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Original Article

The impact of fever/hyperthermia in the diagnosis of Fabry: A retrospective analysis

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ABSTRACT

Background: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by a deficiency of alpha-galactosidase A enzyme, which leads to the accumulation of its substrate, the globotriaosylceramide or Gb3, in many organs and tissues. Main clinical manifestations of FD are neuropathic pain, angiokeratomas, proteinuria and renal failure, left ventricular hypertrophy and stroke. Fever is also a possible symptom at the onset of the disease during childhood and adolescence, but it is frequently misdiagnosed, causing a delay in FD diagnosis.
Methods: We retrospectively analysed the medical records in our series of 58 Fabry patients, focusing on the proportion of patients who exhibited fever as the main symptom at the onset of FD in order to evaluate the diagnostic delay in these patients.
Findings: In our series, we found a significant proportion of patients with a history of fevers at the beginning of their medical history (20.7%; 12/58). 83% of patients with fever also exhibited acroparesthesias (10/12). Inflammatory markers were elevated in few of those cases (2/12). The mean diagnostic delay was 15.6 ± SD 12.8 years.
Interpretation: Fever emerged to be common as part of the FD clinical spectrum and it significantly contributed to the diagnostic delay encountered with this rare disease. Furthermore, our retrospective analysis indicated that FD patients commonly exhibit episodes of fever in association with other symptoms suggestive of FD (such as episodic pain crisis, acroparesthesias, hypo/anhydrosis, heat intolerance, fatigue and gastrointestinal distress). A careful analysis of the medical history in patients suffering fever could lead to an early and correct FD diagnosis. We believe that fever/hyperthermia, acroparesthesias and angiokeratoma should be considered for inclusion in the algorithm for Intermittent Fever of Unknown Origin (FUO) in order to improve the recognition of FD.

1. Introduction

Anderson–Fabry disease (FD, OMIM 301500) is a lysosomal storage disorder due to an inborn deficiency of alpha-galactosidase A hydrolase [1], which is encoded by the *GLA* gene, located on Xq22. FD affects males, but females can also be affected owing to the X-chromosome Lyonization.

The enzymatic defect causes a progressive intracellular accumulation of globotriaosylceramide (Gb3), which leads to the development of multi-organ and tissue dysfunctions [1–4]. Given the progressive increment of accumulation, clinical presentation varies according to age. During childhood, FD usually manifests itself with hypo-hydrosis and distal extremity pain (acral pain, acroparesthesia) [2,5]. During adolescence, acral pain can improve and, usually, angiokeratomas appears around the "bathing suit area", involving thighs, umbilical region and buttocks [6]. *Cornea verticillata*, tinnitus and gastrointestinal symptoms are also frequently reported at the onset of FD [3]. Gastrointestinal symptoms include abdominal pain, difficulty in digestion and changes in bowel habits, alternating constipation with diarrhoea [2,7]. Tinnitus may appear as an earlier neurological manifestation and can worsen over time, degenerating into hearing loss [8]. More severe

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neurological involvement is represented by early stroke [9]. Proteinuria may develop during adolescence and kidney function can degenerate over time leading to renal failure [10]. The storage of lipids in the conduction tissue of the heart can cause rhythm disturbances in the beginning, usually being accompanied, over time, by concentric hypertrophy and valvular dysfunction [2].

Fever is one of the most important symptoms during childhood [5] in male patients who exhibit the classic severe Fabry phenotype, especially in the early stages of the disease or as a trigger for burning-pain crisis in the limbs [11–17]. Although the elevated body temperature in FD is most often described as "fever" by both patients and physicians, it is doubtful whether it is real fever (meaning a temperature rise due to an elevated hypothalamic set-point as part of the acute phase response). The elevated body temperature in FD has been attributed to alterations of the heat-dispersing mechanisms of the body [18]. The hypothesis of abnormal heat dispersion is supported by the evidence that patients suffer impaired sweating due to the deposition of globotriaosylceramide in sweat glands and in the cholinergic nerve cells [18]. Although we are aware of this, for the sake of clarity, we will use the term fever in this manuscript.

Fever represents one of the early symptoms of FD, which is most frequently misinterpreted, leading to a diagnostic delay of FD [11,17]. Owing to the overlap of the FD clinical spectrum with many other diseases, FD has been addressed as "the new great impostor" [19]. Furthermore, FD has been proposed as a rare cause of intermittent fever of unknown origin (FUO) [20].

Based on such observations, we aimed to analyse fever as the presenting symptom of FD, also taking into account the inflammatory markers, in order to evaluate the impact on the diagnostic delay of the disease.

2. Methods

We performed a systematic review of a case series of 58 patients with a biochemical and molecular diagnosis of FD, that have been treated at A. Gemelli Policlinic, Rome, over a period of 27 years, (August 1987–December 2014). We analysed our records of medical histories and charts to gather relevant clinical information. We searched any mention of recurrent febrile episodes with no proved infectious causes. We also focused on symptoms associated with febrile attacks, which are potentially linked to FD. We included acroparesthesia, Fabry abdominal crisis, heat intolerance, hypo-anhydrosis, gastrointestinal distress (as abdominal pain, dyspepsia and/or diarrhoea), tinnitus, vertigo, evidence of proteinuria, *cornea verticillata* and heart involvement (abnormalities of the electrocardiogram and/or signs of concentric hypertrophy on echocardiographs). The frequency of febrile episodes, the timing of onset and the disappearance of recurrent fever were considered. Whenever available, we recorded laboratory results of markers of inflammation such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and beta-2-microglobulin, performed during febrile attacks. Furthermore, we reported the age at which FD diagnosis was confirmed by enzyme assay and genetic testing. For each patient, the diagnostic delay after the onset of fever was calculated. We also searched for previous medical investigations focused on the origin of the fever. No informed consent was necessary as anonymous retrospective data was collected and analysed according to the principles of the Helsinki Declaration. All data obtained are shown in Table 1–2 [21–29].

3. Results

The medical records of 58 patients (30 males, 28 females) with a genetically confirmed diagnosis of Fabry were revised. 12 of them (10 males, 2 females) presented with fever (20.7%). The mean age of fever onset was 7.4 ± 2.0 years. The duration of the period in which they suffered fever was not clearly described, but all of them reported recurrent fever with <1 febrile episode per month. Two individuals had been manifesting febrile attacks lasting a few hours after physical exercise or sun exposure, while two patients reported to have been suffering one feverish episode per month during childhood and each attack lasted 2–3 days with intermittent fever associated with other symptoms previously described and reported in Table 1. All patients described the disappearance of fever. 2/12 patients reported the disappearance of febrile attacks together with growth. 6/12 patients presented a clear disappearance of fever after enzyme replacement treatment was initiated. 4/12 patients did not associate any specific events with the disappearance of febrile seizures.

The recording of inflammatory markers during febrile attacks showed an increment of C reactive protein higher than 10 mg/l in only one patient, while two patients had high values in their erythrocyte sedimentation rate (ESR). A fourth patient manifested high levels of beta-2-microglobulin during a febrile episode: he was simultaneously experiencing renal failure. 8 patients had a history of stable normal values of the inflammatory markers.

Fever episodes were reported in association with symptoms suggestive of FD by all patients. All of them reported intense fatigue and gastrointestinal problems, such as abdominal pain and change in bowel habits (6 patients complained of abdominal pain, 4, diarrhoea, and 2 had both). 10 patients experienced acroparesthesia during febrile attacks (83.3%). 8 patients complained of heat intolerance (66.6%) and 7 of them also had hypo-hydrosis (58.3%). Only 5 patients experienced typical Fabry crises (pain crisis associated with fever).

The occurrence of organ involvement, as represented by proteinuria, myocardial hypertrophy, and dizziness and/or tinnitus, in the years following the first febrile episode was reported in 3 patients: one of the patients exhibited proteinuria with a rapid disease progression, while two patients received a late diagnosis of FD. Eleven patients had a classical phenotype of FD, while one patient had a late onset of the disease.

We calculated the diagnostic delay in this series, which was 15.8 ± 12.8 years. The longest delay occurred in a patient who received the FD diagnosis at 48 years of age. He underwent several medical investigations since fever occurred in his clinical spectrum of manifestations, which was comprised of only few other mild symptoms. The FD diagnosis was established as a consequence of the identification of FD in one of his other family members.

4. Discussion

Our study allowed us to estimate the frequency and the age of the onset of fever in FD on the basis of a small but significant number of patients. We found that 20.7% patients with FD presented with fever at the onset of the disease. Although several articles are available in the medical literature reporting that children affected with FD may present frequently with febrile attacks [12–17], none of them investigated the occurrence of this manifestation in a large series. Our retrospective analysis allowed us to calculate the frequency of fever in FD. We also pointed out that fever could be present in adult patients with FD.

Other interesting outcomes were the absence of a significant increment of systemic inflammation markers during fever and a weak response of fevers to common antipyretics. The latter observation confirms the absence of an underlying inflammatory mechanism by pointing to alterations in heat-dispersing mechanisms of the body. As previously described in FD, the deposits of Gb3 can reduce the Ac and delta fibres [30], which are responsible for the conduction of nociceptive and thermal impulses, but also lead to a reduction in the amplitude of the potential to specific stimuli [31]. Such dysfunctions could affect the reflex mechanisms of thermoregulation through the activation of muscle metabolism or cutaneous vasoconstriction. An endothelial dysfunction has also been widely documented in FD [32–34] that could lead to an altered control of vascular tone even resulting in overt vasoconstriction phenomena (such as Raynaud phenomenon), contributing to further impairments of thermogenesis and heat dissipation. Hence,