

# Fabry Cardiomyopathy: A Global View

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## 1. Introduction

Fabry disease (FD) is a lysosomal storage disease (LSD). It has been stated that the second most common LSD after Gaucher disease is Fabry disease; its worldwide incidence is from approximately 1 in 40 000 to 1 in 117 000 live newborns for the classic form of the disease, but the precise prevalence is unknown. Wide variations in the prevalence of FD have been reported in different countries and, with increasing awareness and screening, it is likely that the actual prevalence may be higher than previously recorded, particularly when late-onset phenotypes are taken into account. An accurate estimation of its epidemiology is difficult to make because FD is clinically very heterogeneous and its early classic manifestations tend to be non-specific and often unrecognized. Patients are therefore frequently mis-diagnosed, or not diagnosed until late in life. Recently a newborn screening showed an incidence of one in 3100 live-newborns, and according to this study, the later-onset forms of FD present a surprisingly high incidence <sup>1</sup>.

Lysosomal biogenesis involves ongoing synthesis of lysosomal hydrolases, membrane constitutive proteins, and new membranes. Lysosomes originate in the fusion of trans-Golgi network vesicles (TGN) with late endosomes. Progressive vesicular acidification accompanies the maturation of the TGN vesicles and this gradient facilitates the pH-dependent dissociation of receptors and ligands, as well as activation of lysosomal hydrolases.

Abnormalities at any stage of the biosynthesis can impair enzyme activation and lead to lysosomal storage disorder. Lysosomal integral or associated membrane proteins are sorted to the membrane or interior of the lysosome by several different signals. Phosphorylation, sulfation, additional proteolytic processing, and macromolecular assembly of heteromers occur concurrently. These are critical to enzyme function, and defects can result in multiple enzyme /protein deficiencies.

The common pathway for LSD is the accumulation of specific macromolecules within tissues and cells that normally have a high flux of these substrates. The majority of lysosomal enzyme deficiencies result from point mutations or genetic arrangements at a locus that encodes a single lysosomal hydrolase<sup>3-5</sup>.

Most LSDs are inherited as autosomal recessive disorders, except Hunter and FD. The latter is an X-linked inherited lysosomal storage disorder that results from mutations in the  $\alpha$ -galactosidase gene. The gene encoding human  $\alpha$ -galactosidase A enzyme ( $\alpha$ -Gal A), located at Xq22.1, spans genomic sequences of approximately 13 kb, containing seven exons, which have been isolated and characterized <sup>6,7</sup>.

Alpha-galactosidase A is a lysosomal exoglycohydrolase. The mature  $\alpha$ -Gal A enzyme polypeptide is 398 amino acids and contains three functional N-glycosylation sites. The active enzyme is a homodimer of approximately 101 kd. This mutation has significant consequences in glycosphingolipid catabolism resulting from deficient or absent activity of the lysosomal enzyme  $\alpha$ -gal A. This enzyme helps to break down and remove glycolipids. The enzymatic defect leads to progressive accumulation of the glycolipid globotriaosyl ceramide (Gb3 or Gl3), or ceramide trihexoside, in the lysosomes in the cells of most organs. Substrate accumulation leads to lysosomal distortion, which has significant pathologic consequences<sup>8-9</sup>.

Up to now, more than 300 mutations that cause FD have been identified, including missense, nonsense, small deletions and insertions, large gene rearrangements, and splice mutations. Most mutations are private and unique, occurring in one or a few affected families. In the cardiac variant of FD all individuals to date have missense or splicing mutations that express residual  $\alpha$ -Gal A activity. All renal variants identified to date have been associated with missense mutations. Three mutations (p.Arg112His, p.Arg301Gln, and p.Gly328Arg) have been identified in individuals with the classic phenotype and the cardiac variant phenotype, suggesting that other modifying factors are involved in disease expression. Therefore it is necessary to sequence the entire  $\alpha$ -gal A gene and adjacent regions to identify the FD mutation in a family<sup>10-14</sup>.

FD is considered highly penetrating in males, although variable in its expression. In affected males, the clinical diagnosis is confirmed by  $\alpha$ -gal A deficiency. The majority of males with FD have absent or very low enzyme activity (1-2% of normal level) and classical phenotype with multiple disease manifestations. Males who show higher residual enzyme activity, approximately 3-10% of normal level, appear to have milder expression of FD. These individuals are diagnosed with FD later in life, after cardiomyopathy of unknown etiology (in most cases, hypertrophic cardiomyopathy - HMC) is discovered<sup>4</sup>.

About 60-70% of females heterozygous for a Fabry disease mutation have some disease manifestations, and approximately 10% of these heterozygous females have severe manifestations, similar to the phenotype in males. Enzyme activity is not reliable for determining female carrier status because women who are obligate carriers have variable levels of  $\alpha$ -gal A that can overlap with enzyme levels found in healthy controls. Therefore it is necessary to sequence the entire  $\alpha$ -gal A gene and adjacent regions to identify the Fabry disease mutation in a family. The absence of family history suggestive of FD, or de novo mutations documented, does not rule out the diagnosis of FD. The rate of new mutations is unknown<sup>8</sup>.

## 2. Cellular physiopathology

Many theories have been proposed with respect to the pathology of FD. It has been hypothesized that the overloading of lysosomes with Gb3 simply leads to the apoptosis of the cell<sup>15</sup>. Another theory argues that the inflammation process is related to the accumulation of Gb3. This theory has been defended based on the parallel structure between Gb3 and CD77, which is supposed to play an important role in apoptosis and necrosis<sup>16</sup>. Finally, Gb3-accumulation has been reported to induce oxidative stress and/or the formation reactive oxygen species (ROS). Another gateway into alteration of endothelial function may be given by the Nitric-Oxide-Synthase-3-genotypes. Endothelium-derived

nitric oxide (eNO), produced by eNO synthase (eNOS), is a key regulator of vessel wall function and cardiovascular homeostasis<sup>17</sup>. Furthermore, the possible relationship between the relative thickness of the left posterior wall and endothelium-derived nitric oxide synthase has been demonstrated. These are the first data showing a significant association of non-GLA-derived sequence variants with the cardiac phenotype in Fabry disease that may, in part, explain the great phenotypic variability of the disease<sup>18</sup>.

### 3. Clinical presentation

Clinically, FD may present as cardiomyopathy, renal disease or neurological small-vessels disease. The age range at which FD presents is quite broad and extends from childhood to the forties, depending on the enzyme residual activity.

Nephropathy is one of the major complications of FD: the nephropathy is progressive and is marked by a persistent insidious development. An analysis of the causes of death reported for 181 affected relatives and 42 patients (699 males and 754 females), enrolled in the Fabry outcome survey (FOS) indicates that the incidence of renal disease as a cause of death appears to be decreasing, while the incidence of cardiac disease is increasing; these trends probably reflect improvements in the management of renal disease in these patients. By adulthood, renal failure frequently becomes a major complication of FD, with more than 50% of male and more than 20% of female patients eventually developing advanced renal disease or end-stage renal disease (ESRD)<sup>19-20</sup>.

Effects on the renal system in FD can and need to be detected in the earlier years of life. Renal involvement has previously been categorized as the second phase of the disease and, as stated by West et al.,<sup>21</sup> older patients are more likely to be diagnosed with severe Fabry nephropathy on their first consultation.

Microalbuminuria is one of the first signs of impairment of renal function, and overt proteinuria may start as early as 10 years of age. Biopsy studies have shown that glomerular and vascular changes are present before progression to overt proteinuria, although chronic kidney lesions may already be present. In young patients, glomerular hyperfiltration can mask the detection of early decline in the glomerular filtration rate (GFR) to the extent that a critical number of nephrons become damaged and cannot maintain adequate glomerular filtration.

The decline in GFR typically commences once proteinuria is established but may precede it. Overt proteinuria is more prominent in men than in women. Proteinuria is a risk factor for progression of nephropathy.

Progression to ESRD is common in hemizygous males (in the third to fifth decades of life), and this population group presents more rapid rates of FD progression than those who do not suffer ESRD. The survival of patients with FD in dialysis is better than that of diabetic patients, but it is clearly decreased compared with uremic patients with other nephropathies, despite a lower mean age of uremia. The outcome of kidney transplantation is similar to that found in other patients with ESRD, despite controversial issues published in the past. The use of a kidney donor with normal  $\alpha$ -Gal-A activity in the control of the metabolic systemic disease is unproven. The recurrence of Gb3 deposits in the kidney graft has been documented only rarely<sup>20</sup>.

Cardiac involvement is very common and is the most frequent cause of death not only in hemizygote males but also in female heterozygote carriers with  $\alpha$ -Gal A deficiency, with a

reduction of life expectancy of approximately 20 and 15 years respectively. The heart may be the only organ affected in the classic phenotype of FD, and this is designated the "cardiac variant". Within the heart, the myocytes, vascular endothelium, conducting system and valves can all be affected. Abnormal storage of the lipid in the blood vessels, with eventual occlusion of the small arterioles, leads to most of the clinical manifestations. Although cardiac involvement of FD begins early, the average age for presenting clinically overt cardiac symptoms (including dyspnea, reduced exercise tolerance, angina, chest pain, palpitations, ventricular arrhythmias, syncope, transient ischemic attacks, stroke and heart failure) has been reported to be 32 years in men and 40 years in women. Cardiovascular manifestations include renovascular and systemic hypertension, aortic root dilatation, mitral prolapse and congestive heart failure <sup>22</sup>.

Although angina is often reported, the incidence of epicardial coronary stenosis is not a dominant feature, and is probably related to coronary microvascular dysfunction. In respect of arrhythmias, a broad spectrum can be seen including shortened or prolonged PR-intervals, AV blocks of different degrees and, sometimes, malignant ventricular arrhythmias. The most frequent cardiac manifestations of the disease are permanent and paroxysmal atrial fibrillation and intermittent ventricular tachycardia. Moreover, an impairment of autonomic control of the heart in boys with FD increases heart variability and may be responsible for the increased cardiac morbidity <sup>23</sup>.

LV hypertrophy is detected in more than 50% of patients. It is more frequent and has an earlier age of onset in males than in females. LVH is a hallmark of FD that can initially present with preserved ventricular function, as has been reported in 3% of men with LVH, and in up to 6% of men and 12% of women with late-onset hypertrophic cardiomyopathy (HCM). LVH is generally symmetrical, although asymmetric septal hypertrophy has been described, and the condition can mimic the phenotypical and clinical features of HCM.

FD is a relatively prevalent cause of HCM and is associated with significant morbidity and early death due to heart failure or ventricular arrhythmias. HCM, mainly characterized by LVH and conduction abnormalities, may in fact be the major presenting feature of the disease.

The electrocardiogram may show LV hypertrophy, P-wave abnormalities, conduction defects, and ventricular dysrhythmias. Typically the echocardiogram shows marked increases in wall thickness and ventricular dilatation later in the disease process. Leaflet and cuspid thickening can be seen, and this produces valve impairment that usually does not require surgical treatment <sup>24</sup>.

Tissue Doppler Imaging (TDI) and strain rate echocardiography represent new echocardiographic tools. In particular, with TDI allowing measuring myocardial contraction and relaxation velocities can be measured, thus providing an objective assessment of both diastolic and systolic ventricular function. In addition, it has been demonstrated that specific TDI parameters (E/Ea ratio) provide a good estimate of left ventricular and atrial filling pressure. The study of left ventricular hypertrophy and cardiomyopathies represents one of the most important fields of application for this imaging technique. TDI can detect the first sign of myocardial damage in a patient with FC and normal cardiac wall thickness. Furthermore, Tissue Doppler (TD) studies have been shown to be useful in detecting cardiac involvement in female carriers with no systemic manifestations of Fabry disease. TDI analysis in mutation-positive patients can enable professionals to recognize preclinical

cardiac damage in Fabry disease: a reduction of TDI velocities may represent the first sign of initial intrinsic myocardial impairment.

The clinical usefulness of TD echocardiography includes a predictive role, in a proper clinical setting. TDI has demonstrated cardiac impairment in patients without LVH, and the correlation between hypertrophy and severity of baseline dysfunction as measured by TDI supports the specificity of this technique. In addition, an inverse relationship between LVH and myocardial systolic velocity (Sa) has been found. Data suggest that Sa correlates very closely with LV wall thickness. In studies, the IVCT was significantly shorter in the group without LVH, compared with the control group, but showed a tendency to be longer in the group with LVH. This may be attributable to the onset of compensating mechanisms as a result of myocardial impairment, due to the stored vacuolated material being mostly confined to the perinuclear zone, with no or only mild instances of fibrosis in this population<sup>26,27</sup>.

Cardiac magnetic resonance imaging (c-MRI) with delayed enhancement may be useful in the non-invasive recognition of myocardial fibrosis, in the context of cardiac involvement of FD. With delayed gadolinium enhancement, c-MRI can identify areas of myocardial damage in HCM and in FD. The evaluation of the myocardial location and distribution patterns of delayed enhancement helps in the identification of the two causes of LV hypertrophy, HCM and LVH associated with Fabry cardiomyopathy.

Furthermore, the myocardial T2 relaxation time is prolonged in patients with Fabry's disease compared with that in hypertrophic patients, and its measurement could be complementary to the delayed enhancement technique<sup>28,29</sup>.

Dermatological lesions usually appear in hemizygous patients, but less frequently in children and women. The earliest clinical signs of Fabry disease often manifest as dermatological disturbances such as angiokeratomas, hypohidrosis, acroparesthesias, and impaired thermal and vibration detection. These disturbances are caused by accumulation of cellular globotriaosylceramide in the skin due to deficient lysosomal  $\alpha$ -galactosidase A activity.

The simplest recognizable, but not pathognomonic, characteristics are angiokeratomas, described mostly (66%) in males but also (33%) in females. Angiokeratomas, which are another hallmark of FD, are red papulomatous lesions occurring in groups on the buttocks and in umbilical areas, the thighs and genital areas. Telangiectasias have been described, again mostly in men. Some authors have described the typical "FD rash" that includes angiokeratomas and telangiectasias. It has been established that there is an association between these dermatological lesions and other early signs such as proteinuria, paresthesias and cornea verticillata. Facial dysmorphism with a characteristic coarsening of the facial features is increasingly recognized<sup>30,31</sup>.

Xeroderma has also been described; reduced production of tears and saliva affect 50 % of this population. Although hypohidrosis/anhidrosis is a classic feature of FD, it has been detected in only 11.9% of females and 6.4% of males, and is also reported in childhood.

With respect to ocular and auditory symptoms, the most characteristic manifestation is increased vascular tortuosity. Located in the superficial layer of the cornea, using a slit lamp, a haze has been described as the most frequent cornea abnormality. Some authors have suggested that the haze is the natural evolution of cornea verticillata. This latter condition has been described in the majority of patients affected with FD (70%); it is termed cornea verticillata because the deposits are distributed in a vortex pattern. Two types of lens

opacity have been described in FD: one type is anterior capsular and subcapsular cataracts, which are always bilateral, and the other type is posterior subcapsular cataracts, which have been described more rarely but specifically, hence these latter have been designated "Fabry cataracts". Vascular lesions are demonstrated using ocular fundus examination<sup>32-34</sup>

High frequency sensorineural hearing loss is common in FD, and affects males earlier in life. Hearing is worse in patients with FD than in the general population, but clinically relevant hearing impairment only affects 16% of patients. Sensorineural hearing loss is less common in children than previously reported, although tinnitus appeared to correlate significantly with severity of clinical presentation in children

The earliest neurological manifestation is painful neuropathy observed in the majority of the patients, mean age of onset 9-14 years in males and 16-20 years in females. Most invalidating neuropathic pain is described as acroparesthesias, which can affect the whole body, but are reported mostly in the hands and feet. Fabry neuropathy has a typical neurophysiological pattern that enables it to be differentiated from other neuropathies. The incidence of carpal tunnel syndrome appears higher than in the general population. Gastrointestinal manifestations of autonomous nervous system involvement may range from abdominal pain to diarrhoea and, more rarely, constipation; in women, abdominal pain may be considered, erroneously, to be of gynecological origin. Altered sweating function is a frequent and classic feature. High temperature increases poor tolerance: fever, and high environmental temperature, as well as physical exercise, can trigger acute pain at the extremities with weakness, which is often intense, and generalized malaise. The central nervous system can be affected, and this contributes to earlier mortality, with a median age of 50 years. As happens with the heart, men will typically be affected in their forties, and women ten years later.

Cerebrovascular events (TIAs, stroke), are present in over 25% of FD cases; in FD they occur at a rather early age and increase progressively. The areas most affected are those supplied by posterior circulation. Renal and cardiac disease can co-exist with cerebrovascular disease, and may predispose patients with FD disease to neurological disability and stroke; however, recent data show that most patients (70.9% of males and 76.9% of females) had not experienced renal or cardiac disease before their first stroke. In addition, 50% of males and 38.3% of females had their first stroke before being diagnosed with FD. In female FD patients, who were for a long time considered to be merely "carriers", and so less affected, the prevalence of cerebrovascular events reported now seems to be as high as in male patients. Differences in cerebral blood velocity have been shown in these patients. These observations have been confirmed after the patients had been treated for a long period of time. Typically, MRI may show lesions attributable to small infarctions, and diffuse alteration of the white matter, especially in deeper sections, with images suggestive of arteriolar involvement of the perforating arteries (lacunar infarctions and leukoariosis). The 'pulvinar sign' is a characteristic MRI manifestation of FD; it is a symmetric hyperintensity image in both pulvinar nuclei<sup>1, 35-36</sup>.

Fabry patients, even those with marked structural alterations of the brain, show only mild cognitive deficits.

Neuro-psychiatric symptoms have been demonstrated in patients affected with FD. Depression is a frequent and under-diagnosed problem. Depression can have a serious effect on quality of life in patients with FD. The high frequency of depression in FD is likely

to be related to the general burden of this chronic multi-organic hereditary disease, but not to the structural brain alterations typical of FD.

Other symptoms associated with FD are gastrointestinal (GI) symptoms. Abdominal pain (often after eating) and diarrhoea are the most frequent manifestations, but other GI symptoms include constipation, nausea and vomiting. The median age of onset of many GI symptoms is before the age of 15 years. FD may be complicated by osteopenia of the lumbar spine and femoral neck.

#### 4. Diagnosis of FD

Diagnosis of FD is often delayed by at least 3 years, and often by 20 years, after the onset of clinical instauration. Male patients with a family member affected need a biochemical analysis in order to measure the plasma or urinary Gb3(lys-Gb3), or  $\alpha$ -galactosidase A activity. In addition, genetic analysis of the GLA gene can confirm the diagnosis.

For suspected heterozygous females, demonstration of markedly decreased  $\alpha$ -Gal A enzyme activity in plasma and/or isolated leukocytes confirms the carrier state in a female. In those women with normal  $\alpha$ -Gal A enzyme activity, molecular genetic testing is necessary to clarify genetic status. Some studies have confirmed the need for direct sequencing in females, instead of other screening strategies.

Those patients with symptoms suggestive of FD require a screening based on the measurement of the accumulated substrate, Gb3, in the urine, especially male patients. Measurement of enzyme levels and assessment of mutational status using blood spots are increasingly utilized. Similarly, quantifying the enzyme in urine samples by enzyme-linked immunoabsorbent assay (ELISA) shows promise, although such diagnostic methods are only reliable in males<sup>3</sup>.

Molecular prenatal diagnosis has become feasible in families with known mutations, or by analysis of intragenetic and closely-linked markers. The prenatal diagnosis of FD is performed using cultured amniocytes, direct and cultured chorionic villi, or blastomeres for preimplantation diagnosis. As soon as the fetal sex is known, the  $\alpha$ -Gal A activity or mutation analyses are performed. Chorionic villus sampling is the optimal procedure, providing fresh fetal tissues after the first trimester<sup>37</sup>.

#### 5. Treatment of FD

Specific pharmacologic therapy for FD with enzyme replacement therapy (ERT) is endorsed by health regulatory agencies. Two authorized drugs are available in Europe for ERT.

ERT supplies recombinant GLA to cells and reverses several of the metabolic and pathologic abnormalities. ERT has been available for the treatment of FD since 2001 with the introduction of two products, agalsidase- $\alpha$  (Repaglal®, ShireHGT Inc) and agalsidase  $\beta$  (Fabrazyme, Genzyme Corp).

Agalsidase- $\alpha$  is purified from a stably transfected human cell line 120 and is infused at a dose of 0.2 mg/kg over a period of 40 min, every two weeks. The extra efficacy of agalsidase alpha administered at 0.2 mg/kg in weekly infusions may be beneficial in some patients.

Agalsidase- $\beta$  is produced in Chinese hamster ovary cells and is infused at a dose of 1.0 mg/kg over a period of up to 4 h, every 2 weeks. The use of a lower maintenance dose of agalsidase beta, 0.3 mg/kg, has been shown to maintain Gb3 clearance in the short term in some patients but not all.

Emerging treatment strategies for FD involve molecular chaperone therapy, and these are very promising for specific mutations. Pharmaceutical chaperones, currently in phase 3 clinical trials, are small molecular ligands that can be administered orally and which bind selectively to the mutant enzyme, promoting correct folding and delivery of the enzyme to the lysosome. In the case of FD, use of the chaperone 1-deoxygalactosyljirimycin hydrochloride has been shown to increase the activity of several  $\alpha$ -galactosidase A-responsive mutants and to reduce urinary levels of Gb3 in those patients who have missense mutations. Recent studies have shown that chemical chaperones can improve the efficacy of ERT.

Substrate reduction therapy (SRT) circumvents enzyme replacement /modification by inhibiting synthesis of globotriaosyl ceramide. This approach involves the use of a glucosyl ceramide synthase inhibitor, which would slow the rate of Gb3 synthesis, and thus decrease lysosomal storage. Combinatorial therapy using ERT and SRT is being considered as a treatment strategy. Enzyme activators may increase the residual activity of mutant GLA in the lysosomes of patients with FD, thereby lessening lysosomal storage of the substrate and alleviating symptoms. However, these activators may not be beneficial if their efficacy is not high enough or if the residual activity of mutant GLA is inadequate.

Specific small molecule promoter activators may increase the amount of GLA in lysosomes by stimulating expression of the target protein. This would result in an increased amount of GLA in the lysosomes, as the enhancement of mutant enzyme expression may proportionally increase protein trafficking to the lysosome. Therefore, in Fabry patients with significant residual GLA enzyme activity, a small molecule promoter activator may correct lysosomal storage by amplifying the amount of enzyme in lysosomes.

Another future treatment strategy involves altering the proteostasis network in cells; this network consists of many highly-regulated biological pathways that influence protein synthesis, folding, trafficking, disaggregation and degradation. In addition, the combination of proteostasis regulators with small molecule chaperones may further increase the amount of folded protein trafficked to lysosomes and thus enhance the therapy, although this hypothesis needs to be tested.

In addition to ERT, the standard treatment strategy, many symptoms of FD can be managed through supportive and palliative approaches. Daily prophylactic doses of neuropathic pain agents, such as phenytoin, carbamazepine, and gabapentin are effective in decreasing the frequency and severity of pain episodes in many patients.

Some patients need more potent analgesics, such as opioids, for pain management while avoiding potential dependency problems. For gastrointestinal disturbances, metoclopramide, H2 blockers, loperamide and hydrochloride can be beneficial. Therapeutic management primarily focuses on the control of blood pressure, lipids, and proteinuria. ACE inhibitors and ARA II /or blockers should be used in patients with proteinuria. Hypertension and hypercholesterolemia should be managed appropriately as usual. Prophylaxis with anti-aggregants is important in patients who have had ischemic attacks or stroke, and permanent cardiac pacing should be considered in high-risk patients. Furthermore, patients need to be encouraged to maintain a healthy lifestyle. While renal failure is the most frequent cause of death in classic FD, in patients with advanced renal disease, dialysis or transplantation can prolong life. However, in FD, even with the engrafted kidneys, other organ system damage continues, particularly vascular disease affecting the heart and brain. It is clear that, even with ERT, other treatments and preventative measures are necessary to manage Fabry disease<sup>38-40</sup>.



## 6. Efficacy of ERT

Generally, ERT normalizes Gb3 levels in a wide variety of organs in most patients, and may be associated with symptomatic benefits. Overall measures of FD severity have shown a general reduction in disease severity after at least 1 year of ERT.

The efficacy of ERT in Fabry cardiomyopathy can be evaluated as the stabilization or decrease of the LV mass and regional myocardial function after 1 year of this treatment, and better exercise capacity at 3 years of therapy in those patients without fibrosis. In addition, clearance of Gb3 from cardiac interstitial capillary endothelial cells has been seen after ERT with agalsidase beta, although not in other cardiac cells such as cardiomyocytes. The long-term effects of ERT on Fabry cardiomyopathy are related to the extent of myocardial fibrosis at baseline, when therapy is started. Fabry patients at an early stage of the disease have virtually no myocardial fibrosis. These patients with no detectable fibrosis and mild hypertrophy at baseline have shown a normalization of LV wall thickness and mass during ERT. Subsequently, the patients with no fibrosis have also improved in exercise capacity, which might be related, at least partly, to the positive effects of ERT on the Fabry cardiomyopathy.

Concerning the optimal time for starting enzyme replacement therapy, prospective clinical trials in affected males and female carriers still in a preclinical phase using TDI and strain rate to assess non-invasively the efficacy of therapy are required to establish the benefits of starting treatment as soon as the diagnosis is reached. Strain-rate imaging based on tissue Doppler is superior to global parameters, like ejection fraction, in monitoring and quantifying LV function in patients with Fabry disease. The increase in peak systolic strain rate appears to be more specific for regional contractility and rather independent of wall thickness.

In relation to renal function, the initiation of ERT before the development of significant proteinuria may be critical for preventing future kidney disease in these patients. Thus, creatinine clearance and eGFR have remained stable after ERT. Treatment with agalsidase alpha for 3 years has been shown to be effective in slowing the deterioration of renal function in patients with Fabry nephropathy. Even in patients with advanced renal disease or in kidney transplant recipients, ERT, by addressing the underlying metabolic deficiency, may slow the progression or development of extra-renal signs and symptoms of the disease. Neither of the synthetic enzymes cross the blood brain barrier (BBB). Treatments can, therefore, only act on the endothelial cells of the cerebral arterial circulation, at least when the BBB is intact (in aggressive and aseptic meningitis-like forms of Fabry disease with lacunar infarcts, BBB may be seriously altered). More studies are necessary to provide evidence of the efficacy of ERT in preventing new cerebrovascular events.

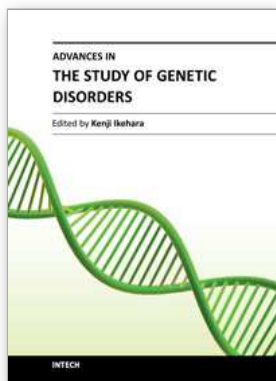
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## **Advances in the Study of Genetic Disorders**

Edited by Dr. Kenji Ikehara

ISBN 978-953-307-305-7

Hard cover, 472 pages

**Publisher** InTech

**Published online** 21, November, 2011

**Published in print edition** November, 2011

The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Rocio Toro Cebada, Alipio Magnas and Jose Luis Zamorano (2011). Fabry Cardiomyopathy: A Global View, *Advances in the Study of Genetic Disorders*, Dr. Kenji Ikehara (Ed.), ISBN: 978-953-307-305-7, InTech, Available from: <http://www.intechopen.com/books/advances-in-the-study-of-genetic-disorders/fabry-cardiomyopathy-a-global-view>

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