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Reviews

Neuropathy and Fabry disease : pathogenesis and enzyme replacement therapy

Raphael SCHIFFMANN
Developmental and Metabolic Neurology Branch
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Abstract

The neurological manifestations of Fabry disease include both peripheral and central nervous system involvement caused by a deficiency of α-galactosidase A and accumulation of α–D-galactosyl moieties, particularly globotriosylceramide accumulation (Gb_3). These are found in Schwann cells and dorsal root ganglia together with deposits in central nervous system neurons. Involvement of the peripheral nervous system affect mainly small Aδ and C fibers and are likely causally related to the altered autonomic function and neuropathic pain found in this disorder. Other related abnormalities to be discussed are hypohidrosis and other abnormalities attributed to autonomic nervous system dysfunction. The function of the peripheral nervous system is somewhat improved by ERT, with reduction in neuropathic pain and an improvement of the detection threshold for cold and warm sensation in the hand and foot. Improvement in sweating and heat tolerance is also noted following ERT. Despite those positive results, ERT does not normalize the function of the peripheral nervous system.

Key words : Fabry disease ; peripheral neuropathy ; neuropathic pain ; enzyme replacment therapy.

Peripheral neuropathy and hypohidrosis in Fabry disease

The peripheral neuropathy in Fabry disease manifests as neuropathic pain reduced cold and warm sensation and possibly gastrointestinal disturbances. Patients with Fabry disease begin having pain towards the end of the first decade of life or during puberty (1, 2). Children as young as 6 years of age have complained of pain often associated with febrile illnesses with reduced heat and exercise tolerance (3). The patients describe the pain as burning that is often associated with deep ache or paresthesiae. Some patients also have joint pain. Although only up to 80% of Fabry patients develop neuropathic pain, they mostly will do so by age 20 years. Female carriers may develop neuropathic pain with the same age range of onset and clinical characteristics (4,5). In general, neuropathic pain in Fabry disease can be continuous or consist of episodic attacks brought about by body or environmental temperature changes and other stressful situations.

The neuropathy of Fabry disease is associated with increased or immeasurable cold and warm detection thresholds in patients that are significantly different from controls in the hand, and foot (6, 7). The latter is measured using a well-established biophysical quantitative sensory testing technique (8). In addition, this neuropathy is associated with severe loss of intraepidermal innervation at the ankle, and to a lesser extent also at the distal thigh (9). Fabry patients also have reduce tolerance to exposure of the limb to a cold challenge (10). The findings described above indicate that Fabry disease is associated with a length-dependent peripheral neuropathy affecting predominantly the small myelinated (A-delta) fibers and unmyelinated (C) fibers. The mechanism of this neuropathy is poorly understood. In general, ischemia of nerves caused by glycolipid accumulation in vasa nervorum or an intrinsic nerve dysfunction have been evoked as potential causal mechanisms (7, 10, 11).

Nerve conductions in patients with normal renal function are generally normal except for an increased frequency of median nerve entrapment at the wrist (carpal tunnel syndrome) in some patients. Although usually in the normal range, compared to controls, nerve conduction parameters are significantly impaired (6). One group found nerve conduction of sympathetic skin responses to be generally preserved but of lower amplitude (6). Vibration thresholds is usually normal in the feet and, in some patients, elevated in the hand only, probably due to frequent median nerve entrapment at the wrist (7). However, another group found vibration threshold to be significantly impaired in the distal forearm and hands (6). Pathological examination of the peripheral nerve typically (such as the sural nerve) shows normal number of large myelinated fibers. There is significant loss

of unmyelinated fibers (9, 12-15). Groups of denervated Schwann cells can also be found. Glycolipid deposits are seen in the perineurium and endothelial cells. The lipid deposits in sensory ganglia have been associated with the peripheral neuropathy itself as well as the neuropathic pain of Fabry disease (11, 14, 16, 17). This abnormality can be seen in heterozygote females as well (16).

Most of the patients who suffer from neuropathic pain also have a deficiency in eccrine sweat gland function, but there is no good correlation between these symptoms (18). As a result, children and young adults often complain of poor exercise tolerance resulting from lack of sweating and severe neuropathic pain (1, 2). Patients with neuropathic pain also tend to have lower residual enzyme activity, and have mutations that lead to non-conservative amino acid substitution or to stop codons (19). The sweating deficiency can be demonstrated using a global sweat test, the thermoregulatory sweat test (20-22) or by an iontophoresis method using acetyl choline (18). One modern form of the latter test is the quantitative sudomotor axon reflex test (23) (QSART) that has shown a marked reduction in sweat output in adults and children with Fabry disease (1, 24).

The involvement of the dorsal root ganglions of the peripheral nervous system and sympathetic nervous system was thought to cause anhidrosis or hypohidrosis (11, 25). However, staining of dermal nerve ending for a pan-neuronal protein such as PGP 9.5 demonstrated no decrease in density of sweat gland innervation (26). Skin biopsy in Fabry patients show the presence of sweat glands containing lipid inclusions, particularly in the myoepithelial cells (27-29). The lack of nerve or sweat gland loss, normal neurophysiologic testing (28), the non-neuropathic distribution of the hypohidrosis (18) and the presence of storage material in sweat glands (29) indicate that a dysfunction of the glands, rather then a destructive process, plays a major role in the hypohidrosis of Fabry disease. Acute improvement in sweating 24-48 after α-galactosidase A (agalsidase alfa) supports the functional impairment in sweat glands of Fabry patients (24). Some authors have suggested that both the peripheral neuropathy and the hypohidrosis are caused by an ischemic process (29-31). Although the vascular elements supplying these systems contain quite a bit of the storage material (29), the clinical, physiologic and pathologic characteristics of these disturbances do not support such mechanism. One indication is that blood flow to the skin was not found to be reduced in patients compared to controls (32).

Some of the manifestations of Fabry disease have been attributed to an autonomic neuropathy (18). There is no evidence of a global autonomic abnormality in Fabry disease, with normal plasma epinephrine and norepinephrine as well as preserved skin sympathetic responses (7, 33). However, there are reports of significant orthostatic hypotension and syncope in patients with Fabry disease suggesting a possible localized autonomic abnormalities possibly at the heart (34-36). Some authors consider the abnormality of vasomotor control in Fabry disease to be an indication of a dysfunction of the autonomic nervous system (37-38).

Despite these pathologic abnormalities, the precise mechanism of neuropathic pain is not known. It is likely that the increased levels of globotriaosylceramide in extra-lysosomal membranous compartments interfere with the function of critical proteins such as ion channels. In general, neuropathic pain, whether of peripheral or central origin, is characterized by a neuronal hyperexcitability in damaged areas of the nervous system (39). The peripheral hyperexcitability may also be due to molecular changes at the level of the peripheral nociceptor, in dorsal root ganglia, in the dorsal horn of the spinal cord, and in the brain (40). The neuronal hyperexcitability and corresponding molecular changes in neuropathic pain have many features in common with the cellular changes in certain forms of epilepsy (41). These changes include increased expression and distribution of sodium channels (42), abnormal responses to endogenous pain producing substances and cytokines such as tumor necrosis factor (TNF), and an alteration of calcium influx into cells (40). This has led to the use of anticonvulsant drugs for the treatment of Fabry neuropathic pain with some therapeutic efficacy (43, 44). However, the mechanisms by which accumulated globotriaosylceramide cause nerve dysfunction is not yet clear.

Effect of enzyme replacement therapy (ERT) on the peripheral nervous system

Our studies, and those of others, focused on neuropathic pain scores, sensory detection threshold for cold, warmth and vibration, sweat function and epidermal innervation density. There was also an attempt to study the effect of ERT on hearing in Fabry disease that we shall briefly allude to.

Neuropathic pain

In the initial NIH 6 months randomized controlled study we found a significant reduction in pain scores, using the Brief Pain Inventory, in patients on enzyme compared to placebo (45). When the placebo patients crossed over to receive agalsidase alfa they exhibited a similar benefit (24). When followed over a longer period of time, however, there was no further reduction in pain scores. For these studies patients were selected for severe neuropathic pain and neuropathic pain medication were stopped one week prior to pain scoring (24).

Our clinical impression since then confirms these initial findings. Neuropathic pain is reduced in patients, including children (unpublished data) but usually it is not eliminated and patients often require the continued pain medications, albeit at a lower dose.

Peripheral nerve sensory function

Using a well-established biophysical method based on computerized automated sensory testing equipment (CASE IV, WR Medical, Rochester, Minnesota) to measure detection thresholds for warmth and cold in the foot, thigh, and hands, patients with Fabry disease had significantly elevated detection thresholds for warm and cold stimuli in the foot and for cold in the hand compared to controls. Warm sensation was found to be normal in the hands (24). ERT with agalsidase alfa had no significant effect on these sensory parameters over the 6-month randomized controlled trial. Over the 3 years of open-label treatment, there was a significant but modest reduction in the cold and warm detection thresholds in the foot in both groups and for warm perception in the thigh. There was also a trend reduction of cold detection thresholds in the hands (24). This effect took more than 18 months to occur and sensory function seemed to stabilize thereafter. Similar results, looking particularly at heat pain thresholds, were obtained by a group treating patients with agalsidase beta (38). These authors also describe improvement in vibration detection thresholds. In two separate studies we found that patients with Fabry disease had normal vibration detection threshold. However, over time there was no change in vibration threshold in the hand, but a significant increase in the foot threshold possibly reflecting uremic neuropathy or just disease progression in some patients. Of note, vibration detection function for the patient group as a whole, remained in the normal range (24). ERT over 18 months was not associated with increased epidermal innervation density in the distal thigh (46).

Overall, although these findings are encouraging, they do not suggest complete normalization of the peripheral nerve function. It is possible that early treatment before irreversible axonal loss, or higher and more frequent dosing may be more effective. Alternatively, as seen also in the Fabry vascular diathesis, perhaps the infused enzyme has insufficient access to affected sensory nerves and ganglia. This hypothesis is supported by the observation of poor storage clearance in non-vascular endothelial cells in a patient who received 2.5 years of infusions of agalsidase beta (47). In the same patient, the dorsal root ganglia cells had marked lysosomal storage identical to the ones seen in non-treated patients (11, 47).

Sweat function

Sweat function in Fabry disease is particularly attractive to study since it is possible to directly measure sweat gland function. Moreover, since the capillaries around the sweat gland are fenestrated, we might expected ERT to improve sweat-gland function relatively early in the course of therapy (48). We studied sweat function using the quantitative sudomotor sweat test (QSART) (23). Since we did not have this technique at our disposal at the start of our initial randomized controlled study, the study of sweat function was possible only at the 3-year time point for this patient cohort. Sweat function was found to improve 24-72 h post-enzyme infusion compared to pre-infusion values while the QSART response normalized in four anhidrotic patients (24). In another study, where we also observed significant improvement in sweat response over time. However, to date, some patients remain anhidrotic despite years of ERT.

In summary, the neuropathy of Fabry disease has all the characteristics of a small-fibre neuropathy similar in many ways to diabetic neuropathy. Elucidating the mechanism by which the glycolipids cause this abnormality may contribute to our general understanding of the pathogenesis of such neuropathies in general and may lead to better therapies. Specific treatment should be improved possibly also by improving the accessibility of the infused α-galactosidase A throughout the organ systems.

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R. Schiffmann, M.D.,
Developmental and Metabolic Neurology Branch,
National Institute of
Neurological Disorders and Stroke,
Building 10 Room 3D03,
National Institutes of Health,
Bethesda, Maryland 20892-1260.
E-mail : rs4e@nih.gov.