REVIEW ARTICLE

Fabry Disease—Often Seen, Rarely Diagnosed

Björn Hoffmann, Ertan Mayatepek

SUMMARY

Background: Data obtained from screened newborns and from persons at known risk for Fabry disease suggest that this condition is much more common in Germany than previously assumed. Its clinical manifestations are very diverse, and its differential diagnosis is correspondingly broad. Thus, there is often a delay before the diagnosis of Fabry disease is established.

Methods: Selective literature search with special attention to studies of large groups of patients with respect to clinical manifestations, diagnostic evaluation, and treatment.

Results: The number of patients carrying the diagnosis of Fabry disease in Germany lies far below what would be expected from published prevalence figures from other countries. Angiokeratoma, acroparesthesia, hypertrophic cardiomyopathy, impaired sweating and corneal opacification (cornea verticillata) are typical manifestations of Fabry disease; many patients also have other, nonspecific complaints, such as gastrointestinal disturbances. It has been clearly shown that women can manifest the entire range of clinical manifestations. Studies involving large groups of patients have improved our understanding of hearing impairment and tinnitus in Fabry disease. Therapeutic trials are currently in progress to determine whether enzyme substitution can delay the occurrence of life-threatening sequelae such as progressive renal failure and cerebrovascular events.

Conclusions: Fabry disease is still underdiagnosed. The average delay from the onset of symptoms to diagnosis is more than a decade. Treatment with human alpha-galactosidase A produced with genetic technology can improve most of the disease's manifestations.

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Key words: lysosomal storage disease, Fabry disease, enzyme substitution, molecular medicine, diagnosis

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Lysosomes are membrane bound organelles that contain 50 to 60 acid hydrolases and constitute a kind of cellular digestive tract. If one of these enzymes is missing, the lysosomal metabolism is interrupted and certain metabolites accumulate. Diseases that are due to a lysosomal enzyme deficiency are known as lysosomal storage diseases. Since lysosomes are present in most cells in the body, storage diseases manifest as multisystem pathologies.

One of the storage diseases is Fabry disease, which is due to X-linked, inherited alpha-galactosidase A deficiency (e1). As a result of the enzyme deficiency, the sphingolipid globotriaosylceramide (Gb3) accumulates in the lysosomes. Fabry disease is still regarded as a rare disease. However, studies of risk groups and prospective data collections from neonatal screening imply a much higher prevalence than hitherto assumed *(Table 1)*. The reasons for the substantial variations in the prevalence rates are complex. The clinical course of Fabry disease is heterogeneous and variable, especially in women. The range of possible differential diagnoses is broad and may touch many medical subspecialties *(Table 2)*. The risk of a delayed or incorrect diagnosis is correspondingly high. The time period from symptom onset to the correct diagnosis is long: 13 years in men and 17 years in women (e7).

This review article shows the clinical diversity of Fabry disease and draws attention to this underdiagnosed and often forgotten pathology. A diagnostic algorithm is presented, as is an overview of therapeutic options.

We conducted a selective literature review, which took into account especially recent studies that describe results from larger patient cohorts or present completely new aspects of pathophysiology, clinical presentation, or treatment.

Clinical picture

The *Box* shows an overview of the range of possible complaints.

Skin

In children, the classic angiokeratoma *(Figure 1)* is found in only about 30% of those younger than 16. In adults, however, the pinhead sized, mostly singly positioned, reddish-brownish efflorescences (2) are seen in two thirds of male patients and more than a third of female patients. The diagnosis is, however, rarely made by a dermatologist (2). Typical locations are the fingertips, the bathing trunk area, the buttocks, and the periumbilical area, but angiokeratoma can also occur on the mucosa—for example, in the gastrointestinal tract (e8). Further

TABLE 1

Prevalence rates of Fabry disease in different populations, 1999–2007

Method	Incidence	Source
Retrospective analysis of diagnosed cases versus numbers of births	1 : 117 000	Meikle et al. 1999 (e2)
Retrospective analysis of known causes of renal replacement therapy using dialysis	~1 : 16 000	Thadhani et al. 2002 (e3)
Secondary screening of patients having renal replacement therapy using dialysis	2 : 1000	Ichinose et al. 2005 (e4)
Secondary screening of patients having renal replacement therapy using dialysis	1.6 : 1000	Kotanko et al. 2004 (e5)
Secondary screening of patients with cryptogenic stroke	5 : 100 (Men) 2.4 : 100 (Women)	Rolfs et al. 2005 (17)
Primary neonatal screening	1 : 3100 (Men)	Spada et al. 2006 (1)
Secondary screening of patients with hypertrophic cardiomyopathy	1.8 : 100 (Men) 5 : 100 (Women)	Monserrat et al. 2007 (e6)

skin manifestations are teleangiectasias, lymphedema, and sweating disturbances. In most cases, hypohidrosis is present (in 53% of men and 28% of women); more rarely, hyperhidrosis or anhidrosis (total absence of sweat secretion) (2). Another indication of Fabry disease may be intolerance to rising environmental temperatures.

The cause is apparently impaired sympathetic innervation of the skin, as well as dysfunction of the sweat glands from deposition of storage material. The development of lymphedema is accompanied by obliteration, vascular ectasias, and/or increased permeability of the lymphatic vessels (e10, e12).

Pain

Male patients tend to experience acute, mostly burning, pain from the 14th year of life, and women from the age of 19 (3). Altogether, more than 70% of patients experience pain (3). In addition to the usual acroparesthesias, any region of the body may be affected. Some 15% to 30% of patients complain about neck pain and headache, and it is not always possible to distinguish such headaches from migraine or cluster headaches because imaging methods usually do not help to explain the pain. Physical activity, rising environmental or body temperatures, and concomitant illnesses may trigger pain crises. Foods such as coffee, meat, and alcohol may trigger pain, as can psychological stress. Not only acute pain, but also chronic neuropathic pain may develop.

The pain and disrupted sensation of vibration and temperature are due to stored sphingolipids in the dermal axons, which are mainly located in the thin myelinated A-δ fibers (e13).

Gastrointestinal symptoms

More than 50% of patients report gastrointestinal symptoms (4). Up to 50% of patients with Fabry disease complain of abdominal pain. The average age at which these symptoms manifest is 14 (4), which is also the age at which acroparesthesias set in (3). Both forms of pain manifestation are accompanied by the same histological changes to the neurons. Patients usually report switches from diarrhea to constipation, which may mimic irritable bowel syndrome (e14). No inflammatory changes are present; the symptoms are due to intestinal neuropathy with storage material on the smooth muscle cells, endothelial cells, and ganglial cells (e8). Meissner's plexuses are vacuolized (e15). The result may be an early sensation of satiety and delayed intestinal passage (e8, e15, e16).

Eyes

Corneal opacities (corneal verticillata) have been described as almost pathognomonic for Fabry disease. As a rule, these changes do not lead to impaired vision (e17, e18). They occur in 75% of women and up to 90% of men with Fabry disease (5, e18). Corresponding corneal changes can be seen prenatally (e19) and are usually easy to detect in the ophthalmological examination using a slit lamp. In addition to treatment with amiodarone, Fabry disease is the most common cause of this form of corneal opacity (e20), and taking a simple medication history often helps clarify the cause.

Independently of corneal changes, up to 75% of men and 20% of women with Fabry disease develop tortuous retinal vessels (tortuositas vasorum) (5, e18). Corresponding changes have even been observed in infants and apparently become more frequent with age (5). Rarer ophthalmological symptoms include uveitis (e21, e22), closure of the central artery (e23), and aneurysmatic vessels in the conjunctiva (e18, e24).

Ears

Sensorineural hearing loss seems to be the most important ear manifestation of Fabry disease. Prevalence rates of acute hearing loss in Fabry disease, which develops within a few hours to days and is initially often reversible, range from 5% to 30% (6, 7, e25). Acute hearing loss is thus 60 times more common in Fabry disease than in the normal population; it affects twice as many men as women (7). Most patients experience slowly progressive hearing loss that permanently affects both ears and all frequencies (6, 7, e28). Onset of hearing loss is in the second decade of life in men and in the fourth decade in

TABLE 2

Range of possible differential diagnoses

Organ (system)	Symptoms of Fabry disease	Possible differential diagnoses and/or misdiagnoses
Skin	Angiokeratoma	Fucosidosis, sialidosis, N-acetylgalactosamine deficiency, acral pseudolymphomatous angiokeratoma of childhood
	Hypohidrosis/anhidrosis	Horner syndrome, therapy with topiramate, acetylcholine intoxication, ectodermal dysplasia
	Hyperhidrosis	Primary hyperhidrosis
	Lymphedema	Chronic venous insufficiency, rheumatic disorders
Peripheral nervous system	(Neuropathic) pain	Rheumatic disorders, fibromyalgia, (cluster) headache, migraine, diabetic neuropathy, recurrent fever syndromes (for example, TRAPS), porphyria, uremic neuropathy, Guillain-Barré syndrome, hereditary neuropathy
Gastrointestinal tract	Abdominal pain, diarrhea, constipation, delayed intestinal passage	Gastritis, duodenal ulcer, celiac disease, gastrointestinal hemorrhage, Crohn's disease, ulcerative colitis, diverticulitis, functional dyspepsia, irritable bowel syndrome, familial Mediterranean fever
Eyes	Cornea verticillata	Therapy with amiodarone, flecainide, tamoxifen; fucosidosis
	Tortuositas vasorum	Diabetes mellitus, arterial hypertension, nephrotic syndrome, neurofibromatosis type 1, fibromuscular dysplasia, Rendu-Osler-Weber disease, velocardiofascial syndrome
	Uveitis	Rheumatic disorders (for example, juvenile idiopathic arthritis, ankylosing spondylitis), tubulointerstitial nephritis and uveitis syndrome (TINU), Behçet's disease, sarcoidosis, Crohn's disease
	Conjunctival aneurysms	Kawasaki syndrom, Diabetes mellitus
Ears	Acute/chronic hearing loss	Apoplexy, multiple sclerosis, leopard syndrome
	Tinnitus	Otosclerosis, borreliosis, sudden deafness, Menière's disease, acoustic neurinoma
	Dizziness	Benign paroxysmal positional vertigo, Menière's disease, vestibular neuritis, cerebellar/brain stem infarction
Heart	Angina pectoris, myocardial infarction	Atherosclerosis
	Palpitations	Atrial fibrillation, Wolf-Parkinson-White syndrome, hyperthyroidism, drug induced palpitations
	Cardiomyopathy	Mitochondriopathies, Long QT syndrome, myocarditis, Pompe disease, Neimann-Pick disease, hemochromatosis, Duchenne/Becker muscular dystrophy, neurofibromatosis type 1, systemic Lupus erythematodes, rheumatoid arthritis, dermatomyositis
	Valvular disorders	Endocarditis, rheumatic disorders, mucopolysaccharidoses
	Impaired variability of cardiac frequency	Arterial hypertension, mitral valve prolapse, diabetes mellitus, Sjögren syndrome, MELAS syndrome, obstructive sleep apnea
Kidneys	Proteinuria/progressive renal failure	Diabetes mellitus, arterial hypertension, glomerulonephritis, systemic lupus erythematodes, hemolytic-uremic syndrome, gout, amyloidosis, diabetes mellitus, Schönlein-Henoch nephritis
Central nervous system	TIA, apoplexy, white matter lesions	Atherosclerosis, multiple sclerosis, mitochondriopathies, CADASIL

TRAPS, TNF-receptor-associated periodic fever;
MELAS, mitochondrial encephalopathy, lactic acidosis, stroke-like symptoms;
CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy

BOX

Range of possible manifestations

- Neuropathic pain*1
- Angiokeratoma*1
- Disturbed sweating*1
- Proteinuria, (progressive) renal failure, abdominal pain, diarrhea, constipation
- Tinnitus, hearing loss
- hypertrophic cardiomyopathy, cardiac arrhythmia, myocardial infarction
- Corneal verticillata, Tortuositas vasorum
- TIA, stroke, depression

*1 may be ubiquitous

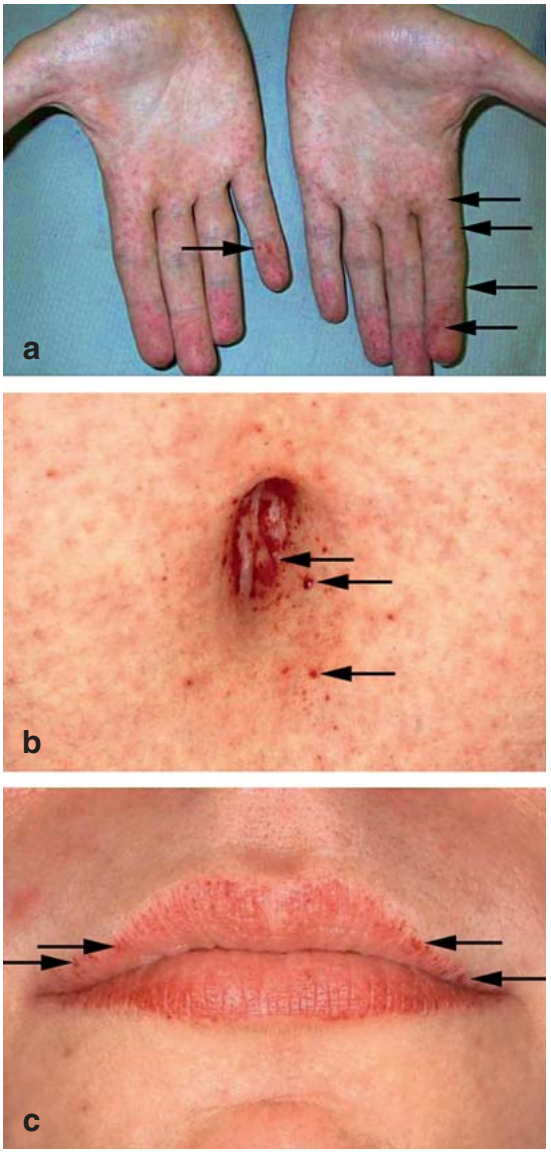


Figure 1: Angiokeratoma a) on the hands; b) periumbilically; c) on the lips, kindly provided by Dr Thomas Jansen, Bochum; reproduced from Beck M: "Fabry disease: clinical manifestations, diagnosis and therapy, 2nd ed. 2007" with permission from Oxford PharmaGenesis Ltd.

women. Hearing loss for higher frequencies develops more rapidly than for the lower frequencies (7). Remarkably, more than a third of patients in whom audiometric tests have shown hearing loss do not report any problems (7). Almost two thirds of women, but only slightly more than 40% of men, with Fabry disease experience tinnitus (6). Independently of the hearing loss or tinnitus, most patients with Fabry disease have damaged auditive functioning of the ear as well as a damaged vestibular organ (8). The most likely cause of the acute hearing loss are microvascular events (8). Chronic hearing loss, however, is usually the result of Gb3 accumulation in the audiovestibular ganglia and vessels of the cochlea and is therefore termed sensorineural (e26).

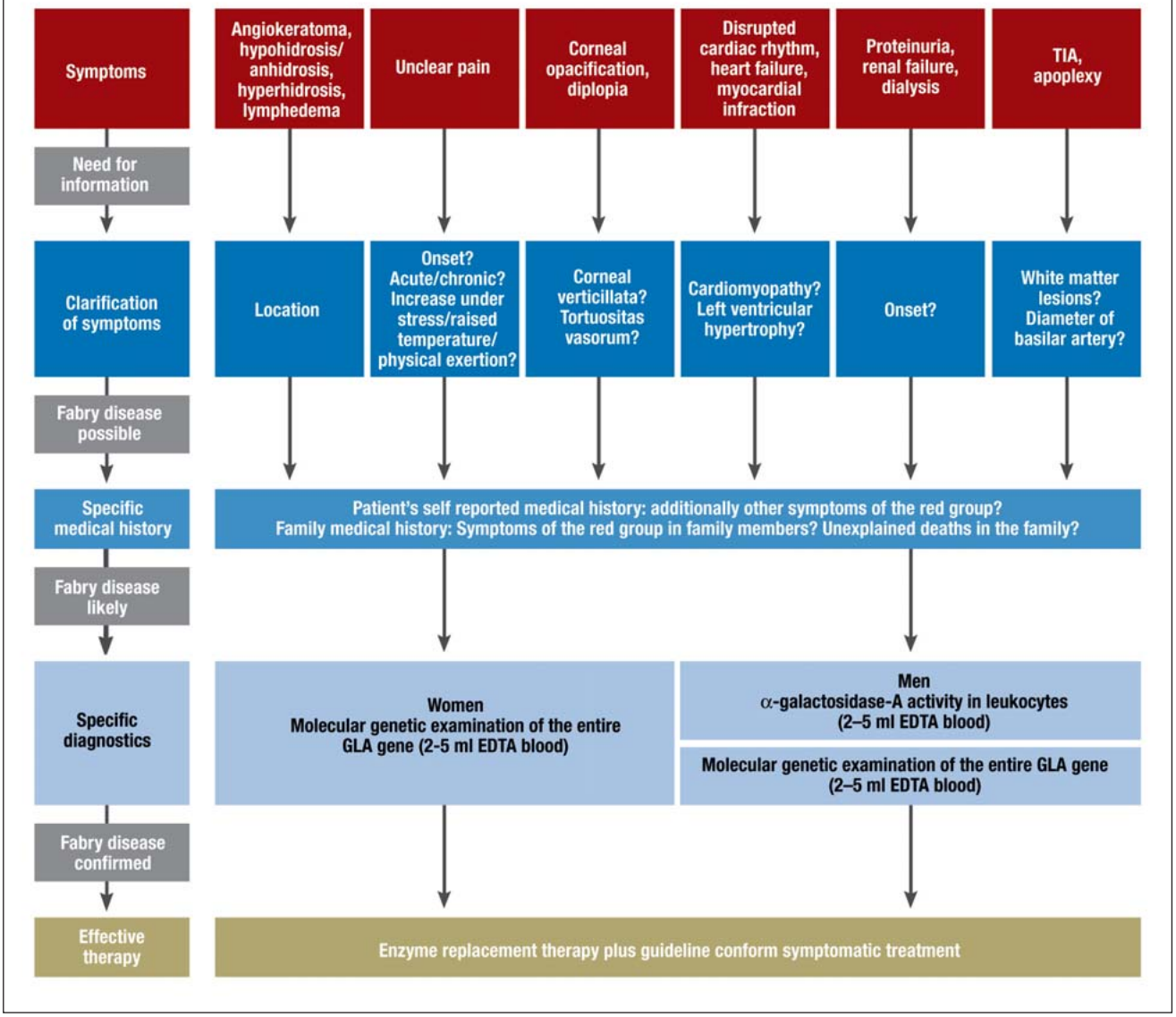
Progressive renal failure, cardiomyopathy, and myocardial infarction, as well as transient ischemic attacks (TIAs) and strokes reduce the survival time for male, untreated patients with Fabry disease to an average of 55 years, for women to 70 years (9).

Cardiovascular system

On average, more than 50% of patients with Fabry disease have cardiac symptoms at the age of 36 (10). Some 33% of women and more than 50% of men with Fabry disease—more with advancing age—who do not receive treatment develop progressive left ventricular hypertrophy (LVH). Conversely, a secondary screening study for left ventricular cardiomyopathy identified Fabry disease in 15 of 508 patients (11). In addition to cardiomyopathy, other cardiac symptoms are common, such as a shortened PR interval, a negative T wave, and a high amplitude. Up to 20% of male and female patients experience cardiac arrhythmias (10, e27); this may also affect children (10). Clinically relevant valvular disorders are present in 15% of patients (12). In spite of the relative frequency of problems associated with angina pectoris, patients with Fabry disease rarely experience myocardial infarctions due to stenosis (e28). Cardiac symptoms do not manifest only in adults but also affect children and adolescents. Manifest left ventricular hypertrophy was found in 7 out of 20 children; the remaining patients had a left ventricular mass above the 75th percentile of healthy children (12). Left ventricular functional disorders can be detected before the myocardium thickens (e29). In childhood, impaired variability of heart frequency may be observed, which is indicative of involvement of the parasympathetic and sympathetic nervous system (12).

Pathophysiologically, storage of Gb3 in myocardial cells, cells of the conduction system (e30), and smaller coronary vessels has been found (e31).

FIGURE 2



Flow chart from (unspecific) symptoms to therapy of Fabry disease

Kidneys

Proteinuria is regarded as the earliest sign of clinically relevant renal involvement in Fabry disease; it is found in 10% of all children younger than 18 years who have Fabry disease. In individual cases, this may occur at the age of 2 years (14). At age 35 it is present in about half of male patients. By age 47, half of all untreated male patients with Fabry disease have developed terminal renal failure. Similar data are also available for female patients (e28), and in individual cases, renal failure develops in adolescence (15). Macroscopic changes to the kidneys are seen in 50% of adults with Fabry disease—for example, as renal cysts—and their prevalence seems to increase with age (e33, e34).The cause of renal failure in Fabry disease is glomerular damage (14, 15). Renal biopsies in children have shown that lipid storage in podocytes and glomerular, interstitial, or vascular changes develop even before clinical renal functional impairment occurs (14).

Central nervous system

The most severe neurological complications in Fabry disease are TIA and (ischemic) stroke. Almost 25% of patients experience a cerebrovascular event over the course of their disease (mean age in men, 34 years; in women, 54 years) (16). Clinical precursors may be hearing loss, dizziness, migraine, and diplopic images. It must be born in mind that not only are patients with

TABLE 3

Positive effects reported for enzyme replacement therapy (ERT) in Fabry's disease

Organ (system)	Symptoms	Effect with enzyme replacement therapy	Study design	Source
Nervous system	Pain	Pain reduction	Double blind, randomized, controlled	23
			Cohort study	3
	Peripheral neuropathy	Improved function of peripheral nerves	Open controlled study	e45
		Improved function of peripheral nerves	Open extension study of a double blind, randomized, controlled trial	e46
	Increased regional blood circulation in the CNS	Reversible	Double blind, randomized, controlled + 12 months open extension study	e47
Gastrointestinal tract	Abdominal pain	Reduction	Cohort study	4
	Diarrhea, constipation	Tendency toward normalization of bowel movement	Cohort study	4
Skin	Sweating	Normalization of sweating	Open extension study of a double blind, randomized, controlled trial	e46
Ear	Hearing impairment, hearing loss	No progression	Open controlled study	8
		Improvement in less severe hearing loss	Double blind, randomized, controlled	19
	Disturbances of equilibrium	Regression	Open controlled study	8
Kidneys	Renal failure	Gb3 storage in glomeruli dissolved	Double blind, randomized, controlled	22
		Creatinine clearance improved; decrease in number of abnormal glomeruli	Double blind, randomized, controlled	23
		Fall in GFR is stopped	Open controlled study	e41
			Cohort study	e42
		Creatinine values fall	Cohort study	25
Heart	Cardiomyopathy	Regression	Double blind, randomized, controlled	20
		No progression	Cohort study	e43
		Regression	Open controlled study	e44
	Disrupted variability of cardiac frequency	Normalization	Open controlled study	21
	Angina pectoris, myocardial infarction	Gb3 storage in endothelial cells dissolved	Double blind, randomized, controlled	22
Quality of life		Improvement	Cohort study	25

Fabry's disease at increased risk of stroke, but that Fabry's disease must be excluded as a possible cause in any patient aged under 55 who suffers a stroke (17).

In 50% of patients aged 33 to 47 years, the central nervous system shows unspecific changes in the form of white matter lesions, in half of these in combination with gray matter lesions (e35). Pathophysiologically, CNS areas with white matter lesions have a lower cerebral glucose metabolism than areas without such changes. There are also indications that the white matter lesions are caused by an imbalance of regional cerebral blood circulation and glucose metabolism (e36). A recent study has shown 87% precision for cranial MR-angiography of the basiliar artery with an increased diameter, which helps distinguish patients with Fabry disease from their peers of the same age (Fellgiebel et al. Neurology 2009; 72: 63–8).

Other complaints

A multisystem disease that is accompanied by chronic pain, that has a far too long diagnostic latency period, and that is associated with a substantially lower life expectancy is necessarily also accompanied by an increased risk of depression (e37). The quality of life of untreated patients with Fabry disease is obviously greatly reduced compared with the normal population (e38).

Diagnosis

A suspected diagnosis of Fabry disease has to be deduced from the individual clinical picture. This is crucial for affected patients; the range of possible differential diagnoses is wide *(Table 2)*. In case of doubt, Fabry disease should be included in the range of possible diagnoses that need clarifying in all patients with atypical clinical courses, uncertain diagnoses, or an unclear clinical picture.

It should be noted that measuring enzyme activity—in affected men, typically <1%—often yields false positive or false negative results in women. The randomized X inactivation is responsible for this; as a result of this, the healthy or faulty GLA gene is switched on or off in each cell, independently of each other and at random. Women with suspected Fabry disease therefore need to undergo a molecular genetic examination with complete sequencing of the GLA gene. Such an examination costs from 70 euros. In principle, histopathological diagnostic tests are possible, but these have been rendered less important by the relatively simple enzyme tests and molecular diagnosis. A diagnostic flow chart for patients with Fabry disease is shown in *Figure 2*. Additionally, prenatal diagnosis is possible, especially by using chorionic villus sampling (e39). After the diagnosis has been made, patients should immediately be referred to human genetic counseling.

Treatment and conclusions

Since 2001, two preparations have been licensed for the causal treatment of Fabry disease in the European Union. Both gene technologically produced alpha-galactosidase A variants are based on human DNA, but they are produced in different ways and have different glycosylation patterns (e40). The treatment is entirely safe; both preparations are administered as infusions every fortnight (22, 23). Differences exist with respect to dosage (0.2 mg/kg for agalsidase alfa and 1.0 mg/kg for agalsidase beta) and infusion time (40 minutes independent of body weight for agalsidase alfa and 15 mg/h for agalsidase beta). Especially in the first 3 months of treatment, adverse medication effects may occur, which should be classed primarily as allergic reactions. Further to headaches, hot flushes, and a raised temperature, patients may develop nausea and vomiting, flushing, and chills. After primary treatment of these problems (stopping the infusion; glucocorticoids, H1-receptor blockers, and, if required, H2-receptor blockers), the infusion can, in all experience, be continued.

The therapy has to be continued for a patient's entire lifetime; the costs are substantial, amounting to 250 000 euros per patient per year, and are independent of which of the two preparations patients choose after receiving comprehensive information. Since this is the only causal therapeutic option for Fabry disease, the German health insurers cover the costs, and the prescription and administration of the therapy are classed as an additional position that does not affect the practice's drug budget.

Table 3 provides an overview of the positive effects of enzyme replacement therapy as described thus far. To enable better understanding, we classified the references by type of study design. Obviously, it has been possible for only very few studies to be conducted in a double blind, randomized, and controlled fashion, as patients with a known diagnosis of Fabry disease were given causal therapy after the preparations had become licensed. The available information about the long term treatment with enzyme replacement therefore comes mostly from cohort studies that were developed from the two available patient registries, or from open extension studies of the phase III trials. Nonetheless, it is clear that patients with Fabry disease benefit from enzyme replacement. Further to an improved quality of life, the function of the vital organs improved significantly, or the progression of the disease was halted. However, even 8 years after enzyme replacement therapy for Fabry disease has been introduced, many therapeutic questions remain unanswered—for example, whether the treatment is able to prevent relevant organ manifestations and reduce mortality due to Fabry disease. These and other questions are currently the subject of clinical research.

Key messages

- Fabry disease is a severe multisystem disorder that starts in childhood and takes a chronic course.
- Progressive renal failure, advancing cardiomyopathy, and cerebrovascular events substantially reduce life expectancy in men and women.
- Recent studies have suggested a much higher incidence of Fabry disease than hitherto assumed.
- Therapy with gene technologically produced human alpha-galactosidase A is safe and effective.
- Fabry disease should be included in the list of differential diagnoses in unclear pathologies and those that take an atypical course.

Conflict of interest statement
Dr Hoffmann and Professor Mayatepek have received unlimited, project bound, research support from Shire Germany GmbH, one of the manufacturers of recombinant human alpha-galactosidase A. Dr Hoffmann has also received honoraria for lectures from Shire Germany GmbH and Genzyme Ltd.

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