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Diagnosing and treatment of Fabry's disease from a neurologic perspective

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Introduction

Despite the surge in our knowledge of Fabry's Disease (FD) and the advancements in diagnostic tools, there is often a significant time between the onset of symptoms and diagnosis. According to the Fabry Registry, 10.5 years is the average age of symptom onset, but 28.5 years is the average age of diagnosis. As a rare disease which shares clinical manifestations with many other disorders, FD can be challenging to recognize. This is a concern because early initiation of enzyme replacement therapy has been found to be important for reduction of disease burden. In order to help clinicians identify FD in its earliest stages, in this review we describe its neurological features, diagnosis and treatment.

Characteristic features of neuropathy in Fabry's disease:

Neuropathy in FD is a small fiber neuropathy (SFN), affecting small myelinated and unmyelinated neurons. The characteristic neuropathy of FD is a symmetrical, length-dependent sensory polyneuropathy which starts in the feet and spreads proximally. In FD the Aδ fibers are preferentially affected, which is in contrast to most other SFNs where both Aδ- and C-fibers are affected[1].

Clinical presentation

Symptoms usually begin between the ages of 3 to 10 years, with males affected earlier and more severely than females[2-4]. FD is divided into "classical" and "non-classical" or "atypical" varieties. Burning pain, hypo or hyperhidrosis, transient ischemic attacks, strokes, angiokeratoma, proteinuria, cardiomyopathy, arrhythmia, cochleo-vestibular and gastrointestinal disorders are the most common presenting features in "classically" affected hemizygous males who have no residual α-galactosidase A activity[4]. Patients with "non-classical" or "atypical" disease who have residual α-galactosidase A activity exhibit milder disease, and typically present in the fourth to sixth decades with clinical manifestations confined to one organ system[5,6].

Pain in FD

Pain is experienced by 60–80% of affected males and females FD patients[7,8] with SFN. Two types of pain associated with SFN have been described. The first type is the episodic painful crisis (Fabry's crisis), which is characterized by agonizing burning pain starting in the extremities and radiating centripetally. It may be precipitated by fever, exercise, fatigue, stress or rapid changes in temperature[9].

The second type is chronic pain, which is characterized by burning, shooting pain or dysesthesias in the hands or feet[9,10]. Decrease in pain with ageing occurs in some patients[11]. This may occur as a consequence of progressive small fiber damage with changes in neural function leading to a decrease in pain[12]. Therefore when pain is not an active symptom, it is important to inquire about a history of acroparesthesias in childhood.

Other sensory manifestations

There is loss of temperature sensation in the hands and feet and reduced tolerance to cold[13].

Autonomic nervous system involvement

There is controversy whether autonomic neuropathy is a major feature of FD. Since FD causes relatively selective damage to Aδ fibers, autonomic functions are usually preserved[14]. Sweat glands[14–19], dermal nerve endings[9], vessel response[20], heart rate variability[21], orthostatic blood pressure, and male sexual function are usually normal[22]. These observations suggest that it is unlikely that FD patients suffer significant autonomic neuropathy. A Four-year prospective clinical trial found remarkable improvement in all heart rate variability indices in boys undergoing agalsidase alfa replacement therapy[23].There are a few reports of orthostatic hypotension and syncope in patients with FD, suggesting localized cardiovascular autonomic abnormalities[24,25]. However, these and other abnormal studies of peripheral hemodynamics might be explained by end-organ failure such as stiffness of vascular smooth muscle and endothelial dysfunction[26].

Cerebrovascular disease

In FD there is a significant incidence of stroke, which is mostly small vessel ischemic event[27], and there is also a predilection for acute ischemia in the posterior cerebral circulation[28,29]. Among different MRI changes, the finding of hyper-intensity in the pulvinar on T1 weighted images ("pulvinar sign") has been found to be a highly specific sign in FD[30] (Fig. 1). The most common angiographic findings are tortuous, elongated, ectatic vertebral and basilar arteries. Increased basilar artery diameter is 87% accurate in diagnosing FD[31]. Cerebral blood flow changes may result in increased white matter interstitial pressure and metabolic impairment[32]. Cerebral involvement is usually widespread. The posterior cerebrum is predominantly involved[32]. Chiari type I malformation has been found in some patients with FD[33].

Hearing loss

There is a high incidence of progressive hearing loss, mainly sensorineural with vestibular dysfunction and sudden deafness in male patients with FD[34].

Diagnosis

When to suspect Fabry's disease

To diagnose FD, further specific tests are recommended by the National Society of Genetic Counselors for patients with any of the factors outlined in Table 1.

Diagnostic testing

In males, the diagnosis is based on typical FD signs and symptoms, very low or completely absent α-galactosidase A (GLA) activity in leukocytes, plasma or fibroblasts, increased globotriaosylceramide (Gb3) and lyso-Gb3 concentrations in plasma and urine and a pathogenic mutation on genetic analysis[29,36,37] (Figure 2)[1]. Females affected by FD have α-galactosidase A levels which can range from deficient to normal[3,38-40]. Therefore, diagnosis must rely upon molecular analysis to identify a disease

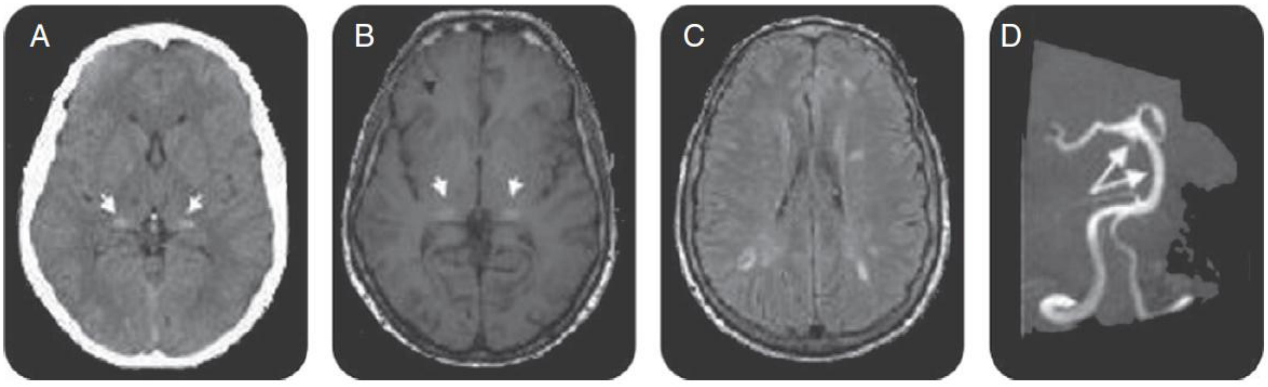

Figure 1: Brain CT, brain MRI, and magnetic resonance angiography for FD patients.
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Axial CT scan demonstrated increased attenuation in the pulvinar region (arrows, A), corresponding to the sites of hyper-intensity on T1-weighted MRI (the pulvinar sign) (arrows, B). Fluid-attenuated inversion recovery–weighted axial MRI section showed multiple white matter lesions in cerebral hemispheres (C). Magnetic resonance angiography shows basilar dolichoectasia (arrows, D).

Test any patient who has	In the absence of factors 1 and 2, test patients with at least two of the features below
1.A family history of Fabry Disease OR 2.Corneal verticillata ("whorls") on slit lamp exam	3. Decreased sweating (anhidrosis or hypohidrosis) 4. Reddish-purple skin rash in the bathing trunk area (angiokeratomas) 5. Personal and/or family history of kidney failure 6. Personal or family history of "burning" or "hot" pain in the hands and feet, particularly during fevers (acroparesthesias) 7. Personal or family history of exercise, heat, or cold intolerance. 8. Patients with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy

Table 1: National Society of Genetic Counselors recommendations for testing patients for FD[35]

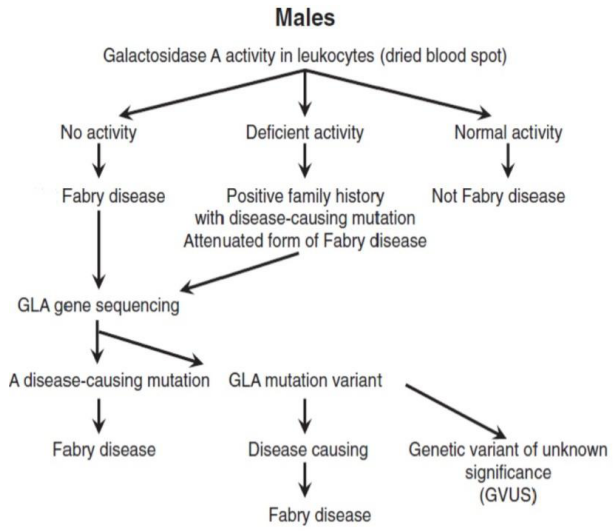

Figure 2: *Proposed algorithm for testing males with suspected Fabry Disease*
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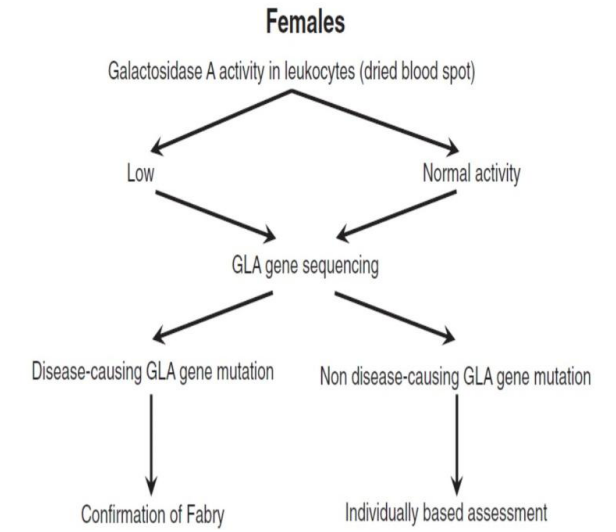

Figure 3: *Proposed algorithm for testing females with suspected Fabry Disease*
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causing mutation in the GLA gene[2,41] (Figure 3)[1]. Prenatal diagnosis is feasible by determining the α-galactosidase A activity in cultured chorionic villi at 10 weeks of pregnancy or in cultured amniotic cells at 14 weeks of pregnancy[42]. Neonatal screening for FD in males is technically feasible by measurement of α-galactosidase A activity in dried blood spot (DBS) using either the fluorogenic or mass spectrometric substrate and will detect cases both with complete deficiency and residual enzyme activity[43].

Neurologic testing

Conventional nerve conduction studies (NCS) assess only large myelinated nerve fibers, and are usually normal in FD unless renal failure is present. Quantitative sensory testing (QST), quantitative sudomotor axon reflex test (QSART) and skin biopsy to assess epidermal nerve fiber density (ENFD) are useful to confirm the presence of SFN. Recently, pain-related evoked potentials (PREPs), where electrical current using special concentric electrodes[44] is used to stimulate A-delta fibers, was described as a suitable and easily applicable new tool for objective small fiber diagnostics[45]. SFN in FD has been demonstrated to be length dependent by using proximal and distal skin biopsy sites[46]. Corneal nerve fiber density (C-fibers) and corneal sensation has been demonstrated to be significantly reduced[47]. Some studies concluded that sensory impairment and SF pathology in FD patients are gender-dependent, associated with reduced renal function, and are progressive in most patients despite ERT[48,49].

Differential diagnosis

For clinicians, it is of utmost importance to distinguishing FD from other causes of painful small-fiber neuropathy (Table 2) [1].

Management

Enzyme replacement therapy (ERT)

ERT is currently the standard of care for FD patients. The most current literature emphasizes that ERT should be instituted upon confirming the diagnosis of FD. Recombinant human α-galactosidase A is commercially available in two forms given as an intravenous (IV) infusion

Other causes of painful small fiber neuropathy	Evaluation
Diabetes and prediabetes	• Fasting glucose, hemoglobin A1C, oral glucose tolerance test
Toxic: Alcohol misuse, heavy metals	• Michigan Alcoholism Screening Test (MAST) • CAGE (cut-down, annoyance, guilt, eye-opener) • Liver function tests • Heavy metal screen
Vitamin B deficiencies or B6 toxicity	• Serum levels of vitamins B12, B1, and B6
Amyloidosis (hereditary or acquired)	• Mutations of transthyretin • Serum and urine protein electrophoresis with immunofixation • Abdominal fat-pad, rectal or nerve biopsy
Acute intermittent porphyria	• Increased urinary porphobilinogen (PBG) • Erythrocyte PBG deaminase activity
Vasculitis	• Antineutrophil cytoplasmic antibodies (c-ANCA, p-ANCA). • Hepatitis panel (especially B) • Erythrocyte sedimentation rate, C-reactive protein • Nerve/muscle biopsy
Connective tissue diseases	• ANA, dsDNA antibodies, SCL-70 antibodies Sm antibodies, RNP antibodies • Anti-Ro, anti-La for Sjogren's syndrome
Immune-mediated	• Serum and urine protein electrophoresis with immunofixation, paraneoplastic antibody screen PET scan for occult neoplasia • Celiac disease antibody panel
Neurotoxic drugs: Antiretroviral agents, vinca alkaloids (vincristine), paclitaxel and docetaxel, cisplatin, carboplatin, and oxaliplatin. Metronidazole and linezolid	• History of exposure, urine or blood levels
Infections	
HIV	• HIV ELISA, HIV RNA
Hepatitis C	• Hepatitis C RNA • Hepatitis C ELISA • Cryoglobulins
Leprosy	• Skin or nerve biopsy
Lyme disease	• Serological tests for Lyme antibodies (ELISA with confirmation by Western blot)
Hereditary sensory and autonomic neuropathy	• Genetic testing for hereditary sensory and autonomic neuropathy types I to IV
Idiopathic	• Other conditions excluded. Can confirm decreased intraepidermal nerve fiber density (IENFD) by skin biopsy

Note : Due to higher incidence of extractable nuclear antigens in FD patients, in comparison to healthy population, presence of an autoantibody may not exclude Fabry [50].

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Table 2: Differential diagnosis of small fiber painful neuropathy

every two weeks. Agalsidase alfa (Replagal) and Agalsidase beta (Fabrazyme) are the two commercially available preparations. Agalsidase beta is approved for use in the United States (US). Agalsidase alfa, on the other hand, is not approved for use in the US. Although complications such as stroke and renal damage may still occur while receiving ERT, patients with FD were found to benefit from ERT, particularly when started at earlier stages of the disease before end organ damage occurs[51].

Infusion related reactions and neutralizing IgG antibodies with ERT

Adverse effects of ERT include fever, chills, facial flushing and rigors. Infusion reactions are managed conservatively with antihistamines and corticosteroids in cases of a severe reaction. Neutralizing IgG antibodies may develop to agalsidase alfa and beta and show cross reactivity between the two enzyme replacements[52–54]. It is recommended that patients receiving ERT should be checked for serum neutralizing antibodies every three months during the first year and then yearly[55].

Pain management

Anti-epileptic drugs are widely used for pain control in patients with FD. Treatment using combinations of anti-epileptic drugs may be necessary for adequate pain control[56]. Treatment with agalsidase beta resulted in decreased neuropathic pain and improved function of Aδ, C and Aβ nerve fibers and intradermal vibratory receptors detected by QST[57,58]. Analgesic medications can also be used, but nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided since they are not effective and potentially harmful to kidneys[59]. In an effort to provide practical pain management guidelines for FD in adults, an FD Expert Panel suggested recommendations that are summarised in Table 3[60].

Peripheral nervous system

Agalsidase alfa therapy has been shown to achieve lower heat pain thresholds, improved cold detection threshold, and improvement of sympathetic skin responses with associated improvement in acroparesthesia and anhidrosis[57,58,61,62]. Treatment with agalsidase beta resulted in improved function of Aδ, C and Aβ nerve fibers and intradermal vibratory receptors detected by QST[57,58].

Cerebrovascular system

Neither agalsidase alfa nor beta has been shown to reduce the frequency of cerebrovascular events[63]. Possible reasons are that neither of the available enzyme compounds cross the blood brain barrier and that irreversible damage to the endothelium typically occurs before the initiation

Indication	Agent	Type of pain	
First-line	Tricyclic antidepressants	chronic neuropathic pain	
	Serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine)		
	Carbamazepine		
	Gabapentin		
	Gabapentinoid pregabalin		
Second-line	Lidocaine patches		
	Topical capsaicin (8%) patches		
	Tramadol	acute pain	
Third-line	Strong opioids	acute pain	
	Cannabinoids		
Fourth-line	Methadone Anticonvulsants with lesser evidence of efficacy (e.g., lamotrigine, lacosamide) Tapentadol Botulinum toxin.		
Other agents to consider			
Acute-pain prophylaxis before physical activity	Lidocaine or capsaicin cream		
During pain crises	Phenytoin	acute pain	chronic neuropathic pain
	Intravenous lidocaine	acute pain	
Nonsteroidal anti-Inflammatory drugs	Ibuprofen Diclofenac	acute pain	
Therapy-resistant neuropathic pain	Opioid Ketamine		
Note: These recommendations are based on an FD Expert Panel that convened in Rome, Italy, in March 2014 and on subsequent discussions.			

Table 3: Recent recommendations for pain treatment in Fabry`s disease[60].

of therapy. Thus, other preventive measures including the administration of antithrombotic agents and control of risk factors are indicated.

Pharmacological chaperone therapy

Migalastat was recently approved by the European commission for treatment of FD patients aged 16 years and older, but not yet approved in the US. It works by facilitating appropriate trafficking of GLA to lysosomes. Migalastat is orally administered, thus it is less invasive than ERT IV infusion. Reduction in plasma lyso-Gb3 levels and improvement in kidneys, heart and gastrointestinal tract functions, have been reported in patients with suitable mutations. No sufficient evidence was found for the effect of Migalastat on neurological manifestations of FD[64].

Conclusion

FD is rare and shows diverse symptoms in the initial stages of manifestation; therefore, the definitive diagnosis is often delayed. However, in recent years, FD has become more widely recognized and there has been a considerable advance in the diagnosis and treatment options. The response to ERT is dependent on the severity of organ involvement, and better results occur when the treatment is instituted early in the disease before major organ damage has occurred.

Conflict of Interest

The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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