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Review

Neuropathic pain in Anderson-Fabry disease: pathology and therapeutic options

John MacDermot [a,*], Kay D. MacDermot [b]

[a] *Medicine and Therapeutics (Division of Medicine), Imperial College School of Medicine, Chelsea & Westminster Hospital, London SW10 9NH, UK*
[b] *Department of Medicine, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK*

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Abstract

An inherited deficiency of the enzyme α-galactosidase A is manifest clinically as Anderson-Fabry disease. Most affected patients present with severe peripheral pain in childhood or early adult life, and frequently progress to multi-organ failure by the 4th or 5th decades. The present review examines the probable mechanisms that contribute to pain in these patients, and outlines some of the treatment options that are currently used. The successful outcome of the first two trials of enzyme replacement therapy suggest that this disease might be amenable in the future to gene therapy. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Anderson-Fabry disease is a rare disorder of glycosphingolipid metabolism in which there is accumulation of globotriaosylceramide (GL-3, Gb_3) in many tissues including endothelial cells, pericytes and smooth muscle cells of blood vessels, renal epithelial cells, cardiac myocytes and numerous neuronal cells (reviewed in Brady and Schiffmann, 2000). The disorder is caused by an inherited deficiency of the enzyme α-galactosidase A, which is transmitted as X-linked recessive, leading to disease in hemizygous males and also variable expression in carrier females. The gene encoding α-galactosidase A has been sequenced, and over 100 different mutations were identified in affected individuals (Ashton-Prolla et al., 2000; Desnick et al., 1995).

Anderson-Fabry disease usually presents in childhood with acroparasthesia (constant burning pain) especially in the toes and fingers, and with painful crises, during which there are extremely severe attacks of sharp pain. In most patients, painful crises are triggered by sudden changes in environmental temperature, and cold or heat exposure (and even the change in skin temperature that follows vigorous exercise) are avoided by patients with the condition. A progressive peripheral neuropathy is usual, and later manifestations of the disease include end-stage renal failure, distressing gastrointestinal symptoms (particularly diarrhoea, vomiting and abdominal pain), cardiomyopathy, and progressive central neurological deficits as a consequence of cerebrovascular disease. The characteristic skin rash in Anderson-Fabry disease consist of numerous tiny red lesions starting in the genital area (angiokeratoma) and later becoming widespread. Patients frequently suffer with hypohidrosis (decreased sweating) and heat intolerance.

2. Structural and functional neuropathology

Storage of Gb3 is widespread within the nervous system of affected individuals with Anderson-Fabry disease. Characteristic Luxol fast blue-positive deposits were observed quite widely in the central and peripheral nervous system, most particularly within selected neurons of the spinal cord, brain stem, amygdala, hypothalamus and entorhinal cortex (deVeber et al., 1992). The extent of the accumulated lipid appears, however, to be underestimated by this technique, and use of a Gb3-specific monoclonal antibody revealed more extensively stored lipid within both cerebral cortex and spinal cord (deVeber et al., 1992). Blood vessels throughout the nervous system have also been examined, and these reveal widespread deposition of Gb3 (deVeber et al., 1992). Peripheral and autonomic neuropathy is a feature of Anderson-Fabry disease, and extensive

* Corresponding author. Tel.: +44-20-8746-8144; fax: +44-20-8746-8887.
E-mail address: j.macdermot@ic.ac.uk (J. MacDermot).

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accumulation of lipid had been described in both dorsal root (Gadoth and Sandbank, 1983) and sympathetic ganglia (Hozumi et al., 1989). The identity of the lipid was confirmed as Gb3, and quantification revealed levels in excess of 30-fold above that found in tissues from unaffected individuals.

The anatomical location of the particular fibres or structures involved in the development of nerve pain in affected individuals has not been fully elucidated, but the typical effect of cold exposure as a trigger for peripheral pain, suggests the involvement of Aδ- and C-fibers, which are implicated in painful responses to changes in temperature (Hensel, 1976; Darian-Smith, 1984). Painful dysaesthesia in affected individuals are however also attributed to the accumulation of lipid in dorsal root ganglion cells. The relative contribution of disordered neuronal activity in dorsal root ganglia versus small peripheral fibres has yet to be clarified. The evidence in support of a primary abnormality in dorsal root ganglia is based on the observation that loss of small peripheral myelinated fibres (in the sural nerve) appears not to correlate with the presence of pain (Gemignani et al., 1984). It was thus inferred that pain sensation most probably originates in structurally abnormal ganglion cells with aberrant discharges in small rather than large fibre input to the dorsal horn of the spinal cord. Inhibitory nociceptive Aδ- and C-afferents might amplify spinothalamic transmission by blockade of the inhibitory input from the substantia gelatinosa according to classic gate theory.

There is evidence, however, supporting the alternative possibility of a more peripheral origin for the pain in Anderson-Fabry disease. In a recent systematic examination of painful responses following cold exposure (Hilz et al., 2000), warm and cold perception thresholds were measured before and after immersion of a lower limb in water at 5 °C. During this study, affected individuals experienced pain, and were only able to tolerate a 30-s exposure to the cold if there were interruptions. Furthermore, following immersion in cold water, there was a striking increase in thermal threshold that was sustained for times up to 80 min. The authors concluded that the most likely explanation for the acute severe pain was a temperature-dependent vasoconstrictor response in stenotic small vessels supplying peripheral tissues. In addition, a critical decrease in blood flow through vasa nervorum might also explain the apparent decompensation of Aδ- and C-fiber function.

Deposition of lipid in both dorsal root and autonomic ganglia might predictably compromise reserve function of peripheral nerves, and biopsies taken from patients with disease reveal quite extensive accumulation of lipid granules in perineural cells and in particular in the exons of unmyelinated fibres of dermal nerves (Cable et al., 1982a). Furthermore, there is an absolute reduction in the numbers of both small myelinated and unmyelinated fibres (Cable et al., 1982a). In the group of patients studied by Hilz et al. (2000), small fibre function was substantially preserved under resting conditions, but decompensated rapidly, and for a substantial period, following the vasoconstrictor challenge with cold water. The author's conclusion that this follows impaired flow through stenotic microvessels, and in particular the vasa nervorum is supported by the observation that patients with Anderson-Fabry disease show delayed recovery of skin temperature after semi-ischaemic forearm exercise, leading to relative hypoxia and accompanying hypothermia (Inagaki et al., 1992). There appear to be no systematic interventional studies directed to an examination of the effects of small vessel dilatation in Anderson-Fabry disease, and whether such treatment might modify painful responses to cold and in particular the altered threshold activity in Aδ- and C-fibres during the recovery phase. Dilatation of major resistance vessels with drugs that block L-type Ca^{2+} channels, α_1-adrenoceptor responses or angiotensin II might predictably make matters worse by diversion of blood away from skin, but dilatation of skin microvessels with prostacyclin (Moncada and Vane, 1978) or similar agents might attenuate the exaggerated vasoconstrictor response to cold seen in patients with Anderson-Fabry disease.

The problems associated with altered sensory responses to quite modest changes in skin temperature may be critical for patients with Anderson-Fabry disease. Many patients have an associated autonomic neuropathy with defective sweating (hypohidrosis), which may lead to reduced capacity for thermoregulation during exercise. The cause of the diminished sweating is most often attributed simply to the autonomic neuropathy, but an examination of autonomic function in Anderson-Fabry disease suggested that this might not explain the problem entirely (Cable et al., 1982b). Examination revealed reduced sweating in all patients studied, but paradoxically the loss was distributed uniformly both proximally and distally, which suggests a primary dysfunction of sweat glands as the likely cause, rather than an associated autonomic neuropathy. Other features of an autonomic neuropathy were noted in about half the patients, and included impaired pupillary constriction with pilocarpine and reduced production of both tears and saliva. Electron microscopic ultrastructural examination of eccrine sweat glands in a patient with Anderson-Fabry disease showed numerous lipid cytoplasmic inclusions in the basal cells and secretory coils of the glands, often associated with cell necrosis. Lamellated inclusions were also present in the unmyelinated axons innervating sweat glands, and the adjacent small blood vessels were narrowed by swollen endothelial cells with heavy inclusions (Lao et al., 1998). These findings appear to confirm a complex mechanism for loss of sweat glands in Anderson-Fabry disease involving both an autonomic neuropathy and local lipid deposition.

Patients with Anderson-Fabry disease may experience a striking intolerance of exercise, which is likely to trigger severe painful cutaneous reactions. It seems probable that

these occur as a consequence of altered skin temperature, but there are very limited experimental data confirming that this is indeed the case.

3. Treatment options

Pain management in Anderson-Fabry disease has proven very difficult, and for many patients there is little relief from unremitting background pain with additional episodes of more severe pain triggered by external stimuli as described above. The mainstay of therapy to date has been based on the long-term use of Na^+-channel blocking agents such as carbamazepine or phenytoin. For purely logistic reasons, there have been no large-scale clinical trials, however, and most data have accumulated in the form of small, uncontrolled, observational studies on less than 10 patients each. Many patients appear to get moderate symptomatic relief with carbamazepine, although exacerbation of pre-existing symptoms associated with autonomic dysfunction may complicate therapy (Filling-Katz et al., 1989). In that study (of only seven patients), urinary retention, ileus and other gastrointestinal disturbances were encountered. The benefit of these drugs in neuralgic pain is very dose-related, and in many individuals the final dose and plasma concentration is limited by ataxia, and may well be in excess of the therapeutic level required for treatment of epilepsy.

There are reports of other therapeutic interventions, including the use of neurotropin in two affected siblings with Anderson-Fabry disease (Inagaki et al., 1990). Neurotropin is found in inflamed skin of rabbits following inoculation with vaccinia virus, and its administration in these patients was accompanied by relief of pain, whether triggered by pyrexia, hot weather, bathing or exercise. In one of the patients, there was no relief of episodic colicky abdominal pain with either carbamazepine or neurotropin monotherapy, whereas a combination of the two was reported to eliminate the pain. The authors inferred from their study that the actions of the two drugs might therefore be complementary, but the absence of any further reports of neurotropin therapy in affected individuals leaves the matter unresolved. The possibility that the benefit might be mediated by activation of central monoaminergic pathways has been considered (Inagaki et al., 1990; Hilz et al., 2000).

A prospective double-blind study of plasma exchange therapy was undertaken in Anderson-Fabry disease (Braine et al., 1981) following the report from a single patient of dramatic improvement in his pain with this treatment modality. The procedure was therefore repeated with an additional placebo or sham arm to the study, in which the patient received back his own plasma. Under these conditions, no benefit of plasma exchange was detected, and the study demonstrates (as the authors highlight themselves) the need for controlled studies in diseases prone to unpredictable exacerbation or spontaneous remission.

Low-dose morphine infusion has proven successful, and was reported in a 7-year-old child with frequent intractable episodes of pain (Gordon et al., 1995), in whom aspirin, paracetamol, codeine and phenytoin were ineffective, although treatment with carbamazepine and phenytoin reduced the frequency of severe painful relapses. In this individual, the infusion of morphine (0.06 and later 0.02 mg/kg/h) during seven acute relapses, followed by evening administration of amitriptyline, was accompanied in each case by immediate pain relief. The use of opiates in chronic pain syndromes associated with diseases such as acute porphyria, sickle cell disease and Anderson-Fabry disease is problematic, especially in the young, and is associated with many difficult cultural and social problems. A fuller discussion of the subject has been presented elsewhere (Pegelow, 1992).

The disappointing response of patients with Anderson-Fabry disease to conventional analgesics, sodium channel blockers or other agents used for the relief of neuropathic pain has been accompanied by equally ineffective measures to prevent or minimise in later life the development of renal failure, stroke and other features of multi-organ failure. The recent publication, however, of two interventional trials of enzyme replacement therapy with α-galactosidase A (Schiffmann et al., 2001; Eng et al., 2001) has renewed hope for a better outcome in these patients, and will no doubt stimulate those in the field to develop methods for gene therapy.

Both trials reported widespread therapeutic benefit and strikingly similar improvement in pain symptoms. Specifically, Schiffmann et al. (2001) described the infusion of 0.2 mg/kg α-galactosidase A ($n = 14$) or placebo ($n = 12$) every other week in hemizygous male patients with Anderson-Fabry disease with neuropathic pain. The patients received a total of 12 enzyme or placebo infusions. Neuropathic pain was assessed with the Brief Pain Inventory (BPI) short form, in which pain severity is recorded on a visual analogue scale (0–10). The mean pain score at baseline was marginally higher in the placebo-treated group, but there was a consistent, progressive and significant decline in the "pain at its worst" scores of the treated group ($P = 0.02$). Similarly, there was a decline in overall pain severity ($P = 0.02$), and an improvement in the pain-related quality of life ($P = 0.05$). Benefit was also observed in terms of the requirement for conventional pain medication. A total of 11 patients in the group receiving α-galactosidase were taking medication for neuropathic pain, and of these, four were able to discontinue therapy during the weeks of α-galactosidase A infusion, whereas none were able to stop pain medication during the period of placebo infusions ($P = 0.03$). Furthermore, those patients remaining on medication for neuropathic pain were able to remain for a mean of 74.5 days without their medication if they were in the group receiving α-galacto-

sidase A, compared with 12.9 days in those patients receiving placebo infusions ($P = 0.02$).

The trial reported by Eng et al. (2001) described infusion of α-galactosidase A into 15 hemizygous male patients, each of whom was recruited into one of five groups receiving a total of five infusions of α-galactosidase A at doses of 0.3, 1.0 or 3.0 mg/kg/14 days, or 1.0 or 3.0 mg/kg/48 h. There were no placebo infusions. There were anecdotal reports from the patients of an increased ability to sweat and less fatigue (an important and common symptom in affected patients). Pain was assessed by the Short Form McGill Pain Questionnaire, and a comparison made of symptoms before and after infusion. There was significant improvement in both "overall pain" ($P = 0.03$) and "present pain intensity" ($P = 0.004$) after five infusions at all doses. In addition, the authors reported that the Short Form (SF-36) Health Survey questionnaire revealed that α-galactosidase A infusion was followed by improvement in bodily pain, general health and vitality.

It was not possible to correlate with confidence the improvement in pain symptomatology with changes in accumulated lipid in any particular tissue. Gb3 levels were however measured by ELISA in pretreatment skin biopsies (free of angiokeratoma), and following enzyme infusions, the Gb3 concentration decreased by ~40%. Histological evaluation showed the greatest improvement in the baseline capillary endothelial score in patients in the biweekly dose cohorts. In contrast, Gb3 deposits in pericytes, perineurium, and the muscular layer of arterioles, as well as the histiocytes and fibrocytes, showed little or no change. A full account of the biochemical changes that accompanied these infusions lies beyond the scope of the present review, but GL-3 levels in plasma and critical tissues were significantly reduced. There was of course no information available from either trial about any changes in the extent of lipid accumulation in most neuronal tissues.

The numbers in each trial were quite small and only one of the two studies incorporated a placebo arm in its design. There was general agreement, however, about the benefit conferred in terms of pain relief and general well-being by α-galactosidase A infusion, even though in each case the period of treatment was quite short.

4. Future studies

In future trials, a systematic and quantitative analysis of neuronal structure and function following α-galactosidase A administration would clearly contribute greatly to our knowledge of both the underlying neuropathology and the mechanism(s) whereby enzyme infusion confers benefit in terms of pain relief. There are a number of options that should be considered, the first being proton MRS imaging, in which abnormalities have been reported in Anderson-Fabry disease (Tedeschi et al., 1999). Signals revealing changes in the concentrations of *N*-acetylaspartate, a putative neuron-specific metabolite, were noted widely in the cortex and subcortical areas, together with more discrete white matter MRI hyperintensities and basal ganglia infarcts. These authors proposed the application of this technology to future clinical trials. Less ambitious and certainly less costly options would also include audiometry and auditory evoked responses. A highly significant reduction in threshold sensitivity to sound with a frequency above 2.0 kHz has been observed in patients with Anderson-Fabry disease (Morgan et al., 1990), and such non-interventional protocols (including also nerve conduction studies and spinal-evoked potentials) should be considered equally with peripheral nerve biopsy as markers of improvement within the nervous system.

The benefit conferred on affected individuals by infusion of α-galactosidase A gives reason for cautious optimism that gene therapy, providing a sustained enzyme source, in Anderson-Fabry disease would be a reasonable option in years to come. Life expectancy is reduced in this disease by approximately 20 years (MacDermot et al., in press) and for many patients, there is a considerably reduced quality of life also. It is a rare disorder, affecting probably no more than a few hundred patients in the UK, but the presentation in many affected individuals with severe pain from early childhood makes it a legitimate target for such an expensive therapeutic option.

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