Assessing small fiber neuropathy and subtle cardiac involvement in Fabry disease

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Abstract

Fabry disease (FD) is an X-linked lysosomal storage disorder characterized by reduced or absent activity of the enzyme α-galactosidase A. Due to systemic accumulation of glycolipids, FD phenotype is diverse, and diagnosis may be challenging. Clinical manifestations include small fiber neuropathy, renal dysfunction, cardiac involvement, cerebrovascular disease, among others. In the present study, we describe biopsy proven small fiber neuropathy and subclinical cardiac involvement in two cousins diagnosed with FD secondary to a recently described pathogenic variant, highlighting the importance of diagnostic tools to document organ damage and allow early treatment.

Keywords

Fabry disease, small fiber neuropathy, cardiomyopathy.

Introduction

Fabry disease (FD) was originally described as "angiokeratoma corporis diffusum" by the dermatologists Johannes Fabry and William Anderson, in 1898 [1–2], being currently recognized as the most frequent systemic lysosomal storage disorder [3]. Markedly reduced or absent activity of the enzyme α-galactosidase A (α-Gal A) results in progressive accumulation of glycolipids, primarily globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (lyso-Gb3), within lysosomes in a variety of cell types, including vascular endothelial cells, cardiomyocytes, renal, arterial smooth muscle cells and nerve cells [4–5]. The X-linked nature of the disease was first recognized in 1965, and α-Gal A is a homodimeric glycoprotein encoded by the *GLA* gene located on the long arm of the X chromosome [6–7]. By this pattern of inheritance men are characteristically affected, and prediction of disease course in female patients is challenging, since this depends on the occurrence of random inactivation of the X chromosome [8]. The phenotype of male patients with FD was initially described as the classic form, manifested with a severe and early onset resulting from the absence or significant reduction (< 1% of mean normal) of α-Gal A enzyme activity. Nonetheless, a proportion of patients will manifest with late onset disease, with varying residual levels of enzyme activity and clinical manifestations [4,7].

In classic FD, neuropathic pain and pain attacks are often the presenting symptoms, typically emerging during childhood, and are usually described as burning or shooting pains or painful pins and needles in hands and/or feet [9–10]. Cardiac damage usually starts early, progresses sub-clinically and classically manifests as left ventricular hypertrophy (LVH) mimicking hypertrophic cardiomyopathy (HCM). Cardiac involvement is the main cause of impaired quality of life and death in those patients, wherein adequate evaluation with cardiac imaging is essential for diagnosis and staging of FD [11–12].

In the present study, we describe subclinical cardiac involvement and small fiber neuropathy in two cousins diagnosed with FD secondary to a recently described likely pathogenic variant [13]. Family history is resumed in Figure 1.

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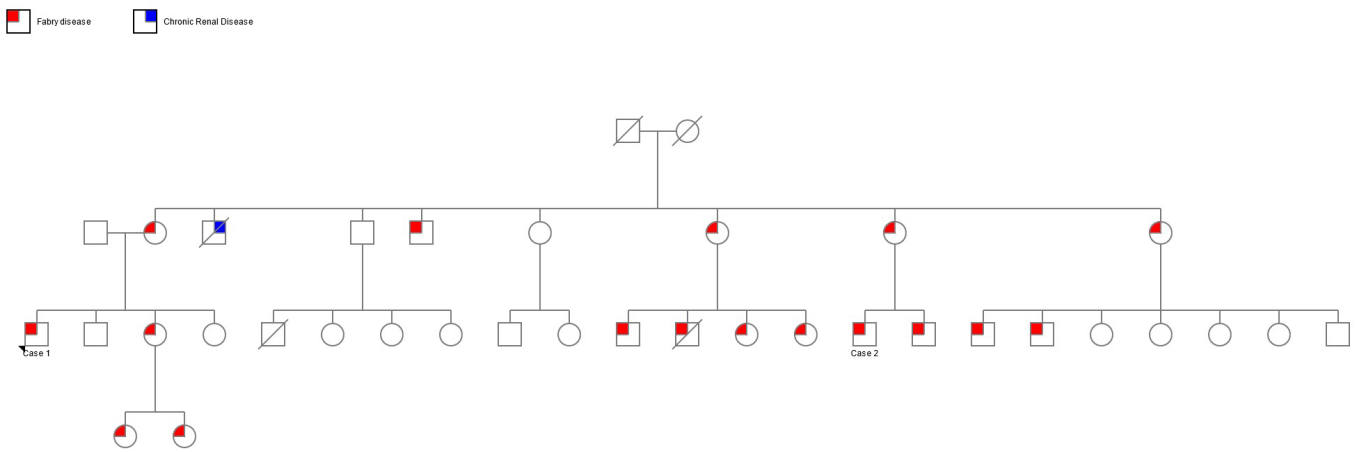

Figure 1. Family pedigree.

Case 1

A 34-year-old man reported that at the age of 11 he started burning sensation in hands and feet during physical activity, improving with rest and when he placed his hands under ice water. These symptoms have improved in frequency and intensity, and he only keeps burning sensation in hands when exposed to heat. Since childhood he has intestinal constipation, evacuating only twice a week, and also postprandial vomiting after a fatty meal. Neurological examination revealed painful hypoesthesia in the feet. Nerve conduction studies were normal. Family history was positive for Fabry disease. Since genetic testing of family members was not available, *GLA* gene was sequenced and identified a variant of unknown significance (PM2, PP3) NM_000169.2: c.454T>G, p.Tyr152Asp (GRCh37). Further studies were performed; MLPA of *GLA* gene didn't reveal any copy number variants, GLA enzyme activity was 0,10 µmol/L/h (normal ≥ 15,3 µmol/L/h) and the serum level of Lyso-Gb-3 was elevated at 41,3 ng/ml (normal ≤ 1,8 ng/ml).

Information from other family members [13], enzyme activity and serum level of Lyso-Gb3 in this patient and his cousin where helpful to stablish PP1 as a further criteria and reclassify this variant as likely pathogenic [14]. Also, a different variant in the same codon has been reported as pathogenic and related to classic FD by Duro *et al* [15] (PM5).

Considering the current diagnostic impression of small fiber neuropathy, a skin biopsy was performed and showed a significant reduction of intraepidermal nerve fiber density (IENFD) in the samples from the distal leg, with an average density of approximately 1,2 IENFD/mm in the evaluated cuts (Figure 2). The observed densities are below the expected values for the patient's age and sex, thus confirming the diagnosis of small fiber neuropathy. A cardiological investigation was also carried out with 12-lead ECG showing sinus rhythm with short PR interval and 24-hour Holter with periods of junctional rhythm. Transthoracic echocardiography (2D-echo) showed mild left ventricular dilatation without increased thickness, but with increased ventricular mass index (LVMI=121.9 g/m2), compatible with eccentric hypertrophy. Traditional measurements of diastolic function showed no abnormalities except for a slight increase in left atrial volume. In speckel-tracking echo evaluation, global longitudinal strain (GLS) was also borderline (-16.9%), and it was reduced, mainly in basal segments with a relative apical sparing pattern, confirming apparent initial cardiac involvement. Cardiac magnetic resonance (CMR) was further performed and demonstrated normal function with boundary thickness of septum and posterior wall of left ventricle. There was a reduction in myocardial native-T1 time, calculated between 759ms and 869ms (normal >900ms) and no alteration in extracellular volume (ECV). In addition, it was described late gadolinium enhancement (LGE) with inferolateral basal uptake, mid-myocardium distribution pattern and total fibrosis estimated in 2% (Figure 2). Audiometry was within normal range. Ophthalmologic evaluation revealed cornea verticillata (Figure 2) and increased vascular tortuosity.

Case 2

A 30-year-old man reported that at the age of 13 he started burning sensation in hands and feet and lipothymia triggered by excessive heat. Such symptoms improved when he lay on the cold floor for 15-30 minutes. He mentions that there was complete improvement of this condition before the age of 25, remaining asymptomatic until the present moment. Neurological examination was normal. Genetic testing identified, as expected, the familial variant on *GLA* gene. The GLA enzyme activity was < 0,8 µmol/L/h (normal ≥ 15,3 µmol/L/h) and the serum level of Lyso-Gb3 was elevated at 45,8 ng/ml (normal ≤ 1,8 ng/ml). Cardiac assessment with 12 -lead ECG and 24-hour Holter were unremarkable. 2D-echo showed mild increased left ventricular inferolateral wall thickness. The longitudinal strain was reduced in lateral wall, but GLS still preserved. CMR has also demonstrated slight thickness of septum and posterior wall of left ventricle and reduction in myocardial native-T1 time. ECV was preserved and subtle LGE was present in inferolateral basal segment, showing underlying fibrosis with mid-myocardium distribution.

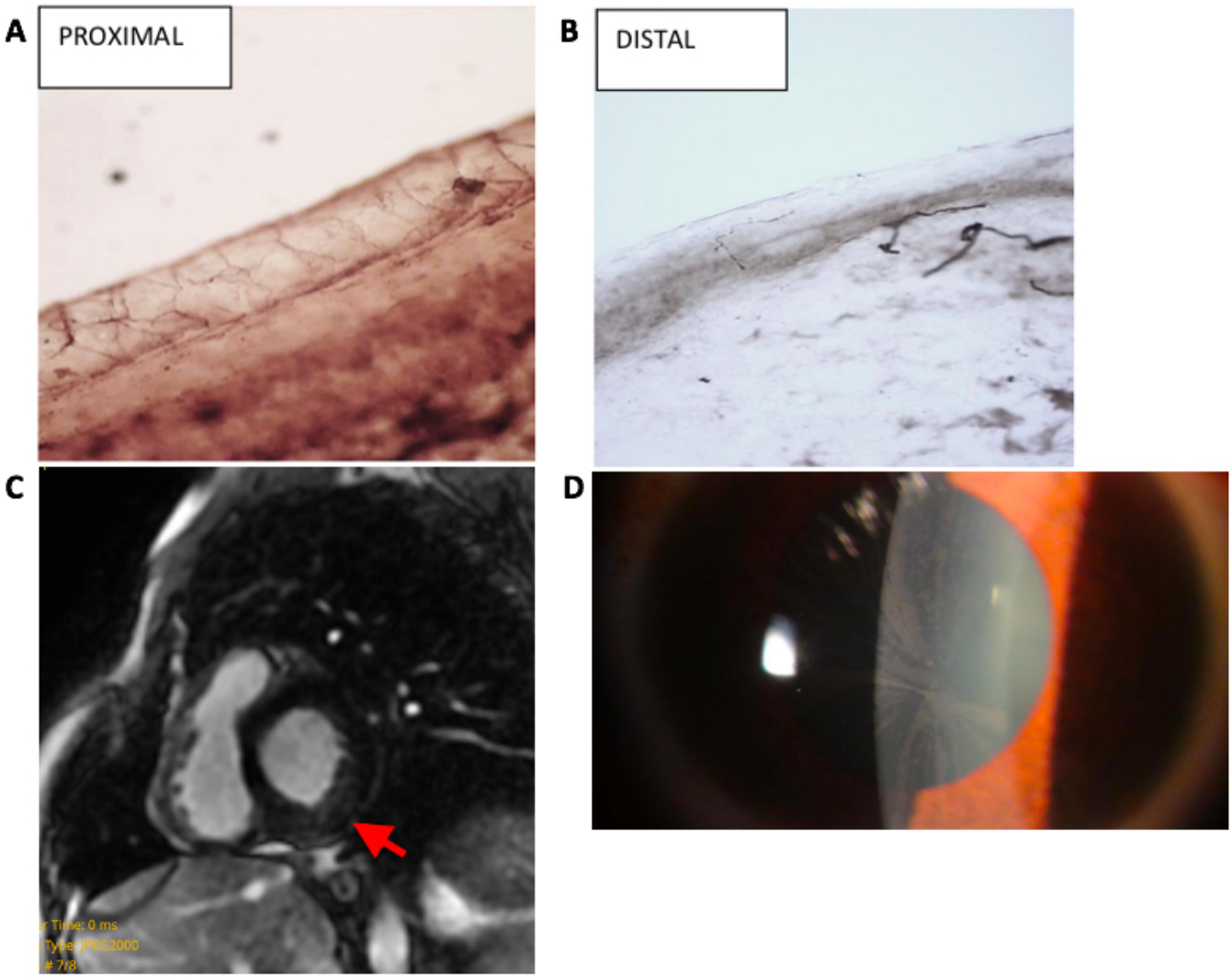

Figure 2. A and B: Skin biopsy showing a significant reduction of intraepidermal nerve fiber density in the samples from the distal leg, in comparison with proximal leg. C: Cardiac magnetic resonance imaging showing late gadolinium enhancement with inferolateral basal uptake. D: Cornea verticillata.

Discussion

In FD, as a consequence of an abnormal function of the lysosomal enzyme α-Gal A, Gb3 starts to accumulate within several tissues including blood vessels, kidneys, nervous system and heart, accounting for the corresponding clinical manifestations [16]. Considering the peripheral nervous system, early neural damage involves small nerve fibers of the peripheral somatic and autonomic systems [16–17]. Neuropathological studies reveal loss of cell bodies in the dorsal root ganglia together with a pronounced reduction of small, thinly myelinated (Aδ) and unmyelinated (C) nerve fibers in sural nerve biopsy specimens [18–19]. The preferential involvement of these nerve fibers characterizes the common finding of small fiber neuropathy (SFN), with onset of related symptoms generally occurring at an earlier age in boys than in girls [20]. Neuropathic pain is a frequent feature of SFN, described in 60-80% of classically affected boys and girls, and can manifest as episodic crises (known as "Fabry crises") of burning pain in hands and feet, usually precipitated by fever, exercise, fatigue, stress, and rapid changes in temperature, and chronic pain with burning and/or tingling sensations [21–22]. In both cases described in the present study, patients manifested with typical "Fabry crises" during childhood/adolescence, in which the painful symptoms were precipitated by specific triggers. As pain may become less prominent in adulthood, it is important to search for a previous history of acroparesthesia in infancy/adolescence during the first examination of a newly diagnosed adult patient, as well as suspect of FD in an adult patient with previous neuropathic symptoms in infancy [23]. Autonomic dysfunction also composes SFN, often starts in childhood and usually remain present during adulthood. It frequently manifests with gastrointestinal involvement, as abdominal pain (often after eating), diarrhea, nausea, and vomiting, possible related to the deposition of Gb3

in the autonomic ganglia of the bowel and mesenteric blood vessels [24–25]. In addition, sweating disorders (anhidrosis or hypohidrosis) are also common and can cause heat and exercise intolerance [25–26]. Despite more extensive knowledge about the phenotype of SFN in FD, the exact underlying pathophysiological mechanism remains unknown, and it is uncertain whether the neuropathy arises from deposits of lipids in ganglia leading to dying-back neuropathy, or from direct damage to small nerve fiber axons [9]. Moreover, diagnosing SFN remains challenging as a golden standard is not yet available [27]. Skin biopsy with linear quantification of intraepidermal nerve fibers density (IENFD) is a reliable and efficient technique to confirm the clinical diagnosis of SFN and should be based on the comparison with normative reference values adjusted by age and possibly gender [28]. In previous studies, reduced IENFD were described in 19 out of 20 male patients [29] and in 27–53% of female patients with FD [30]. Further studies showed that 100% of male and 57% of female patients had an abnormal IENFD [9], together indicating that almost all male and about half to three quarters of female Fabry patients have diagnostic features compatible with SFN. In both cases reported in the present study, symptoms suggestive of SFN were present early, being later confirmed by normal nerve conduction studies and reduced IENFD in the patient who underwent skin biopsy. The diagnostic documentation of SFN allows the establishment of specific organ damage by FD and the indication of early specific treatment.

Although the classically described cardiac involvement is LVH, more common after 40 years of age, cardiac disease is progressive, affects both genders, but in men it occurs earlier than in women [12,31]. With the introduction of new technologies and their use in clinical practice, it is reasonable that we can detect intermediate phenotypes between patients without evidence of heart disease and those with classic signs [32]. Assessment of GLS and T1 mapping /CMR were pivotal at presented cases. GLS (obtained by speckel-tracking echo or CMR) has been shown to add diagnostic value in heart disease associated with FD [32–33]. Although nonspecific, reduced GLS can present including reduced longitudinal strain in the basal inferolateral segment, and it has been described as useful to detect subclinical cardiomyopathy [34]. A reduced regional longitudinal strain involving basal segments with a relative apical sparing was recently described in patients with FD [35]. CMR can be useful, in addition to 2D-echo, in the detection of LVH, specially from apical segments and to assess papillary muscle hypertrophy, described as an early marker [12]. Beyond that, myocardial native T1 mapping is usually altered. It represents a quantitative myocardial signal which is reduced by the sphingolipid storage tissue, representing an initial phase of cardiac involvement and risk factor for disease worsening [36,37]. On the opposite, the ECV is classically normal and can be useful as differential diagnosis from other infiltrations myocardium conditions where the ECV is increased [38]. Here, we described reduced regional longitudinal strain and a native myocardial T1 decreased in patients with FD even before evident and classical LVH. The use of these diagnostic tools is actually recommended [39]. In both cases, tenuous fibrosis was detected through the subtle LGE with a mid-myocardial non-ischemic pattern [40], reaffirming cardiac FD.

Diagnosis of FD is always challenging. The stand-alone identification of a *GLA* variant is not sufficient for diagnosis of this condition. In men with clinical symptoms, the first diagnostic testing should be enzyme activity, unless the familial variant has been identified and has a well stablished classification of pathogenic/likely pathogenic [41–42]. The variant identified in this family has been previously reported by Dias *et al* [13]. However, the authors didn't report which criteria were used to classify this variant nor enzyme activity levels. The case reported by Dias *et al* is the uncle of the patients reported here. Additionally, in this study we provide detailed evidence that this variant is associated with <5% enzyme activity, accumulation of Lyso-Gb3 and organ damage consistent with classical FD.

Conclusion

In the present study we describe male patients from the same family, both with neuropathic and autonomic symptoms that started in childhood, molecular testing and laboratory findings consistent with FD. Non-invasive tests were conclusive in the unequivocal diagnosis of SFN with proven histological evidence in one of them. Despite the absence of cardiac symptoms, it was possible to diagnose early-stage cardiac FD assessed by techniques available but not widely used in daily clinical practice. We hope that reports like this can be useful to encourage screening and follow-up routines in FD patients, enabling early diagnosis and adequate treatment. Up to the moment this variant has not been included in specialized Fabry disease databases (International Fabry disease Genotype-Phenotype database and the Japanese Fabry Database). Therefore, the evidence provided in this study may help to improve the variant classification and refine genotype-phenotype correlations in FD.

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Authors' Contributions

CBB, FS, and MAFDL participated in Conception and design; Acquisition and interpretation of data; Medical writing; Critical revision; and Final approval. APCSN, KMPS, ABVF, and JCN participated in Acquisition and interpretation of data; Technical procedures; Critical revision; and Final approval.

Declaration of Conflicting Interests

The authors declare that the is no conflict of interest.

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