Fabry disease is a rare condition; however, it is associated with a high incidence of stroke, particularly in young adults. At a symposium held during the 4th European Stroke Organisation Conference in Gothenburg, Sweden, an expert panel gave an overview of Fabry disease, including its pathogenesis and management, and provided practical guidance to help identify Fabry disease in patients with stroke.
Professor Reisin started the symposium by giving an introduction to Fabry disease. Fabry disease is caused by a deficiency of the enzyme α-galactosidase A (α-Gal A), resulting in multi-systemic accumulation of globotriaosylceramide (Gb3). The α-Gal A (GLA) gene is found on the X-chromosome, but, because of random X-inactivation, symptoms in some females can be as severe as in males. Many patients present with neuropathic pain, which is a hallmark of Fabry disease and exacerbated by heat and exercise. Neuropathic pain is frequently misdiagnosed as rheumatic fever, bone pain or rheumatologic disease.

Prof. Reisin noted that two key signs give neurologists an enhanced opportunity to recognise Fabry disease – the presence of small skin lesions called angiokeratoma, and cornea verticillata, which can be identified by asking an ophthalmologist to perform a slit lamp examination.

Diagnostic confirmation can be achieved in male patients by α-Gal A activity testing alone, but the presence of a disease-causing mutation in the GLA gene is required for the diagnosis of female patients.

As Fabry disease progresses, the three main organs affected are the kidney, heart and cerebrovascular system. Patients with Fabry disease can lose up to 10 mL/min/1.73 m² of glomerular filtration rate every year, ultimately resulting in kidney failure.

All cardiac cell types are affected in Fabry disease. Hypertrophic cardiomyopathy is a frequent finding and cardiac fibrosis can lead to severe arrhythmia and cardioembolic stroke.

Prof. Reisin highlighted that stroke is important in Fabry disease because it occurs frequently. Fabry disease should be considered in cases of haemorrhagic as well as ischaemic stroke – in patients with Fabry disease and stroke, ~17% of males and 7% of females had a haemorrhagic stroke. Up to half of all patients have a stroke before the diagnosis of Fabry disease, highlighting the importance of screening studies. Even without a stroke, more than 40% of Fabry patients have white matter lesions, and more than 10% have haemorrhagic bleeds.

Patients with late-onset Fabry disease may not have all the signs and symptoms of classical Fabry disease, and screening studies are one way to identify these patients. The Stroke in Young Fabry Patients (SIFAP) study screened more than 5000 young adults (18–55 years) with cerebrovascular events, and identified GLA mutations in ~1%, with the majority of these patients having late-onset or oligosymptomatic forms of Fabry disease.

Prof. Reisin concluded that unless neurologists actively look for Fabry disease, they will miss it.
Fabry disease is highly heterogeneous, requiring individual assessment and monitoring

Genotype-phenotype correlations in Fabry disease: a neurologist’s view
Dr Tobias Böttcher

Dr Böttcher looked at the mutations that cause Fabry disease (genotype), and how this corresponds to disease manifestations (phenotype). There is a very high proportion of private mutations (that is, mutations occurring in just one family), and a high degree of clinical variability, both among patients from the same family and among those from unrelated families with the same mutation.

In X-linked diseases such as Fabry, heterozygous females are commonly referred to as ‘carriers’, but this designation does not provide any information on the disease phenotype. Many female heterozygotes are symptomatic, usually with a slower course of disease than observed in males.

More than 900 GLA mutations causing a variety of clinical manifestations have been identified. Mutations leading to a non-functional or absent enzyme, such as mutations affecting the active site of the enzyme, are associated with classic Fabry disease. Disease signs and symptoms develop in the first decade of life, typically with multi-organ involvement.

Mutations that cause a mild phenotype affect residues that tend to be on the surface of the protein. Non-classical Fabry disease has a less aggressive phenotype with a later onset, and may have oligo- or mono-symptomatic manifestations. An Italian newborn screening study found that the ratio of non-classical to classical variants was ~10:1.

Dr Böttcher highlighted that it is important to identify patients with atypical variants and their affected family members, because they may develop manifestations in one or more organ systems.

It was explained that there are also gene variants of unknown significance (GVUS), and that classifying variants is an ongoing discussion. Dr Böttcher noted that neurology screening often finds variants that are non-classical, under discussion or GVUS. An algorithm to evaluate GVUS is available, but one challenge with this algorithm is determining which organ to biopsy for those patients with enzyme activity in the ‘grey zone’ (>25%–<40% of normal), especially as some Fabry variants may manifest in just one organ.

Dr Böttcher then discussed the controversial D313Y mutation, and presented two case studies of patients with this mutation. These patients had definite Fabry disease, as shown by skin biopsies. A third case also had the D313Y mutation, but no evidence of Fabry disease, highlighting the importance of follow-up.

Dr Tobias Böttcher

Genotype-phenotype correlations in Fabry disease:
- Very complicated!
- High proportion of private mutations (most families carry different mutations)
- High degree of clinical variability
  - among patients from the same family
  - among those from unrelated families with the same mutation
- Part of the phenotype may be due to non-genetic factors
- Clinical features of Fabry disease are frequently observed in the general population (neuropathic and abdominal pain, headache, tinnitus, hearing loss, diarrhoea, cardiovascular disease)

Problems

Dr Böttcher noted that the biomarker globotriaosylphosphinosine (lyso-Gb3) can differentiate classical Fabry disease from atypical α-Gal A mutations, but that it is not predictive of the disease phenotype.

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Dr Tsivgoulis gave a highly visual lecture about neuroimaging and Fabry disease. He reminded the attendees that Fabry stroke can be both ischaemic and haemorrhagic, and that infarctions and white matter lesions – as well as depression – are common.5,36-38 A variety of mechanisms can lead to stroke in Fabry disease, but the most common are small vessel disease and cardiothrombotic causes.39

Dr Tsivgoulis explained that patients with Fabry disease may have some or all of the following neuroimaging findings:

(i) The pulvinar sign (T1 hyperintensity in the lateral pulvinar region)
- Originally considered to be prevalent (25%) and 100% specific for Fabry disease,40 but now recognised to have a prevalence of 3% in unselected patients, and to be observed in some other diseases.41,42

(ii) Diffuse white matter lesions and lacunar infarctions
- The volume of white matter lesions increases steeply with age, but early treatment with enzyme replacement therapy (ERT) can reduce the white matter load.43

(iii) Cerebral microbleeds
- Occur with high prevalence (6-30%), and are typically deep supratentorial.44-46

(iv) Vertebral basilar dolichoectasia
- Occur with high prevalence (56% of male and 35% of female patients with Fabry disease).45 Unlike other causes of stroke, the underlying mechanism is thought to be vascular remodelling.47

Dr Tsivgoulis highlighted that 3-Tesla imaging is a promising tool for Fabry disease, and can reveal the enlarged dorsal root ganglia which occur as a result of Gb3 accumulation.48

Individual clinical and neuroimaging findings can help to distinguish Fabry disease from four other hereditary cerebral small vessel diseases. These findings include migraine with aura, apathy and dementia (CADASIL), alopecia and back pain (CARASIL), progressive vision loss (RVCL) and porencephalic cysts (COL4A1).49

It is important to consider Fabry disease in the differential diagnosis of multiple sclerosis (MS). Several studies have reported the misdiagnosis of Fabry disease as MS.26,50-52 Although two-thirds of patients with Fabry disease fulfill the McDonald criteria for the diagnosis of MS,50 diagnostic red flags for Fabry disease include the absence of oligoclonal bands, a low intraepidermal nerve fibre density on punch biopsy, an abnormal cold detection threshold, and the absence of corpus callosum involvement.50,53,54

Ophthalmological and skin manifestations and peripheral nervous system involvement may help in the differential diagnosis of Fabry disease.5,36,55 Dr Tsivgoulis noted that in his experience a punch skin biopsy together with sensory testing has high diagnostic value.

If Fabry disease is suspected, men can be screened for low α-Gal A activity, but women require molecular genetic screening.56 Dr Tsivgoulis re-iterated the value of a skin or kidney biopsy, and noted that lyso-Gb3 levels may be helpful.57 He concluded with the observation that there should be a low threshold for testing for Fabry disease.
Early diagnosis of Fabry disease can allow appropriate management

Stroke in Fabry disease: pathogenesis and treatment
Prof. Ricardo Reisin

The final presentation looked at the pathogenesis and treatment of stroke in Fabry disease. Professor Reisin began by explaining that stroke in Fabry disease can be caused by vasculopathy and/or cardioembolic events.58-60

Several mechanisms are involved in the vasculopathy of Fabry disease. Gb3 induces the release of pro-inflammatory cytokines by acting through toll-like receptors (TLR) on antigen-processing cells.61 TLR are also found on the endothelium, and Gb3 may cause a prothrombotic state,62,63 and induce an endotheliopathy through oxidative stress and damage of mitochondria.62-65 Endothelial dysfunction may also be caused by Gb3 acting via second messengers to decrease the expression of KCa ion channels in the endothelial cell membrane.66,67

Endothelial dysfunction does not explain all the features of Fabry vasculopathy. In patients who received ERT, the endothelium was cleared of Gb3, but vasculopathy was still observed.68 This may be because of damage to the medial muscular layer. Lyso-Gb3 may promote hypertrophy, lead to oxidative stress through hyper expression of angiotensin receptors, and cause fibrosis through activation of transforming growth factor-beta (TGF-β), the ‘master switch of fibrosis’.69 Prof. Reisin highlighted that fibrosis is not treatable, and is the point of no return.

“Fibrosis is...the point of no return”

There are many reasons for cardioembolic stroke in Fabry disease, including left ventricular hypertrophy, valve thickening, wall thinning, fibrosis and arrhythmia.70

Available treatment options for Fabry disease include ERT and chaperone therapy,71-74 but all patients will also need adjunctive or concomitant therapies.75

Prof. Reisen then focused on ERT, which has been shown to have benefits on pain and quality of life, and has been associated with improved or stabilised cardiac and renal functions.71-73

There is an increasing burden of white matter lesions with age, which has been shown to be stabilised or reduced in patients treated with ERT.76 It has been reported that patients with both Fabry disease and factor V Leiden (FVL) deficiency have a 5-fold higher risk of stroke compared with Fabry patients without FVL.77 The risk of thromboembolic events was 3 times higher in patients with Fabry disease who were not receiving ERT.77 Prof. Reisin commented that these studies suggest that ERT may have a protective effect on small vessel disease.77 However, the results need to be confirmed in randomised, controlled clinical trials, and should be interpreted with caution due to the limitations of the study designs.

Brain MRI lesions in Fabry disease are often misdiagnosed as other conditions, such as MS.70,78 Stroke is frequent in Fabry disease,12 so it is important to consider screening young stroke patients (18–55 years) for Fabry disease,4 and to consider Fabry disease in the differential diagnosis of other conditions such as MS and CADASIL. If Fabry disease is suspected, physicians should look for angiokeratoma, cornea verticillata, relevant family history and cardiomyopathy.13,70,79,80

Prof. Reisin noted that “effective treatment requires early diagnosis”, and that “every time you identify one patient, you identify a family”. 

WHEN YOU SUSPECT FABRY DISEASE LOOK FOR:

ANGIOKERATOMA CORNEA VERTICILLATA FAMILY Hist CARDIOMYOPATHY

DIAGNOSTIC CONFIRMATION TREATMENT

MALLeS: a-Gal ABO testing FEMALLeS: Screening testing ERT CHAPERONE + CONCOMITANT

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