Original Article

Small Fiber Neuropathy in Fabry Disease: a Review of Pathophysiology and Treatment

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Abstract

Fabry disease is an inherited metabolic disorder characterized by progressive lysosomal accumulation of glycolipids 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 a young age. Neuropathic pain and pain attacks are often the presenting symptoms of the disease and start at an average age of 9 years in male patients and 16 years in female patients, but currently a systematic literature review in early childhood showed the presence of these symptoms before the age of 5 years. Clinical studies have shown that enzyme replacement therapy may improve the overall pain scores and pain intensity in patients; improvements in pain outcomes have been sustained during the long-term follow-up, allowing many patients to reduce their use of pain medication. Some indirect evidence from dose-switching studies suggests that enzyme replacement therapy dose may be of relevance to pain outcomes. Considering that damage to small nerve fibers occurs early, prompt treatment is important in order to limit damage to the peripheral nervous system. In this article a comprehensive overview of the existing literature on small nerve fiber pathophysiology and the relationship with neuropathic pain and treatment response in children and adults with Fabry disease is presented.

Keywords

Fabry disease, small fiber neuropathy

Introduction

Small fiber neuropathy (SFN) is a hallmark of Fabry disease (FD), and neuropathic pain is one of the first symptoms in most patients.[1,2] Pain is experienced by 60% to 80% of boys and girls[3,4] with SFN. Two types of pain have been described. The first type is the episodic painful crises, also known as "Fabry crises," characterized by agonizing burning pain starting in the extremities and radiating centripetally. It may be precipitated by fever, exercise, fatigue, stress, or rapid changes in temperature.[5,6] The second type is chronic pain (classically referred as "acroparesthesias") characterized by burning, shooting pain, or dysesthesias in the hands or feet. Although these 2 types of pain are widely accepted, recently the Würzburg Fabry Center in Germany developed and validated the Fabry Pain Questionnaire for adult patients.[7]

In children with SFN due to FD, reductions in feelings of well-being, school attendance, and 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 in the quality of life in both males and females.[8,9]

The early neurologic manifestations of FD 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 nonspecific gastrointestinal pain.[10] Although first symptoms appear in childhood, correct diagnosis may be delayed well until adulthood.

Recently, Laney et al, reported that neuropathic pain (including chronic pain and acute pain crises) in the hands and feet (acroparesthesia) and tingling are usually intermittent in pediatric population, which are triggered by extreme temperatures, fever, fatigue, stress, overheating, or exercise.[11] There are published reports of 10 children in the early childhood age-group with acroparesthesia/neuropathic pain, ranging in age from 2.0 to 4.0 years. There are also reports of pain crises

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specifically in one 2.5-year-old and one 4.0-year old. Although not as common in the population younger than 5 years of age, children with FD can exhibit reduced sweating or hypohidrosis, as found and reported in 4 children of 2.5 to 4.0 years. This may combine with autonomic dysfunction to result in exercise and heat intolerance, although it has not been studied in children younger than age 5.[11]

The suspicion of FD is extremely low, if not absent in patients presenting with SFN without concomitant symptoms or signs compatible with FD (skin lesions, gastrointestinal complaints, hearing loss, cardiac, or renal involvement). Knowledge of "extraneurological" manifestations is imperative to increase the suspicion index, because in adult patients with isolated SFN routine screening for FD does not seem warranted.[12]

Even when the central nervous system involvement was rarely described in children with FD, this topic is out of the scope of the current paper. The authors recommend Tuttolomondo's reviews to address this specific disease manifestation.[13,14]

Pathophysiology

Small sensory nerve fibers are either thinly myelinated Aδ fibers which transmit mechanical pain sensitivity to pinprick stimuli or unmyelinated C fibers which transmit warm sensation and pain sensitivity to heat. In FD, small fiber hypofunction preferentially affects Aδ fibers.[15-17] Thermal sensation deficits are initially more pronounced in the feet than in hands and gradually progress to more proximal parts. In early stages, impairment of thermal stimuli primarily involves cold perception (Aδ fibers), rather than warmth perception (C fibers),[18] suggesting that the thinly myelinated Aδ fibers are more vulnerable to globotriaosylceramide (Gl_3)-induced damage.[19]

Autonomic small fiber damage in FD is likely to be related to the patients' gastrointestinal dysmotility (eg, abdominal cramps, bloating, diarrhea, and nausea), hypohidrosis, impaired pupillary constriction, decreased tear, and saliva formation, Raynaud phenomena, reduced heart rate acceleration upon exercise and, in advanced stages, orthostatic hypotension.[20-22] The cutaneous response to scratch can be diminished,[23] and baroreflex-mediated vasoconstriction can be deficient due to sympathetic vasomotor nerve fiber dysfunction.[24] Both autonomic sudomotor nerve fibers and sweat gland function are impaired in untreated patients.[25] Of note, the generally accepted assumption that autonomic neuropathy plays an important role in the pathophysiology of FD has recently been questioned by 1 group of investigators.[26] The observation of nearly normal male sexual function and autonomic control of the cardiovascular system in patients with FD led the investigators to suggest that end-organ damage, rather than autonomic dysfunction, might play a prominent role in this disorder.

Sural nerve biopsy reveals selective decrease in small myelinated and unmyelinated nerve fibers.[27-29] Glycolipid deposits are seen in the perineurium, sensory ganglia, vascular smooth muscle cells (SMCs), fibroblasts, and endothelial cells. Reported nerve biopsy analysis indicates a severe loss of nerve fibers according to age, systemic compromise, and kidney involvement. The pathophysiology which leads to neuropathy is not fully understood. One hypothesis is that Gl_3 deposits in dorsal root ganglion (DRG) neurons may conclude in neuronal damage with a dying back neuropathy in terms of a ganglionopathy and may result in reduced intraepidermal nerve fiber density (IENFD).[30] At the same time, Gl_3 deposition in DRG may also interfere with the function of cellular membrane proteins, such as ion channels, thus altering cellular excitability and leading to cytotoxicity resulting in nerve fiber dysfunction and damage. This hypothesis fits well with the observed general reduction in intraepidermal nerve fibers in patients with FD also found in the skin at the back, which is normally preserved from intraepidermal fiber loss in length-dependent peripheral neuropathies.[31,32] A second hypothesis concerns chronic nerve ischemia secondary to Gl_3 deposition within the endothelial cells of the blood vessels supplying nerve fibers.[28] Lyso-Gl_3 has been shown to promote SMC proliferation in vitro and has been proposed to play a role in the development of vascular pathology in FD.[33] Another possible hypothesis is that the increase in the number of small regenerating unmyelinated fibers as seen in some cases[34] in spite of the pattern of nerve fiber depletion generates hyperexcitability and spontaneous firing of sprouting unmyelinated neurites arising from nociceptive axons.

Recently, Choi et al. investigated the direct effects of Gl_3 and lyso-Gl_3 on sensory neurons and pain production.[35] Firstly, the effects of intraplantar hind paw injection of Gl_3 and lyso-Gl_3 on healthy wild-type mice were studied by measuring mechanical withdrawal thresholds to von Frey hairs. In comparison with saline injected controls, Gl_3 and lyso-Gl_3 resulted in robust mechanical allodynia with significantly reduced pain thresholds that lasted for up to 6 hours. Next, exogenous lyso-Gl_3 was applied to DRG sensory neuronal cultures derived from wild-type mice. This resulted in an increase in cytoplasmic Ca^{2+} levels within the sensory neurons in a lyso-Gl_3 concentration-dependent manner.

Diagnosis

Conventional nerve conduction studies assess only large myelinated nerve fibers, thus they are usually normal in FD unless renal failure is present.[15] Previous reports concluded that the neuropathy of FD is characterized by an increased prevalence of median nerve entrapment at the wrist.[36,37] Quantitative sensory testing, quantitative sudomotor axon reflex test, and skin biopsy to assess IENFD are useful to confirm the presence of SFN.[16-18] A prospective single-center study investigated 120 patients with FD for small fiber pathology and peripheral nerve function and followed them for 4 years.[31] At baseline, patients had mostly normal neurological and electrophysiological examinations. In male patients, a strong positive correlation was found between the glomerular filtration rate and distal IENFD. Lower leg IENFD was reduced to 46% in patients compared to controls and to 12.5% in men with impaired renal

function. Women with normal renal function were spared from the deterioration over time. They concluded that sensory impairment and SFN in patients with FD are gender dependent, associated with reduced renal function, and progressive in most patients despite enzyme replacement therapy (ERT). Nevertheless, nerve fibers in proximal skin areas may regenerate in patients with normal renal function, under ERT.

The relation of small nerve fiber involvement and pain has been studied only scarcely. Moreover, 5 studies showed conflicting results. One study in 30 male patients showed more severe small nerve fiber impairment with older age, while no correlation between thermal thresholds and pain severity was found[15]; another study in 19 females found a positive correlation between age and pain severity but no association between IENFD, thermal sensation, and pain severity[38]; a third did not reveal an association between small nerve fiber function and age or disease severity in the 22 male patients studied[39]; the fourth study did not demonstrate correlation between age, pain severity, and nerve fiber function in 12 women with FD, although they did find an association between IENFD and pain intensity[37]; and the last study in 20 males could not demonstrate a correlation between disease severity and IENFD.[40] Thus, the relation of SFN, age, and pain in FD has been unclear so far.

Treatment

Enzyme Replacement Therapy

Clinical research programs of ERT for FD led to commercial availability of agalsidase alfa (Replagal; Shire Human Genetic Therapies, Inc, Cambridge, MA, USA) and agalsidase beta (Fabrazyme; Genzyme Corp, Cambridge, MA, USA) in most European countries in 2001, and only for agalsidase beta in the United States in 2003.[41,42]

In the first randomized, controlled trial investigating pain outcomes as a primary end point, authors reported that 4 of 11 adult patients treated with agalsidase alfa who were taking neuropathic pain medications at baseline discontinued these medications after 1 to 8 weeks of the study (mean 30.5 days) compared with none of the 11 patients receiving placebo.[42] However, when US Food and Drug Administration's Center of Biologic Evaluation and Research reviewed the source of data, including the pain medication dosage records, no evidence was found that the pain outcomes indicated a treatment-associated effect.[43]

In a cohort of patients with low pain scores at study entry, Wilcox et al reported that 5 (8.6%) of 58 patients stopped all pain medications and 6 (10.3%) of 58 had a reduction in dose and/or frequency of their pain medications after 30 months of open-label agalsidase beta treatment.[44] Other report where 22 patients underwent open-label treatment with agalsidase beta for 18 to 23 months, all patients reported a subjective reduction in frequency and intensity of pain.[45] Measures of neuropathy, including detection thresholds of vibration, heat pain onset, and intermediate heat pain severity, were significantly improved following agalsidase beta treatment, with intermediate heat pain in particular normalizing in 16 of 20 patients with initially abnormal thresholds.

Recently another descriptive and observational retrospective cohort study of 10 children, who underwent regular systematic investigations for 1 year to 8 years after initiation of ERT with agalsidase beta, was published.[46] All patients reported acroparesthesias at baseline, 8 had decreasing symptoms during the study period, and 2 patients had a moderate increase in symptoms after an initial improvement. Seven of 10 patients reported abdominal pain at baseline, and 5 had decreasing pain during the study period. All patients experienced an increased level of energy and 9/10 patients reported increased physical exercise performance compared to baseline.

Concomitant Therapies

Painkillers are commonly used to reduce pain in neuropathic pain disorders, including diabetic neuropathic pain.[47] Carbamazepine alone, or in combination with pregabalin, is recommended as the first-line treatment in Fabry neuropathic pain. The presence of spontaneous pain (shooting and burning) indicates an increased excitability of axons (Na+ ectopic channels) and the current demonstration of an increase in the expression of transient receptor potential cation channel (TRPV1) and Nav1.8, supports the use of carbamazepine as the most effective painkiller in FD.[48]

Antidepressants, particularly dual reuptake inhibitors of both serotonin and norepinephrine (Serotonin -norepinephrine reuptake inhibitors [SNRIs]: venlafaxine and duloxetine, and black-box warning for use in the pediatric age-group) are also viable options. Because of their anti-cholinergic effect, tricyclic antidepressants have potential concomitant and difficult side effects in patients with Fabry (eg, accentuation of autonomic instability). The 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.[5] Topical application of anesthetics may provide relief of burning pain or hyperalgesia.

Dietary recommendations to avoid gastrointestinal symptoms mainly involve adjustments to meal content and frequency. Smaller and more frequent meals have also been found to be very helpful. Loperamide has been used to reduce diarrhea crises. Nausea and vomiting can be treated with metoclopramide and domperidone initially, but in cases of gastroparesis or severe symptoms the motilin receptor agonists could be added.[49]

Conclusions

Small fiber dysfunction accounts for many of the incapacitating complaints reported by most children, adolescents, and young adults with FD. These early manifestations (eg, chronic burning peripheral pain and attacks of acute excruciating peripheral pain) should prompt the clinician to consider the diagnosis and to perform appropriate tests. When treatment is indicated before the renal function decline, ERT may improve small nerve fiber function and help decrease pain. The early initiation

of ERT and good supportive pain management using adjunctive therapies may improve the patient's quality of life as well as reduce or delay the likelihood of life-threatening renal and cardiac complications.

Declaration of Conflicting Interests

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