

Poikilothermia in a 38-year-old Fabry patient

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Abstract A Fabry patient with poikilothermia is described. Laboratory investigations, neuro-imaging and autonomic function tests did not disclose a cause. Assessment of intra-epidermal nerve fibre density and quantitative sensory testing revealed small fibre neuropathy with a highly impaired cold sensation. We speculate that the poikilothermia is either caused by a vascular lesion in the hypothalamus not visible on MRI or by small fibre neuropathy leading to disturbed body temperature perception and therefore impaired thermoregulation.

Keywords Autonomic nervous system diseases · Metabolic diseases · Peripheral nervous system diseases

Introduction

Fabry disease (OMIM 301500) is an X-linked glycolipid storage disease caused by deficient activity of the lysosomal enzyme α -galactosidase A. This leads to accumulation of specific glycosphingolipids and results in multi-system disease. Early Fabry symptoms and signs are angiokeratomas, corneal opacities, hypo- or anhidrosis and acroparesthesias.

Later in life renal failure, stroke and cardiomyopathy occur [1]. Most physicians take care of few Fabry patients, and some symptoms have only become apparent upon studying larger patient groups. Hearing loss, for instance, was only recently shown to occur frequently in these patients [2]. Here, we report on an additional possibly related symptom: poikilothermia.

Case report

A 38-year-old man was hospitalised because of malaise in December 2008. He was diagnosed with Fabry disease at the age of 18 years [3], and at that time he had mild proteinuria, ankle oedema and left ventricular hypertrophy with normal cardiac function. In addition, white matter lesions in the right parietal and temporal lobes on MRI, sensory hearing loss and tingling paresthesias of the hands and feet were noted. He has been treated with human α -galactosidase A (Replagal, Shire Inc.) at a dose of 0.2 mg/kg since 2001. He was stable until March 2008 when he was evaluated because of transient hypoalbuminemia. At this time, hypothermia was noted. A few months later, he complained of malaise, slurred speech and difficulty with walking. At admission, physical examination revealed a bradyphrenic man with a body temperature of 34°C. Repeated measurements over the next weeks showed temperatures between 32.9 and 34.3°C. He declined feeling cold. Laboratory investigations, including electrolytes, vitamins, thyroid function and adrenocorticotrophic hormones, were unremarkable except for minimal changes in thyroid hormones [TSH 9.70 mE/L ($N = 0.50$ – 5.00), fT4 12.5 pmol/L ($N = 10.0$ – 23.0)] with negative anti-thyroxine peroxidase (aTPO). Structural lesions of the hypothalamus or its efferent pathways were not seen on cerebral and

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cervical MRI. A forced breathing test, supine-standing up test and Valsalva's manoeuvre were performed and demonstrated normal cardiovascular autonomic function: the difference between maximal and minimal heart rates during the forced breathing test (inspiratory-expiratory difference) was 9 beats per minute, the highest heart rate in the first 15 s from the onset of standing minus the heart rate at baseline ($\Delta\text{HR}_{\text{max}}$) was 20 beats per minute, and the ratio between the highest and lowest heart rate in the first 30 s from the onset of standing ($\text{HR}_{\text{max}}/\text{HR}_{\text{min}}$ ratio) was 1.3. The Valsalva manoeuvre showed a normal heart rate and blood pressure response with a Valsalva ratio of 2.9. Small nerve fibre function was assessed with quantitative sensory testing: a special device that warms or cools the skin was placed over the patient's left hand and right foot. The patient was asked to press a button as soon as he felt the slightest change of temperature to warm or cold. These tests showed a highly impaired cold sensation at the upper and lower limb (see Fig. 1). A skin biopsy taken 10 cm above the lateral malleolus showed an intraepidermal nerve fibre density (IENFD) of 0.71 fibres/mm which is lower than healthy controls (median IENFD 8.4 fibres/mm, 0.05 quantile 4.7 fibres/mm [4]), but similar to other male Fabry patients (median IENFD 0.5 fibres/mm, unpublished data).

During the following summertime, temperature normalised, and the accompanying symptoms resolved. The subsequent decrease of body temperature to 34°C during

the next winter (2009) and again normalisation during the summer of 2010 suggested poikilothermia rather than hypothermia. Poikilothermia is defined as fluctuation in core temperature of more than 2°C due to changes in ambient temperature. Temperature stress tests were not performed. Heat stress testing was considered unethical due to the possible provocation of painful acroparesthesias that occur in Fabry patients.

To find out whether poikilothermia is more prevalent in Fabry disease than previously recognised, we measured body temperatures routinely in 60 Fabry patients (22 males, mean age 43 years) at the outpatient clinic (ambient temperature of 21°C) from September to December 2009. Only one other patient (female, 50 years old, known with white matter lesions, left ventricular hypertrophy and renal failure) had a temperature below 35°C. She also declined feeling cold.

Discussion

Except for heat intolerance due to sweat gland dysfunction, temperature disturbances have not been reported previously in Fabry disease. Maintenance of a constant body temperature is mainly governed by the thermoregulatory centres in the hypothalamus that contain warm-sensitive neurons. These neurons are activated by increase of body temperature and inhibited by input from cold receptors in the skin [5]. Integration of temperature information leads to heat loss responses or to heat conservation and production. Aside from hypothalamic lesions (e.g. vascular, multiple sclerosis and trauma), old age and thyroid disorders are the most common causes of impaired thermoregulation presenting symptoms as described in our patient (malaise, bradyphrenia, slurred speech and disturbed gait). Autonomic neuropathy may contribute to disturbed thermoregulation by impaired control of cutaneous circulation. We studied the autonomic nervous system in our patient showing normal cardiovascular autonomic function. This is in line with our recent study in 48 Fabry patients, where the generally accepted assumption that Fabry patients suffer from overt autonomic neuropathy was rejected [6]. In that paper, we suggested that symptoms and signs compatible with autonomic dysfunction in Fabry patients are mainly caused by end-organ failure due to continuous accumulation of glycosphingolipids. However, other investigators argue that functional autonomic neuropathy is a key feature of Fabry disease due to accumulation of glycosphingolipids in central and peripheral autonomic structures. A recent report on cardiovascular responses to orthostatic challenge in Fabry patients using spectral analysis revealed a reduced sympathetic activation and a limited cardiovagal withdrawal upon standing, suggesting subtle dysfunction of the autonomic nervous system [7]. However, none of the

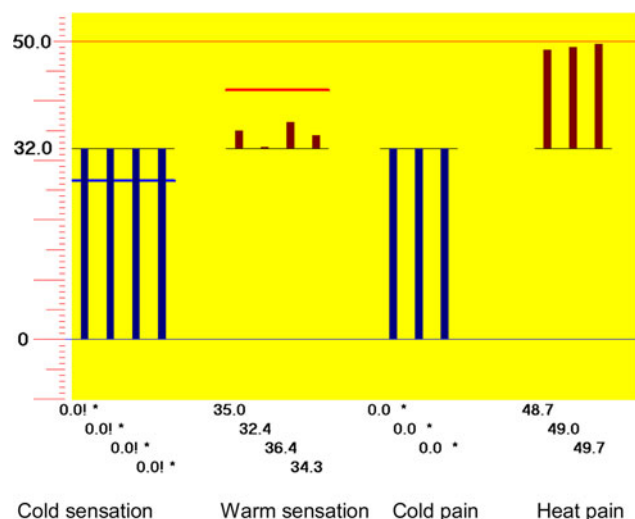


Fig. 1 Quantitative sensory testing results at the lower limb. Quantitative sensory testing consisted of thermal detection and thermal pain thresholds. These tests were performed using a TSA 2001-II thermal sensory testing device. Normative values have been well established in our laboratory. Each test was done four times. This figure shows that our patient has a highly impaired cold sensation at the lower limb: a temperature decrease to 0°C was not perceived as cold or pain. Warm sensation was normal. The horizontal lines represent normative values. Values with exclamation mark indicate abnormal value

studied Fabry patients had overt orthostatic hypotension, whereas this is seen invariably in patients with autonomic neuropathy due to other diseases accompanied by peripheral neuropathies [8]. Abnormalities at the level of the heart, the vascular walls or the baroreceptors themselves could have accounted for the abnormal cardiovascular responses in that study.

Common causes of poikilothermia are hypothalamic lesions or thyroid disorders. In 1996, four women with poikilothermia were described [9]. It was concluded that in these subjects, who had normal blood pressure responses to standing up and Valsalva manoeuvre, poikilothermia had to be attributed predominantly to disorders of the central thermoregulatory pathways, being a trauma, a tumour and an empty sella. Possibly, the poikilothermia in our patient is also caused by a central nervous system abnormality. We cannot exclude for example that the white matter lesions found elsewhere in the brain of our patient point to a small localised vascular episode in the appropriate part of the hypothalamus not visible on MRI. The minimal changes in thyroid hormones are a consequence rather than a cause of the poikilothermia, as shown by its spontaneous normalisation.

Finally, we propose that the small nerve fibre dysfunction could underly the abnormal temperature regulation. Quantitative sensory testing and skin biopsy results showed the presence of a severe small fibre neuropathy, which is a common finding in Fabry disease [10]. These tests were done during summertime when body temperature and thyroid hormones had normalised spontaneously. Possibly, the conduction of ‘cold’ information by small fibres from peripheral thermoreceptors to the hypothalamus is insufficient, while increases in body temperature are detected normally by the hypothalamic warm-sensitive neurons. This imbalance may lead to impaired feedback and therefore to a lower body temperature, especially during the cold winter time. However, if this was the true cause of poikilothermia in our patient, it is remarkable that poikilothermia has not been noted in other equally affected Fabry patients with small fibre neuropathy.

Conclusion

Poikilothermia in Fabry disease may have various causes. In our patient, the disturbed thermoregulation is either

caused by a vascular lesion in the hypothalamus not visible on MRI or by his small fibre neuropathy with highly impaired cold sensation leading to impaired feedback and a low body temperature. More clinical observations and studies are awaited.

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