  $\alpha$ -gal A, but they are produced differently and are approved for administration at different doses.<sup>38,39</sup> Agalsidase  $\alpha$  is produced in a human cell line by gene activation. It is administered by intravenous infusion at 0.2 mg/kg every 2 weeks over approximately 40 minutes, usually without routine premedication. Agalsidase  $\beta$  is produced in Chinese hamster ovary cells by recombinant techniques and is administered by intravenous infusions at a dose of 1.0 mg/kg, with premedication (antipyretic and/or antihistamine). There are several evidences, in literature, of symptoms improvement, improvement of quality of life, and reduction in disease progression in AFD patients who undergo ERT.<sup>40</sup> An early start of treatment remains essential to obtain the therapeutic goals.<sup>41</sup> ERT has poor effectiveness on some neurological manifestations: this was attributable to the fact that either formulation agalsidase  $\alpha$  or  $\beta$ , do not cross the blood–brain barrier, and to irreversible vascular damage owing to late initiation of treatment.

The incidence of stroke remains high despite several studies have demonstrated significant functional changes in the vasculature of the brain with agalsidase  $\alpha$ <sup>42</sup> and a slowed progression of cerebrovascular complications with agalsidase  $\beta$ .<sup>43</sup> Increases in the number of white matter lesions, detected by MRI, have been reported during ERT.<sup>44</sup> Painful neuropathy, hearing loss, vestibular dysfunction and hypo-/anhidrosis have been found to improve after ERT, even if there is no evidence of intraepidermic nerves regeneration.<sup>45</sup> However, despite convincing evidence that improvements in pain occur, they do not always translate into reduction in analgesic requirements.<sup>46</sup> As for renal and cardiac complications, early initiation of treatment may provide an improvement or

preservation of peripheral nerve function. Beyond ERT, for the management of pain in patients with AFD, it is important to take preventive measures and avoid triggers.

The goal of pharmacological management of neuropathic pain should be to decrease pain to a tolerable and functional level and, thereby, to improve the patient's quality of life, activities of daily life, and psychosocial function. Currently, there are no available randomized controlled trials of any analgesic therapy for the treatment of painful peripheral neuropathy in AFD. To achieve optimal pain management, multiple medications, targeting different aspects of the complex pathways might be considered in patients with advanced disease. It is recommendable to start pain medication(s) at low dose, and to evaluate the tolerability and effectiveness of a change in medication(s) after 2 to 3 weeks.

Anticonvulsants are commonly used to reduce pain in neuropathic pain disorders, including diabetic neuropathic pain.<sup>47</sup> Carbamazepine alone, or in combination with pregabalin (rather than gabapentin), is recommended as first-line treatment in Fabry neuropathic pain. Prescription of opioids implies the risk of drug dependence or abuse. Although, they should only be prescribed if other therapeutic options are ineffective, opioids may be helpful in the acute management of intolerable pain crises.

With increasing disability and unpredictability and difficulty of controlling the pain, patients are at a risk of chronic depression. Patients should be evaluated for psychosocial and behavioral deficits and appropriately treated. Antidepressants, particularly dual reuptake inhibitors of both serotonin and norepinephrine are also viable options. Because of their anticholinergic effect, tricyclic antidepressants have potential concomitant and difficult side-effects in Fabry patients (e.g., accentuation of autonomic instability).

## Conclusions

AFD is a rare and probably underdiagnosed disorder, because, due to its variability in phenotypic expression, diagnosis can often be delayed, if not overlooked.

The neurological features of AFD, particularly the cerebrovascular disease, occur in more than 40% of AFD patients: 4.9% of patients with young stroke have AFD.

Thus, neurologists could play a pivotal role in early instrumental and clinical detection of organ damage in AFD. Clinicians, neurologists in particular, should try to increase their awareness of the wide spectrum of neurological manifestations of AFD to consider this monogenic disorder in the differential diagnosis of stroke and painful neuropathies.

The diagnosis of AFD could improve a patient's quality of life, also making it possible to avoid unnecessary further investigations to detect the origin of stroke or neuropathies. Moreover, ERT for AFD is a major step forward for affected patients and has revolutionized their care.

Although data from the available studies do not completely support the benefit of ERT in improving or preventing neurological manifestations in adult patients, it may nevertheless be reasonable to hypothesize that ERT, if started at an early age, may slow, or even prevent the development of irreversible changes, including neurological manifestations.

#### Conflict of Interest

None.

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