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EXPLORING NEUROPATHIC PAIN IN FABRY DISEASE: A REVIEW OF PATHOGENESIS, DIAGNOSTIC PITFALLS AND MANAGEMENT STARTING FROM CLINICAL CASES

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***ABSTRACT* – Background:** Fabry disease is a multisystem disease, with the most serious clinical impact observed in the heart, kidneys and central nervous system (CNS). Neuropathic pain is a key symptom in children with Fabry disease since it is often the earliest manifestation, and it has a considerable impact on overall quality of life.

Case Series: Here we report the cases of two young boys presenting with pain as the only clinical manifestation of Fabry disease, both receiving enzyme replacement therapy. The first patient experienced a partial symptom improvement and is currently under clinical monitoring to detect whether adjunctive symptomatic treatment is needed. The second one showed a progressive worsening of pain over time despite treatment escalation and developed drug dependence and associated significant psychological burden.

Conclusions: These two cases underline the need for accurate and objective pain measurement tools to define the correct time to start supportive treatments and to monitor treatment efficacy. Moreover, the second case remarks on the difficulties in pain management due to the lack of specific guidelines, the risk of overtreatment, and the importance of a multidisciplinary follow-up, including a thorough psychological evaluation in these patients. National and international collaborations are needed to standardize pain measurement modalities and improve symptomatic treatment management, ideally through prospective clinical studies.

Keywords: Neuropathic pain, Fabry disease, Pain measurement, Analgesic drugs.

INTRODUCTION

Fabry disease (FD, OMIM 301500) is an X-linked lysosomal storage disease caused by absent or deficient activity of lysosomal exoglycohydrolase α-galactosidase A due to mutations in the galactosidase alpha (*GLA*) gene[1,2]. This results in an accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids (galabiosylceramide) within lysosomes, leading to a multisystemic involvement with potential complications in various organs, including the nervous system[3]. First clinical symptoms may manifest since 2 or 3 years of age with acroparesthesias, chronic neuropathic pain, hypo- or anhidrosis, and gastrointestinal involvement[4]. These symptoms can negatively affect patients' quality of life (QoL)[5,6]. Pain is often associated with febrile illnesses and involves approximately 60-80% of children with FD[7-9].

Although neuropathic pain may be an early neurological sign of FD, clinical suspicion remains remarkably low in patients lacking typical systemic features, such as angiokeratomas, gastrointestinal disturbances, or cardiac and renal involvement[1]. Its prompt recognition is critical to timely diagnosis and treatment, preventing irreversible organ damage and preventing or slowing the progression of neuropathic pain[10]. Starting from the clinical cases of two patients who initially presented with persistent acroparesthesias and were subsequently diagnosed with FD, we propose a review of the pathophysiology and main features of pain in this rare disease, and current therapeutic approaches for effective symptom management.

CASE PRESENTATION

Case 1

F, a Caucasian male with normal psychomotor development, began experiencing recurrent febrile episodes with exudative pharyngotonsillitis at the age of 3 years. Fever temporarily resolved around age 7 years during the COVID-19 lockdown but recurred a year later with the reintroduction to community life, accompanied by acroparesthesias. He referred to pain primarily affecting the toes, often associated with transient pallor of the extremities and limping. The episodes lasted 3-4 days and occurred 4-5 times per year, with a positive response to paracetamol. At the age of 11 years, F developed motor tics, characterized by neck flexion, facial grimacing and shoulder elevation. Elevated anti-streptolysin O titers supported a presumptive diagnosis of pediatric autoimmune neurologic dysfunction syndrome (PANDAS), leading to monthly intramuscular benzathine penicillin administration with subsequent reduction in both fever and tic frequency. Inflammatory markers and autoantibody panels, including ANA and ENA antibodies, were normal, and rheumatologic evaluation excluded active rheumatic disease. The patient did not report muscle pain or fatigue after sporting activities, which he performed regularly. Moreover, the neurological examination yielded no significant impairments in strength, tone, coordination, or gait, and no indications of neuropathy, dysautonomia, or thermal sensitivity abnormalities were reported, aside from febrile episodes. At the age of 11 years, due to the persistence of episodic extremity pain and poor thermal tolerance during fever, alpha-galactosidase A activity was assessed, revealing a markedly reduced activity (0.9 nmol/mg/h; normal value 45 ± 15.5). Lyso-Gb3 was elevated as expected (35.1 ng/mL), and genetic testing confirmed a hemizygous pathogenic variant (c.999+2T>C) in the *GLA* gene. The diagnosis of FD was established, and enzyme replacement therapy (ERT) with agalsidase beta was immediately initiated without adverse reactions. Three months after the start of ERT, a significant reduction of Lyso-Gb3 was obtained (7.6 ng/ml). After a 12-month period of therapy, febrile episodes completely resolved. Pain persisted, mainly in the toes, but acroparesthesia episodes decreased in frequency, intensity, and duration, occurring 1-2 times monthly and lasting about 1-2 minutes, often triggered by walking on uneven surfaces. Considering that symptoms were overall well controlled, further specific neuropathic pain therapy was not deemed necessary. Moreover, the patient did not report any alteration in skin color or sensory loss, and motor tics did not recur following targeted treatment.

Case 2

IL, the first-born child of healthy, non-consanguineous parents with an unremarkable family history, was delivered at term *via* spontaneous vaginal birth following an uneventful pregnancy. Psychomotor developmental milestones were achieved at the appropriate age, and he was in good health until he was 8 years old. At this age, the patient began to experience recurrent episodes of burning pain localized in the hands and feet. Temperature changes, physical exertion, or intercurrent infections precipitated these episodes. Initial orthopedic evaluation, including foot radiographs, was unremarkable and symptomatic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) was initiated. At the age of 10 years, due to persistent pain, a rheumatological assessment was conducted under suspicion of juvenile idiopathic arthritis. No signs of arthritis were found, and inflammatory markers were within normal limits. However, physical examination revealed angiokeratomas and hypohidrosis. Enzymatic testing demonstrated reduced α-galactosidase A activity in leukocytes (1.8 nM/mg/h; reference: 54 ± 15.5 nM/mg/h), and molecular analysis identified a hemizygous c.979C>A (p.Q327K) mutation in the *GLA* gene, confirming the diagnosis of FD. Cardiac and renal assessments, including echocardiography and proteinuria evaluation, were unremarkable. ERT with agalsidase alfa (0.2 mg/kg biweekly) was initiated at the age of 10 years, along with paracetamol as needed, resulting in initial symptomatic relief. Nevertheless, over the following year, the patient required three hospitalizations for pain crises unresponsive to oral analgesics, necessitating morphine administration. Chronic fatigue, persistent pain, and mood disturbances significantly impaired his quality of life. Thus, at the age of 11, gabapentin and tramadol were introduced, initially on demand and later regularly. At the age of 12, ERT was switched to agalsidase beta (1 mg/kg biweekly), with transient improvement of pain. Within 3 months, pain crises recurred, requiring intravenous administration of tramadol. Subsequently, tramadol was replaced with gradually increasing doses of oxycodone. The patient still reported mild pain during intercritical periods [Numerical Rating Scale (NRS) 3/10]. At the age of 13 years, amitriptyline was subsequently introduced, providing a transient benefit. However, due to recurrent pain crises, both amitriptyline and oxycodone required dose escalation. At follow-up evaluations, the patient still reported severe chronic pain resulting in social withdrawal and increased use of opioid analgesics. In the suspicion of a functional component of pain, a gradual discontinuation of opioids was advised, but was not implemented by the patient. Intensified physiotherapy and psychological support provided partial relief. Chronic pain remained the predominant clinical feature for many years, in the absence of cardiac or renal complications.

DISCUSSION

FD is a multisystem disease, with the most serious clinical impact observed in the heart, kidneys and central nervous system (CNS)[11,12]. Neuropathic pain is a key symptom in children with FD for different reasons. First of all, it is often the earliest manifestation of the disease, and its prompt recognition may lead to an early disease diagnosis and start of treatment, preventing irreversible heart and kidney damage. Moreover, it has a considerable impact on overall patients' QoL, since it is often persistent over time and associated with fatigue, anxiety, depression, and school absences[13]. Its correct evaluation and treatment are still a challenge in FD management and require an accurate evaluation by a multidisciplinary team in an experienced reference center.

Pathogenesis of Pain in FD

Neuropathic pain represents a hallmark of FD. It primarily results from small fiber neuropathy due to the dysfunction and progressive degeneration of thinly myelinated Aδ nerve fibers, mediating pricking pain and cold perception, and, to a lesser extent, unmyelinated C nerve fibres, mediating slow pain, warmth and heat perception, while large-diameter myelinated Aβ fibres are typically spared[14-17].

The accumulation of Gb3 in myelinated and unmyelinated fibres, as well as within the perineurium and endoneurium, results in dysregulation of voltage-gated ion channels and subsequent axonal degeneration, particularly in dorsal root ganglia (DRG) neurons[18,19]. In particular, Gb3 content exceeds 10 times in DRG than in other brain areas, including the frontal cortex, the temporal lobe, and the hippocampus, resulting in neuron stress and death[19-21]. Furthermore, in FD, lipid inclusions are found not only in DRG neurons but also in peripheral nerve axons, correlating with morphological abnormalities such as axonal enlargement and myelin irregularities[20,22]. Moreover, the Gb3 accumulation in keratinocytes has been demonstrated to favor the disruption of intraepidermal small nerve fibers, thereby explaining the typical burning pain and acroparesthesia observed in childhood[4]. The loss of small fibers in Fabry disease primarily affects the distal lower limbs, with the most significant degeneration observed in the feet. However, proximal regions, such as the thighs, may also demonstrate reduced innervation[14,23]. Although not yet directly demonstrated in FD, a length-dependent "dying-back" pattern of axonal degeneration – commonly observed in other small fiber neuropathies, such as diabetic neuropathy – is likely responsible for the greater loss of nerve fiber density in distal compared to proximal regions[24,25]. It has been hypothesized that potassium channel abnormalities and increased sensory neuron depolarization may be associated with pain severity in FD, based on an indirect assessment of potassium channel function[26]. Experimental studies have suggested that some of the spontaneous types of pain in patients with FD may be explained by hyperexcitability of peripheral nociceptive neurons mediated by upregulation of sodium ion channels, transient receptor potential cation channel subfamily V member 1 (TRPV1), or a lyso-GL-3-dependent increase in calcium influx. Since increased lyso-GL-3 levels are directly associated with pain in FD, timely initiation of ERT at adequate doses is a key component of pain-reduction strategy[27]. However, further research is required to investigate these ion channel dysfunctions and their potential contribution to the pathogenesis of the disease. Moreover, the clinical efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in a substantial proportion of patients suggests the presence of nociceptive or inflammatory pain in FD[28]. Furthermore, patients with FD may also experience abdominal pain and diarrhea, primarily due to damage to the small autonomic fibers of the intestinal myenteric plexus caused by glycolipid accumulation, leading to dysregulated smooth muscle activity throughout the gastrointestinal (GI) tract. Additionally, vasculopathy affecting the GI circulation and tissue inflammation related to Gb3 accumulation further contribute to these symptoms[29,30].

Pain Clinical Manifestations and Differential Diagnosis in FD

Pain in FD exhibits a significant interindividual heterogeneity. It can present as acute episodic events, known as “Fabry crises”, characterized by severe burning pain originating in the distal extremities and radiating proximally, often triggered by fever, physical activity, emotional stress, fatigue, or fluctuations in ambient temperature. Conversely, chronic neuropathic pain, referred to as acroparesthesias, is characterized by persistent burning, shooting, or dysesthetic sensations, predominantly affecting the hands and feet[31-33]. Although pain predominantly presents a glove and stocking distribution, specifically the fingers, palms, and soles, episodes of high-intensity pain may also extend to the legs, arms, back, shoulders, joints and head[5,28]. The most prevalent symptoms of FD in the pediatric population under 5 years of age are neuropathic pain, heat sensitivity and digestive symptoms, including abdominal pain and diarrhea[33]. Also, headache, priapism and chest pain have been described in the literature[12,34,35]. Due to the nonspecific nature of pain in FD, it is important to distinguish FD-associated neuropathic pain from other etiologies of small fiber neuropathy in order to avoid delays in diagnosis and treatment. These conditions include diabetic polyneuropathy, autoimmune neuropathies, postherpetic neuralgia, fibromyalgia syndrome, rheumatic diseases, growing pains, especially in preschool-aged children, radiculopathy, traumatic or postoperative neuropathic pain, complex regional pain syndrome, paroxysmal extreme pain disorder, erythromelalgia, idiopathic small fiber neuropathy and celiac disease[27,30,36].

The prevalence of FD has been estimated in several series of “high-risk” patients presenting possible manifestations of FD, such as renal failure, left ventricular hypertrophy and early onset stroke[37-39]. However, diagnosis should be established before irreversible organ damage occurs.

In 2017, a disease screening program[40] was conducted in Russia examining the prevalence of Fabry disease in children with chronic pain in the distal limbs or acroparesthesia, without finding any affected patient. In 2025, the DOUFAB and DOUFABIS studies[41] explored the prevalence of FD in a population of nearly 1,000 patients affected by chronic pain. They were followed in a secondary or tertiary expert center, leading to the diagnosis of FD in one patient and providing an estimated prevalence of about 1/1,000 for the studied population. Consequently, the estimated prevalence of FD did not appear to be higher in this type of population, and it does not seem justified to systematically search for FD in patients with chronic pain who have no other relevant personal or family symptoms that could be FD-related. Nevertheless, as in the cases reported above, in case of pain with characteristics compatible with small fiber neuropathy (burning, tingling, prickling), FD should be excluded, especially in the presence of accompanying symptoms, such as hypohidrosis, impaired heat tolerance and gastrointestinal disturbances[41].

Pain Assessment and Impact on Quality of Life in FD

In previous studies[42], pain was recognized as the most persistent and debilitating symptom of FD, with half of the patients experiencing moderate to severe pain, especially in their hands and feet. Moreover, many studies[43,44] showed that chronic pain is linked to significant psychological burden and diminished

QoL over the long term. In particular, neuropathic pain and anhidrosis have been shown to be predictors of a poorer QoL[43,44]. Polistena et al[45] confirmed that Italian FD patients have a poor average QoL, also lower if compared with patients presenting other inflammatory chronic disorders, such as Crohn's disease, chronic hepatitis, cirrhosis and multiple sclerosis.

Close and prospective monitoring of pain in as many patients as possible is important to gain a better understanding of the natural history of the disease and the rate of disease progression. Additionally, pain quantification is needed to assess the impact of treatments[46].

In the past, many nonspecific scales, such as the Brief Pain Inventory (BPI), the Joint Pain Questionnaire, the Visual Analogue Scale (VAS) for pain and the Numerical Rating Scale (NRS) for pain, have been used in different studies, with variable results in different patients' populations[47]. However, general pain questionnaires fail to cover the entire scope of Fabry pain, and most of them have been developed for adult patients[28].

In 2012, the Fabry-specific Paediatric Health and Pain Questionnaire (FPHPQ)[46] was developed and was used to address the most commonly reported symptoms experienced by children with FD, followed in a Fabry registry – the Fabry Outcome Survey (FOS). The questionnaire included three subscales: pain associated with heat or exertion, pain associated with cold, and abdominal pain and fatigue symptoms. Preliminary results indicated that the measurement properties of FPHPQ were valid and reliable for assessing patient-reported symptoms of FD. Other disease-specific tools have been proposed over time, such as the FabryScan[48] and the Wurzburg Fabry Pain Questionnaire[49].

The availability of a valid and reliable measure is crucial to accurately assess the severity of this disabling symptom, especially when aiming to correctly modulate ERT and the other supportive treatments. In fact, an underestimation of pain may lead to a significant decrease in patients' QoL. On the contrary, an overestimation could cause the administration of unnecessary treatments, with the risk of adverse effects and, in some cases, the development of drug dependence, as in our second case report.

The development of a unified FD pain scale and its validation in a multicentric study on a sufficiently wide cohort of patients would be very useful to improve the knowledge of the disease and the definition of response to treatments, even in different centers and countries.

Another challenge in the evaluation of FD patients with pain is the evaluation of small nerve function, since nerve conduction studies are inadequate as they only assess large, myelinated fibers and, therefore, will be normal in most FD patients. 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 settings. Skin biopsy is simple to perform and well tolerated. It 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[50]. It can also be repeated multiple times to monitor disease progression or treatment efficacy[51]. Still, clear indications on the correct timing of skin biopsy and its role in treatment tailoring in FD are currently lacking to our knowledge. Moreover, in case of previous structural nerve fiber damage, improvements in response to ERT or chaperone therapy will be difficult to detect. Novel techniques for assessing small fiber function, such as microneurography, are needed to improve detection and monitoring of small fiber neuropathy during treatment[52].

Finally, in our first case report, a rapid and significant reduction of Lyso-Gb3 after the start of ERT was noticed, in parallel to pain improvement. The possible correlation of Lyso-Gb3 levels with pain as an expression of accumulation in nervous fibers should be explored in a large patient cohort.

Pain Treatment in FD

Clinical studies[53-57] have shown that ERT may improve overall pain scores and pain intensity in patients with FD. Considering that damage to small nerve fibers occurs early, prompt treatment is important to limit damage to the peripheral nervous system[16]. Nevertheless, other studies[28,58,59] report no, or a limited, effect of ERT on pain, and in clinical practice, persistent pain is still a therapeutic challenge in FD and compromises significant health-related QoL (HrQol)[60-63]. Interestingly, a survey of 367 FD patients found that the occurrence of pain was irrespective of the use of ERT, ranging up to 80% in patients who received ERT[44]. This suggests that the healthcare needs of FD patients are not being fully met, and adjunctive pain-management strategies are required alongside ERT.

One of the cornerstones in pain management in FD is lifestyle modification with avoidance of possible pain triggers, such as air conditioning, good hydration, rapid treatment of fever and avoiding some types of strenuous activity. However, in many cases, these strategies alone are not sufficient and have to be combined with symptomatic therapy with analgesic drugs. Clinical caution in the selection of analgesics for symptomatic treatment of neuropathic pain is important to avoid undesirable side effects and potential addiction risks[27,64]. Unfortunately, there have so far been no controlled prospective interventional trials that have evaluated adjunctive pain therapies in FD. As a consequence, current recommendations mainly derive from small observational studies, expert panel discussion and from existing data on related neuropathic conditions (predominantly diabetic peripheral neuropathy and trigeminal neuralgia)[31,50]. Moreover, since conditions that cause neuropathic pain in children are relatively uncommon, data on general neuropathic pain treatment in children are limited by small numbers and few randomized controlled trials, leaving clinicians with many unanswered questions regarding clinical practice[65]. Despite the paucity of evidence, a treatment algorithm for the treatment of neuropathic pain in children with FD was published in 2015 by the US group[50], proposing an escalation of symptomatic medications following a stepwise, managed approach that allows for optimization of therapeutic/side effects before adding or switching to an alternative medication[50].

The majority of the proposed therapeutic algorithms indicate that carbamazepine could be used as the first monotherapy agent in case of chronic neuropathic pain[50,64,66]. Another possible first-line agent is gabapentin, even if little evidence is available on its real efficacy in FD[64,66].

Other medications that are used for Fabry pain include tricyclic antidepressants (TCA), amitriptyline and nortriptyline, as well as the selective serotonin-noradrenaline reuptake inhibitors (SSNRI) duloxetine and venlafaxine. Their use is suggested in patients with pain associated with a diagnosis of anxiety and depression[66]. However, caution is recommended in the use of antidepressants due to their anticholinergic effects (e.g., constipation, anhydrosis, palpitations) and the potential to worsen autonomic symptoms[50].

Lidocaine patches and high-strength capsaicin patches are second-line options[67]. Opioids are shown to be effective in the treatment of painful crises, but they should be used with great caution since their chronic use may cause constipation, drowsiness, dependence and involve the risk of substance abuse[64], as in our second case report. The same case remarks on the importance of periodic psychological evaluation and of non-pharmacologic approaches, including psychological and physical treatments. As previously reported, these treatments should be implemented, since they have been proven effective in the relief of pain and the treatment of comorbid disorders, including anxiety and depression. Among the psychological treatments, cognitive-behavioral therapies are most implemented to treat chronic pain[27].

The first case report, on the contrary, raises the question of the correct time to start the supportive treatments in relation to the severity of pain, which should be periodically measured in a standardized way to get an early detection of possible subtle deteriorations that could undermine patients' QoL.

Moreover, since ERT or chaperon treatment alone may improve pain in FD patients, in case of mild symptoms, a time interval between the start of ERT and symptomatic treatment would be advisable to prevent the risk of overtreatment.

The key points of pain management in FD have been reported in Figure 1. However, pain management strategy should be tailored to each patient, considering many factors in a holistic perspective with a multimodal treatment approach. Even though it might not always be possible to fully eliminate pain, a realistic treatment goal should be to reduce pain to manageable levels, avoid pain progression, and reduce the number of pain crises, in order to help patients to successfully cope with everyday life[67].

CONCLUSIONS

In conclusion, pain is a major symptom in FD due to its frequency and impact on patients' QoL. Since pain is one of the earliest manifestations of FD, its prompt recognition has a key role in early FD diagnosis, leading to timely treatment initiation and disease outcome improvement. Proper pain evaluation and management are crucial to improve patients' QoL, but they can be very challenging and heterogeneous in different centers. National and international collaborations are needed to standardize pain measurement modalities and improve symptomatic treatment management, ideally through prospective clinical studies.

Pain in FD diagnosis

- FD should be excluded in each patient with unexplained neuropathic pain, even in the absence of other disease manifestations
- Accompanying symptoms, such as hypohidrosis, impaired heat tolerance and gastrointestinal disturbances, should be sought to guide the diagnostic process
- Acute pain crises, triggered by fever, physical activity, stress or fluctuations in ambient temperature, should raise the suspicion of FD

Pain management in FD

- Enzyme replacement therapy should be started immediately
- Lifestyle modifications (e.g., air conditioning, hydration, rapid treatment of fever and avoidance of strenuous physical activity) are recommended
- Psychological treatments, such as cognitive–behavioral therapies, and physical treatments should be implemented since the earliest stages of pain treatment

Acute pain crises

- First treatment: acetaminophen/anti-inflammatory agents
- Non-responsive crises: possible trial with lidocaine or capsaicin patches
- Opioids: effective but they should be used with great caution

Chronic neuropathic pain

- First monotherapy agent: carbamazepine or gabapentin
- Other possible medications: tricyclic antidepressants and selective serotonin–noradrenaline reuptake inhibitors, but caution is recommended in their use

Figure 1. Key points in the diagnosis and management of pain in Fabry disease. (FD: Fabry disease).

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Annalisa Madeo has served as a speaker or an advisory board member for Sanofi and Takeda. Alessandro La Rosa has served as a speaker for Sanofi. The other authors have no conflicts of interest to disclose.

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