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Minireview

The management and treatment of children with Fabry disease: A United States-based perspective

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ABSTRACT

Fabry disease is an inherited X-linked disorder that presents during childhood in male and female patients. Young patients may initially experience pain, hypohidrosis, and gastrointestinal symptoms. Other manifestations of Fabry disease, such as renal and cardiac disease, manifest later in adolescence or adulthood. In the pediatric population, renal damage is typically subclinical and identifiable only through biopsy. Specialists from the United States with expertise in Fabry disease convened during 2013–2014 in order to develop these consensus guidelines about the management and treatment of children with Fabry disease. The presence of symptoms in boys and girls of any age is an indication to begin therapy. Early treatment before the onset of potentially irreversible vital organ pathology is ideal. Asymptomatic children with Fabry mutations should be followed closely for the development of renal, cardiac, neurological, or gastrointestinal signs, symptoms, or laboratory changes, which would warrant treatment initiation. A comprehensive care plan should be implemented by the treating physicians to guide the management of children with Fabry disease.

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Abbreviations: α-GAL, α-galactosidase A; CNS, central nervous system; ERT, enzyme replacement therapy; FD, Fabry disease; GFR, glomerular filtration rate; GL-3, globotriaosylceramide; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; TIA, transient ischemic attack; QST, quantitative sensory testing.

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1. Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by a deficiency in the enzyme α-galactosidase A (α-GAL) due to mutations in the *GLA* gene. This enzyme deficiency results in an accumulation of globotriaosylceramide (GL-3) and related glycolipids, which begins a cascade of events often resulting in fatal end-organ damage to the kidneys, heart, and brain [1]. The first debilitating clinical symptoms of FD emerge in childhood and include neuropathic pain, hypohidrosis, and gastrointestinal discomfort [2–6] (Table 1). However, the symptoms of FD in childhood may be non-specific, often resulting in a delay in diagnosis for decades [9,10]. Early differential diagnosis of Fabry disease is therefore important, and the testing of family members and newborn screening allows patients to be diagnosed in infancy or early childhood. Once diagnosed with FD, comprehensive regular monitoring with tracking of disease progression is important and may contribute to the decision of when to start therapy.

As expected for a rare disease, large-scale, prospective randomized controlled trials testing the long-term efficacy of proactive interventions, including assertive management of symptoms and early disease-specific treatment initiation, remain limited. Nevertheless, there is broad expert-level consensus, supported by recent and emerging studies [11–13], that treatment of FD should be initiated sufficiently early to limit or prevent significant, irreversible end-organ damage. Treatment should be started early, ideally when Fabry-related symptoms emerge or significant organ pathology is detected, in order to achieve maximal impact on the long-term consequences of FD, reduce suffering, and increase quality of life.

Timely initiation of enzyme-replacement therapy (ERT) is important because some early pathological changes are potentially reversible by ERT [11]. Importantly, the impact of ERT is reduced if extensive irreversible pathological changes (e.g., fibrosis) have already occurred in major organs [12]. A 10-year study of the effectiveness of agalsidase beta in patients with classic FD has shown that adults who initiated treatment at a younger age and with less renal involvement (urine protein to creatinine ratio ≤ 0.5 g/g and < 50% sclerotic glomeruli) benefited more from therapy [13].

Females with Fabry mutations manifesting FD clinical symptoms should be managed identically to males with symptomatic FD. It has been established that females are not just carriers of *GLA* mutations, but that they may develop multi-organ injury similar to male FD patients [14,15]. In addition to active symptomatic management (see below), symptomatic female patients should be treated with ERT. However, female FD patients, including those with active renal or cardiac disease for whom treatment is clearly indicated (and long overdue), are less likely to seek treatment, and they often receive treatment much later than their male counterparts [16], thus often missing a crucial window of opportunity to intervene prior to the development of irreversible end-organ damage.

This document, which began with discussions held at a meeting of the Fabry Expert Panel of United States Fabry specialists convened in November 2013, reviews current practices and available assessment techniques for the monitoring of pediatric patients with FD, and presents consensus recommendations regarding the timing of initiation of ERT and symptomatic therapies in these patients. Other than face-to-face panel discussions, no specific method was used to reach consensus among authors, and areas of disagreement are noted in the text. Although there is considerable overlap with management practices followed in other countries [17,18], these guidelines address the practices of Fabry specialists in the United States only.

Table 1
Signs and symptoms of Fabry disease observed in childhood.
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Signs and symptoms	Earliest report of symptoms
Storage of globotriaosylceramide found in organs on biopsy	Prenatal
Presence of pathological albuminuria[a]	7.0 years [8]
Presence of pathological proteinuria	>14.0–20.0 years [3]
Corneal whorls/cornea verticillata	Prenatal/newborn
Gastrointestinal problems, including nausea, vomiting, diarrhea, constipation, and abdominal pain	1.0 year
Slow growth in boys (mean height/weight < 50th percentile)	2.0 years
Intermittent acroparesthesia/neuropathic pain triggered by stress, heat, fatigue, or exercise	2.0 years
Hypohidrosis or anhidrosis	2.5 years
Fabry crises of agonizing neuropathic pain typically begin in the hands and feet and may radiate proximally	2.5 years
Heat, cold, and/or exercise intolerance	3.5 years
Retinal vascular tortuosity	4.0 years
Tinnitus/vertigo	4.0 years
Low glomerular filtration rate	4.0 years
T-wave inversion on electrocardiogram	4.0 years
Trivial cardiac valve disease	4.0 years
Angiokeratoma	4.0 years

[a] Persistent values (at least 2 of 3 consecutive values) for 1st morning voids above 12 μg/min could be considered to be abnormal [7].

2. Screening and monitoring

2.1. Newborn screening

FD is not currently included in the United States Advisory Committee on Heritable Disorders in Newborns and Children Recommended Uniform Screening Panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html) and its inclusion was not addressed. However, Fabry newborn screening programs have been initiated in Missouri, Washington State, New York State, Pennsylvania, and Illinois, with programs approved, but not yet initiated, in New Jersey and New Mexico [19,20]. Newborn screening raises challenges in defining the most appropriate way to counsel families of infants diagnosed with FD, and how to effectively monitor and manage those infants in order to optimize clinical outcomes. Guidelines published by the American College of Medical Genetics [21], provide an excellent educational resource to guide the confirmatory testing and clinical management of asymptomatic individuals diagnosed with lysosomal storage diseases such as FD. The National Society of Genetic Counselors has also published guideline recommendations on the role of genetic counselors in FD management [19].

Mutation testing is indicated for all infants identified with α-GAL deficiency. Knowing the specific Fabry mutation is important, both for the screening of family members and for the prediction of likely disease severity, thus helping to guide decisions on the timing of ERT initiation. Nonsense, splicing, and frame-shift mutations typically result in

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effectively absent enzyme activity; most male patients with such mutations will develop a classic Fabry phenotype with symptom onset in childhood or early adolescence. Onset of first symptoms in females with these mutations usually occurs later, but still frequently in late childhood or adolescence [2]. Adult females with FD are at much higher risk of experiencing renal, cardiovascular, and/or cerebrovascular clinical events than similarly aged females without FD [15].

The phenotypes associated with other mutations (including, but not limited to, the non-classic or later onset phenotypes) can be quite variable and often include genetic variants of unknown clinical significance [22]. In such cases, although the ability to predict the development and progression of symptoms and important organ injury is limited, evaluation of relatives with the mutation may be useful to guide decision-making about the management and treatment of the infant or child. A variant of unknown significance that is de novo or in the context of inadequate family members to assess pathogenicity and severity is particularly problematic. There is insufficient experience to know if FD biomarkers are always elevated in the newborn period with classical FD mutations, but they can be with later-onset FD [23].

Finally, it is crucial that discussions regarding the implications of FD for a newborn (age 0–28 days) be managed by a physician and/or genetic counselor familiar with the impact of sex and the specific Fabry mutations on disease manifestations. These infants should be closely followed by a management team familiar with FD. However, further research is urgently needed to provide evidence-based guidance on the optimal monitoring and management of infants diagnosed with FD as newborns.

2.2. Current recommendations on monitoring and assessment of pediatric patients with FD

Guidelines on the evaluation and management of FD published by Eng et al. in 2006 [24] remain important benchmarks that set standards for the diagnosis, monitoring, and treatment of patients with FD of all ages. However, since 2006 substantial advances in the understanding of FD pathology and increased experience of treatment with ERT have impacted the management of FD, particularly in children and, therefore, warrant an update of these guidelines.

The Fabry Registry provides a recommended schedule of monitoring and assessments for pediatric Fabry patients (http://fabrycommunity.com/en/Healthcare/Registry.aspx). Other guidelines recommend a similar level of monitoring to that of the Fabry Registry (UK: http://collections.europarchive.org/tna/20080102105757/dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_4118404; France: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-12/ald_17_pnds_fabry_vd.pdf) [18]. However, the lack of clinically validated biomarkers that can accurately reflect the underlying preclinical progression of early FD major end-organ damage represent limitations common to all available guidelines. This hampers the delineation of the optimal monitoring and management strategy, especially in children with FD and in patients with non-classic clinical phenotypes. The recommended assessments for children and adolescents with FD are summarized in Table 2 [25,26].

Table 2
Recommended assessments in children and adolescent patients with Fabry disease.

	Assessment(s)	Schedule of monitoring
General	Complete physical examination including evaluation of quality of life, school performance, level of depression anxiety	At diagnosis and yearly
	Genotyping	At diagnosis
	Genetic counseling	At diagnosis and as needed during maturity
Kidney	Measured GFR (preferred); eGFR to be calculated using age-appropriate formulae (abbreviated Schwartz formula [25]) for patients aged <18 years	At diagnosis and at regular intervals (at least annually) and 6-monthly in patients on enzyme replacement therapy
	Urine test to detect albuminuria/creatinine ratio	Overnight or first morning, performed annually
	Kidney biopsy	If clinically indicated; can be a useful tool to guide management
Heart	Blood pressure and cardiac rhythm	Every clinic visit
	Echocardiogram and electrocardiography	Diagnosis and every 2 years starting at age 10 years, and as clinically indicated
	Cardiac MRI	No routine studies are recommended (may be useful in detection of latent fibrosis)
	Holter monitoring	Carried out if an abnormal rhythm is suspected or palpitations are reported; if arrhythmias detected then more frequent/detailed rhythm surveillance should be instituted
Central nervous system	MRI	No routine studies are recommended Perform promptly if a pediatric patient experiences any neurological change that could potentially relate to stroke or transient ischemic attack
Neuropathic pain	Pain evaluation and history Pain measurement scale such as the Neuropathic Pain Symptom Inventory or pediatric Brief Pain Inventory Fabry-specific Pediatric Health and Pain Questionnaire [26]	At diagnosis and at each follow-up clinic assessments
Gastrointestinal tract	Medical history focusing on bowel habits, nausea/vomiting, weight gain, and diet Radiographic or endoscopic evaluation may be helpful to exclude non Fabry-related causes of severe abdominal pain	At diagnosis and at least annually

eGFR, estimated GFR; GFR, glomerular filtration rate; MRI, magnetic resonance imaging.

2.3. Renal monitoring

There is compelling histological evidence that kidney damage due to the accumulation of GL-3 occurs prenatally in renal cells [27], years before the development of measurable abnormalities using routine measures of urinary protein or albumin, or estimates or measures of glomerular filtration rate (GFR). In this context, it is important that clinicians are aware that albuminuria is an earlier pathological sign than proteinuria, and is a more sensitive marker of glomerular and podocyte injury.

Biopsy studies in children have shown accumulations of GL-3 in all renal endothelial cells, and in glomerular mesangial cells and podocytes, distal tubular cells, and vascular smooth muscle cells [6,28,29]. Perhaps of special interest, given the correlation with early increases in urinary protein levels, GL-3 accumulation in podocytes in children is associated with widening of podocyte foot processes in both boys and girls with FD; these histopathological changes are observed in patients with normal GFR levels and before the development of pathological albuminuria [6,28,29]. Importantly, podocyte GL-3 accumulation, unlike accumulation in endothelial and mesangial cells, increases with age and may precede increases in urinary albumin or total protein. This may represent

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an important preclinical histological progression parameter which could help guide disease prognosis and the timing of ERT institution [8,29]. A comprehensive evaluation of renal function of all children with FD should be made, including formal baseline measured GFR (mGFR) and longitudinal estimated GFR (eGFR), as well as measurements of urinary albumin and protein excretion [30]. It is important to note that the presence of pathological albuminuria (or proteinuria) is sufficient to indicate a diagnosis of chronic kidney disease, even in the presence of normal GFR (Supplementary Table 1) (Table 1).

eGFR formulae using serum creatinine, cystatin C, or both are relatively imprecise at early stages of progressive renal disease [6,31]. mGFR using iohexol and timing specific collection is the most precise and accurate approach [6]. However, it may be technically challenging in very young children and may not be universally available outside of academic institutions. It is also crucial to consider that even such close longitudinal functional monitoring will fail to detect early renal structural progression in many children with FD [32]. eGFR from serum creatinine using an age-appropriate formulae for eGFR and urinary protein and albumin should be assessed at diagnosis, and then 12 months thereafter for untreated patients and every 6 months for ERT patients. mGFR at baseline allows for determination of whether the formulae for eGFR are accurate estimates for that patient. Nevertheless, subsequent eGFR could detect changes in true GFR, with the caveat that mGFR is a much more sensitive way to detect GFR changes over time [33].

Recent studies have highlighted significant limitations of using routine measures of renal function, such as eGFR [11,28,29] and albuminuria or proteinuria [11,28] to identify children with early renal injury. As noted above, GFR and urinary protein and albumin levels typically remain normal or near normal during childhood in FD despite progressive renal injury [8,11,28,29,]. For example, in a recent study of renal pathology none of 8 children with histological evidence of renal damage had pathological albuminuria [8]; earlier studies by the same group reported albuminuria in only 5 of16 children despite these patients all having significant podocyte GL-3 accumulation [28]. Serum creatinine and eGFR only become abnormal when there is clinically quite advanced structural renal damage [34]. As such, these late markers of kidney damage are inadequate to monitor progression of renal injury in children and adolescents with FD. Therefore new, widely available, non-invasive, safe, and easily performed biomarker assessments of early kidney injury are urgently needed.

Renal biopsy can provide direct assessment of the level of pathological structural changes, including cellular substrate accumulation, podocyte foot process effacement, glomerular scarring, vasculopathy, interstitial fibrosis, and tubular atrophy among patients for whom the decision of whether to initiate treatment is unclear. At present there is no direct evidence that initiation of treatment based on histopathological evidence of injury alone will improve clinical outcomes such as end-stage renal disease. However, a recent study suggests that early treatment initiation is associated with improved clearance of podocyte GL-3 accumulation and proteinuria [11]. Thus, renal biopsy is a reasonable consideration in selected clinical settings, particularly where evidence of the level of renal disease would have an impact on the decision to start ERT. This circumstance may be particularly relevant in the management of female patients where the degree of podocyte mosaicism for GL-3 accumulation is related to the severity of podocyte stress, as indicated by foot process width [35]. Although severe renal disease can develop during childhood in some patients with FD, such rapid progression is uncommon. Thus, for children with FD who have significant proteinuria or declines in renal function, renal biopsy is essential for ruling out alternative or additional renal diseases.

Currently the role of routine renal biopsy in the clinical care of children with FD remains an area of intense debate, with some experts advocating its use and others questioning its utility. Although biopsy is invasive and carries some risk of complications, it is generally considered safe [36] and is carried out routinely in the management of other chronic kidney conditions that have a much lower risk of end-stage renal disease than FD.

2.4. Cardiac monitoring

FD patients may develop a range of cardiac complications, including left ventricular hypertrophy (LVH), arrhythmias, and heart failure [1]. In some patients with non-classic FD, cardiac symptoms manifest at an older age without other typical symptoms of FD such as skin lesions, pain crises, and renal impairment. Most FD cardiac complications manifest in adulthood, but evidence of early progressive heart damage can be seen in young male and female patients underscoring the need for regular comprehensive monitoring of all young patients with FD (Table 2). In a cohort study of 22 children with FD, 3 children had progressive LVH [37] and an analysis of the Fabry Registry also revealed cardiac abnormalities in boys and girls during follow-up assessments [2]; the most common abnormality being valvular dysfunction, followed by conduction abnormalities, arrhythmias (including sinus bradycardia), and LVH [2].

The schedule of assessments recommended for pediatric patients with FD, summarized in Table 2, includes blood pressure and cardiac rhythm monitoring at every clinic visit, and echocardiogram and electrocardiography at diagnosis and then every other year, starting at age 10 years. Currently there is no recommendation for the use of cardiac magnetic resonance imaging (MRI) among pediatric FD patients. Further research on the use of cardiac MRI as an assessment for monitoring progression of cardiac pathology is required.

2.5. Central nervous system monitoring

Stroke and transient ischemic attacks (TIAs) are significant clinical manifestations commonly affecting adults with FD [38]. However, cerebrovascular events are extremely uncommon among children with FD and regular central nervous system (CNS) monitoring using serial MRI is not recommended in children. MRI should be performed promptly if a pediatric patient experiences any neurological change that could potentially relate to stroke or a TIA. Mood disorders (particularly depression) are prevalent among patients with FD [39], and there is some evidence of increased difficulties with cognitive and executive functions in pediatric patients with FD [40]. Therefore, parents/caregivers must be vigilant for early signs of depression or problems at school, and the initiation of appropriate management (particularly psychology or psychiatry referral) may be warranted, particularly among adolescent patients.

2.6. Evaluation of Fabry-related neuropathic pain

Pain is an important and early symptom in both female and male patients with FD [2,3,5]. Fabry-related pain is typically localized to the feet and hands, but may progress in a length-dependent manner to more proximal aspects of the extremities. It may also manifest in atypical locations including the joints, teeth, and abdomen. The pain in FD is predominantly related to dysfunction of the small myelinated Aδ-fibers, distinguishing it from other small fiber neuropathies that affect both Aδ- and C-fibers [4,41–46].

The nature of the pain associated with FD is similar to classical neuropathic pain, with a prevalence of 'burning' used as a descriptor. Other descriptions include 'stabbing', 'squeezing', 'pressing', 'prickling', or 'soreness' [46]; these phenomena are often in the setting of hyperalgesia or allodynia (evoked pain). In addition to chronic/permanent pain, FD patients experience episodic, profound exacerbations of pain (attacks or crises) triggered by stress, extremes of temperature, exercise, or fever [3,4,46]. Both pain and small fiber function appear to decrease with age and severity of disease [46]. This is presumably due to complete loss of small fibers with loss of sensation, implying that pain is a

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result of ectopic discharge from injured nerve cells with preserved but altered function.

The evaluation of suspected small-fiber neuropathy in patients with FD should be based on a thorough pain history and examination (Table 1). General pain scales such as the Brief Pain Inventory and Neuropathic Pain Symptom Inventory are often employed to monitor pain symptoms and severity among children with FD. Furthermore, pain scores can be captured as part of the Fabry-specific Pediatric Health and Pain Questionnaire [26]. Although several Fabry-specific pain/quality of life assessment scales are currently in development, there are no validated pain scales specific for children with FD.

The evaluation of the FD patient with pain may include tests of intraepidermal small nerve function, where available and feasible. Nerve conduction studies are inadequate as they only assess large myelinated fibers and, therefore, will be normal in most FD patients without renal dysfunction. Skin biopsy, quantitative sudomotor axon reflex testing, and quantitative sensory testing (QST) are all appropriate in the assessment of small nerve fibers but may not be available in all clinics. Skin biopsy is simple to perform, well tolerated, and can provide unequivocal evidence for loss of small fibers, which can be useful in the differential diagnosis of Fabry-related pain in patients not yet diagnosed. QST provides evidence for dysfunction of small fibers in FD, but is not as readily available as skin biopsy and more typically used in clinical research settings. QST typically yields impairments in cold sensation (reflecting Aδ-fiber dysfunction) with relatively less involvement of warm sensation (C-fiber function), as would be expected with the preferential involvement of myelinated Aδ-fibers in FD [41–43,47,48].

2.7. Abnormal regulation of sweating

Both hyperhidrosis and hypohidrosis have been reported in association with FD [49]. Hyperhidrosis is most common in females and rarely occurs in males; it does not usually require intervention. Hypohidrosis is more common in males than females and results in heat intolerance that may contribute to pain crises triggered by hot temperatures, increased physical activity, or fever. The age of onset of hypohidrosis is not well established, but it has been reported as early as age 2–4 years [5]. Hypohidrosis is recognized based on history and physical examination. Testing to quantify sweat production is possible, but can be technically challenging and may not be readily available in many centers. The pathogenesis of the condition is unclear and several mechanisms of action have been proposed. Functionally, hypohidrosis contributes to decreased exercise tolerance, pain crises, and decreased quality of life.

2.8. Gastrointestinal tract monitoring

Gastrointestinal disturbances, such as abdominal pain and diarrhea, are among the most common symptoms reported by pediatric Fabry patients [2]. Assessments of gastrointestinal symptoms should be performed at diagnosis and at least annually thereafter. In particular, initial patient evaluation should include weight gain, bowel habits, nausea/vomiting, and diet history. Radiographic or endoscopic analysis may be helpful to exclude non Fabry-related causes of severe abdominal pain.

3. Medical management

3.1. Clinical management of pediatric patients

Due to the multiple organ systems affected by FD and the complexity of disease management, it is recommended that multidisciplinary clinical teams should be established wherever possible to oversee the management of pediatric patients with FD [19]. The team should be coordinated and led by a single physician experienced in FD management, often a geneticist. This lead clinician can coordinate patient care with the assistance of cross-specialty colleagues. These include, as appropriate, a pediatric cardiologist, a pediatric nephrologist, a pediatric neurologist/pain specialist, a genetic counselor, and potentially other subspecialty services such as gastroenterology, psychiatry and psychology, as well as the patient's primary care physician, ideally in a treatment center that has experience treating FD.

The genetic implications of FD screening are also important. It has been reported that when the first family member is diagnosed with FD an average of 5 additional family members are also affected by the disease [50]. Therefore a detailed family history should be taken by an experienced health professional or genetic counselor in order to identify at-risk family members who should be tested. At-risk family members and other family members with plausible FD inheritance should receive genetic counseling and be encouraged to have genetic testing for FD.

3.2. Management of Fabry-related pain in pediatric patients

Management of pain in FD is based on: trigger management; symptomatic therapy; and ERT.

3.2.1. Trigger management

Behavioral management is crucial in the management of pain. The most important aspect of this is the avoidance of triggers. To avoid needless precipitation of pain crises, children with FD need appropriate guidance regarding athletic activities. Trigger management strategies to avoid overheating include use of air conditioning or cooling vests, removing shoes and socks when pain starts, rapid treatment of fever, water spray as a surrogate for sweat when there is hypohidrosis, and avoiding some types of strenuous activity (e.g., long-distance running) that go beyond the patient's tolerance level and capability. Expert management is crucial in order to optimize care for FD patients: a specialist with expertise in management of chronic pain should be involved to create a planned, stepwise approach to the management of pain.

3.2.2. Symptomatic therapy

3.2.2.1. Management of neuropathic pain. Any pain management program should involve the judicious use of neuropathic and general pain-reducing agents. Medications should be escalated following a stepwise, managed approach that allows for optimization of therapeutic/side effect before adding or switching to an alternative medication (Fig. 1) [46]. Strategies for both chronic pain and pain crises should be developed.

As studies of the impact of specific neuropathic pain treatments to manage Fabry-related pain in both the adult and the pediatric setting are lacking, guidance regarding the use of different agents is derived from considerable experience from adult patients with painful polyneuropathy, post-herpetic neuralgia, trigeminal neuralgia, spinal cord injury, and other neuropathic entities. Possible treatments to manage Fabry-related pain include antiepileptic drugs, antidepressants, and topical agents. An algorithm for the selection and use of these agents is detailed in Fig. 1. Neuropathic pain medications should be started as single agents at a low-dose and escalated to therapeutic or adverse effect. Fabry-specific data regarding the use of specific agents do not exist, so recommendations were derived from the expert panel discussion and from existing data on related neuropathic conditions (predominantly diabetic peripheral neuropathy and trigeminal neuralgia). As such, Fabry-specific considerations should be kept in mind when selecting neuropathic pain agents. These include caution with the use of tricyclic antidepressants due to their anticholinergic effects and the potential to worsen autonomic symptoms [51]. Topical agents may be considered in the setting of pain crises, a phenomenon unique to the management of pain in FD patients; this modality allows for temporary relief of localized pain without the need for dose escalation as with oral medications or their side effects [51,52]. Opioids, such as tramadol, also have good evidence for efficacy and may be effective as breakthrough agents during crises or when permanent pain flares [52]. Some specialists favor

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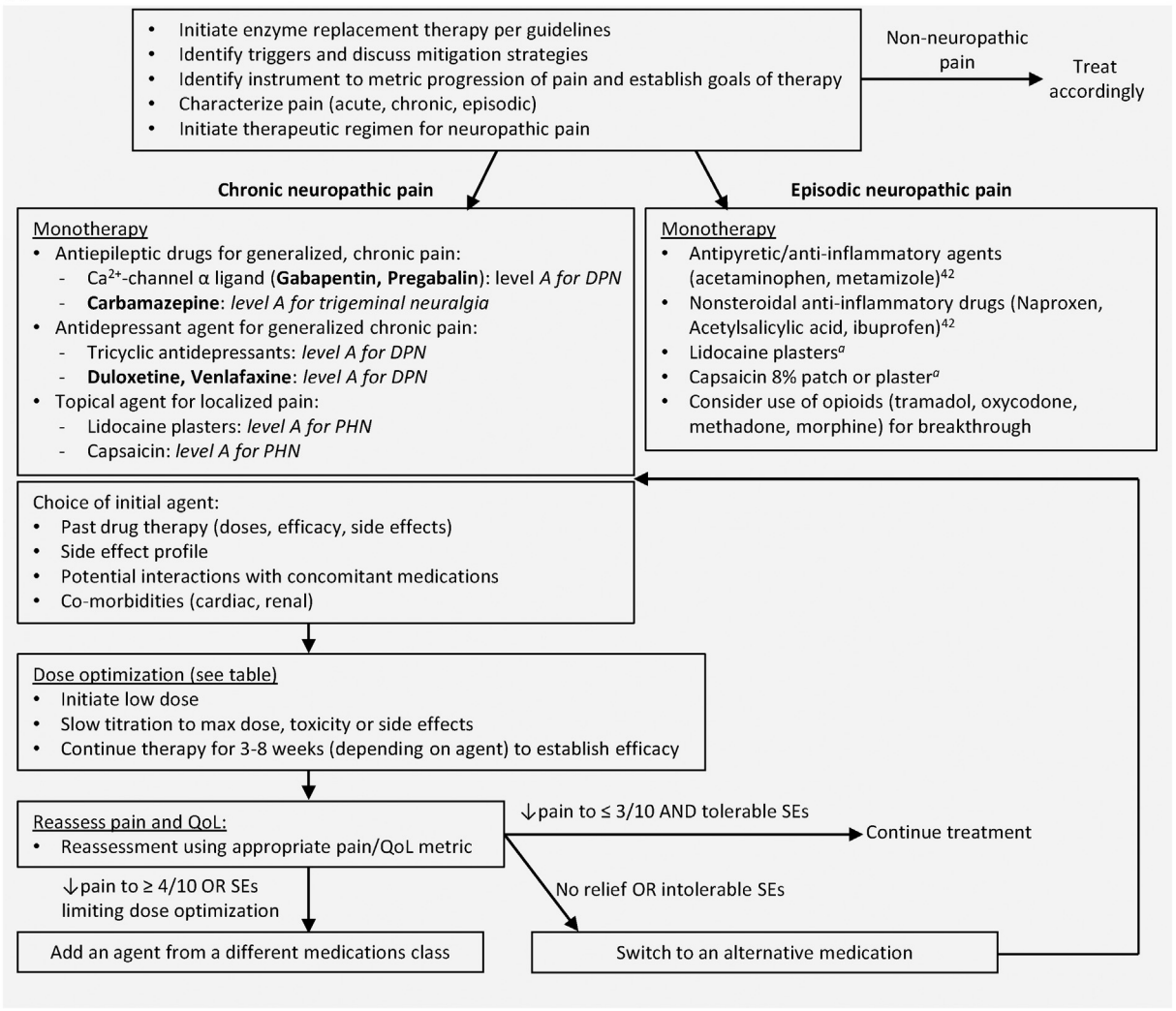
A



B

	Initial dose	Dose titration	Max dose (normal renal function)
Carbamazepine	> 12 y: 200 mg/d bid – qid 6–12 y: 200 mg/d bid – qid < 6 y: 10–20 mg/kg/d	> 12 y: ↑ 200 mg/d qwk 6–12 y: ↑ 100 mg/d qwk < 6 y: ↑5 mg/kg qwk (per level)	> 12 y: 1200 mg/d 6–12 y: 1000 mg/d < 6 y: 35 mg/kg/d
Duloxetine	> 7 y: 30 mg/d	7 y: ↑ 60 mg qd after 1 wk	> 7 y: 60–120 mg/d
Gabapentin	≥ 12 y: 100 mg qhs – 100 mg tid 3–11 y: 10–15 mg/kg/d in 3 div. doses	≥ 12 y: ↑ 100–300 mg q1–7d AT 3–11 y: 5 mg/kg/d q3d	≥ 12 y: 4800 mg/d 3–11 y: 50 mg/kg/d
Pregabalin	Adult: 50 mg tid Children: **NOT APPROVED**	Titrate per adult recommendations	Adult: 200 mg tid Children: **NOT APPROVED**
Tricyclic Antidepressants (amitriptyline, imipramine, nortriptyline)	Adult: 10 mg qhs Children: A: 0.1 mg/kg/d I: 0.2–0.4 mg/kg/d N: 0.05–1 mg/kg/d	Adults: ↑ 10 mg q4–7d AT Children: A: ↑ 0.5–2mg/kg/d over 2–3wk I: ↑ by 50% q3d N: ↑ q3d to effect	Adult: 150 mg qd Children: A: 2–3mg/kg/d I: 2.5mg/kg/d N: 3mg/kg/d
Venlafaxine **First line**	>17 y: 37.5 mg/d > 40 kg: 25 mg/d < 40 kg: 12.5 mg/d	> 17 y: ↑ 75 mg qwk > 40 kg: ↑ 25 mg/wk < 40 kg: ↑ 12.5 mg/wk	> 17 y: 225 mg/d > 40 kg: 75 mg/d < 40 kg: 50 mg/d

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carbamazepine for the control of Fabry pain; however, it has not been shown to be superior to other anticonvulsant agents in clinical trials for neuropathic pain, with the exception of trigeminal neuralgia [53]. Therefore its utility in FD patients has yet to be well defined.

There is an urgent need for comparative randomized controlled trials of pain medication in patients with Fabry neuropathy, including pediatric patients.

3.2.2.2. Management of gastroenterological disturbances. Children with FD commonly experience significant gastrointestinal disturbance, including episodic abdominal pain; severe, explosive diarrhea; and periodic constipation. Patients who experience significant abdominal pain or motility issues should be evaluated and managed by a pediatric gastroenterologist; it is particularly crucial that Fabry patients with gastroenterological problems receive an effective evaluation to exclude other potential causes of their symptoms, such as celiac disease [54]. Significant gastrointestinal disturbances warrant consideration of initiating ERT, as it has been reported to improve the gastrointestinal symptoms [55,56].

3.2.2.3. Management of psychological disturbances. As noted above, mood disorders are exceedingly common among patients, particularly children, with FD; this is particularly true among teenage patients. Psychological disturbances in FD likely reflect both a primary impact of the disease on the CNS and the secondary manifestations of living with a chronic illness throughout childhood [40]. The limited physical activity secondary to pain and decreased exercise tolerance are particularly likely to contribute feelings of being isolated or left out. Boys with FD are commonly slight of build and stature, and are at risk of being bullied or socially marginalized in school during their teen years. Close attention to the psychosocial risks associated with FD and appropriate management should be offered to FD children.

3.2.3. ERT

There are currently two forms of ERT manufactured: agalsidase beta (Fabrazyme; Genzyme, a Sanofi company, Cambridge, MA, USA) and agalsidase alfa (Replagal; Shire Human Genetic Therapies Inc., Cambridge, MA, USA). Agalsidase beta is the only product approved by the Food and Drug Administration for use in the United States. In Europe and many other countries worldwide both products are available [57]. Pediatric studies of both products have found that ERT is safe for use in children [58–60].

ERT treatment during childhood may positively impact school attendance, exercise performance, energy levels, and pain with subsequent improvements on quality of life [58,61,62]. In a recent small study, children receiving ERT experienced a significant improvement in neuropathic pain scores [11]. When correlating pain with disease severity and age, the effect of ERT on neuropathic pain was more significant when ERT treatment was started early [11]. The effect of ERT treatment on pain can be maintained in the long-term as recently seen in a 6.5 years extension study carried out children [63].

3.2.3.1. Timing of ERT initiation. Early initiation of ERT could delay, prevent, or mitigate long-term organ damage to the kidney and heart. A recent study correlated the dose and duration of ERT and the clearance of GL-3 from the kidney: after 65 months of treatment, patients who received a 1 mg/kg agalsidase dose every other week had substantial clearance of podocyte GL-3 inclusions. The greatest clearance was observed in the youngest patient treated, beginning at age 7 years [11]. Although such observations provide indirect evidence that early treatment provides the greatest likelihood of optimal long-term outcome for the disease, there is little consensus on what defines 'early'. Certainly, delaying therapy into adulthood may reduce the potential benefit of ERT in terms of slowing disease progression [11].

The initiation of lifelong ERT infusion therapy is a major decision with important implications for both the child and the family. Considerations include potential interruptions to school activities, the impact of 'medicalization' of a child during his or her social and emotional development, need for repeated venous access (peripheral intravenous cannulation or implanted infusion port) in young patients, and the potential for infusion reactions. However, these factors must be balanced against the possible clinical benefits to be gained from reducing disease progression and preventing irreversible organ damage. Therefore, the decision to initiate ERT should be based on the full range of available diagnostic tests and a thorough dialogue with patients and their families regarding the implications of treatment.

Providing specific recommendations for very young patients identified via newborn or family screening programs is even more challenging. This is because for patients with a predicted non-classic variant or variant of unknown significance, the spectrum of organ involvement and natural history is broad and not fully characterized. However, investigation of family members with the mutation (unless it is de novo) may provide some indication as to severity and the need for treatment.

3.2.3.2. Recommendations for ERT initiation

3.2.3.2.1. Symptomatic patients. Recommendations for ERT initiation are provided in Table 3. Patients reporting Fabry-related symptoms should consider treatment, regardless of age or sex. This includes patients with mild symptoms, as any symptoms reflect underlying disease progression. We cannot recommend using other medications to control Fabry symptoms in order to postpone initiation of ERT. Symptoms such as pain may be less reversible with time and end-organ damage will have progressed. Consensus was reached (primarily based on personal clinical experiences) on the recommendation to treat and manage symptomatic girls and boys in the same way, with the same goal of decreasing symptomatology and reducing the risk of disease progression. These recommendations are quite similar to those independently reached by the European Fabry Working Group [17].

3.2.3.2.2. Asymptomatic patients. Clinicians should consider starting ERT around age 8–10 years in asymptomatic boys with classical Fabry mutations. This consensus recommendation was reached based on data from renal biopsy studies and response to ERT, as reviewed in Section 2.3, which noted greater difficulty in initiating infusions in children younger than this. In addition, a recent report of early disease status in 31 asymptomatic boys with classical Fabry mutations revealed histological evidence of GL-3 accumulation and cellular and vascular injury in renal tissue prior to the onset of albuminuria or other clinically significant renal findings [6]. When to initiate ERT should be a joint decision between clinicians and the family with the inconvenience of infusions and potential medicalization of an asymptomatic child balanced against the desire to prevent damage and the possible reversal of GL-3 storage in podocytes. As some children with Fabry can have significant damage by young adulthood [10], these United States consensus recommendations do not concur with the European Fabry Working Group recommendations for treatment initiation at 16 years [17].

FD patients with non-classic/attenuated/late-onset variants, or those identified through family or newborn screening programs should be monitored closely and treated only once symptoms or signs emerge, or initiation of ERT is suggested by biopsy evidence.

Fig. 1. A stepwise approach to the management of neuropathic pain in pediatric Fabry disease patients. These consensus recommendations are based on the discussions held at the Fabry Expert Panel of United States Fabry specialists meeting. Part (A) shows the recommendations for therapy selection [46]. Part (B) shows the recommendations for monotherapy dose optimization for the treatment of chronic neuropathic pain. [a]Based on recommendations for PHN. A, Amitriptyline; bid, two times a day; d, day; DPN, diabetic peripheral neuropathy; I, imipramine; N, nortriptyline; PHN, post-herpetic neuralgia; qd, every day; qhs, at bedtime; qid, four times a day; QoL, quality of life; qwk, every week; SEs, serious events; tid, three times a day; wk, week; y, years.

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Table 3
Recommendations for initiation of ERT in pediatric patients with FD.

	US Consensus panel recommendations
Symptomatic male or female pediatric patient	• Treatment with ERT should be considered and is appropriate if Fabry symptoms are present in boys or girls at any age • Signs and symptoms warranting treatment suggest major organ involvement – Neuropathic pain crises/Fabry neuropathy – Renal disease (decline in eGFR, pathological albuminuria or pathological proteinuria, creatinine elevation, cellular GL-3 accumulation or evidence of tissue damage such as podocyte effacement on renal biopsy) – Cardiac disease (cardiomyopathy or arrhythmia (including sinus bradycardia) attributable to FD) – Recurrent abdominal pain and diarrhea (excluding alternative causes) – Exercise intolerance and impaired sweating
Asymptomatic male patients with classical (severe) mutations	Timing of ERT depends on individual case (balancing risks and benefits of therapy) Serious discussion regarding the timing of ERT initiation is recommended by age 8–10 years for boys with classical mutations
Asymptomatic female patients and asymptomatic male patients with late-onset mutations or variants of unknown significance	Decision to defer ERT should be based on comprehensive longitudinal monitoring for the development of clinical symptoms and signs of disease, as defined above Family history of the female patients should also be considered

eGFR, estimated GFR; ERT, enzyme-replacement therapy; FD, Fabry disease; GL-3, globotriaosylceramide.

Asymptomatic girls with Fabry mutations should be followed closely using the same schedule of comprehensive clinical assessments as male patients (Table 2). Girls with FD commonly develop non-specific early symptoms such as abdominal pain, diarrhea, and neuropathic pain, around the age of 9–10 years [2]. These symptoms should be considered adequate evidence of progressive disease to recommend the initiation of ERT. However, there is currently insufficient evidence to advocate initiation of ERT for girls with FD who do not have indication of damage on assessments and biopsies, or clinical signs or symptoms of the disease. Nevertheless, they should receive appropriate, proactive treatment early, prior to the development of irreversible end-organ damage.

4. Limitations

Due to the lack of large controlled studies and a formal evidence review, most of the recommendations in this document are Grades C and D.

5. Conclusions

Optimizing the care of young patients with FD is difficult because our knowledge about the condition is incomplete. However, we do know that the first stages of organ damage begin at a very early age and affect both boys and girls. Early diagnosis of patients with symptoms of FD is therefore vital, and it is important to routinely and systematically monitor both male and female children with FD using a comprehensive, longitudinal approach. There is strong circumstantial evidence and increasing clinical recognition of the crucial importance of early treatment initiation to mitigate the long-term impact of the disease. In this context, the appearance of early or mild symptoms suggesting major organ involvement, such as neuropathic pain, exercise intolerance, hypohidrosis, and gastrointestinal problems not due to other causes, should alert the clinician to consider treatment or, at least, to increase vigilance for more objective symptoms prompting treatment initiation. ERT is recommended for all symptomatic pediatric patients, regardless of their sex and the severity of their symptoms. For asymptomatic boys and girls with classical FD mutations, a thorough diagnostic assessment and regular monitoring are important from an early age. Treatment should be considered for asymptomatic boys with classical FD mutations by age 8–10 years, in the context of active, supportive discussions about the risks of long-term organ damage with the family and patient. Asymptomatic girls need to have regular, ongoing monitoring that is maintained throughout their lives with clinical vigilance for non-specific signs such as pain and gastrointestinal signs that could indicate the onset of active disease.

Most importantly, the management of FD requires a coordinated, multidisciplinary care approach, with overarching leadership from a clinician who is an expert treating this rare genetic disease.

Conflicts of interest

Robert J. Hopkin: consults with Genzyme and Shire, and has been an investigator in clinical trials sponsored by Genzyme, Shire, and Amicus. These activities have been monitored and found to be in compliance with the conflict of interest policies at Cincinnati Children's Hospital Medical Center.

John L. Jefferies: declares no conflicts of interest.
Dawn A. Laney: is on the Fabry Registry Board, consults with Genzyme, and has been an investigator and/or coordinator in clinical trials sponsored by Genzyme, Shire, Protalix, and Amicus. These activities are monitored and are in compliance with the conflict of interest policies at Emory University School of Medicine.
Victoria H. Lawson: consults for Genzyme. These activities are monitored and regulated by Ohio State University conflict of interest policies.
Michael Mauer: consults for Genzyme and Amicus, and has reviewed grants for Shire. This interest has been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policy.
Matthew R. Taylor: has been an investigator in clinical trials and research projects sponsored by Genzyme, Shire, and Amicus.
William R. Wilcox: consults for Genzyme and Shire, and is an investigator in clinical trials sponsored for Fabry disease by Genzyme, Amicus, and Protalix. These activities are monitored and are in compliance with the conflict of interest policies at Emory University School of Medicine.

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