Especially in young patients – think about Fabry disease

Unexplained peripheral neuropathic pain and/or stroke

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Summary

Fabry disease is a rare X-linked lysosomal storage disorder caused by the absence or deficiency of the hydrolase alpha-galactosidase A activity. As a consequence, accumulation of globotriaosylceramide occurs in a wide variety of cells throughout the human body. Specific gene mutations determine disease severity and different phenotypes.

Fabry disease is a multisystemic disease with nonspecific initial manifestations. Neuropathic pain and acroparaesthesia are one of the earliest symptoms, already reported in childhood or adolescence. Later signs and symptoms involve the heart, kidney and brain, resulting in life-threatening complications such as cardiac and renal failure as well as cerebral strokes. Early treatment initiation can ameliorate disease progression and potentially prevents long-term complications.

Based on its diverse and nonspecific manifestation, it can take up to 15 years between the onset of the first symptoms and the final diagnosis of Fabry disease. Recognition of early symptoms, such as neuropathic pain and acroparaesthesia, and considering Fabry disease in young patients with stokes, is important.

As such, neurologists may play a key role in early diagnosis of this disease.

Key words: Fabry disease; central nervous system; peripheral nervous system; enzyme replacement therapy

Introduction

Fabry disease, also called angiokeratoma corporis diffusum, ceramide trihexosidosis, or Anderson-Fabry disease, is a rare lysosomal storage disorder due to the absence or deficiency of hydrolase alpha-galactosidase A (alpha-Gal A) activity in lysosomes. This dysfunction results in progressive accumulation of glycosphingolipids, especially of globotriaosylceramide (Gb3), within lysosomes in a wide variety of cells throughout the human body: vascular endothelial cells, neurons, astrocytes, meningeal cells, smooth muscle cells, as well as podocytes and other kidney cells, myocytes, etc., resulting in major organ system damage [1–3].

More than 400 mutations have been identified in the alpha-Gal A gene (*GLA* gene) situated on the long arm of the X chromosome. For decades, Fabry disease was believed to be an X-linked recessive disorder. However, actual data suggest an X-linked dominant inheritance with variable penetrance. Specific gene mutations determine disease phenotypes and severity [4]. Classical or typical Fabry disease is present in 1:40 000 to 1:60 000 men and usually occurs when alpha-Gal A activity is less than 1%. Milder phenotypes occur when gene mutations result in residual alpha-Gal A activity [4]. Heterozygous women, 1:6000 to 1:40 000, may also be affected with variable penetrance and manifestations. They can exhibit severe disease manifestation similar to that seen in men [4, 5]. Hwu et al. reported results from a programme for newborn screening for Fabry disease in 171977 infants. They found an incidence of Fabry disease of approximately 1 in 1250 males, of whom 86% carried mutations associated with a later-onset phenotype [6]. Underdiagnosed atypical phenotypes and mutations with limited alpha-Gal A activity might indicate that the actual incidence could be higher.

Measuring alpha-Gal A enzyme activity in plasma, leucocytes, cultured skin fibroblasts, biopsied tissue or a dried blood spot is a diagnostic tool in men. In contrast, women with Fabry disease may have enzyme activity levels within the normal range, as a result of

Abbreviations

ARB	=	angiotensin receptors blocker
CNS	=	central nervous system
ERT	=	enzyme replacement therapy
FOS	=	Fabry Outcome Survey
Gb3	=	globotriaosylceramide
GFR	=	glomerular filtration rate
alpha-Gal A	=	hydrolase alpha-galactosidase A
MRI	=	magnetic resonance imaging
PNS	=	peripheral nervous system
SFN	=	small fibre neuropathy
TIAs	=	transient ischaemic attacks

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random X chromosome inactivation [7]. Molecular genetic testing is thus the most reliable method to establish the diagnosis in females who are symptomatic or carriers. Prenatal testing is possible by means of DNA testing using chorionic villus sampling (at 9–10 weeks) or cultured amniotic cells (amniocentesis at approximately 15 weeks) [8].

Fabry disease is a multisystemic disorder, and signs and symptoms may appear in childhood and adolescence. Among the earliest and most important organ manifestations are those in the nervous system. The focus of this article is, therefore, to review the neurological manifestations and to enhance awareness of this entity. We reviewed the current literature using a MedLine search and congress abstracts.

Clinical manifestation

Neurological involvement

The sphingolipid deposition can affect the entire peripheral (PNS) and central (CNS) nervous systems involving small and large cerebral vessels, neurons, ganglia, nerve sheaths and perineurium.

Involvement of the peripheral nervous system

Small fibre neuropathy (SFN) is the main manifestation of Fabry disease in the PNS [9]. The pathophysiology of SFN is not fully understood. Gb3 accumulation has been demonstrated in dermal vascular endothelial and perineural cells of thin myelinated Aδ and unmyelinated C fibres involved in mediating pain and temperature misperception [10–13]. Electron microscopy of skin biopsies revealed a decreased density of Aδ and C fibres [13]. With progression of the disease, large fibre involvement and nerve conduction abnormalities may develop [14]. Patients with SFN present with somatosensory discomfort and neuropathic pain as prominent manifestations. Typically, burning pain dysaesthesia, and paraesthesia, defined as acroparaesthesia, of the hands and feet occur. They may present as recurrent painful episodic crises triggered by stress, fever, heat, fatigue or exercise [15, 16]. The duration may vary from a few minutes up to several days and extreme pain attacks known as "Fabry crises" may be accompanied by fever, joint pain and elevated erythrocyte sedimentation rate, and may require hospitalisation [17]. During a crisis, the distal extremities may be livid and swollen. Neuropathic pain with acroparaesthesia is often the earliest manifestation of Fabry disease reported by patients. Pain has been reported as early as 3 years of age in boys and 6 years in girls [18]; mean age at onset is 14.8 years in men, 19.8 years in women [19] (table 1). The Fabry Outcome Survey (FOS) reports a high frequency of neuropathic pain in Fabry disease (76% men, 64% women) [3, 20]. Intolerance of cold and warmth is another manifestation of SNF. Quantitative sensory testing may show increased or unmeasurable thermal and, specifically, cold detection thresholds, as well as increased vibration detection thresholds [12, 21]. Up to 63–100% of men and 16–33% of women have impaired sensory perception [3, 9, 22, 23].

Table 1: Natural course of neurological involvement in Fabry disease (age in years, mean ± SD).

	Men	Women	Ref.
Strokes	39.8 ± 11.9	45.7 ± 14.8	[20]
Small fibre neuropathy/ neuropathic pain	14.8 ± 1.0	19.8 ± 1.4	[19]

Hypohidrosis, reduced saliva and tear production, impaired pupillary constriction, heart conduction defects, sexual dysfunctions such as priapism, and gastrointestinal disturbances may be signs and symptoms of peripheral autonomic dysfunction in Fabry disease [3, 24, 25].

Involvement of the central nervous system

Diffuse glycosphingolipid deposits in endothelial cells of small and large vessels and vascular smooth muscle cells may result in stenosis and occlusion as well as vasodilatation and, hence, lead to impaired cerebral perfusion [3, 26–29]. The vertebrobasilar territory is preferentially affected and increased basilar artery diameter has been shown to be a sensitive indicator of Fabry disease [30]. The higher frequency of ischaemic lesions in this area, furthermore, explains the typical CNS manifestations of vertigo, anopsia, diplopia, nystagmus, dysarthria, hemiparesis, hemiataxia, and gait ataxia [26].

The mechanism linking glycosphingolipid accumulation to ischaemic tissue damage is not fully understood. Endothelial dysfunction, vessel wall irregularities leading to compromised cerebral blood flow velocities and cerebral autoregulation, and immunological and cellular changes leading to, among others, a prothrombotic state probably contribute to cerebral ischaemia [26–29, 31, 32]. Fabry disease predisposes to valvular heart disease and arrhythmia, and kidney disease, cardiogenic embolism and hypertension could also be contributory factors.

Data from FOS revealed that 13.2% (15.1% men, 11.5% women) of Fabry patients developed an ischaemic stroke or transient ischaemic attacks (TIA), and that cerebrovascular events typically occur at an earlier age

in Fabry patients than in the general population [20]. Median age of first stroke in men was 39.8 years and in women 45.7 years (table 1). The observed number of ischaemic strokes in men aged between 25 and 44 years was about 12 times higher than expected in a comparable general population [20, 33]. Most Fabry patients did not experience hypertension and atherosclerotic plaques before their first stroke. Approximately 50% of men and 38.5% of women experienced their first stroke before renal or cardiac events and diagnosis of Fabry disease [3, 34–36]. In a recent meta-analysis of nine studies, the prevalence of Fabry disease ranged from 0.6 to 11.1% among patients with cryptogenic strokes and from 0.4 to 3.5% in all stroke aetiologies [37].

Development of neuropsychiatric symptoms such as depression and memory deficits are frequently observed in Fabry disease patients. Unlike the general population, men with Fabry disease report a higher prevalence of severe depression than women (36% men; 22% women) [38]. The mechanism is unclear and, besides a primary origin, a secondary cause due to the persistence of neuropathic pain has been discussed [38]. A large proportion of patients with Fabry disease also report progressive hearing impairment, tinnitus and dizziness and/or vertigo, presumably due to the involvement of central and peripheral vestibulocochlear system [39, 40].

Neuro-imaging

Nonspecific white and grey matter lesions, as well as vascular abnormalities, are often seen in brain magnetic resonance imaging (MRI). The most common structural abnormalities are found in the deep white matter, mostly in the posterior periventricular and centrum semi-ovale region [32, 41], and occur at a comparable frequency in male and female patients [33]. It is hypothesised that glycosphingolipid deposition leads to increased interstitial pressure in deep white matter and to metabolic alterations resulting in gliosis, demyelination and increased interstitial water content [42]. Calcification in the pulvinar and posterior thalamic regions, on the other hand, has been shown to result from cerebral hyperperfusion [43, 44]. Calcification of the pulvinar, best seen in T1-weighted MRI (fig. 1), represents a characteristic, although not pathognomonic, neuroradiological feature of Fabry disease. Additional structures to be involved by dystrophic calcification are the dentate nucleus and basal ganglia [43]. Dolichoectasia (fig. 2) is detectable with MRI and magnetic resonance angiography. A vessel diameter exceeding 3.2 mm for the basilar artery is able to distinguish between Fabry disease patients and normal controls with a sensitivity of 87% and specificity of 86% $p < 0.001$ [45]. With the relative risk of stroke elevated by 12.2 for men and 4.2 for women in the 35 to 45 year age category, strokes with either lacunar infarcts (fig. 3) or territorial infarction are usually the first serious complication seen in Fabry disease patients [35, 36].

Other organ involvement (fig. 4)

Kidney involvement is reported in about 50% of patients. Kidney lesions result from deposition of Gb3 and other sphingolipids in the podocytes, mesangial

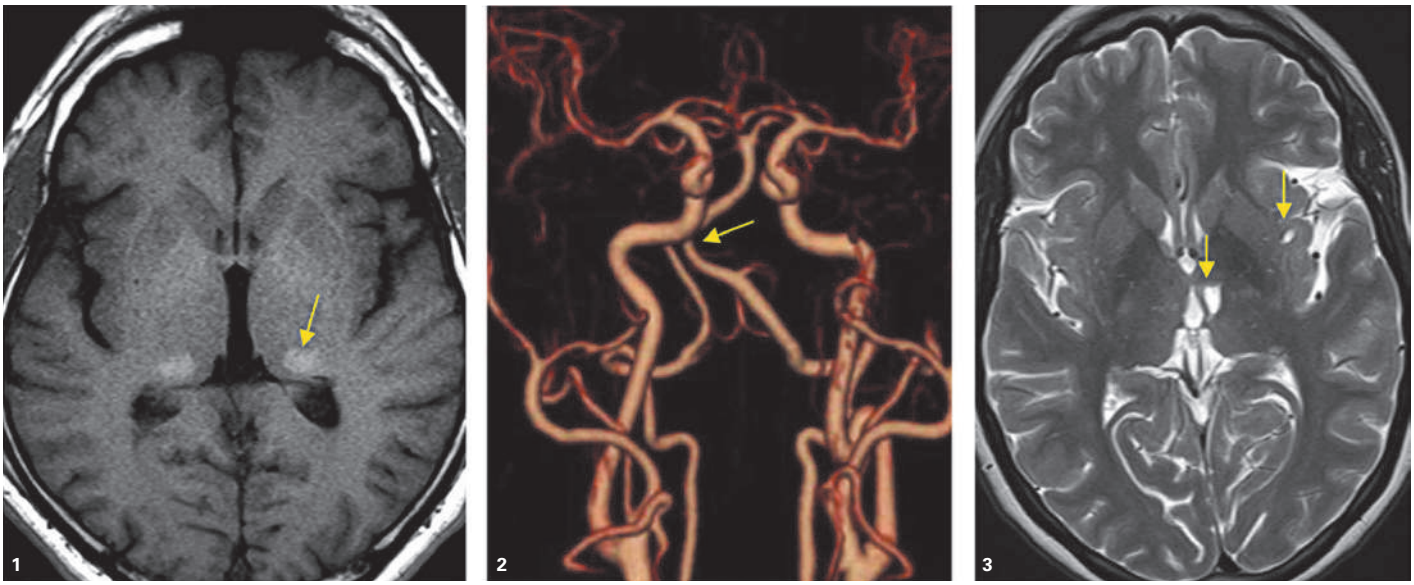

Figure 1, 2: T1 magnetic resonance image (fig. 1) of a 33-year-old male with typical hyperintense pulvinar sign indicating hyperperfusion-induced dystrophic calcification and magnetic resonance angiography (fig. 2) with mild elongation and dolichoectasia of the basilar artery (diameter 3.8 mm).
Figure 3: Axial T2w magnetic resonance image of a 38-year-old female with left thalamic and subinsular infarctions.

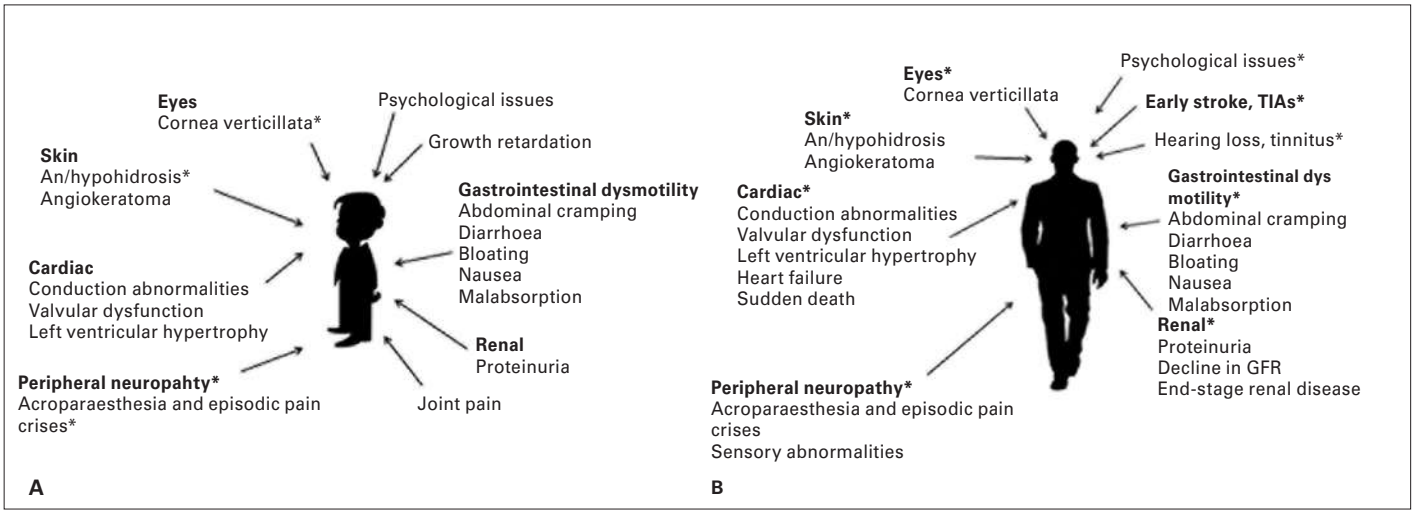

Figure 4: Multi-organ involvement in children **(A)** and adults **(B)** [174, 175]. * Frequent manifestations.
GFR = glomerular filtration rate; TIA = transient ischaemic attack

and glomerular endothelial cells, tubular cells, vessels and interstitial cells. It results in cellular changes, typically in prominently vacuolated podocytes and tubular cells by light microscopy (fig. 5A). Electron microscopy reveals lysosomal inclusions with lamellated structure, called myelin or zebra bodies (fig. 5B). There may be peritubular capillary inclusions, vascular intimal and medial inclusions and vascular smooth muscle cell hypertrophy in the kidneys. Vasculopathy has also been observed, probably due to local upregulation of the renin-angiotensin system [46]. Glomerular sclerosis and tubulointerstitial fibrosis are the histological features that best correlate with progression of kidney disease in humans with Fabry disease [47]. Kidney impairment often begins with microalbuminuria and proteinuria in the second to third decade of life [8, 10]. Disease-related tubular and glomerular alterations lead to proteinuria and loss of glomerular filtration rate, resulting in chronic kidney disease. It should be noted that glomerular compensation (hyperfiltration) can mask impairment of kidney function for years. For this reason, gradual deterioration of kidney function usually becomes apparent in the third to fifth decades of life. At this stage, fibrosis, sclerosis and tubular atrophy dominate the disease activity. By the age of 40 years, end-stage renal disease has usually been reached [36, 48].

Cardiac involvement is common, affecting more than 50% of all Fabry patients [49, 50]. It may affect all cardiac structures. Intracellular accumulation of Gb3 occurs within myocytes, valves and vascular endothelium of the heart [51]. Interstitial remodelling, due to intracellular lysosomal storage of Gb3 and an increase of trophic factor such as lyso-Gb3, is an important feature of Fabry cardiomyopathy [51]. In most Fabry patients with cardiomyopathy, concentric left ventricular hypertrophy without left ventricle outflow tract obstruction and normal left ventricular systolic

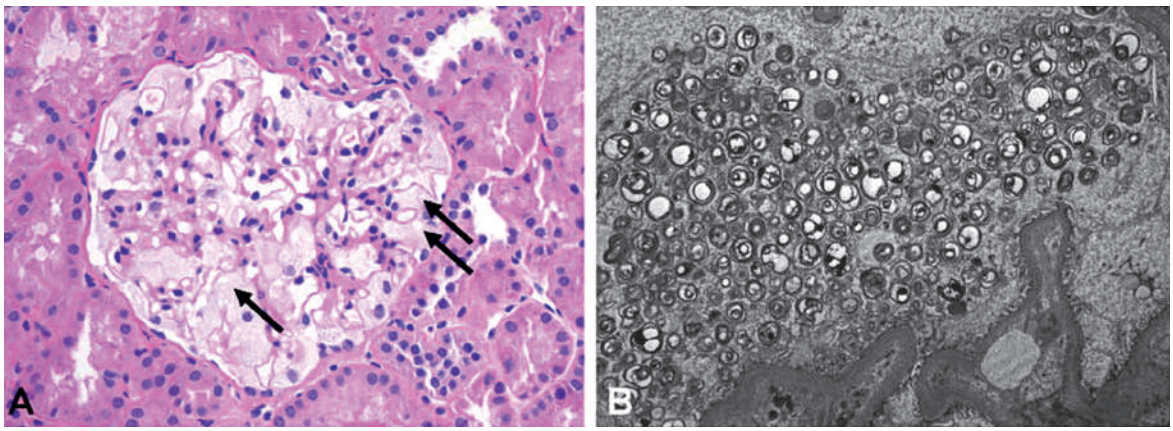

Figure 5: Histological findings in a kidney biopsy: **(A)** Glomerulus with prominent, vacuolated podocytes (arrows) (H&E, ×200). **(B)** Lysosomal inclusions with lamellated structure – myeloid or zebra bodies in podocytes (TEM, ×2800).

function is found [36, 52]. Other findings in Fabry cardiomyopathy are prominent papillary muscles and early stages of diastolic dysfunction. Few Fabry patients exhibit mild aortic, mitral and tricuspid insufficiency, especially in end-stage cardiomyopathy [50, 52]. End-stage Fabry cardiomyopathy is characterised by intramural fibrosis, detectable by late gadolinium-enhanced MRI [53] and echocardiography [51]. This fibrosis leads to wall motion abnormalities and arrhythmias [51, 54].

Glycosphingolipid deposition in intestinal ganglia and small vessels causes *gastrointestinal dysmotility*: episodic diarrhoea, nausea, vomiting, bloating, cramping abdominal pain and/or malabsorption. The median age of onset for these symptoms is before 15 years and, overall, 50% of patients with Fabry disease complain about gastrointestinal symptoms [55].

Skin involvement with angiokeratomas, clusters of individual punctate (fig. 6) or scattered (fig. 7) dark red to blue-black angiectases, is a hallmark of Fabry disease [56]. These benign tumors, characterised by ectasia of blood vessels in the papillary dermis and possibly associated with acanthosis and hyperkeratosis of the epidermis, are commonly localised on the lower trunk, palms, around the mouth and umbilicus. They are observed in 40–60% of patients and may appear already during childhood [57]. Hypo/anhidrosis, rarely hyperhidrosis, occurs in Fabry disease [58].

Cornea verticillata is a typical *ophthalmological* manifestation with bilateral keratopathy occuring in over 70% patients (fig. 8). It is identifiable during slit-lamp examination as whirl-like white-to-golden-brown opacities extending from centre to periphery of the cornea and corresponds to glycosphingolipid accumulation in the basal epithelium of the cornea [59]. Two types of lenticular changes may also be present in Fabry disease: anterior capsular or subcapsular cataract, and radial posterior subcapsular cataract [60]. Posterior subcapsular cataract is rare and specific for Fabry disease, and hence called "Fabry cataract". Other possible ocular abnormalities are retinal and conjunctival vessel tortuosity [60].

Lung involvement with mild to severe airway obstruction, manifesting as chronic bronchitis, wheezing or dyspnoea, is present in 25% of women and up to 60% of men [61].

Although Fabry disease may present in childhood or puberty, given the rarity of this disease and the nonspecific presenting symptoms, the disease is often not even considered by clinicians. As a consequence, diagnosis of this deadly disease is delayed in a majority of affected patients until the underlying pathology is already advanced [36, 62].

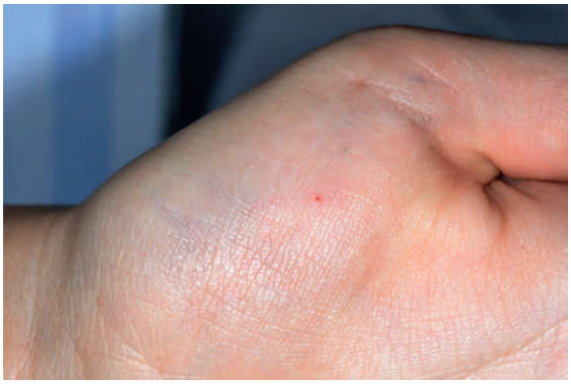

Figure 6: Angiokeratomas.

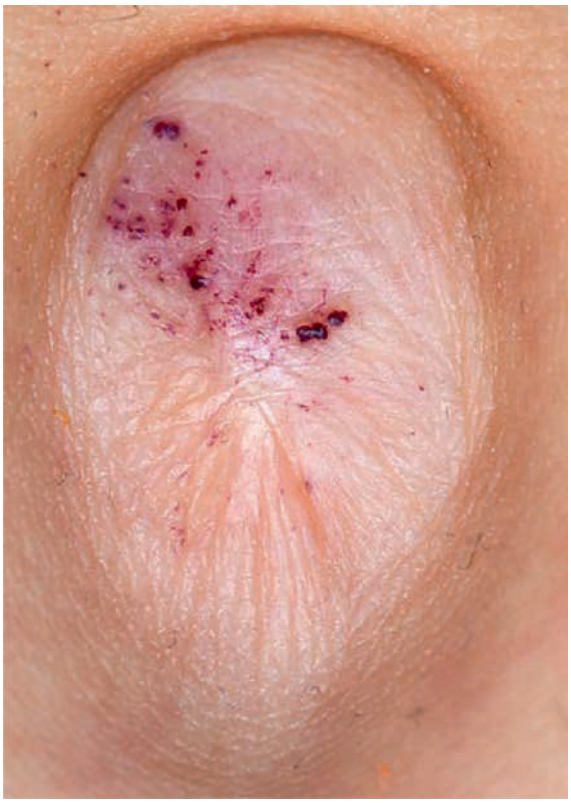

Figure 7: Angiokeratoma in the navel.

Management

Treatment of patients with Fabry disease primarily focuses upon substitution of alpha-Gal A enzyme.

Enzyme replacement therapy (ERT) with alpha-Gal A has been used to treat Fabry disease in Europe since 2001 and in the USA since 2003. Recombinant human alpha-Gal A is available in two forms: agalsidase-alfa (Replagal®, Shire HGT) and agalsidase-beta (Fabrazyme®, Genzyme Corp.). Both proteins have the same amino acid sequence as the native human enzyme. They differ in glycosylation pattern. Agalsidase-alfa

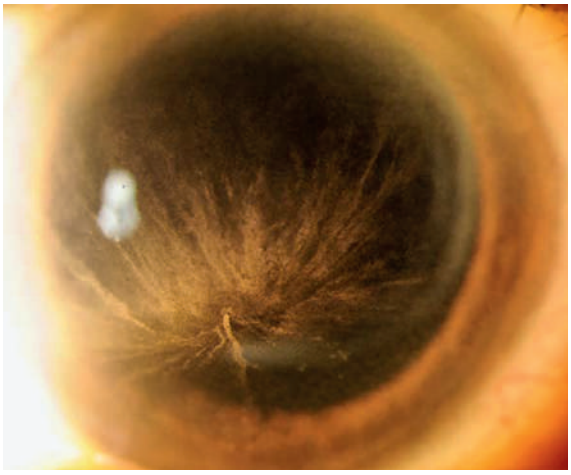

Figure 8: Cornea verticillata.
Courtesy Dr. R. Kovacs, Ophthalmology Department, University Hospital Zürich.

is purified from a stable transfected line of cultured human skin fibroblasts and is infused at a dose of 0.2 mg/kg every 2 weeks [63]. Agalsidase-beta is produced by expression of human alpha-Gal A DNA in Chinese hamster ovary cells and is infused at a dose of 1.0 mg/kg every 2 weeks [64]. The use of a lower maintenance dose of agalsidase-beta, 0.3 mg/kg, has been evaluated and has been shown to maintain Gb3 clearance in some, but not in all patients. Long-term clinical effects of this lower dose of agalsidase-beta, however, have not been evaluated. Common side effects with ERT include infusion reactions and seroconversion (i.e., development of antibodies to either agalsidase-alfa or agalsidase-beta) [65, 66]. Studies suggest that there are no significant differences between the two forms in terms of efficacy and safety profiles [67].

Neurological symptoms ameliorate with ERT. Significant improvement of small nerve fibre function has been shown, resulting in decreased pain and consequently less analgesic consumption [16, 65, 68, 69]. Improvement in intradermal vibration and temperature perception thresholds is reported [70]. Intraepidermal innervation density does not increase, suggesting that epidermal nerve fibres do not regenerate during ERT treatment. A hypothesis is that structural damage to small fibres is irreversible, whereas function of remaining fibres may improve on ERT.

CNS studies have demonstrated significant functional vascular changes under ERT treatment, with a tendency to normalisation of cerebral vessel autoregulation and regional perfusion [32, 71]. However, effects of ERT on white matter lesions or incidence of cerebrovascular events have not yet been demonstrated [67, 68, 72]. Studies have reported recurrence of strokes despite long-term ERT [73, 74]. The explanation may be the inability of ERT to pass the blood-brain barrier [75].

ERT leads to decreased left ventricular mass, heart rate variability and Gb3 in cardiac endothelium, as well as improved left ventricular function [76, 77]. It has been shown to stabilise kidney function and to reduce proteinuria [74, 78–80].

Although there is, to date, no consensus on treatment initiation, studies have shown that ERT reverses Gb3 accumulation in cells and tissues particularly when started at an earlier stage of the disease, whereas advanced disease stages such as advanced nephropathy and myocardial fibrosis do not respond to ERT [65, 72, 78]. Furthermore, ERT does not cure Fabry disease and adjunctive conventional medical treatment and therapy may be required. Symptomatic neuropathic pain management includes acetaminophen (paracetamol), gabapentin, carbamazepine and lamotrigine as well as tricyclic antidepressants such as amitriptyline. Opioids should be used carefully in Fabry disease patients, in particular those with gastrointestinal motility disorders; nonsteroidal inflammatory drugs are not recommended because of their nephrotoxicity. Additional measures include lifestyle changes with avoidance of stimuli such as stress, intense physical exertion and extreme temperature changes. Prophylactic therapy is particularly important in stroke prevention. It could include the use of antiplatelet agents (i.e., aspirin, clopidogrel, or a combination of aspirin with dipyridamole), antihypertensive agents and statins. It is important to note, however, that the efficacy of antiplatelet and anticoagulant therapy has not been proven at the present time. Avoidance of smoking, obesity, dyslipidaemia and arterial hypertension is likely to reduce the risk of stroke as in the general population. They also prevent heart failure and pulmonary symptoms. Angiotensin converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in reducing proteinuria and controlling hypertension [80]. Patients may require renal replacement therapy, such as dialysis or kidney transplantation. Diuretics, ACE inhibitors, ARBs, beta-blockers, and implantable cardiac devices need to be considered in patients with cardiovascular involvement. Heart transplantation may be necessary in cases of advanced congestive heart failure.

Ongoing trials are investigating novel approaches such as chaperone therapy [81], gene therapy [82] and substrate reduction therapy [83]. Further evaluations and pharmacological studies are needed as efficacy and safety in humans need to be demonstrated.

Table 2: Common misdiagnoses of Fabry disease (not an exhaustive list).

Fabry disease symptoms	May be diagnosed as	
Diarrhoea and abdominal pain	Gluten/lactose intolerance, noninflammatory bowel diseases	[84]
Acute pain in extremities	Erythromelalgia, "growing pains"	[85, 86]
Angiokeratomas	Lupus, petechiae, Osler disease	[3, 87]
Elevated erythrocyte sedimentation rate	Juvenile or rheumatoid arthritis, rheumatic disorders, fibromyalgia, rheumatic fever	[87]
Joint pain	Juvenile or rheumatoid arthritis, rheumatic disorders	[87]
Stroke-like events in brainstem structures	Multiple sclerosis	[88–90]

Conclusions

Fabry disease is a rare multisystemic genetic disorder characterised by progressive accumulation of glycosphingolipids in tissues, leading to ischaemia and irreversible vital organ damage. Neurological involvement by Fabry disease, presenting at the end of the first decade of life or during puberty, is comparable in men and women and is one of the most frequent and earliest manifestations of Fabry disease reported by patients. Neurological involvement is also one of the earliest, potentially life-threatening, complications of Fabry disease with an average age of onset for cerebrovascular ischaemia and premature stroke around 35–40 years.

Because of its variable nonspecific symptoms, diagnosis of Fabry disease is challenging. Misdiagnoses, especially with rheumatic disorders and neurological disease, are frequent (table 2) and the delay between first symptoms and diagnosis could reach 10–15 years. Adequate care management and treatment are promising to slow or even reverse disease manifestation. However, organ damage is usually irreversible if treatment is started too late, underscoring the importance of early recognition of this devastating disease.

Among patients enrolled in FOS – the Fabry Outcome Survey – the medical specialists who most often establish the diagnosis of Fabry disease were nephrologists followed by dermatologists and paediatricians; fewer cases are diagnosed by neurologists [3]. The earlier the diagnosis is suspected and confirmed and the earlier treatment, including ERT, is initiated, the more effective is the therapy.

Recognition of early neurological symptoms, in particular unexplained peripheral neuropathic pain typically in the hands and feet, and considering Fabry disease in the case of unexplained stroke in young patients is important.

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To avoid misdiagnosis and to start treatment early, young patients with unexplained stroke should be evaluated for presence of other systemic problems in their personal medical and family history such as (i) gastrointestinal disturbance, (ii) recurrent tingling or burning in hands or feet, (iii) pain crises of pain possibly accompanied by fever remaining of unexplained origin, (iv) trouble sweating, (v) difficulties to tolerate heat or cold, and (vi) a family history of kidney/cardiac failure, ischaemic attack or stroke and early death. A complete physical examination should be performed to look for angiokeratomas, reddish-purple spots particularly in the bathing trunk area. Neurological examination should focus on sensations mediated by peripheral small fibres, such as cold, heat, light touch, pressure and vibration perception testing. Proteinuria has to be sought (table 3).

Table 3: Signs and symptoms suggestive of Fabry disease.

Personal medical history
Gastrointestinal disturbance
Acroparaesthesia, burning pain in hands or feet
Neuropathic pain of unknown cause
Trouble sweating
Vertigo, dizziness
Heat/cold intolerance
Transient ischaemic attacks
Stroke
Family history
Kidney disease
Cardiac disease
Transient ischaemic attacks
Stroke
Early death
Physical examination
Angiokeratomas
Cold, heat and vibration perception testing
Laboratory examination
Proteinuria

In conclusion, Fabry disease requires a multidisciplinary approach, including neurologists, nephrologists, cardiologists, dermatologists, gastroenterologists, geneticists, pathologists and clinical pharmacologists. Neurologists play a key role in the early diagnosis of this deadly disease and may be the first clinicians to identify Fabry disease.

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The full list of references is included in the online version of the article on www.sanp.ch.

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