Clinical Characteristics of the GLA N215S Variant and Implications for the Diagnosis and Management of Nonclassic Fabry Disease

Chloe Reuter, MS; Julia Platt, MS

Our understanding of Fabry disease continues to evolve since its first description as a dermatologic disorder over a century ago, and the more we learn, the more it becomes clear that this complex disorder defies simple categorizations. A progressive inborn error of lysosomal glycosphingolipid metabolism caused by disruption of the X-linked GLA gene, Fabry disease exhibits a wide spectrum of severity and clinical findings. The phenotype that is most likely to be recognized clinically is the well-described classic form that manifests in boys or young men with neuropathic pain and paresthesia, angioderatomas, hypohydrosis or anhidrosis, corneal verticillata, hypertrophic cardiomyopathy, renal failure, and cerebrovascular strokes. However, the diagnosis remains challenging in people with nonclassic presentations, such as female heterozygotes, who may have a milder course or later onset but are still at risk for life-threatening complications of the disease, and cases of variant Fabry, where clinical involvement is largely confined to a single organ. For example, cardiac variant Fabry can mimic sarcomeric hypertrophic cardiomyopathy. These diagnostic challenges are of particular concern to providers who are likely to encounter nonclassic presentations, such as those working in cardiology clinics. Fabry disease-specific treatments, such as enzyme replacement therapy or chaperone treatment, can only be initiated after an accurate diagnosis is established, and the efficacy of treatment may be limited in those with advanced disease.

See Article by Oder et al

In this issue, Oder et al describe a cohort of patients who were referred for evaluation of apparently isolated hypertrophic cardiomyopathy but who on further workup and genetic testing were diagnosed with nonclassic Fabry disease. This article describes 26 patients (13 men and 13 women) with the N215S (c.644A>G, p.Asn215Ser) variant in the GLA gene. The N215S variant is a common cause of Fabry, occurring in 4.8% of people in a large cohort of primarily North American and European descent. The deep phenotyping of the cohort reported by Oder et al contributes to our understanding of the natural history of N215S-related Fabry disease, with implications for management and setting patients’ expectations about the prognosis for themselves and their families.

Pathogenesis and Pathophysiology

Fabry disease is caused by impaired activity of the α-galactosidase A enzyme. This dysfunction leads to accumulation of globotriaosylceramide (also known as Gb3, GL-3, or ceramide trihexoside) and other related glycosphingolipids, such as Ga2 and lyso-Gb3. These compounds build up in the lysosomes, particularly in vascular endothelial cells, renal cells, and cardiomyocytes. The classic hemizygous Fabry phenotype is caused by extremely low or absent enzyme activity, whereas nonclassic hemizygotes may have enzyme activity as high as 25% or 30% in plasma. Enzyme levels in heterozygous women do not always correlate with clinical disease in this X-linked disorder.

The N215S variant is located in exon 5 of the GLA gene, and the asparagine residue at this codon is the active site for N-linked glycosylation—a type of post-translational modification that affects protein stability, solubility, and trafficking. The asparagine to serine amino acid substitution disrupts glycosylation at this site and has been shown to impair enzyme activity, solubility, and transport from the endoplasmic reticulum to the lysosome. N215S is associated with residual enzyme activity above the classic range, which is consistent with reports that most people with this genetic variant exhibit a nonclassic phenotype.

Clinical Features of N215S-Related Fabry Disease

Davies et al reported the N215S variant in a man with unspecified classic Fabry disease symptoms without renal involvement. Other early case reports described both men and women with N215S as having a mild phenotype with primarily cardiac manifestations, including cardiomegaly and left ventricular hypertrophy. Analysis of registry data has yielded additional insight into the spectrum of the N215S phenotype. In one registry study of 125 patients with the N215S variant, the degree of cardiac left ventricular hypertrophy was found to be comparable with patients with classic Fabry disease, with age of onset in the third or fourth decade of life. Renal involvement was reported in 17% of men, although the degree
of renal impairment is unclear. In another report of 84 individuals (37 men and 45 women) with the N215S variant, the majority presented with cardiac hypertrophy (mean age of diagnosis of 52.5 years in men and 72 years in women). Three percent of N215S men had strokes. Patients with N215S can also present with renal failure.

In this issue, Oder et al describe the cardiac characteristics of a cohort with the N215S variant and compare them to an age- and sex-matched group of classic Fabry patients. Although some larger cohorts of people with the N215S variant have been reported, this is the first example of detailed multisystem phenotyping in a cohort of more than a few people. Oder et al report no significant difference in degree of left ventricular ejection fraction or morphology, the frequency of implanted cardiac devices (pacemaker or defibrillator), or presence of late gadolinium enhancement on cardiac magnetic resonance imaging between those with N215S-related disease and classic Fabry. Consistent with previous reports, these data suggest that cardiac involvement in N215S-related disease may be as severe as that in patients with classic Fabry disease. The authors found no clinically significant renal and neurological impairment in their cohort.

Biochemical and Genetic Diagnosis of Nonclassic Fabry Disease

The accurate diagnosis of heterozygous and variant Fabry disease can be extremely challenging compared with that of classic hemizygous disease. Delays to diagnosis have been well described for classic cases, but once the characteristic clinical findings are recognized, the diagnosis can be corroborated by the results of appropriate follow-up studies. Although some notable exceptions have been reported, diagnostic testing for the vast majority of classic cases will demonstrate absent or nearly absent α-galactosidase A enzyme activity, evidence of substrate accumulation via elevated Gb3 levels, signs of storage on a biopsy of an affected tissue, and a variant in the GLA gene. In contrast, diagnostic testing for heterozygous and people with variant phenotypes is much more likely to be equivocal and may complicate decisions about the appropriateness of Fabry-specific treatment.

In heterozygous women, for example, GLA sequencing is the diagnostic standard because enzyme activity is prone to yield false-negative results in this population. However, the usefulness of DNA testing is limited if the result shows a novel or rare genetic variant. Throughout the genome, rare benign variants are much more common than supposed previously. If a clear clinical or biochemical diagnosis is not present in a female proband, establishing pathogenicity of a genetic variant requires collecting case data to demonstrate the presence of the variant in multiple unrelated people with the disease. However, most disease-causing GLA variants are present in only one or a few families. If a female patient does not have an affected male relative whose clinical and biochemical data can be used to establish pathogenicity of a variant of uncertain significance, clinical interpretation of a GLA variant may be limited.

Clinical diagnosis of nonclassic Fabry is equally fraught with ambiguity. The pathogenicity of several genotypes has been debated in the literature. In addition, analysis of newborn screening programs and populations at risk for unrecognized nonclassic Fabry have demonstrated a high proportion of variants of uncertain significance in the GLA gene. It is useful to have a well-established genetic variant like N215S to act as a representative model for the natural history and diagnostic parameters of this class of genetic variants. For example, several reports indicate that clinically affected N215S hemizygotes and heterozygotes may have normal α-galactosidase A activity, plasma and urine Gb3, and lyso-Gb3 levels, indicating the need for better understanding of disease biomarkers and their relationships to clinical findings.

Looking Forward

The N215S variant exemplifies the phenotypic and biochemical complexity of Fabry disease and the limitations in our ability to categorize these clinical findings. The concept of a cardiac variant phenotype is helpful in guiding the expectations of clinicians and patients, but this term may lead to a sense of false reassurance. The data of Oder et al and others provide a reminder that a diagnosis of variant Fabry disease does not necessarily equate to late-onset or mild disease. It may lead to cardiac dysfunction that is as severe as that seen in classic Fabry and occurring as early as the third decade of life. The literature also demonstrates what seems to be a much less frequent but real possibility for life-threatening extracardiac manifestations, including end-stage renal disease and stroke.

As genetic testing for Fabry disease becomes more widespread, ascertainment of nonclassic phenotypes will continue to increase, along with our understanding of the variable expressivity of GLA variants. Inclusion of Fabry disease on newborn screening panels is already demonstrating that the incidence of impaired α-galactosidase A activity with a GLA variant may be as frequent as 1 in 3100 male newborns—a much higher figure than the traditionally quoted incidence of disease of 1 in 40000 to 60000 men. However, better presymptomatic ascertainment leads to more questions. What is the threshold of evidence required to establish a clinical diagnosis? How and with what frequency should patients undergo surveillance for manifestations of disease? When is the appropriate time to start enzyme replacement or chaperone therapies? Additional longitudinal studies are needed to quantify the frequency and severity of clinical findings in patients with nonclassic Fabry disease.

Disclosures

J.P. has served on an advisory panel for Shire.

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