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Case Report

The Many Faces of Anderson - Fabry Disease

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Abstract

The diagnosis of Fabry Disease at the initial presentation can be challenging, given the spectrum of nonspecific symptoms that can mimic other common disorders requiring high clinical suspicion and careful physical examination. For patients presenting with multi-organ involvement: acroparesthesias, hypohidrosis, angiokeratomas, and signs and symptoms of cardiac, renal, cerebrovascular involvement, it is essential to include Fabry Disease in the workup. Impediment in diagnosis leads to delay in treatment and, thus, significant morbidity and mortality not just to the patient but also to other at-risk family members. Our report raises the awareness of early recognition of Fabry Disease manifestations and subsequent management initiation to reduce morbidity and mortality. It also alerts health care providers of the importance of screening at-risk relatives.

Keywords: Fabry disease; Angiokeratoma; Heat intolerance; *GLA* gene; α(alpha)-galactosidase A; Enzyme replacement therapy

Abbreviations

FD: Fabry Disease; GLA: α-Galactosidase A; Gb3: Globotriaosylceramide; ERT: Enzyme Replacement Therapy

Introduction

Fabry Disease (FD) is an X-linked lysosomal storage disease due to pathogenic variants in α-Galactosidase A (GLA) gene that codes for lysosomal enzyme alpha-galactosidase A (α-Gal A) [1]. Based on the residual enzyme activity, the presentation of FD can range from severe classic phenotype (most common) to atypical forms that present later in life and maybe under diagnosed. The classic form typically presents in childhood or adolescence with acroparasthesia, angiokeratomas, sweating abnormalities, corneal opacities, and proteinuria. Later onset types may result in end-stage renal, cardiac (left ventricular hypertrophy, cardiomyopathy, arrhythmia), and/or cerebrovascular (stroke, transient ischemic attack) diseases [2]. Acroparesthesia is thought to be due to length-dependent and Aδ (delta) small fiber neuropathy secondary to the accumulation of Gb3 [3].

Our report describes an adolescent male diagnosed with FD after presenting primarily with persistent acroparesthesia and diffuse rash. We highlight the diagnostic odyssey and the subsequent diagnosis of his six family members. This case emphasizes the importance of careful physical examination and consideration of FD in patients presenting with nonspecific symptoms, thus reducing the delay in starting Enzyme Replacement Therapy (ERT).

Case Presentation

A 15-year-old, previously healthy male, born to non-consanguineous parents of Southeast Asian (Cambodian) descent, was evaluated for burning sensation in his four extremities, a diffuse whole-body rash, and nonspecific symptoms, including anxiety, reduced sweating, and heat intolerance that started six months prior to seeking medical advice. He experienced episodic paresthesia described as warm, pinprick sensations over the hands and feet, which worsened during emotional states, extremes of heat or cold or physical exertion. Upon careful examination, multiple red-blueish angiokeratomas over the trunk and extremities were observed with an overlying eczematous rash that partially obscured the angiokeratomas (Figure 1). Together with a careful assessment of his presenting complaints, FD was considered. Subsequent biochemical testing revealed significantly reduced plasma α-Gal A activity (0.016 U/L, reference range (RR): 0.074-0.457) and markedly elevated lysosomal Gb3, confirming the diagnosis of FD. Molecular testing revealed a previously reported hemizygous, likely pathogenic, maternally inherited variant in the *GLA* gene (c.640-801G>A). Further evaluations, including ophthalmologic, cardiac, and audiology exams, were unremarkable. However, his urinalysis revealed microalbuminuria and a slightly reduced Glomerular Filtration Rate (GFR) with normal plasma creatinine (Cr) and electrolytes. He was soon started on ERT (agalsidase beta, Fabrazyme) infusions in addition to the Gabapentin that was started earlier to help with the acroparesthesia. Overall, his symptoms have been alleviated, allowing his daily functioning and school activity to return to normal with ERT initiation. Following the diagnosis, at-risk relatives were screened for the same variant in GLA, which was detected in his mother, asymptomatic 23-year-old brother, two maternal aunts, and their offspring, as shown in the pedigree (Figure 2). The maternal grandfather was reported to have renal disease. Unfortunately, both maternal grandparents passed away, and genetic testing was not possible. Other at-risk relatives declined testing. Summary of the clinical manifestations and our

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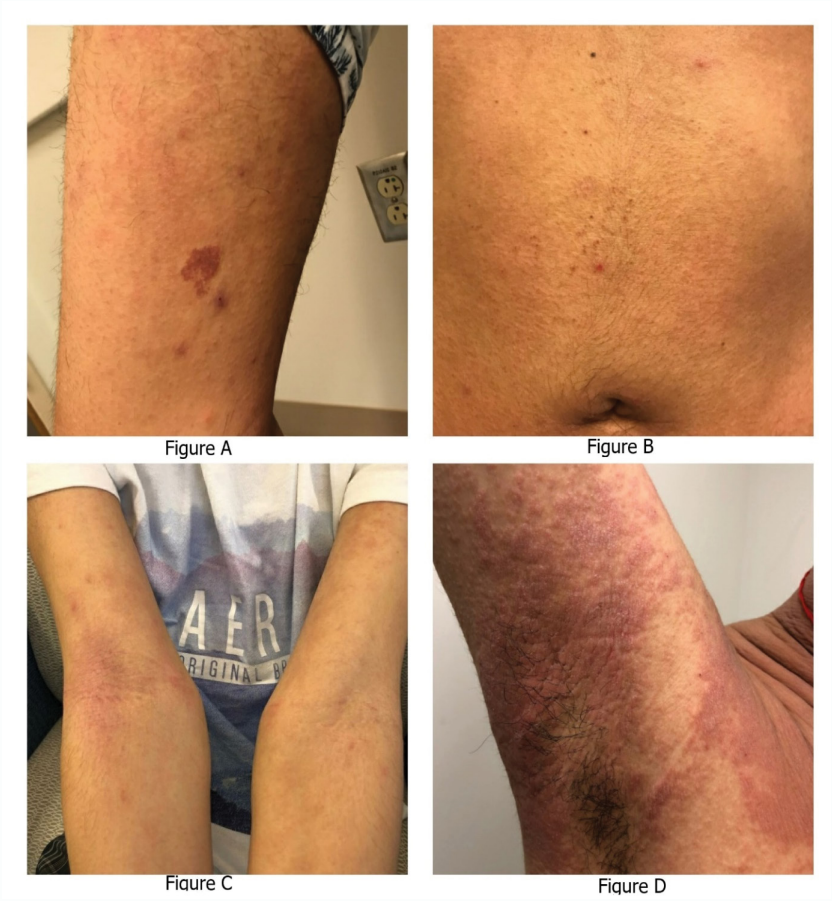

Figure 1: Inflammatory changes and bowel wall thickening centred.

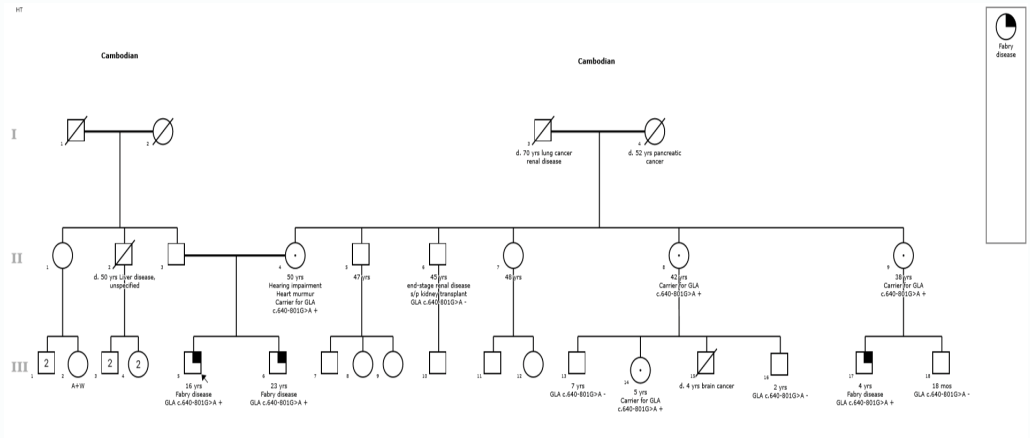

Figure 2: The family pedigree of demonstrating the affected family members with the phenotypies.

subject's laboratory findings are presented together with his six family members in Table 1.

Discussion

The *GLA* gene, located on chromosome Xq22, encodes α-Gal A enzyme that, when deficient, leads to systemic accumulation of lysosomal Gb3 in various tissues including kidneys, heart, dorsal root ganglia, nerves resulting in a multi-system disease with a wide array of clinical presentations [1,2]. There are more than 500 *GLA* variants reported [4] with poor genotype-phenotype correlations.

The variant detected in our case, (c.640-801G>A), also known as IVS4+919G>A, results in a cryptic splice site leading to the insertion of a 57 base pair pseudoexon sequence from intron 4, resulting in a premature termination codon and thus an aberrant protein. This variant has been reported in individuals with a late-onset cardiac phenotype of FD, especially of Taiwanese and Japanese descent [5,6].

Intrafamilial variability in FD is documented in the literature [7]. Our case demonstrates that GLA c.640-801G>A variant also exhibits variability amongst relatives as our proband is symptomatic

Table 1: Clinical manifestations and laboratory values of the proband and his six family members carrying the GLA variant (c.640-801G>A), as illustrated in the pedigree.

Subject	Age at presentation/Sex	Clinical manifestations	A-Gal A1	Lyso-GB32	Urine Microalbumin	Cardiac evaluation
II-4	50 year/F	Right-sided hearing loss, Hypertension	ND	1.04	ND	Trace TR
II-8	42 year/Female	None	ND	1.16	Normal	ND
II-9	38 year/F	Acroparesthesia(mild)	ND	0.85	Normal	ND
III – 5 (Proband)	16 year/M	Acroparesthesia, heat intolerance, angiokeratoma	0.016	2.25(pre-ERT) 1.06(post-ERT)	34	Normal
III-6	23 year/M	None	0	2.1	Normal	Normal
III-16	5 year/F	None	ND	0.39	Normal	Very mild aortic root dilation, mild MR
III-17	4 year/M	None	0.021	1.43	Normal	ND

M: Male, F: Female, TR: Tricuspid valve Regurgitation, MR: Mitral Regurgitation, ND: Not Determined, ERT: Enzyme Replacement Therapy

[1]Alpha Galactosidase (α-Gal A) - Reference range: 0.074-0.457 U/L

[2]Globotriaosylsphingosine (Lyso-GB3) - Normal level≤1.00 ng/ml

[3]Urine Microalbumin Reference range: Children 0-30 µg/ml; adults 0-25 µmg/ml

in adolescence, while his older brother is completely asymptomatic (Figure 2).

Males with the classic form of FD typically present in childhood or early adulthood. Such individuals would have nonsense, splice site, or frame-shift variants resulting in absent enzyme activity. The clinical presentation of carrier females, on the other hand, can range from being completely asymptomatic to severely symptomatic as affected males, a variation that can be explained by random X-chromosome inactivation [8].

Further, the onset of symptoms in carrier females might be later, but still frequently present in late childhood or adolescence [9] with multi-organ damage as seen in affected males, thereby prompting similar clinical management. Adult females with FD are at much higher risk of developing renal, cardiovascular, and/or cerebrovascular clinical events than similarly aged, unaffected females [2]. The diagnosis of FD is typically established in males based on absent or diminished α-Gal A enzyme activity. However, in heterozygous females, the diagnosis is based mainly on molecular testing as enzyme activity is unreliable. The patient's mother is a 50-year-old with a history of hearing deficits and hypertension but normal renal function: Cr.0.68 (RR 0.44-1.03 mg/dl), blood urea nitrogen 16 (RR 8-20 mg/dl), GFR>60 ml/min/1.73 m^2.

A new diagnosis of FD has implications for family members of the affected individual. Once a diagnosis is made in a proband, an average of 5 additional family members are then diagnosed [10]. This was observed in our case, with six other family members identified.

Given the ERT's significant clinical benefit for FD, intravenous agalsidase beta infusion was initiated soon with a dose of 1 mg/kg every two weeks. ERT substitutes the deficient α-Gal A enzyme and has been found to prevent major organ complications [11,12]. This is important as organ damage has been noted in very young children with classic FD. Timely initiation of ERT in symptomatic patients is crucial to limit or prevent significant, irreversible, end-stage organ damage [13]. Early treatment can potentially reverse some early pathological changes and improve school attendance, exercise performance, neuropathic pain, and overall life quality [14,15]. According to the current recommendations per the US consensus panel [13], treatment with ERT should be considered if FD symptoms are present regardless of sex or age. Asymptomatic heterozygous females should be followed closely, and ERT should only be initiated if symptoms develop, including nonspecific symptoms such as abdominal pain, diarrhea, or neuropathic pain, which might occur early, around the age of 9 to 10 years.

In conclusion, the phenotype of FD is highly variable, leading to under diagnosis and delay in management and disease progression. Therefore, high clinical suspicion and careful physical exam are crucial to reduce the associated morbidity and mortality.

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Conflict of Interest

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