Review Article

Stroke and Chronic Kidney Disease in Fabry Disease

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Fabry disease is an X-linked lysosomal storage disorder caused by pathogenic variants in the GLA gene leading to a deficiency of the enzyme alpha-galactosidase A (α-Gal A). Multiple organ systems are implicated in Fabry disease, most severely the cardiac, kidney, and central nervous systems. In this brief review, we will focus on the kidney and central nervous system involvement.

Key Words: Fabry disease—Chronic kidney disease—Stroke—Chronic white matter hyperintensities

Introduction

Fabry disease (FD) is an X-linked inherited metabolic disorder, caused by a deficiency of the lysosomal enzyme alpha-galactosidase A (α-Gal A). Absent or deficient enzyme is a result of pathogenic variants in the GLA gene which lead to progressive accumulation of the substrate globotriaosylceramide (Gb3 or GL3).[1] There are over 900 pathogenic variants reported, most of which are family specific variants[2] The incidence is estimated to be 1 in 40,000 males, however data from newborn screening has shown that the incidence may be much higher particularly for non-classic disease.[3] FD affects both males and females, but females tend to have a wider range of disease phenotypes, predominantly due to random X-chromosome inactivation.[4] Females range from being asymptomatic to being as severely affected as males, however the majority tend to fall somewhere in between.

FD presentation tends to be classified as either "classic" or "non-classic," with classic disease encompassing more severe disease presentation. "Classic" disease presentation usually results from little to no working α-Gal A enzyme, disease onset is typically in childhood, multiple organ systems tend to be affected and symptoms progress to a more acute extreme. By contrast "non-classic" disease presentation usually results from residual α-Gal A enzyme- activity, disease onset is typically in adulthood, fewer organ systems tend to be affected, and symptoms tend to be milder.[6]

Symptoms of FD include involvement of various organ systems as a result of Gb3 build up in endothelial cells, initiating a downstream cascade of events leading to inflammation and organ damage.[5] Earlier disease presentation tends to involve neuropathic pain, gastrointestinal involvement, hypohidrosis, auditory abnormalities, optical abnormalities, and early cardiac and kidney involvement. Major organ involvement becomes apparent in adulthood with progressive cardiac and kidney presentation along with central nervous system involvement.[2]

There are currently two available FDA approved treatments that mitigate disease progression. Enzyme replacement therapy (ERT) is available in the USA in the form of agalsidase beta (Fabrazyme ®) which is administered at a dose of 1 mg/kg body weight once every two weeks as an intravenous infusion.[7] Chaperone therapy (CT) works by reversibly binding to the active site of α-Gal A, stabilizing specific mutant forms of the enzyme to facilitate their proper folding and cellular trafficking from the endoplasmic reticulum to lysosomes where dissociation of migalastat allows α-Gal A to breakdown accumulated Gb3. CT is available in the form of migalastat (Galafold ®) which is a 123 mg tablet taken orally every other day, however is only indicated for patients with amenable mutations and is not recommended for patients with

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estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2.[8] Both have been shown to be effective in reducing the accumulation of Gb3 in the body. Primary therapies do not address all the symptoms of FD, and patients also require secondary adjunctive treatment to manage specific complications such as neurogenic pain and hypertension, and aspirin to prevent strokes.[2]

Kidney involvement

Kidney disease is a major complication of FD and is related to glycosphingolipid accumulation of Gb3 throughout the nephron. Gb3 deposits can be found in most kidney cell types prior to loss of GFR, and continuous buildup throughout life leads to progressive kidney failure. Gb3 primarily accumulates in the podocytes of glomeruli, leading to foot process effacement that precedes pathological albuminuria.[9] Deposits can be visualized on light microscopy via the characteristic honeycomb appearance while resembling zebra bodies on electron microscopy[10] (Fig. 1). Albuminuria typically begins in the second to third decades of life. Gb3 accumulation increases over time resulting in fibrosis, tubular atrophy, and chronic kidney disease in the third to fifth decades of life; and ultimately end-stage kidney disease in the fifth decade of life. Decline in kidney function if further exacerbated by coexisting arterial hypertension.[9]

Primary treatment such as ERT or CT can slow and delay the progression of kidney disease, having a more significant impact the earlier treatment is initiated relative to the disease course.[15] Pediatric and adult patients should have regular monitoring of GFR (using an age appropriate formula in children), as well as monitoring of urine albumin/creatinine ratio at regular intervals. A renal biopsy may be considered at baseline to determine the severity of underlying tissue injury, to identify possible kidney comorbidity if there is a sudden decrease in kidney function, or to provide additional insight into unexpected low eGFR.[2]

Central nervous system involvement

Individuals with FD have an increased risk for transient ischemic attack and stroke, and an earlier age of onset when compared to the general US population.[11] The majority of FD-related strokes are ischemic, less frequently hemorrhagic.[2] Blood flow is augmented in Fabry vasculopathy which leads to altered cerebrovascular reactivity.[2] Additionally, chronic white matter hyperintensities (CWMH) are common (Fig. 2). They can be single, multiple, or confluent, and can occur in the subcortical, deep and periventricular white matter, usually in a symmetrical manner. CWMH tend to increase in number with age and are not usually associated with any neurological abnormalities. Resulting CWMH are thought to be a result of microvascular injury due to Gb3 related medial arteriolar damage, however CWMH seem to be distinct and not related to white matter strokes.[11]

ERT does not cross the blood-brain barrier thus the impact on CWMH and acute neurological deficits is unclear.[2] There does seem to be some evidence that treatment with agalsidase beta was associated with a lower incidence of cerebrovascular events compared to those receiving no treatment or receiving agalsidase alfa.[12] There is no recommended cerebral monitoring for pediatric patients. Adult patients should be monitored approximately every three years with brain magnetic resonance imaging (MRI) ideally using T1, T2/fluid attenuation inversion recovery (FLAIR), apparent diffusion coefficient and diffusion weighted images. Additionally, magnetic resonance angiography (MRA) should be done at first assessment in males over 21 years and females over 30 years. Computed

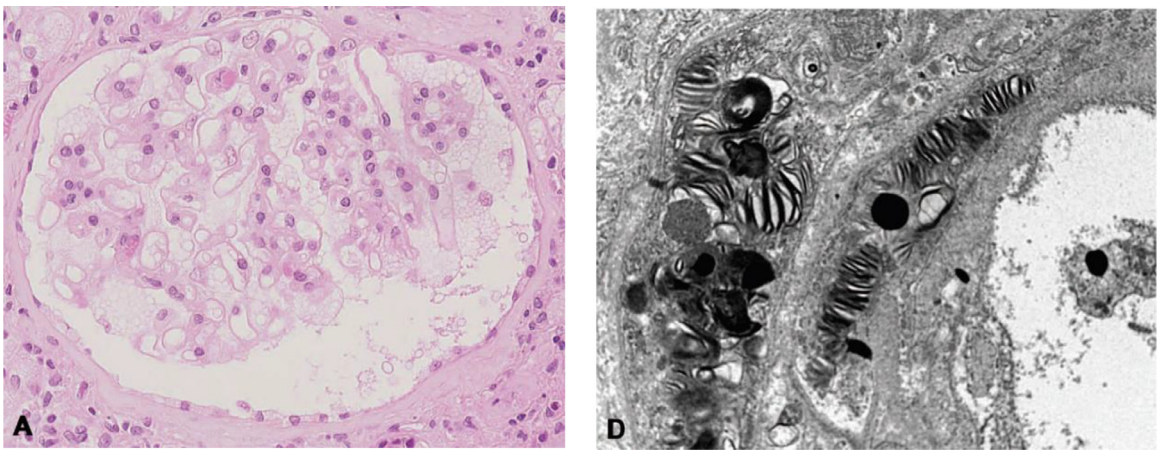

Fig. 1. *Kidney biopsy. A, Fabry nephropathy on light microscopy. Cytoplasm of podocytes appears expanded, foamy, pale, and lacy owing to lipid deposits. (original magnification X200). D, Fabry nephropathy by electron microscopy showing zebra bodies in an arteriole (frozen tissues, original magnification X3597). Reprinted from Colpart and Felix, Fabry Nephropahty,* Arch Pathol Lab Med. *2017;141(8):1127-1131 with permission from* Archives of Pathology & Laboratory Medicine. *Copyright 2017. College of American Pathologists.*

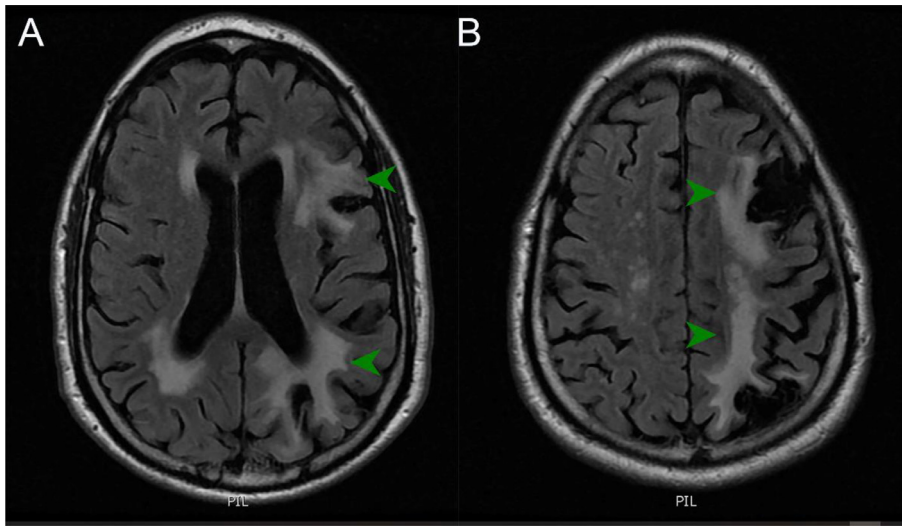

Fig. 2. *Cerebral white matter hyperintesities and stroke. A, Axial FLAIR at the level of the lateral ventricles demonstrating severe confluent white matter abnormalities involving the left frontal lobe and parietal lobe. B, Axial FLAIR above the ventricles again shows severe confluent white matter abnormalities as well as left parietal and left frontal encephalomalacia from prior ischemic infarctions. Courtesy: Dr. Daniel S. Chow, assistant professor-in-residence, Dr. David Floriolli, program director of diagnostic radiology and Associate Clinical Professor, department of radiological sciences at the University of California Irvine.*

tomography should only be used in the event of acute stroke or if MRI is contraindicated.[2]

Overlap between the kidney and central nervous system

The kidney and brain share similar hemodynamic properties, such as vasoregulation of the microvasculature in both organs. They also share common vascular risk factors that can complicate organ involvement, hypertension and diabetes mellitus.[11] Studies found that a lower eGFR was associated with increasing severity of CWMH,[13] and patients with more stable eGFR had fewer strokes than those with rapidly progressive kidney disease.[14]

Conclusions

Chronic kidney disease and acute cerebrovascular events are major complications seen in FD. Gaining a better understanding of the pathology underlying these symptoms can lead to prevention of major complications.

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