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Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel

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Abstract

Background: Fabry disease is an inherited metabolic disorder characterized by progressive lysosomal accumulation of lipids in a variety of cell types, including neural cells. Small, unmyelinated nerve fibers are particularly affected and small fiber peripheral neuropathy often clinically manifests at young age. Peripheral pain can be chronic and/or occur as provoked attacks of excruciating pain. Manifestations of dysfunction of small autonomic fibers may include, among others, impaired sweating, gastrointestinal dysmotility, and abnormal pain perception. Patients with Fabry disease often remain undiagnosed until severe complications involving the kidney, heart, peripheral nerves and/or brain have arisen.

Methods: An international expert panel convened with the goal to provide guidance to clinicians who may encounter unrecognized patients with Fabry disease on how to diagnose these patients early using simple diagnostic tests. A further aim was to offer recommendations to control neuropathic pain.

Results: We describe the neuropathy in Fabry disease, focusing on peripheral small fiber dysfunction - the hallmark of early neurologic involvement in this disorder. The clinical course of peripheral pain is summarized, and the importance of medical history-taking, including family history, is highlighted. A thorough physical examination (e.g., angiokeratoma, corneal opacities) and simple non-invasive sensory perception tests could provide clues to the diagnosis of Fabry disease. Reported early clinical benefits of enzyme replacement therapy include reduction of neuropathic pain, and adequate management of residual pain to a tolerable and functional level can substantially improve the quality of life for patients.

Conclusions: Our recommendations can assist in diagnosing Fabry small fiber neuropathy early, and offer clinicians guidance in controlling peripheral pain. This is particularly important since management of pain in young patients with Fabry disease appears to be inadequate.

Keywords: Diagnosis, Fabry Disease, Neuropathy, Pain, Treatment

Review

Fabry disease is a life-limiting genetic lysosomal storage disorder with distressing early clinical symptoms related to small fiber neuropathy [1-3]. The deficiency of lysosomal α-galactosidase A activity results in the progressive accumulation of glycolipids in a variety of cell types [4]. A cascade of overlapping pathologic events usually leads to multisystemic disease. First symptoms (see Table 1) typically arise in childhood or adolescence and include, among others, peripheral pain, angiokeratoma (Figure 1), and cornea verticillata (Figure 2) [1-3]. Serious complications developing in adulthood include progressive renal insufficiency, cardiac complications (arrhythmia, hypertrophic cardiomyopathy), and/or cerebrovascular complications (e.g. early stroke), and have been reviewed elsewhere [5-9]. Although Fabry disease is transmitted in an X-linked fashion, females commonly manifest symptoms, presumably as a result of skewed X-chromosome inactivation [10,11]. Their phenotypic presentations, however, are far more variable as compared to males [7,10].

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Table 1 Possible early symptoms of Fabry disease

Organ system	Sign/Symptom
General	Reduced quality of life; reduced well-being; reduced school/work performance and engagement in leisure activities, including sports
	Psychosocial and behavioral deficits
	Poor weight gain
Nervous system	Chronic burning pain
	Attacks of excruciating pain
	Paresthesias/dysesthesias
	Sensory losses
	Hypohidrosis/anhidrosis
	Abdominal cramp, (post-prandial) diarrhoea, bloating, nausea
	Tinnitus, hearing loss
	Dizziness
Skin	Vascular lesions (angiokeratoma, Figure 1)
Eyes	Corneal/lenticular opacities (seen on slit lamp examination, Figure 2)
	Vascular tortuosity (retina, conjunctiva)
Kidneys	Microalbuminuria, proteinuria
	Impaired concentration ability
	Increased urinary GL-3 excretion
	Renal hyperfiltration (early), decrease in glomerular filtration rate
Heart	ECG abnormalities (for example, short PR interval)
	Arrhythmias, hypertrophic cardiomyopathy (young adults)

The first neurologic symptoms reflect damage to the small fibers of the peripheral and autonomic nervous systems. Peripheral neuropathic pain in young patients with Fabry disease can manifest as chronic, burning pain and superimposed attacks of acute excruciating pain (described in more detail later), dysesthesias, thermal sensation deficits (primarily cold perception), and paresthesias (e.g., painless tingling) [12-14]. Symptoms related to autonomic nervous system dysfunction may include hypohidrosis, impaired pupillary constriction and saliva and tear production, gastrointestinal dysmotility (abdominal cramping pain, bloating, diarrhea, nausea), and sensory losses.

The primary neuropathic insult in Fabry disease is presumably due to a combination of factors that are linked with accumulation of GL-3, and possibly with deposition of its deacylated form [15]. Accumulated GL-3, migrated from the plasma into neural cells or synthesized in situ, can interfere with the function of critical proteins, e.g., ion channels, thereby causing nerve injury and dysfunction [12]. GL-3 inclusions have been demonstrated 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 less often in Schwann cells [16-25]. The dorsal root ganglia have fenestrated blood vessels and appear particularly vulnerable for GL-3 accumulation (Figure 3) [26,27]. Also in the central nervous system, GL-3 appears to accumulate in regions where the blood-brain barrier is more permeable (e.g., supraoptic, paraventricular and preoptic hypothalamus nuclei, dorsal nucleus of the vagus) [26].

Luminal encroachment and occlusion of the vasa nervorum of the peripheral nerves due to endothelial GL-3 storage, disturbed balance between vasodilatative and vasoconstrictive mechanisms, and thrombotic complications are factors that may contribute to ischemic neural damage [28,29]. Also, GL-3 accumulation in skin cells may interfere with the function of intradermal sensory receptors.

Although still insufficiently understood, peripheral nerve injury may induce a variety of peripheral and central mechanisms, e.g., axonal sensory hyperexcitability, ectopic spontaneous firing, and central sensitization that have been described elsewhere [12,13,30,31]. The extent of overlap of these mechanisms in the various stages of Fabry disease is uncertain.

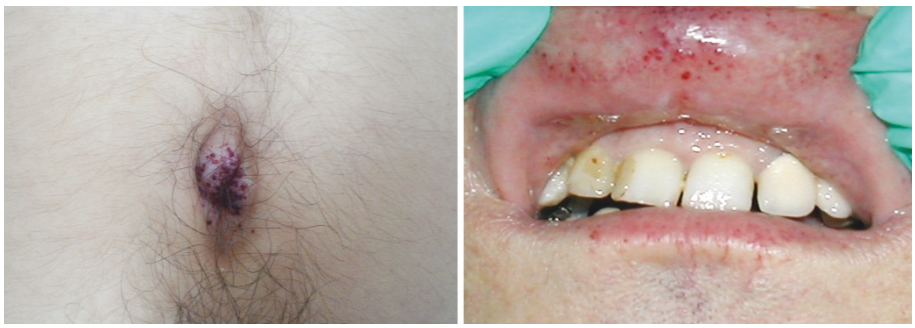

Figure 1 Red-purple, non-blanching vascular skin lesions. Angiokeratoma are usually distributed on the buttocks, groin, umbilicus (left figure) and upper thighs (bathing trunk distribution), and occasionally on lips and oral mucosa (right figure).

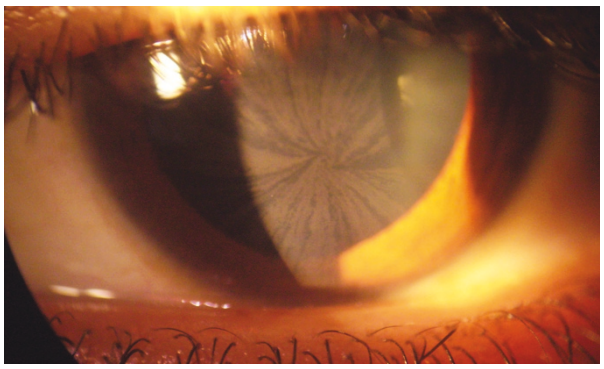

Figure 2 Cornea verticillata. A bilateral, whorl-like corneal pattern of cream colored lines in a patient with Fabry disease.

An International Expert Panel on Neuropathy in Fabry Disease convened on January 12th, 2009, in Rome, Italy. The Panel was composed of 8 experts (7 physicians/physician scientists, 1 scientist) in the area of Fabry disease and/or peripheral neuropathy from the US, Canada, South America, and Europe. The aim of the meeting (sponsored by Genzyme Corp.) was to develop guidance on the clinical evaluation of early stages of small fiber neuropathy in Fabry disease, focusing on simple diagnostic tools that can be quickly applied by the practitioner, and on treatment of the neuropathic pain. The recommendations are supported by a review of relevant medical literature published up to September 2010. Given the well manageable number of relevant publications, no specific criteria for literature review were used. Our recommendations can assist in diagnosing Fabry small fiber neuropathy early, and offer clinicians guidance in controlling peripheral pain. This is particularly important since management of pain in young patients with Fabry disease appears to be inadequate [1].

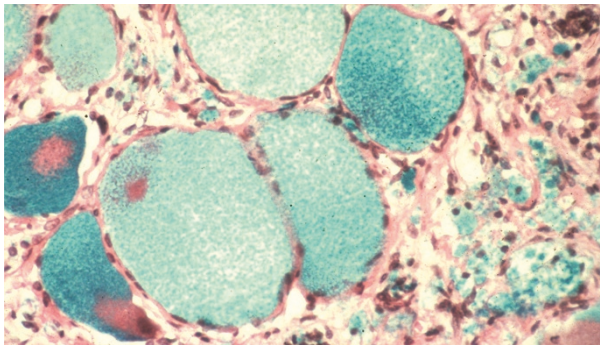

Figure 3 Dorsal root ganglion cells from a Fabry patient. The ganglion cells are swollen by accumulation of glycolipids and stained with Alcian blue (photo courtesy of E. Kaye).

Clinical course of neuropathic pain in Fabry disease

Burning, nagging pain with a symmetric distribution pattern in the palms of the hands and soles of the feet of children or adolescents and peripheral dysesthesias are the first symptoms to raise alarm. 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 [12,32]. They can be so intense that the patient is confined to bed [12], and episodes can occur daily [4]. They may be triggered by a rapidly changing core body temperature (e.g., fever, stress, physical activity) presumably due to a decreased ability to sweat [12,32], although they have been noted even in patients with hyperhidrosis [33]. Additional triggering factors include sudden exposure to cold, rapid changes in humidity, and fatigue [34]. Deep ache, significant joint pain, bouts of unexplained fever, and elevated erythrocyte sedimentation rate can accompany a pain crisis [12,35,36].

Neuropathic pain was reported by ~60 and 80% of the affected boys enrolled in the two Fabry disease registries, usually beginning in childhood, and by ~40 to 60% of affected girls, often a few years later than in boys [1,2]. Most adult males and 60 to 90% of females experience some form of Fabry pain [13,37-39]. Over time, neuropathic pain appears to diminish, perhaps due to progressive loss of nerve fibers, but can also become more severe [40,41].

It has recently been proposed to abandon the use of "acroparesthesia" in the description of Fabry neuropathic pain because, by definition, paresthesias are painless tingling sensations [42]. In fact, paraesthesias appear to be rather uncommon in Fabry disease as they were reported by only ~10% of affected adults [42].

In children with Fabry small fiber neuropathy, reductions in feelings of well-being and in school attendance and a reluctance to participate in sports, gymnastics, and leisure activities are of particular concern. As the patient ages, the symptoms lead to increasing neurological disability and impairment of quality of life in both males and females [7,10,43-45].

As in other conditions with chronic neuropathic pain, pain medication dependence (e.g., opioids) and substance abuse can occur [46]. Patients may develop social-adaptive or psychological functioning deficits [47,48] and many become depressed, with the presence of neuropathic pain being the strongest predictor of depression [49]. Suicidal ideation has been reported in patients with Fabry disease [49-51].

Small fiber dysfunction in Fabry disease

The pattern of small fiber dysfunction in Fabry disease is seen in various other diseases characterized by peripheral neuropathy, including diabetes mellitus [52,53].

However, if provoked crises of excruciating pain occur, the diagnosis of Fabry disease should be highly suspected. The neuropathy in Fabry disease is a length-dependent neuropathy [12,54] typically associated with a marked reduction of thinly myelinated Aδ fibers (mediating sharp pain, cold perception), unmyelinated C fibers (pain, warmth perception), and loss of unmyelinated autonomic fibers [17,19,21,23,24,40,55-59]. Female patients, even when asymptomatic, may also be affected by loss of small fiber function [39,54,60].

The thermal sensation deficits are initially more pronounced in the feet than in hands, and gradually progress to more proximal parts (Figure 4) [12,39,59,61]. In early stages, impairment of thermal stimuli primarily involves cold perception (Aδ fibers), rather than warmth perception (C fibers) [62], suggesting that the thinly myelinated Aδ fibers are more vulnerable to GL-3-induced damage [36,40,63,64].

Disappearance of pain may not necessarily reflect nerve recovery but rather degeneration of nerve fibers and the sensory neuropathy may progress to numbness and hypoalgesia. Recently, an association between the severity of small fiber neuropathy, determined by cold perception in the feet, and progressive sensorineural hearing loss has been reported, both in male and female patients [65].

Autonomic small fiber damage in Fabry disease is likely to be related to the patients' gastrointestinal dysmotility (e.g., abdominal cramps, bloating, diarrhea, nausea), hypohidrosis, impaired pupillary constriction, decreased tear and saliva formation, Raynaud phenomena, sensory losses, reduced heart rate acceleration upon exercise and, in advanced stages, orthostatic hypotension [17,37,66]. The cutaneous response to scratch can be diminished [17,67], and baroreflex-mediated vasoconstriction can be deficient due to sympathetic vasomotor nerve fiber dysfunction [68].

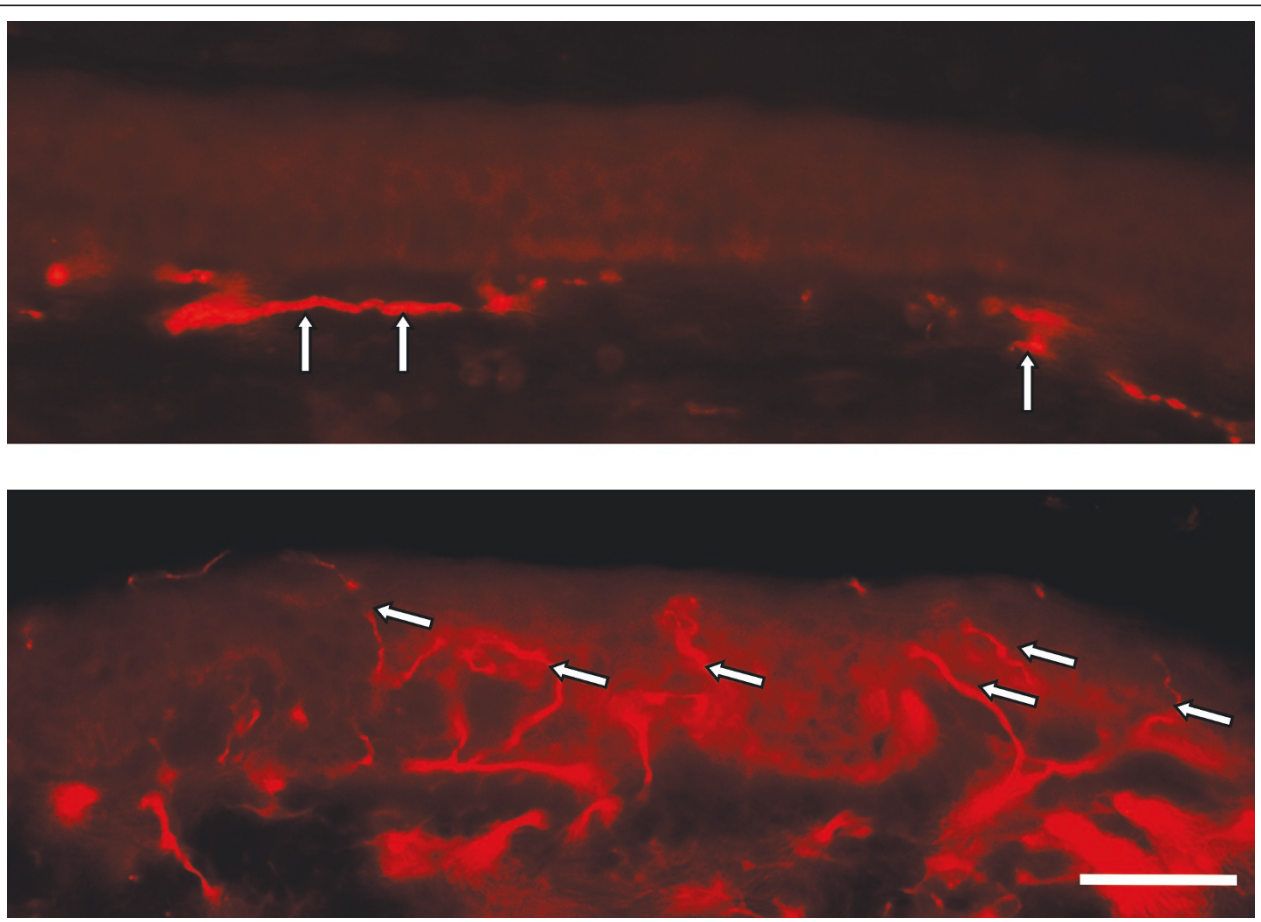

Figure 4 Photomicrographs of frozen skin sections (50 μm) from a Fabry patient. Samples immunoreacted with PGP 9.5 and were processed for fluorescence microscopy with Cy3 labelled secondary antibodies. Note the lack of intraepidermal nerve fibers and persistence of fibers pertaining to the subepidermal nerve plexus (arrows) in the sample from the lower leg skin of a Fabry patient (upper figure). Note the dense innervation of the epidermis (arrows) in the sample from the back of the Fabry patient, taken at the dermatome Th 12 (lower figure). Bar = 50 μm.

Pancreatic parasympathetic dysfunction may cause post-prandial diarrhea after consumption of a high-fat meal [69]. Both autonomic sudomotor nerve fibers and sweat gland function are impaired in untreated patients [37,70]. Hyperhidrosis can also be recognized in patients with Fabry disease, mainly in females. If present, it often manifests in childhood or adolescence [33].

Of note, the generally accepted assumption that autonomic neuropathy plays an important role in the pathophysiology of Fabry disease has recently been questioned by one group of investigators [71]. The observation of nearly normal male sexual function and autonomic control of the cardiovascular system in patients with Fabry disease led the investigators to suggest that end-organ damage, rather than autonomic dysfunction, might play a prominent role in Fabry disease.

Large fiber dysfunction in Fabry disease

As large Aα and Aβ fiber modalities (e.g., motor function, position, and vibration sensation) are generally spared in early stages of Fabry disease, it is not surprising that the results of motor and sensory nerve conduction tests have mostly been normal [19,21,34,36, 40,57,61,66,72,73]. With progression of the disease, however, large fiber involvement with associated nerve conduction abnormalities may develop. Reductions of compound muscle action potential amplitudes are seen more often than the slowed conduction velocities [40]. Impaired vibration perception may be a consequence of disturbed transmission of the synchronized impulse volleys in large myelinated afferent Aβ fibers, or by GL-3-induced dysfunction of intradermal corpuscles (mainly Pacinian corpuscles and Meissner bodies [74,75]) mediating the vibratory stimuli [40,73]. With age, more severe abnormalities involving large fibers are expected to occur as demonstrated by a significant influence of age on vibratory perception [40].

The mechanisms contributing to development of large nerve fiber abnormalities in a subset of patients are as yet unclear. It has been suggested that Schwann cell pathology due to GL-3 accumulation might account for slowing of conduction velocities [40]. Uremia due to Fabry end-stage renal disease and overuse of alcohol may add to the large fiber pathology [40,55,66,76].

Median nerve conduction abnormalities may indicate median nerve entrapment caused by GL-3 accumulation in carpal tunnel structures. A prevalence of carpal tunnel syndrome of ~25% has been reported for both male and female patients with Fabry disease [36,55].

Diagnosis and simple assessments

The early neurologic manifestations of Fabry disease are initially often subtle and affected children are frequently misdiagnosed as having rheumatism, viral infection, growing pains, "bone problems", psychogenic pain, cryptogenic pain, food intoxication, or non-specific gastrointestinal pain [77]. Although first symptoms appear in childhood, correct diagnosis may be delayed until well into adulthood. Data from the Fabry Registry shows that the mean diagnostic delay was approximately 11 years for both genders [10]. While still undiagnosed and untreated, the disease increasingly impairs the young patient's well-being.

Children and young adults with unexplained peripheral neuropathic pains may be referred to the pediatrician, or the pediatric/general rheumatologist or neurologist. Therefore, they play a critical role in recognizing the array of distinct early features of Fabry disease (Table 1), of which several are related to the small fiber neuropathy. The importance of their role is underpinned by a recent Fabry screening study among individuals with small fiber neuropathy of unknown aetiology; several previously unrecognized patients were diagnosed with Fabry disease [53]. The differential diagnosis of peripheral neuropathy can be significantly narrowed by taking a detailed medical history (Table 2). This should include information on the onset, quality, intensity and distribution of pain symptoms, abnormal responses to normally non-painful stimuli, triggering and exacerbating factors, psychological factors, changes of symptoms over time, and coping skills. Previous and current use of pain medications (prescription, non-prescription and recreational drugs) and smoking habits should be documented. The patient's general status, energy level, comorbidities, school, work and sport performance, and lifestyle should be explored. Gastrointestinal problems (abdominal pain, post-prandial diarrhea, number of bowel movements per day, bloating, nausea) and hearing problems need to be documented, as well as the family history (e.g., renal/cardiac failure, transient ischemic attack (TIA) or stroke, early death).

A neuropathy pain assessment scale should be used at the initial assessment and follow up examinations. The Neuropathy Symptoms and Change Questionnaire evaluates the number, severity and change of symptoms, as well as motor, autonomic, large fiber and small fiber sensory nerve function [78]. Other available neuropathic pain evaluation tools include the Leeds Assessment of Neuropathic Symptoms and Signs, Neuropathic Pain Questionnaire, Neuropathic Pain Symptom Inventory, Douleur Neuropathique en 4 questions, pain DETECT, and ID-pain [79]. The Total Symptoms Score has been used for grading of neuropathic pain in clinical studies in diabetes and Fabry disease patients with peripheral neuropathy [73,80].

The patients can also be asked to keep a (weekly) pain diary. A more general pain assessment can be performed by using, for example, the Pediatric Pain Questionnaire

Table 2 Medical history and examinations in young patients with Fabry disease

General status	Decreased stamina and exercise; psychologic co-morbidities; school, work and sport participation and performance; smoking
	SF-36® Health Survey or PedsQL™
Pain	Onset; quality; intensity; distribution; abnormal responses to stimuli; exacerbating factors; pain meds (past, current), McGill Pain Questionnaire, Brief Pain Questionnaire, Pediatric Pain Questionnaire
Gastrointestinal	Abdominal cramps; (post-prandial) diarrhea; number of bowel movements/day; bloating; nausea
Family history	Renal/cardiac failure; TIA or stroke; early death
Complete physical examination	
	Including height; weight; pulse irregularity; supine and standing blood pressure; vascular skin lesions (Figure 1); cornea clouding (requires slit lamp exam, Figure 2)
Neurologic examination	
	Thermal perception (cold/warm water tubes, a cold and warm tuning fork or reflex hammer, or thermal discs at dorsal foot, e. g., "Minnesota Thermal Disks" [81])
	Pain perception (pinprick to skin of limbs and trunk)
	Light touch perception (cotton swab or lightly touching skin, e.g., on legs vs. feet, testing distal vs. proximal sensation)
	Vibration perception (vibrating tuning fork (Rydell-Seiffer®) to 1st metatarsal bone)
	Sensorineural hearing loss (Rinne test, three-tone audiometry)
Definitive diagnosis	
	α-Galactosidase A enzyme activity in leukocytes or whole blood in males
	GLA mutation analysis in females (known family mutation testing or full gene sequencing)
Genetic risk assessment	Diagnosis should be followed by genetic testing of the entire family
Severity scoring	
	Neuropathy Staging Scheme [91], Neuropathy Symptoms and Change Questionnaire [78]

or the McGill Pain Questionnaire. The quick version, the Short-form McGill Pain Assessment Questionnaire [81], is particularly easy to administer. Quality of life can be assessed by using the Short Form-36 (SF-36®) Health Survey (http://www.sf-36.org) or Pediatric Quality of Life Inventory (PedsQL™) [82].

A complete physical examination should be performed as it may provide clues to the diagnosis of Fabry disease (Table 2). It should include measurement of height and weight, heart rate (irregular pulse) and supine and standing blood pressure to determine orthostatic hypotension (defined as a drop in systolic blood pressure by at least 20 mmHg, or in diastolic blood pressure by at least 10 mmHg, within the first three minutes upon active standing up from the sitting or supine position, or upon passive head-up tilt) [83]. The skin should be inspected for presence of vascular skin lesions (angiokeratoma, Figure 1), particularly in the bathing trunk area. Cornea verticillata (Figure 2) is readily detectable by slit lamp examination and present in almost all males and 70% of females with Fabry disease [32,84]. Routine blood work-up is usually normal. Albuminuria may be detected in young patients and is an antecedent to progressive Fabry nephropathy [85].

The neurologic examination in children, adolescents and young adults should focus on sensations mediated by peripheral small fibers, as overt central nervous system involvement is usually not yet present (Table 2). Relevant, easy to perform and non-invasive sensory perception tests include cold, heat, light touch, pinprick, pressure and vibration perception testing. Assessment of allodynia and hyperalgesia should preferably be carried out in the area of maximal pain. All tests should be performed under comfortable ambient conditions and temperature at the distal lower limbs.

Early in the course of small fiber neuropathy, impaired appreciation of thermal stimuli primarily involves cold perception rather than warm perception [39,62]. A rather crude test of thermal perception consists of placing tubes filled with cold and warm water, a cold and warm tuning fork, the handle of a reflex hammer, or thermal discs with a polyvinyl surface on one side and a metal surface on the other side (similar to the "Minnesota Thermal Discs" [86]) on the patient's foot. Cold sensation can also be assessed by using acetone spray, or by immersing one leg up to the mid thigh (or one forearm) for 30 seconds into ice-cold water [34]. Normal subjects report little discomfort to a brief immersion of a limb in ice water, but the Fabry patient experiences intense burning pain within 10-30 seconds.

Pain perception and hyperalgesia can be tested by applying just enough pressure with a sharp pin to indent the skin. Loss of discrimination between pinprick sensation and application of a blunt pressure sensation points towards small fiber neuropathy.

Perception of light touch and mechanical allodynia can be tested by lightly rubbing the skin with a cotton swab or by lightly squeezing the patient's leg. Vibration

can be assessed by placing a scaled (8/8), vibrating 128 Hz tuning fork to the first metatarsal bone [87].

Symmetrical sensorineural hearing loss can be explored by performing the Rinne test. The stem of a vibrating tuning fork (512 or 256 Hz) is placed on the mastoid process until sound becomes inaudible; the fork is then immediately placed outside the ear. In case of sensorineural hearing loss, bone conduction and air conduction are both equally reduced. However, to reliably assess or rule out hearing loss, three-tone audiometric testing needs to be performed [88].

Abnormal results of the tests described above may lead to more comprehensive examinations trying to document the sensory abnormalities qualitatively and quantitatively. A standardized quantitative sensory testing (QST) protocol to assess the somatosensory profile within 30 minutes and diagnose a small fiber neuropathy is available [53,56,89]. The QST battery consists of 7 tests measuring thermal detection, thermal pain and mechanical detection thresholds and mechanical pain sensitivity. An abbreviated version of this protocol assessing cold and warm detection thresholds can be applied within approximately 10 minutes and may facilitate the development of new screening strategies for Fabry disease. Methods to test nerve conduction velocities, sympathetic skin response, quantitative sudomotor axon reflex sweating, saliva and tear formation, and other autonomic dysfunction are not further discussed in this manuscript that focuses on simple bedside tests. Given the availability of an accurate diagnostic laboratory test, nerve or skin biopsies are not required for diagnosing Fabry disease, although skin biopsy can detect small fiber disease in yet asymptomatic patients and may be used to quantify loss of skin innervation [39].

Measuring α-galactosidase A enzyme activity in leukocytes is the gold standard assay of diagnosis of Fabry disease in males [4]. Many females with Fabry disease, however, may have enzyme activity levels within the normal range. Diagnosis in females, therefore, requires genetic studies to detect or confirm the Fabry mutation. Extended familial assessment identified, on average, five family members with Fabry disease for every proband [90]. Therefore, the importance of taking a family history and genetic testing in all members of the family of a newly identified patient cannot be underestimated.

Evaluation and monitoring of the small fiber neuropathy are important as the elicited signs and symptoms may provide insight into possible pathophysiological mechanisms and, in turn, may provide guidance on optimal pain management. Given the progressive nature of Fabry disease, regular objective and comparable monitoring of the neuropathy and its progression using reproducible measures of staging is required for therapy adjustment. Particularly useful may be the neuropathy staging scheme developed by Dyck [91] as it scores sensory, autonomic, and motor components separately, and provides an overall stage. Other available methods to score severity include the Total Symptom Score for grading of pain [73,80], and the Neuropathy Impairment Score [92].

Treatment

Current management of pain in pediatric patients with Fabry disease appears to be inadequate. This is as illustrated by the fact that the majority of children in the Fabry Registry who had neuropathic pain reported not to have received any pain medication [1].

Given the episodic and provoked nature of many of the painful crises, it should be emphasized that identification of individual provocateurs is important for conservative management. Patients can change their lifestyle and take preventive measures to avoid exposure to, for example, rapid changes in temperature. 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 psycho-social function.

We are not aware of any randomized controlled trial of an analgesic for the treatment of painful peripheral neuropathy in Fabry disease; only some empiric use of drugs has been reported [93-95]. However, a substantial body of evidence exists for the treatment of other types of painful neuropathy and this may serve as a guide for the physician treating the Fabry disease patient [96-99]. Pain treatment should generally consider the most likely mechanism in each case. However, in the attempt 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 2-3 weeks.

Anticonvulsants are commonly used to reduce pain in neuropathic pain disorders, including diabetic neuropathic pain [96-99]. Carbamazepine alone [95], or in combination with pregabalin (rather than gabapentin) [99], is recommended as first-line treatment in Fabry neuropathic pain. Symptoms suggestive of autonomic dysfunction should be monitored as dose-dependent exacerbation of autonomic dysfunction has been reported [95]. Antidepressants, particularly dual reuptake inhibitors of both serotonin and norepinephrine (SNRIs; venlafaxine, duloxetine; black-box warning for use in pediatric age group) are also viable options. Because of their anti-cholinergic effect, tricyclic antidepressants have potential concomitant and difficult side-effects in Fabry patients (e.g. accentuation of autonomic instability). Prescription of opioids carries the

risk of drug dependence or abuse. Although they should only be given if other therapeutic options are ineffective, opioids may be helpful in the acute management of intolerable pain crises [96-99]. Topical application of anesthetics may provide relief of burning pain or hyperalgesia.

With increasing disability and unpredictability and difficulty of controlling the pain, patients are at risk of chronic depression [49]. Patients should be evaluated for psychosocial and behavioral deficits and appropriately treated.

Common non-neurologic symptoms of Fabry disease and risk factors should be carefully monitored and treated as outlined in the general guidelines for the management of Fabry disease patients [100]. Co-morbidities must be addressed and smoking discouraged as it may aggravate airflow obstruction commonly found in patients with Fabry disease [101], and further increase the risk of cardiovascular and cerebrovascular events. Anti-platelet drugs (aspirin, clopidogrel) are recommended for patients at risk of thrombotic events. Dyslipidemia should be treated with statins [100], and recently the use of statins to prevent stroke in Fabry disease has been discussed [102].

Enzyme replacement therapies (ERTs) are available for treatment of patients with Fabry disease and several clinical studies have reported pain outcomes [45,73,103-112]. For example, the Total Symptom Score improved with biweekly ERT at the dose of 1 mg/kg for 18 or 23 months [73], and some adults were able to discontinue their pain medication(s), or doses of pain medications could be tapered [105,112]. Improvements in the Bodily Pain scale of the SF-36 during 2 to 3 years of treatment with ERT (1 mg/kg), particularly in younger patients, have recently been reported [45]. Signs of recovery of small nerve fibers have been noted. Significant improvements in vibration, heat-pain, and cold perception thresholds, indicating recovery of Aβ, Aδ- and C-fiber function, have been reported in adults treated biweekly with 1 mg/kg agalsidase beta for 18 or 23 months [73].

As for the renal [107,113] and cardiac complications [114] of Fabry disease, early initiation of treatment may provide a better outcome, i.e., improvement or more optimal preservation of peripheral nerve function. Additional studies are needed in pediatric patients to assess if early-stage treatment can prevent the often devastating peripheral neurologic burden of Fabry disease.

Conclusions

Small fiber dysfunction accounts for many of the incapacitating complaints reported by most children, adolescents and young adults affected by Fabry disease. These early complaints (e.g., chronic burning peripheral pain, attacks of acute excruciating peripheral pain, and manifestations of autonomic dysfunction, such as gastrointestinal dysmotility and hypohydrosis) should prompt the clinician to consider the diagnosis Fabry disease and to perform appropriate tests. The burden of the progressive neurologic disease should be assessed early, comprehensively and regularly as the neurologic disability in Fabry disease increases with age, both in males and females. Adequate management of the pain is essential for improving the quality of life of young patients, as are multidisciplinary management and timely intervention with disease specific enzyme replacement therapy.

Abbreviations

GL-3: globotriaosylceramide; lyso-Gb3: globotriaosylshingosine; TIA: transient ischemic attack; SF-36: Short Form-36; PedsQL: Pediatric Quality of Life Inventory; ERT: enzyme replacement therapy.

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Written informed consent was obtained from patients for publication of the clinical photographs (Figures 1 and 2). Copies of the written consents are available for review by the Editor-in-Chief of this journal.

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Authors' contributions

This review is based on discussions of the available evidence by an international panel that met in January 2009 at the 1st International Expert Panel on Neuropathy in Fabry Disease, Rome, Italy. All authors are member of this Expert Panel. APB and MJH were involved in drafting the manuscript and all other authors have contributed important scientific content. All authors have approved the final draft.

Competing interests

APB has been in receipt of honoraria for lectures on Fabry disease from Genzyme Corporation and Shire HGT. KBS is a consultant to Amicus Therapeutics and has received clinical trial support from Amicus and Genzyme Corporation, and research support from Genzyme Corporation. JMP has been in receipt of honoraria for lectures on Fabry disease from Genzyme Corporation. GJB has received a consulting fee from Genzyme Corporation. RB has received grants and research support from Genzyme Corporation. CS has received financial support from Genzyme Corporation for lecturing and research support. ATM received travel assistance and speaker's fees from Genzyme Corporation. MJH has received financial support from Genzyme Corporation for lecturing, consulting activities, travel assistance, and research support. APB and KBS have received honoraria for participation in the European and North American Fabry Registry Board of

Advisors, respectively, from Genzyme Corporation, and JMP for serving as a Latin American Fabry Registry Coordinator. The Fabry Registry is sponsored by Genzyme Corporation.

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