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NEUROLOGICAL COMPLICATION OF ANDERSON-FABRY DISEASE AND IMPACT OF ENZYME REPLACEMENT

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ABSTRACT
In the central nervous system (CNS), diffuse lipid storage occurs in the cerebral vasculature and neurons of Fabry patients. The most prominent CNS manifestations consist of cerebrovascular events such as transient ischaemic attacks (TIAs) and (recurrent) strokes. Another common symptom of youg Fabry patients is neuropathic pain and it can manifest as chronic, burning pain and recurrent attacks of acute excruciating pain, dysesthesias, thermal disperception (primarily cold perception) and paresthesias. Other sympotomatology due to to autonomic nervous system involvement may include hypohidrosis, impaired pupillary constriction and saliva and tear production, gastrointestinal dysmotility-like syndromes such as abdominal cramping pain, bloating, diarrhea, nausea.

KEYWORDS: hypohidrosis, sympotomatology, dysesthesias.

INTRODUCTION
Anderson-Fabry Disease (AFD) is a rare genetic X-linked disorder with deficient activity of the lysosomal enzyme alpha-galactosidase A.[1] Fabry disease results from mutations in the GLA gene that encodes the lysosomal enzyme a-galactosidase A. A functionally relevant reduction of enzyme activity results in the accumulation of globotriaosylceramide (Gb3) within lysosomes. A wide variety of progressive clinical symptoms are seen in patients with Fabry disease and many of these are seen first in early childhood. These symptoms include burning sensations, particularly in the hands and feet (acroparaesthesia), gastrointestinal (GI) problems, angiokeratomas and temperature intolerance. Signs and symptoms that tend to develop later in adolescence and early adulthood are associated with the resultant progressive and diffuse accumulation of neutral glycosphingolipids, especially of globotriaosylceramide (Gb3) in vascular endothelium, kidneys, heart, brain, skin, cornea and other tissues leads to multiorgan pathology.

Characteristic clinical manifestations of AFD such as acroparesthesias, angiokeratoma, corneal opacity, hypo/ and anhidrosis, gastrointestinal symptoms, renal and cardiac dysfunctions can occur in male and female patients, although heterozygous females with AFD usually seems to be less severely affected.[2,3] In the central nervous system (CNS), diffuse lipid storage occurs in the cerebral vasculature and neurons.[4,5] The most prominent CNS manifestations consist of cerebrovascular events such as transient ischaemic attacks (TIAs) and (recurrent) strokes.[6,7] For the most part, CNS complications in AFD have been attributed to cerebral vasculopathy, including anatomical abnormalities (e.g. small vessel occlusive disease, and large vessel ectasia and tortuosity)[8,9] impairment of endothelial function.[12 13] and dysregulation of cerebral blood flow.14 15 Gb3 storages within neurons, 5 6 cerebrovascular risk factors[10,11] and genetic factors13 might increase additionally the likelihood of developing cerebrovascular disease. Brain magnetic resonance imaging (MRI) results often altered in AFD patients[12-14] In detail, neuroradiological findings include periventricular white matter signal intensity abnormalities and single or multiple lacunar infarcts (alterations typical of small vessel disease), large ischemic cerebral infarctions[15,16] and posterior thalamus involvement (the so-called pulvinar sign).[17]

Although clinical features of the disease are mostly displayed in affected males, female carriers may suffer from Fabry related complications as well. The principal clinical manifestations in Fabry disease consist of artery associated complications (such as cerebral disease and nephropathy), but the pathophysiology of this specific vasculopathy is unclear. Several studies indicate that the specific vascular lesions that are present in Fabry disease occur as a result of vascular dysfunction with major

components being endothelial dysfunction, alterations in cerebral perfusion and a pro-thrombotic phenotype.[18]

Possibly, other cardiovascular risk factors may contribute to enhanced athero-thrombogenesis and a worsening of arterial performance. Although some patients with Fabry disease may suffer from stroke by involvement of larger arteries, small-vessel disease causes cerebral complications and probably contributes to complications of the kidney and the heart.[19-21] Controversy exists whether the storage in the endothelial cells and the pro-thrombotic state is the origin of arterial damage or whethe r smooth muscle cell proliferation in the arterial media layer is the initiating step in the cascade that leads to Fabry vasculopathy.[22,23] In addition, small fiber neuropathy could influence vascular reactivity as well, by abnormal innervation or stimuli located in the adventitial layer of the arteries. Abnormal intima media thickness and vascular reactivity as well as smooth muscle cell proliferation and atherosclerosis have all been described in patients with different ages and degrees of organ damage. For instance, advanced renal disease could markedly enhance atherosclerosis, which makes it difficult to delineate these different processes in arterial walls.

Progress has been made in the treatment of AFD thanks to the introduction of enzyme replacement therapy (ERT) in June 2001 in Europe. ERT has been shown to markedly reduce the cellular storage deposition of Gb3 in vascular endothelial cells.[24,25] However, the long-term clinical effects of ERT, especially on cerebrovascular disease, remain to be fully assessed. Since its introduction in 2001, ERT has been shown to be effective in alleviating many of the signs and symptoms of the disease and to slow or even reverse disease progression.[26-33]

Several studies underlined the presence of specific vascular lesions that are present in Fabry disease and that are pathogenetically related to a summa of vascular dysfunction and major components being endothelial dysfunction, alterations in cerebral perfusion and a pro-thrombotic phenotype.[34] Nevertheless it is not possible to exclude the role as additional pathogenetic factors of come classical atherogenic risk factor that may contribute to enhanced athero-thrombogenesis with a subsequent worsening of arterial performance. In some cases of ischemic stroke in subjects with Fabry disease it is possible to observe an involvement of larger arteries whereas small-vessel disease causes other cerebral complications such ad white matter hyperintensity lesions (WMHLs) and probably contributes to complications of the kidney and the heart.[35-37]

Still controversial it appears the tole of endothelial storage the pro-thrombotic state in a direct pathogenesis of arterial damage or whether smooth muscle cell proliferation in the arterial media layer is the initiating step in the cascade that leads to Fabry vasculopathy.[38,39]

Ischemic stroke in Anderson-Fabry Disease

Stroke is a typical neurological complication of Fabry disease. Some studies[6, 7] and informations about natural history of Fabry derived from postmarketing surveillance databases of Fabry patients treated with enzyme replacement therapy, reported that ischemic stroke may affects even young patients and that stroke has been reported as the first disease event.[7] Although patients with Fabry disease are known to experience transient ischaemic attacks (TIAs) and strokes at an early age[8, 9], there are some markers of disease burden in the central nervous system such as white matter hyperintensity lesions (WMHLs) . Fabry patients frequently show brain MRI findings of white matter lesions.[10] which can be detected by conventional neuroimaging methods but that have been reported as quantificable by means magnetic resonance diffusion tensor imaging.[11]

However, the risk of clinical cerebrovascular manifestations, such as stroke and TIAs, is difficult to predict. Thus, because of the various ways by which different studies defined cerebrovascular complications, the stroke incidence and median age at first stroke cannot be readily compared across studies.

Several studies[40-44] analyzed stroke frequency in several cohorts of patients with Fabry disease. Vedder et al.[40] showed how 12 of 25 males (48%) and 13 of 41 females (32%) experienced a previous cerebrovascular event such as TIA, stroke or lacunar stroke and that the median age of cerebrovascular event onset 46 years in male subjects and 52 years in females.

Furthermore Gupta et al[41] showed how 4 of 54 female Fabry patients (7%) with a median age of 51 years. were affected from a previous ischemic stroke, whereas Mehta et al[42] reported that 24 of 216 males (11%) and 27 of 172 females (16%) suffered from TIA or a stroke.

Grewal in a systematic revision of various types of stroke-suggestive neuroimaging data showed how 8 of 33 Fabry patients (24%) had a stroke at a median age of 26.5 years[43] and another study screened 721 young patients (age 18 to 55) with previous ischemic stroke of unknown pathogenesis showing how 4.9% of males and 2.4% of females had Fabry disease.[44]

On this basis it has been reported and estimated by the same authors how 1% to 2% of all stroke patients within this age range could have Fabry disease.

Nevertheless other researchers reported how this percentage should be underestimated or otherwise underestimated and the real number of Fabry patients among young subjects with ischemic stroke may be higher.[45] or lower[46]

Among possible mechanisms of stroke pathogenesis in Fabry have been reported a progressive accumulation of GL-3 within the endothelium of intracranial blood

vessels as a mechanism with a primary role in the vasculopathy and risk of ischemic stroke.[47] but other pathogenetic factors such as abnormalities in cerebral blood flow velocity, a prothrombotic state and increased intravascular production of reactive oxygen species have also been reported as involved in development of stroke due to intracerebral vasculopathy in Fabry disease.[48-50]

Recently, a German study reported previously unrecognized α--Gal A deficiency in 4.9% of 432 young men with initial and recurrent cryptogenic ischemic strokes[51] 21 of 432 (4.9%) male stroke patients and seven of 289 (2.4%) women had a biologically significant mutation within the alpha-GAL gene. The mean age at onset of symptomatic cerebrovascular disease was 38.4 years (SD 13.0) in the male stroke patients and 40.3 years (13.1) in the female group. The higher frequency of infarctions in the vertebrobasilar area correlated with more pronounced changes in the vertebrobasilar vessels like dolichoectatic pathology (42.9%vs 6.8%). Thus authors reported a high frequency of Fabry disease in a cohort of patients with cryptogenic stroke, which corresponds to about 1.2% in young stroke patients. Fabry disease must be considered in all cases of unexplained stroke in young patients, especially in those with the combination of infarction in the vertebrobasilar artery system and proteinuria.

However, Brouns et al[52] in a smaller study of 64 Belgian men with cryptogenic strokes did not identify any patients with α-Gal A deficiency. n a population of 103 young patients with cryptogenic stroke that met the in- and exclusion criteria,authors were unable to identify any patient with Fabry disease. Based on the results of alpha-galactosidase A and beta-glucuronidase activity, genetic sequencing and the low prevalence of clinical signs and symptoms of Fabry disease in this population, we believe that the true prevalence of Fabry disease in patients with cryptogenic stroke may be less than currently accepted in literature. Thus, the prevalence of unrecognized Fabry disease among young patients with ischemic strokes remains unclear, particularly among patients with first stroke or strokes attributed to other causes.

Moore and coworkers[53,54] reported a predominance of cerebrovascular abnormalities in the posterior arterial territory in Fabry's disease. These authors showed a significantly increased resting regional cerebral blood flow of the posterior circulation due to a vascular dysfunction of arteriolar smooth muscle and endothelial cell components. Nevertheless, the exact pathogenesis of cerebrovascular complications has not been completely elucidated. Complex multifactorial mechanisms have been proposed which may lead to endothelial dysfunction, vessel wall dilatation, induce procoagulant and abnormal flow states, which in turn may increase the incidence of emboli or thrombosis.

Some authors[55-58] analyzed pathogenetic pathways able to explain cerebrovascular diseases in patients with Fabry disease reporting a higher prevalence of brain posterior circulation subsequent Megadolichobasilar anomaly with thrombosis in subjects with Fabry disease. Megadolichobasilar anomaly (MDBA) is an extremely dilated, elongated and S-forming basilar artery that was first described by Dandy as 'S' aneurysm in 1947 and subsequently by Boeri and Passerini .[55] 150 cases have been described in the literature until 1985, but only single descriptions in patients with Fabry's disease.[56]

More recently Garzuly et al[57] described a family with MDBA occurring in five men and a woman with Fabry's disease caused by a novel mutation in the a-galactosidase gene A (GLA), the c.47T!C missense mutation resulting in L16P in the amino acid sequence of the a-galactosidase protein . These authors have found a mutation in the a-galactosidase gene in three family members. This mutation is c.47T-C missense mutation resulting in the replacement of leucine at amino acid position 16 by proline in the amino acid sequence of the a-galactosidase protein has not been reported before in patients with Fabry's disease, reporting similar enzyme activity levels in these patients. This finding suggests that the type of mutation may influence expression of enzyme activity in this family.In the absence of sufficient a-galactosidase, GL-3 accumulates in lysosomes of many cell types, mainly in the endothelium and smooth muscle. In its classical form, cerebrovascular events accompany serious renal and cardiac dysfunction in the last stage of the disease. Authors reported a prevalence of Cerebral ischaemia or infarction in 68% of 50 classical Fabry patients by using MRI.). Only one family with Fabry's disease and prominent basilar artery aneurysm has been reported.[58] In the present family, however, MDBA was also pathologically verified and is an almost consistent feature. Previous studies have reported how in Fabry Disease pathogenesis of brain ischemia could be related to a prothrombotic state due to the presence of endothelial activation markers and leucocyte integrin expression in the peripheral blood[59]
A very recent study[60] analyzed data from 2446 patients in the Fabry Registry were analyzed to identify clinical characteristics of patients experiencing stroke during the natural history period (ie, before enzyme replacement therapy). A total of 138 patients (86 of 1243 males [6.9%] and 52 of 1203 females [4.3%]) experienced strokes. Median age at first stroke was 39.0 years in males and 45.7 years in females. Most patients (70.9% of males and 76.9% of females) had not experienced renal or cardiac events before their first stroke. Fifty percent of males and 38.3% of females experienced their first stroke before being diagnosed with Fabry disease. Thirty patients (21 males and 9 females) had strokes at age <30 years. Most patients (86.8%) had ischemic strokes, but 16.9% of males and 6.9% of females had hemorrhagic strokes, among those for whom stroke type was reported. At the most recently available follow-up examination after their first stroke, 60% of males and 25.5% of

females exhibited stage 3 to 5 chronic kidney disease and 66.1% of males and 59.5% of females had left ventricular hypertrophy. On this basis authors concluded that All patients with Fabry disease, regardless of age or gender, should be monitored for possible cerebrovascular complications, as stroke can occur in the absence of other key signs of the disease.

White-matter lesions (WMLs)

The most prevalent structural imaging of fabry patients with neurological involvement are progressive white-matter lesions (WMLs), which develops even in early age.Two studies analyzed of white matter lesions (WMLs) distribution in male and female patients with Fabry disease reporting a comparable frequency and severity of WMLs in both sexes.[61,62] In the first study 36% of female and 31% of male patients had MRI findings of WMLs[62], whereas in the other study[62] a comparable prevalence of WMLS has been reported showing this MRI finding in 27% of women and 34% of men. Nevertheless a third study reported WMHs in only 7% of women with symptomatic Fabry disease with a mean age of 43 years.[64] and this finding appears as unexepected owing to the reported the high frequency of neurological complications in female patients with Fabry disease[65,66] although in this study the overall prevalence of MRI angiographic disease was of 20%.

With regard of pathogenesis of WMLs although the most reported suggestive pathogenetic mechanism is Endothelial accumulation of Gb3, it appears to be unlikely that this pathogenetic mechanism could to be the only pathogenetic pathway involved in the WMLs lesions observed in Fabry disease and this point of view seems to be underlined by the observed prevalemnce o only 14% (2/14) of women in a study by Fellgiebel and colleagues[62] that showed had reduced α-galactosidase A activity, with further evidence that circulating enzyme is able to clear lipid from endothelial cells.[67]

Another recent study[68] to quantify brain structural changes in clinically affected male and female patients with Fabry disease (FD) using Diffusion-Tensor Imaging (DTI) study in 27 adult Fabry patients and 21 age-matched controls. Authors reported that global mean diffusivity (MD) was increased in FD whereas global Fractional Anisotropy (FA) did not differ significantly between FD and controls. Authors also reported that FD patients without significant WMLs showed increased global MD Regions of interest with significant MD elevations were located in the frontal, parietal and temporal white matter, whereas no differences of thalamic and hippocampal DTI measurements could be detected between FD and controls. DTI parameters did not differ between male and female patients. These findings offer the first evidence of a pattern of marked structural brain tissue alterations in adult FD male and female patients even without WMLs. This DTI appear to be a useful technique to quantify brain tissue integrity in FD and possibly favorable for longitudinal assessment of brain structure alterations in FD and for monitoring the effects of enzyme replacement therapy on brain abnormalities markers such ad MRI findings.

A further study[69] analyzed independent and sensitive quantification of structural changes in the brain in clinically affected men and women with FD by means a voxel based analysis of diffusion tensor images (DTI) in 25 patients with FD and 20 age matched normal controls. In this study DTI findings revealed significant increases in cerebral white matter mean diffusivity (MD) in patients with FD, which were pronounced in the periventricular white matter. The subgroup of patients without significant WMLs load (n = 18) showed increased diffusivity in the cerebral white matter. In gray matter areas, MD elevation was detected only in the posterior part of the thalamus, independent of the visible pulvinar alterations on T1 weighted images whereas voxel based fractional anisotropy measurements did not differ significantly between patients and controls.

Thus the present the present study demonstrates the clinical feasibility of voxel based analysis of DTI as a sensitive tool to quantify brain tissue alterations in FD. The pattern of increased brain tissue diffusivity is probably due to microangiopathic alterations, mainly affecting the long perforating arteries.

A prospective MRI study of 50 Fabry patients with a mean age of 33 years showed that more than 50% had MRI findings indicating WMLs whereas, older are patients higher is prevalence of WMLs.[76] Furthermore a recent report indicated as this type of neuroimaging findings have been observed also in children.[77]

The most accepted pathogenetic explanation of WMLs in subjects with Fabry disease[78] is based on the concept of an increased cerebral blood flow and altered vascular reactivity due to Gb3 deposition or Gb3- induced cellular dysfunction leading to increased interstitial pressure in the deep white matter with subsequent gliosis, demyelination and increased interstitial water content resulting in white matter hyperintensities Other authors have reported to enrich this pathogenetic theory a decreased cerebral blood flow by transcranial Doppler in patients with the disease[79] and in a murine model of Fabry disease.[80]

Nevertheless, there is broad agreement that, besides α-galactosidase A deficiency, some authors underlined the role of other genetic cofactors in modulation of vasculopathy of pathogenesis of WMLs in Fabry disease, such as single nucleotide polymorphisms of genes involved the nitric-oxide pathway and in inflammatory and prothrombotic possible pathogenetic mechanisms.[81]

The deep cerebral white matter susceptibility to ischemic damage is probably due to its blood supply in perforating arteries and in particular posterior circulation perforant

branches seems at higher risk of vascular damage and perfusion impairment in this disease.[82]

Pulvinar Hyperintensity

A study[70] analyzed the presence of hyperintensity in the pulvinar region on T1-weighted images in the present retrospective study of 94 hemizygous patients with Fabry disease suggests a distinctively characteristic MR finding related to this disease. Endogenous substances that commonly cause hyperintensity on T1-weighted clinical MR images include fat, calcium.[71,72], iron (ferric form as found in methemoglobin)[73], melanin[73,74], free radicals and elevated protein concentrations.[15]

Although calcification on CT scans is most typically associated with signal intensity loss on MR images, the T1 shortening effect resulting in hyperintensity on T1-weighted images is well described.

This finding has been explained by a mechanism of surface interaction of protons with calcified tissue[75,76] At lower concentrations of calcium, T1 shortening effects dominate, resulting in hyperintensity, whereas at higher concentrations (above 30–40%) susceptibility effects and decreases in proton density dominate, leading to signal intensity loss.

It is unclear at present why only about a third of the patients with Fabry disease eventually develop this MR abnormality. The correlation of this finding with elevated posterior circulation CBF has not definitively confirmed owing to the fact that in a larger series of patients, as does the coincidental occurrence of Fabry leukoencephalopathy and dolichoectasia. It on the other hand, may be attributed to chronic lowgrade insult with an accumulation of damage over time. Thus finding of increased signal intensity in the pulvinar on T1-weighted images as a very sensitive sign of diagnosis of Fabry disease it appears not fully defined.

Very recently a study[83] investigated the typical imaging features of classic Fabry disease in patients with IVS4A (mutation, IVS4 + 919 G>A) Fabry disease.These authors analyzed MRI findings of Twenty-six patients with IVS4-type Fabry disease (20 men and 6 women; age range, 43-71 years; median age, 61 years) and 26 age- and sex-matched healthy controls (age range, 44-68 years; median age, 60 years) evaluating the presence of white matter hyperintensities, the pulvinar sign, and basilar artery diameter. The volumes of white matter hyperintensities were calculated by comparison with an in-house data base of 276 controls. Infarctions were found in 9 patients with IVS4 Fabry disease (35%) and in none of the healthy controls (P = .001). A pulvinar sign was found in 8 patients with IVS4 Fabry disease (30%) and in none of the healthy controls. No significant difference was found in Fazekas scale scores for white matter hyperintensities; however, white matter hyperintensity volume in the deep white matter was higher in patients with IVS4 Fabry disease than in those from the healthy control data base. Along with its involvement of the cardiac system, IVS4-type Fabry disease has features similar to those of classic Fabry disease and a higher frequency of deep white matter hyperintensities and a higher incidence of infarctions and pulvinar signs than in healthy controls.

Peripheral nerve involvement

Fabry disease first neurologic symptomatology usually reflect an involvement of small fibers of the peripheral and autonomic nervous systems. A common symptom of youg Fabry patients is neuropathic pain and it can manifest as chronic, burning pain and recurrent attacks of acute excruciating pain, dysesthesias, thermal disperception (primarily cold perception) and paresthesias.[84-87] Other sympotomatology due to to autonomic nervous system involvement may include hypohidrosis, impaired pupillary constriction and saliva and tear production, gastrointestinal dysmotility-like syndromes such as abdominal cramping pain, bloating, diarrhea, nausea, sensory deficits.

The primary neuropathic damage in Fabry disease has been reported as due to a combination of factors strictly related to accumulation of GL-3 or a deposition of its deacylated form.[88] GL-3, migrate into neural cells or synthesized in situ, cause a dysfunction of some critical proteins, e.g., ion channels, furtherly impairing nerve injury and dysfunction.[84] GL-3 accumulations have been described in dermal vascular endothelial and smooth muscle cells, endothelial and perithelial cells of epineural and endoneural small blood vessels, perineural cells, myelinated and unmyelinated axons, and also in Schwann cells[88-95] In Fabry patients dorsal root ganglia exhibit fenestrated blood vessels and appear particularly vulnerable for GL-3.[96]

Other pathologic findings have been reported such as luminal encroachment and occlusion of the vasa nervorum of the peripheral nerves due to endothelial GL-3 storage, disturbed balance between vasodilatative and vasoconstrictive mechanisms and thrombotic complications are factors that may contribute to ischemic neural damage.[97,98]

Peripheral nerve damage has been reported as associated with a variety of peripheral and central mechanisms, e.g., axonal sensory hyperexcitability, ectopic spontaneous firing and central sensitization that have been described elsewhere.[99,100]

A recent study.[101] evaluated large and small nerve fiber function in a homogeneous group of Fabry patients. In 24 of 30 Fabry patients with creatinine below 194.7 mmol/L the authors assessed median, ulnar and peroneal motor conduction velocity (MCV) and median, ulnar, and sural sensory conduction velocity (SCV) nerve conduction to study the function of thickly myelinated nerve fibers. In addition, the authors studied sympathetic skin responses (SSR) at both hands and feet in 24

patients. To evaluate A beta nerve fiber function, the authors determined vibratory detection thresholds (VDT) at the first toe in 30 patients. Function of A delta and C fibers was assessed by quantitative sensory testing of cold detection threshold (CDT) and heat-pain detection thresholds (HPDT). Nerve conduction studies showed significantly decreased amplitudes of MCVs and SCVs in Fabry patients as compared to controls. However, individual results of MCV and SCV studies were only mildly impaired. SSRs were present in all tested patients but SSR amplitudes were significantly decreased in Fabry patients in comparison to controls. VDT, CDT and HPDT were significantly elevated in Fabry patients as compared to controls. However, only six patients had pathologic VDT, 19 had increased CDT and 25 had elevated HPDT at a high level of stimulation. In Fabry patients, small fiber dysfunction is more prominent than large fiber dysfunction, confirming previous findings of sural nerve biopsies. The results suggest a higher vulnerability of small-diameter nerve fibers than of the thickly myelinated fibers.

Pain and somatosensory disturbances are prominent manifestations of this disease. Until recently disease manifestations in female carriers of Fabry disease have been questioned. To explore the frequency of symptoms and the functional and structural involvement of the nervous system in female patients Moller et al.[102] examined the presence of pain, manifestations of peripheral neuropathy and nerve density in skin biopsies in 19 female patients with Fabry disease and 19 sex- and age-matched controls. Diaries, quantitative sensory testing, neurophysiologic tests and skin biopsies were performed. Daily pain was present in 63% of patients, with a median VAS score of 4.0. Tactile detection threshold and pressure pain threshold were lower and cold detection thresholds increased in patients. Sensory nerve action potential amplitude and maximal sensory conduction velocity were not different, whereas there was a highly significant reduction in intraepidermal nerve fiber density. Authors found no correlation between pain VAS score, quantitative sensory testing and intraepidermal nerve fiber density. This study shows that careful evaluation of symptoms in female Fabry patients is important as small fiber disease manifestations are present, which in some cases is only detected by skin biopsy.

Another study[103] analyzed the neurologic and neurophysiologic findings and neurologic symptoms in 12 women with Fabry disease and to evaluate the relationship between the subjective symptoms and the findings on the various tests done. Authors used neurography, vibratory and thermal quantitative sensory testing (QST), skin biopsy for measuring intraepidermal nerve fiber density (IENFD). Heart rate variability (HRV) and sympathetic skin response (SSR) tests for detecting autonomic dysfunction, pain-, depression- and somatic symptom questionnaires and clinical examination. Neurological examination was normal in most patients. Five patients had decreased IENFD or thermal hypoesthesia in QST. In QST, Adelta-fiber function for innocuous cold was more often impaired than C-fiber function. Conventional nerve conduction studies were mostly normal. Carpal tunnel syndrome (CTS) incidence was increased, 25% had symptomatic CTS.

Authors concluded that heterozygous women carrying the gene for Fabry disease have symptoms and findings of small-fiber polyneuropathy more often than has previously been considered. The prevalence of CTS is also increased. Thus in the the diagnostic yield the diagnosis of small-fiber neuropathy is can be increased using a combination of thermal QST and IENFD measurements.

Common neuropathic symptoms are usually burning, nagging pain with a symmetric distribution pattern in the palms of the hands and soles of the feet of children or adolescents and peripheral dysesthesias. Other common symptoms linked to peripheral nerve involvement are recurrent attacks of pain ("pain crises"), of distal parts of the extremities and may radiate proximally.[104]

These peripheral pain crises are often triggered by a rapidly changing core body temperature (e.g., fever, stress, physical activity) presumably due to a decreased ability to sweat[104], although they have been noted even in patients with hyperhidrosis.[105] Additional causal factors include rapid exposure to cold, rapid changes in humidity and fatigue.[106]

Neuropathic pain frequence has been reported of~60 and 80% of the affected boys enrolled in the two Fabry disease registries, of ~40 to 60% of affected girls, often a few years later than in boys.[107,108]

It has recently been proposed to abandon the use of "acroparesthesia" in the description of Fabry neuropathic pain because, by definition, paresthesias are painless tingling sensations.[42] In fact, paraesthesias appear to be rather uncommon in Fabry disease as they were reported by only ~10% of affected adults.[109]

Enzyme replacement therapy (ERT) in neurological complications of Fabry disease

Clinical natural history of Fabry disease in patients prior to receiving enzyme replacement therapy (ERT) may be useful to better understand pathophysiology, for assessing outcomes once ERT is initiated. Some authors conducted.[110] a chart review of 447 patients to document the severity and progression of their nephropathy, as well as cardiovascular and cerebrovascular events and death before enzyme replacement therapy (ERT). This study evaluated as pre-defined study endpoints progression of renal, cardiac and cerebrovascular involvement and/or death before the initiation of enzyme replacement therapy.

Authors reported that advanced Fabry nephropathy was more prevalent and occurred earlier among males than females and that cardiac events (mainly arrhythmias), strokes and transient ischaemic attacks occurred in 49, 11, 6% of males, and in 35, 8, 4% of females, respectively. The mean age at death for 20 male patients was 49.9 years. This study extends the existing knowledge of the natural history of Fabry disease prior to the initiation of ERT and, in particular, describes the progression rates of the Fabry nephropathy for patients stratified by gender and baseline proteinuria.

The development and approval of recombinant human α-Galactosidase A (r-hα-GAL-A) treatment induced clinicians to start in affected individuals although several crucial questions have been never fully answered by randomized placebo controlled trials. It explains that many obtain future long-term data derived from postmarketing surveillance databases run by the pharmaceutical companies who market the enzyme products, that is, Fabry Outcomes Survey (Shire Inc) and Fabry Registry (Genzyme Inc) that are ongoing observational collecting data abour clinical findings and outcome events of patients with Fabry disease. Patient and physician participation is voluntary. Outocome events registered in these databases encompasse assessments of cerebrovascular and neurological manifestations of the included patients with Fabry disease.

Although these databases provide only surrogate informations of outcome of these patients with Fabry they offer more conclusive evidences more conclusive than clinical experience with singular cases providing definitive informations about the baseline phenotype in women.[111.112]

The understanding of the pathophysiology of the vasculopathy in Fabry disease is still not fully addressed as recently reviewed by Rombach et al.[113] although a removal effect of glycosphingolipid from various cell types has been reported in studies investigating the efficacy of enzyme replacement therapy.[114-116] Nevertheless several studies reported that the removal of stored glycosphingolipid from the endothelial cells, demonstred as histological finding, does not prevent the progression of vascular disease in many patients.[117-118] This finding put in doubt the traditional concept that storage in endothelial cells may represent the main pathogenetic event of vascucular dysfunction in Fabry disease. This paradox may be related to the fact that normal function mechanisms of GL-3 is still not fully understood thus suggesting further potential contribution of secondary metabolic phenomena to the evolution of Fabry disease.[119]

Enzyme replacement therapy with intravenous infusion of r-hα GALA has been reported as effective in lowering GL-3 levels in plasma and this effect is also been observed in clear lysosomal inclusions from vascular endothelial cells but wether this occurs to the same extent in brain vasculature is unknown. The effects of enzyme therapy on other tissues have not been univocally reported and therefore recommendations for the treatment include commencement early in the course of the disease in order to be optimally effective in preventing initial or progressive organ failure and to establish which complications of the disease that do not respond to intravenously delivered enzyme.[D120]

Enzyme replacement therapy (ERT) is the only availanle therapy for Fabry disease but owing to the fact that it is available only since less of 10 years it is still no possible to do definitive conclusions about whether this therapy can reduce the morbidity associated with CNS disorders, such as stroke. and this issue is also related to the particular characteristics of neurological complications of Fabry disease. In Fabry disease neurological complication could be viewed as potentially reversible deficits/abnormalities, such as hypohidrosis, neuropathic pain or thermal sensation deficits, and non-reversible but preventable deficits, such as ischaemic stroke.[121] Furthermore, the relatively low rate of stroke events and the effects of general therapies, such as antiplatelet agents and statins, make difficult a possible prospective analysis of effectiveness of ERT on stroke incidence. Furthermore, are highly effective in stroke prevention impairing the identification of the specific effects of ERT.[121]

In an early trial of ERT, overall pain, pain intensity and some aspects of quality of life were apparently improved after only five injections five infusions[122] and subsequent large-scale, long-term studies show that these improvements are maintained for up to 54 months.[123] In the largest cohort of patients assessed to date, pain severity was significantly reduced in 81 patients on ERT for 2 years and in 62 patients on ERT for 3 years and all dimensions of pain perception were improved.[124] As in the initial assessments of ERT, improvements in pain were accompanied by improvements in health-related quality of life, which were maintained after 24 month of ERT.[124-125]

In classical form of Fabry disease patients with essentially no detectable α-Gal A activity and progressive accumulation of globotriaosylceramide (Gb3) in microvascular endothelial and smooth muscle cells results in microvascular ischemia and infarction leading to neurologic symptomatology such as transient ischemic attacks (TIAs) and stroke. Double-blind, placebo-controlled multicenter Phase 3 and 4 clinical trials reported that enzyme replacement therapy (ERT) with agalsidase beta clears the accumulated glycosphingolipid in the vascular endothelial cells of the kidney, heart and skin.[126] and slows the progression of combined renal, cardiac and cerebrovascular events in patients with advanced FD.[127] However, central nervous system (CNS) symptoms remain a therapeutic challenge

in both untreated and treated patients, particularly in those with advanced classical form of FD.

Owing to the fact that vasculopathy of Fabry disease is linked to abnormalities in blood components, blood flow and endothelial dysfunction, some authors tested whether this vascular sysfunction should represent a possible therapeutic target to improving with disease-specific therapy thus serving as a surrogate indicator of cardiovascular event reduction such as ischaemic stroke.[122]

Authors reported that a prothrombotic condition exists in patients with Fabry disease and causing cerebral hyperperfusion an impaired vasodilation to acetazolamide[123], increased nitrotyrosine staining in dermal blood vessels and a delayed decrease in cerebral perfusion in response to ascorbate.

Authors evaluated the effect of ERT on cerebral vascular perfusion in two 6-month randomized controlled trials of agalsidase alfa conducted at the National Institutes of Health evaluating cerebral perfusion by means $H_2{}^{15}O$ and positron emission tomography (PET). These authors showed a significant decrease in resting cerebral blood flow in patients on ERT compared with the placebo group due to a partial reversal of the cerebral hyper-perfusion previously observed in patients with Fabry disease.[123]

Other studies confirmed this finding using two other methods, measuring blood perfusion and the and cerebral blood flow velocity by means transcranial Doppler.[124,125]

Another randomized placebo-controlled trial evaluated the pathogenetic role of reactive oxygen species (ROS) in cerebral hyperperfusion of Fabry patients by an analysis of the response of cerebral blood flow to the intravenous infusion of 1 g ascorbate, a known scavenger of ROS.[126] Authors by means imaging of arterial spin tagging and magnetic resonance underlined cerebral hyperperfusion also reporting how controls and fabry patients on ERT responded in a similar manner to ascorbate infusion by a decrease in cerebral blood flow, but controls showed a delay in the reduction of cerebral blood flow due to an impaired vessel reactivity, possibly due to an excess production of ROS in Fabry disease.[127]

Another study focused on peripheral nerve involvement in Fabry disease assessing neuropathic pain scores, sensory detection threshold for cold, warmth and vibration, sweat function and epidermal innervation density. Authors reported a significant reduction in pain scores, using the Brief Pain Inventory, in patients on ERT compared with those on placebo.[128]

In the same study authors used a computerized automated sensory testing equipment to evaluate detection thresholds for warmth and cold in the foot, thigh and hand reporting that patients with Fabry disease experienced significantly elevated detection thresholds for warm and cold stimuli in the foot and for cold stimuli in the hand, compared with controls.[129] Authors also reported no significant effect on these sensory parameters over the 6-month period of the randomized controlled trial in fabry patients treated with ERT with agalsidase alfa. And a significant but modest reduction in the cold and warm detection thresholds in the foot in patients receiving ERT and for warm perception in the thigh. There was also a trend for reduction of cold detection thresholds in the hand. Similar results, looking particularly at heat pain thresholds, were obtained by a group treating patients with agalsidase beta[130] also reporting an improvement in vibration detection thresholds. In two other studies,[131,132], authors reported that patients with Fabry disease had a normal vibration detection threshold with no change in vibration threshold in the hand, but a significant increase in the foot threshold and vibration detection within the normal range whereas the functional improvement in cold perception of about 10% was not associated with an increase in epidermal innervation density.

Enzyme replacement therapy (ERT) has shown beneficial effects on renal, cardiac and peripheral nerve function in FD, but the ERT effect on the progression of WMLs, or the reduction in cerebrovascular events is not fully studied.

A recent study[133] evaluated the effects on the WML burden and the effect of agalsidase beta 1 mg/kg biweekly on WML progression 4 agalsidase-beta placebo-controlled analysis of untreated and treated FD patients reporting that the WML burden in patients on ERT was more likely to remain stable, compared with patients on placebo. Thus, ERT may reduce the progression of vascular disease, even in advanced FD patients, suggesting that early treatment may stabilize WML progression and stroke risk.

Expert commentary

Real prevalence of cerebrovascular complications of Fabry disease remains worthy of further analysis, although a recent study[133] reported previously unrecognized α-Gal A deficiency in 4.9% of 432 young men with initial and recurrent cryptogenic ischemic strokes. Nevetheless prevalence of FD[135] among nonselected adults 60 years of age or younger with acute ischemic stroke or TIA is not to date well negligible and a systematic evaluation for FD in a stroke setting, using a comprehensive clinical, biochemical, and genetic screening protocol, may be useful.

Nevertheless, neurological complication of subjects diseases represent a real health problem in these patients although the actual weight of the cerebral ischemia in patients with Fabry disease remains in many ways still to be determined it is likely to think that the role of cerebrovascular neurological complications and do not

appear to have an increasing role with increasing age of the patients and particularly likely in males and in so-called variant forms Since its introduction in 2001, ERT has been shown to be effective in alleviating many of the signs and symptoms of the disease and to slow or even reverse disease progression.[136-137]

The enzyme replacement therapy agalsidase alfa has an amino acid sequence identical to that of native α-galactosidase A and intravenous agalsidase alfa 0.2 mg/kg every other week is indicated for the long-term treatment of patients with confirmed Fabry disease. Agalsidase alfa had beneficial effects in adult men with abnormalities in functional cerebral blood flow and cerebrovascular responses that has been reported as also reversed with agalsidase alfa therapy[138] and it has been reported a significant reduction in cold and warm detection thresholds and a significant improvement in sweat function were seen after 3 years' therapy.

Recommendations and guidelines for ERT in patients with Fabry disease have been published previously in 2003[139] and 2006.[140] These guidelines, however, require updating, particularly when considering indications for commencing treatment in females and children owing to the fact that comparison of the percentage of females and males included in a registry of patients with Fabry disease has shown that 82% of males have been given ERT compared with just 34% of females; importantly, this difference was not justified based on the extent of major organ involvement.[141]

Thus considering high prevalence of neurological symptoms in females with variant form of the disease need an appropriate remark about the real effectiveness of ERT in these subset of patients and another not fully explained issue is that although enzyme replacement therapy (ERT) has been reported as effective in adults, there are, as yet.

No published data regarding the long-term effects of ERT in children. Therefore In our opininion, in order to continue collecting data of the effects of treatment in children with Fabry disease, it is essential that patients be diagnosed as early as possible.[142,143,144,145]

Another related issue is due to the X-linked inheritance of Fabry disease that implies that the prevalence of this disorder is likely to be twice as high in females as in males. However, data from patient registries[146,147] indicate that females only make up approximately half of the patient population, suggesting that Fabry disease is underdiagnosed and thus undertreated in females. Owing to the fact that severity of disease phenotype in females has been reported to correlate with age in our opinion an early intervention with ERT may be more beneficial than later intervention and this issue may be particularly in clinical setting of neurolical complications of Fabry disease.[148-150]

Furthermore in our opinion it may be desirable that future studies will be addressed to furthering understanding of the parameters that predict more severe disease in females thus to ameliorate our ability to identify patients who are more likely to benefit from early therapy.

In recent years, our knowledge of the pathology and natural course of Fabry disease has improved significantly and now it is well known that deficiency of the lysosomal enzyme α-galactosidase A is results in accumulation of globotriaosylceramide in bodily tissues, probably contributing to the tissue dysfunction associated with Fabry disease.

Nevertheless the precise relationship between sphingolipid metabolism and cellular dysfunction is not clear particularly in clinical setting of central neurological complications of Fabry patients whereas more precise knowledges seem to be confined to the role of globotriaosylceramide accumulation in the peripheral nerve involvement with more significant effects of ERT on symptoms such as pain and dysesthesias.

Thus enzyme replacement therapy (ERT) is currently the primary treatment for Fabry disease and it is based on the intravenous administration of recombinant human α-Gal A (rhα-Gal A), of which Fabrazyme (agalsidase β; Genzyme, Cambridge, MA) and Replagal (agalsidase alfa; Shire Pharmaceuticals, Cambridge, MA) are the only two approved products. These therapies are generally well-tolerated, and in some patients reduce plasma, urine and microvascular endothelial GL-3 levels, stabilize kidney function,[7] and alleviate neuropathic pain, reverse or improve hypertrophic cardiomyopathy, and increase the ability to sweat. Unfortunately delivery and uptake of ERT to some cells, tissues, and organs is insufficient in certain cases, as suggested by the inability of infused rhα-Gal A to significantly reduce GL-3 in cardiomyocytes, renal tubules, and glomerular podocytes, as well as the central nervous system and in addition, the infused enzymes can be immunogenic, which may limit efficacy and sometimes adversely affect tolerability.

Recent evidences[152] indicate that a pharmacological chaperones (PCs) such as iminosugar, 1-deoxygalactonojirimycin (AT1001) may ameliorate stability and total cellular and tissue levels of exogenous rhα-Gal A, translating to greater enzyme activity and substrate turnover *in situ*reporting in cell-based studies, the efficacy AT1001 coincubation on rhα-Gal A uptake and GL-3 reduction in cultured fibroblasts derived from different male Fabry patients.

Thus in our opinion AT1001 coadministration may represent a future therapeutic option to mprove therapeutic management possibly applicable to several groups of Fabry patients and future trial should be

addressed on the basis of these encouraging findings to confirm these findings.

Five-year view

A targeted screening for Fabry disease among young individuals with stroke seems to disclose unrecognized cases and may therefore very well be recommended as routine in the future. Furthermore, ischemic stroke is related to inflammation and arterial stiffness and no study had addressed this relationship in patients with AF disease and cerebrovascular disease, so this topic could represent a possible future research line.

Nevertheless, thus, it is important to add primary stroke prevention including lifestyle counseling, blood pressure and lipid-lowering drugs and additionally ACE inhibitors, angiotensin I and II receptor antagonists.

Continued research and the collection of efficacy data will contribute to the increased knowledge concerning Fabry's disease diagnosis and management with ERT whereas even better understanding of the disease specifics and its treatment will increase the likelihood that some important questions regarding important issues such as the advisability to treat asymptomatic females to be treated, the possibility to reverse organ damage or to consider these findings as a "point of no return", the role of ERT in restorgin organ histology and function or in stabilizing and preventing further organ deterioration, will be answered.

An important step in the improved management of Fabry disease in the future will be increased awareness of Fabry disease among a wide range of specialists and general physicians. The provision of specialist-specific algorithms for the diagnosis and treatment of Fabry disease, together with comprehensive international management guidelines, will be key to optimizing individual patient care.

Molecular chaperone therapy Although ERT remains the major approach for the treatment of patients with Fabry disease and other LSDs, other therapies have been investigated. Of these, pharmacological chaperones are showing the most promise for patients with specific mutations resulting in misfolded or unstable enzymes.

Pharmaceutical chaperones are small molecular ligands that can be administered orally and which bind selectively to the misfolded enzyme, promoting correct folding and delivery of the enzyme to the lysosome.

In the case of Fabry disease, use of the chaperone 1-deoxygalactojirimycin hydrochloride has been shown to increase the activity of several a-galactosidase A responsive mutants and to reduce urinary levels of Gb3 in those patients who have missense mutations.

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