Summary: Fabry Disease, a Uniquely Different Lysosomal Storage Disorder

Deborah Elstein

Abstract  Lysosomal storage disorders (LSDs) can be viewed as unified by their pathology; however, clinical presentation in each of the LSDs is uniquely variable, often even among those with the same genotype Nonetheless, there are areas of commonality within the sub-types of LSDs (infantile, juvenile and late-onset forms) as well as among the various LSDs. Having said that, Fabry disease may, nonetheless, be the one LSD that is least like the others, possibly because it is X-linked. This chapter will review what is currently known about Fabry disease and put this in the context of the other LSDs.

Keywords  Lysosomal storage diseases · Fabry disease · Diagnosis · Clinical symptoms · Enzyme replacement therapy

Introduction

Lysosomal storage disorders (LSDs) can be viewed as unified by their pathology which involves abnormal accumulation of partially degraded glycosphingolipids derived from the plasma membranes of eukaryotic cells and intracellular lysosomal and Golgi apparatus, in various organs. In each of these diseases a specific lysosomal hydrolase which should have been destined for post-translational modification and catabolism is putatively way-laid (by virtue of mis-folding) because of mutation(s) in its sequence. Virtually all of the LSDs can be considered within the context of the sequential breakdown of ganglioside A1 (GA1), myelin gangliosides (GM1, GM2, and GM3) and globoside, all of which devolve on the lactosylceramide pathway that would normally produce ceramide and eventually sphingosine.
LSDs can also be viewed clinically as so rare as to often escape the immediate attention and care of medical practitioners (‘the diagnostic odyssey’) which inadvertently leads to widening of the therapeutic gap as symptoms and signs progress and in many cases become irreversible.

Finally, LSDs had been difficult to manage historically because of the multiple organs involved and the fact that symptomatic treatment and palliation did not in fact impact the trajectory of the disease. However, within the past 2 decades, there has been a radical change in the natural course of several of these LSDs by virtue of the commitment of some pharmaceutical companies to take on the challenge of producing specific enzyme replacement therapy (ERT), substrate reduction therapy (SRT), and most recently, pharmacological chaperones (PC). Moreover, with better understanding of the underlying mechanisms and concerted efforts to identify patients prior to onset of irreversible organ damage, particularly neurological and cognitive deterioration, the future for patients with LSDs can be viewed with greater, albeit guarded, optimism.

Fabry disease is well-positioned within the above overview of LSDs: importantly, it has been targeted for ERT, SRT, and PC. Nonetheless, it is distinctly different than most LSDs by virtue of the myriad of organs involved that are not comparable to other LSDs vs. other organs that are critically involved in other LSDs but are spared in Fabry disease. This chapter will compare Fabry disease to the bulk of other LSDs in order to highlight its unique pathology.

**Diagnosis**

Deficient enzyme production in many LSDs is generally interpreted as <15% of enzymatic activity relative to that in unaffected individuals. It has been presumed that in cases with even abysmal levels of activity, should exogenous enzyme be provided continually, some normalization of pathology can be achieved; males with classic Fabry disease, however, lack (or have undetectable levels of) $\alpha$-galactosidase A activity. This may imply something about the early evolution of Fabry organ pathology in utero.

Accumulated storage material in LSDs is seen to be the nexus for system pathology, yet there is no apparent correlation between the degree of accumulation and organ involvement. This is a conundrum that appears to be common to Fabry disease as well.

There are apparently only rare instances of tight genotype-phenotype correlation among the LSDs. Fabry disease is marked by more than 300 mutations and almost as many private and rare genotypes, making prediction of disease severity highly problematic even between patients with the same genotype. As in other LSDs, epigenetic and environmental factors including life cycle events also impact the phenotype.

Early identification of pre-symptomatic patients is a goal of the medical community, and for most LSDs, screening of at-risk populations, as well as large-scale screening of newborns and even amniotic fluid, is available. In the case of Fabry
disease, screening of the extended pedigree of an index case (male or female) as well newborn screening is encouraged. The rationale for extensive newborn screening for Fabry disease is the probability that disease prevalence may be greater than suspected based on current numbers of identified patients, and since, unlike some LSDs where there is also some ethnic predilection such as among Ashkenazi Jews for Tay-Sachs disease and Gaucher disease, GM1 gangliosidosis in natives of Malta, or Metachromatic Leukodystrophy among Navajo Indians and Muslim Arabs, Fabry disease is panethnic. Moreover, with the availability of the Chamoiles filter paper method of screening many LSDs simultaneously, and efficient multiplexing, accurate and timely evaluations are realistic expectations.

It should be noted that whereas most LSDs are recessive disorders, Fabry disease (and Hunter syndrome) is an X-linked disorder.

For many LSDs, there are no adjunct lab measures to support enzyme and mutation analysis and assess disease severity changes over time relative; for Fabry disease as well as four Mucopolysaccharidoses (MPS) disorders and Gaucher disease, there are enzyme or macrophage biomarkers, and for Fabry disease and six other LSDs, there are substrate markers.

### Clinical Features

Clinical presentation in each of the LSDs is uniquely variable, often even among those with the same genotype. Among all LSDs, there is probably only one well-described example of tight genotype-phenotype correlation: D409H homozygosity and the Gaucher cardiac variant. Nonetheless, there are areas of commonality within the sub-types of each LSD (infantile, juvenile and late-onset forms) as well as among the various LSDs. Having said that, Fabry disease may nonetheless be the one LSD that is least like the others, possibly because it is X-linked, although MPS II (Hunter syndrome) is also X-linked and shares many features with other MPSs, especially MPS I (the Hurler-Scheie syndromes).

Among some LSDs it is axiomatic that the earlier the onset of symptomatic disease, which usually means emergence of neurological signs, the more probable a severe and fulminant course. In Fabry disease, many of the symptoms and signs that are seen in the youngest boys (and sometimes girls), particularly those of a gastrointestinal etiology, albeit very debilitating, are not actually indices or predictors of ultimate disease severity. In addition, cardiac involvement in Fabry disease although progressive (in most affected boys) from before puberty and is a marker of overall disease severity, the aggressive effects of renal involvement which usually only manifest in young adulthood, intervene and dominate the clinical picture so that the sequelae of proteinuria and hypertension are more often the cause of severe morbidity and eventual mortality.

Clinical disease severity in LSDs is invariably correlated with progressive and devastating neurological involvement, marked by intellectual decline (with only a few exceptions), neurogenic spasticity, problems with speech and hearing, disrupted
gait, and eventually clonus and seizures. This clinical trajectory is true in all the infantile forms of LSDs that are fatal within the first decade of life. There is no acute infantile form that is lethal in Fabry disease and this is unique among the LSDs. With regard to central nervous system involvement, Fabry disease has predominantly small vessel involvement that occurs after the first decade of life and is expressed as abnormal vasodilatative and vasoconstrictive forces and result in thrombosis or thromboembolism. Unlike in other LSDs, ischemic and hemorrhagic strokes in Fabry disease, often with consequent white matter lesions, as well as the predictable clinical consequences of strokes, can be seen in many adult patients (males more than females).

Delayed acquisition of developmental milestones and/or regression and/or impaired intellectual ability is usually evident within the 1st year of life among the infantile and juvenile forms of the LSDs. For the chronic forms of some LSDs including Fabry disease and Gaucher disease (but not in the late-onset forms of Tay-Sachs disease or Metachromatic Leukodystrophy where cognitive regression often leads to confusion and dementia in early adulthood), cognitive function is unaffected. It therefore is to be recommended that for children with Fabry disease who are incapacitated by their disease to the extent that they are unable to attend school regularly, home instruction should be instituted to prevent cognitive decline.

Neuropathic pain, while rare in other LSDs, is very common in Fabry disease and often is an early manifestation (even in young children); acroparesthesia, another finding that is common in Fabry disease but much less so in other LSDs, is both an early and concerning complaint of patients but is not correlated with involvement of other organs such as the heart, kidney, or lungs.

The eyes are noted to be affected in virtually all LSDs, particularly corneal opacities are commonly seen because of storage material as in Fabry disease, but also gaze palzies (horizontal or vertical) and nystagmus are present in many infantile forms but not so in Fabry disease.

There is progressive hearing loss in several LSDs including in Fabry disease where it is because of sensori-neurological involvement.

Peripheral neuropathy including autonomic involvement (hypohidrosis, orthostatic hypotension, and the gastrointestinal disturbances) is basic to the issues that reduce quality of life for patients with Fabry disease, but it is relative rare among LSDs other than in Niemann-Pick disease, Krabbe disease, and Metachromatic Leukodystrophy.

Involvement of the skin such as angiokeratoma (albeit in areas that are mostly clothed) is an overt sign of Fabry disease that has no parallel among other LSDs. There are, however, examples of discoloration of the skin such as the ochre color of patients with Niemann-Pick type A who also may have xanthomas.

The facial dysmorphism (coarsening) that is pathognomonic of some of the LSDs, and is actually an interesting feature of commonality that may help in diagnosis of MPSs, is less dramatic in Fabry disease males and has been described as ‘gargoyloid’ facies.

Cardiomyopathy with fatal congestive heart disease is noted in infantile forms of some LSDs like GMI gangliosidosis, but cardiac involvement which is progressive and marked by left ventricular hypertrophy is nearly universal in Fabry disease and
this is unique. There are some examples of cardiac valve involvement in LSDs such as in a cardiac variant of Gaucher disease with progressive calcification of heart valves, and some cardiac valvular disease in the MPSs, especially MPS I and II.

Storage in the glomerular and tubular apparatus of the kidney is not a universal finding in LSDs: the kidneys may actually be small albeit fatty in Niemann-Pick disease and there may be hyper-filtration in MPS II and in a benign form in Gaucher disease. In Fabry disease renal end-stage failure is a major component of the pathology, it is both age-related and a marker of severity once proteinuria is detectable.

Hepatosplenomegaly which is characteristic of Gaucher disease and less massively in patients with the sub-types of Niemann-Pick disease as well as some of the MPS disorders, is distinctly uncommon in Fabry disease. Abnormal liver function is rarely noted in LSDs other than the neonatal jaundice of Niemann Pick disease, whereas hypersplenism is characteristic of Gaucher disease but no other LSD.

There seems to be a degree of pulmonary infiltrative disease in many LSDs especially infants with Niemann-Pick (type A) but also in the adults with Niemann-Pick (type B); pulmonary involvement in Gaucher disease and some of the MPSs is a very poor prognostic sign. The etiology of lung involvement may be accumulation of storage material in the alveolar and/or macrophages of the lungs, and/or in the epithelial and smooth muscle cells. Progression of lung pathology is unabated by symptomatic treatment but also disease-specific therapy seems not to greatly alter the course especially in the younger patients who are severely affected with Gaucher disease; this is equally true in pediatric and adult patients with Fabry disease.

Skeletal involvement takes a myriad of pathological forms among the LSDs. Avascular necrosis seen in some of the chronic forms such as Gaucher disease and also in younger patients with MPS I (Hurler and Scheie sub-groups), II (Hunter syndrome), and IV (Morquio syndrome), but is virtually missing among the remaining LSDs. The joint and muscle pain of Fabry disease, on the other hand, may be vascular in origin and/or due to lack of exercise (walking, climbing stairs) and/or because of intolerance due to cardiac and pulmonary involvement. In contradistinction, the lack of joint (especially shoulder) mobility seen in MPS I, II, and especially VII (Maroteaux-Lamy syndrome) is dissimilar because it may be due to storage in these sites and is not correlated with severity of other organs or with age. Neuromotor decline and gait/ataxia abnormalities may mark the disease course of many older patients with LSDs but this is not seen in Fabry disease.

Finally, adult patients with Fabry disease describe long-standing feelings of depression. This is quite distinct from behavioral changes and emotional lability which precedes the dementia of late-onset Metachromatic Leukodystrophy. It is also dissimilar to the psychiatric disturbances that mark the early stages of late-onset forms of Tay-Sachs disease as well as Metachromatic Leukodystrophy. In the LSDs with intellectual decline from childhood, the patient can not be described as feeling depressed; in LSDs such as type 1 Gaucher disease where intelligence is not affected, depression is rather infrequent. However, in Fabry disease (and in MPS IV and IX) where intelligence is intact, depression is no doubt a reflection of the reality of living with a multi-systemic disorder that is not sufficiently appreciated by those with whom the patient comes in contact.
Management

Beyond recommendations for symptomatic therapy and palliation, beyond physiotherapy, and beyond ancillary treatments which should include vitamin supplementation as needed, non-specific management of LSDs can probably be as exclusive or as inclusive as required by the condition of any individual patient. There may also be a place for non-traditional, alternative forms of medicine such as acupuncture, herbal medicine, and even ozone therapy. However, the great advantage that LSDs enjoy over other rare disorders is that enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are currently available. Infusible ERT, since its seminal trials in Gaucher disease type 1, has been the immediate therapeutic goal for other LSDs including Fabry disease and MPS I, II, and VI. In general, these molecules are safe, although there are some inimical issues such as those related to infusions per se, to antibody formation, and even to the high cost of ERT. Efficacy is also considered good, although here too there are problems of not all patients responding optimally, of some organ systems (beside the central nervous system) being more impervious to improvement, and of course, not actually curing the underlying disease.

SRT with miglustat has the one advantage of being capable of traversing the blood-brain barrier, and although its safety is not as high as for ERT, it provides hope for patients with neurological forms such as the late-onset form of Tay-Sachs disease, Niemann-Pick disease type C, and Gaucher disease type 3; there may be a rationale for the use of glucosylceramide synthase inhibitors in Fabry disease based on animal studies.

Finally, because of the possible chaperoning effects of SRT, new classes of pharmacological chaperones have been developed for use in both neurological and non-neurological forms of various LSDs including Fabry disease, although the disappointing results in Gaucher disease trials needs to be taken into consideration.

Summary

Fabry disease is a rather prevalent rare disease, but it has stymied researchers and clinicians since its recognition. The extent of the multi-system involvement is particularly confusing since specific ERT does not seem to halt progression of any of these. There are no acute forms with early demise, but rather an inexorable and irreversible worsening of all systems from early childhood to a pain-filled adulthood. This is still the sad reality for patients with Fabry disease. As in the Dedication page at the start of this textbook, I would like to conclude by quoting Orison Swett Marden: ‘There is no medicine like hope, no incentive so great, and no tonic so powerful as expectation of something better tomorrow.’ We pray for a better tomorrow.
**Fabry Patient Associations**

**AIPAF Onlus – Italian Association of Anderson-Fabry Patients**  
Via Tino Corzani  
3 - 47026 San Pietro in Bagno - Forlì - Cesena  
Italy  
info@aipaf.org  
[www.aipaf.org](http://www.aipaf.org)  
Tel: +39 (0)543 917434  
Fax: +39 (0)543 901260

**APL – Associação Portuguesa das Doenças Do Lisosoma**  
Av. Defensores de Chaves, 33-5º  
1000-111 Lisboa  
Portugal  
geral@aplisosoma.org  
[www.aplisosoma.org](http://www.aplisosoma.org)  
Tel: 213 194 710  
Fax: 213 194 719

**BOKS, Belgian organization for metabolic disease**  
Floralaan 35A  
B 9120 Beveren  
Belgium  
[www.boks.be](http://www.boks.be)  
Tel: 03 775 48 39

**Brazilian Association of Fabry Disease (ABRAFF)**  
Rua Irene Palma  
212 - Ch.São José 13054-060  
Brazil  
Fabry@fabry.org.br  
[www.fabry.org.br](http://www.fabry.org.br)  
Tel: 19 3224-4210  
Fax: 19 3224-4210

**Canadian Fabry Association**  
9011 - 142 Street NW  
Edmonton, Alberta T5R 0M6  
Canada  
amkoning@telus.net  
[www.fabrycanada.com](http://www.fabrycanada.com)  
Tel: 780-489-0012  
Fax: 780-443-4959
Canadian Organization for Rare Disorders (CORD)
151 Bloor Street West, Suite 600
Toronto, Ontario M5S 1S4
Canada
info@raredisorders.ca
www.raredisorders.ca
Tel: 416-969-7464 (877) 302-7273
Fax: (416) 969-7420

CLIMB National Information Centre for Metabolic Diseases
Climb Building,
176 Nantwich Road
Crewe, CW2 6BG
Great Britain
info.svcs@climb.org.uk
www.climb.org.uk
Tel: 0800 652 3181

Danish Organization of Fabry Patients
www.fabry.dk

Fabry Disease Patient Association – France
Mme Nathalie Triclin
9 rue de la Gare
08160 Vendresse
contact@apmf-fabry.org
www.apmf-fabry.org

Fabry – Hungary
www.fabry.mnsza.hu

Fabry International Network
Søre Titlestad 111
FANA, 5243
Norway
finpresident@myconnect.org
www.fabryintnetwork.com

Fabry Onlus – Italian Fabry Patient Group
Gruppo Italiano Pazienti Fabry
C/da Caravotti 3
66020 Paglieta (CH)
Italy
www.fabryonlus.org
Tel: +39 0872.809890
Fax: +39 0872.808605
**Fabry Patient Association – Norway**
www.fabry.no

**Fabry Suisse**
Willikon 58
CH-8618 Oetwil am See
Switzerland
info@fabrysuisse.ch
www.fabrysuisse.ch
Tel: +41 (0)44 929 05 74

**Fabry Support Center of China**
zhangasiaafrica@sina.com
www.fabry.org.cn

**Fabry’s Support Group**
PO Box 269
Willoughby NSW 2068
Australia
info@fabry.net.au
www.fabry.net.au
Tel: 03 9497 8017

**Fabry Support & Information Group (FSIG)**
108 NE 2nd St. Ste C
P.O. Box 510
Concordia, MO 64020
info@fabry.org
www.fabry.org
Tel: 660-463-1355 866-30-FABRY (32279)
Fax: 660-463-1356

**Fabry Support & Informatie Groep Nederland**
Boelenkamp 10
8431 BL Oosterwolde
Netherlands
FSIGN@fabry.nl
www.fabry.nl
Tel: 06-25488090

**Lysosomal Disease New Zealand**
125 Cuba St
Petone
Lower Hutt City
New Zealand
john.forman@xtra.co.nz
www.ldnz.org.nz
Tel: 04 566 7707
Fax: 04 566 7717

**MPS Society – UK**
MPS House, Repton Place
White Lion Road
Amersham, Buckinghamshire, HP7 9LP
Great Britain
mps@mpssociety.co.uk
www.mpssociety.co.uk
0845 389 9901

**MPS Society – Spain**
info@mpsesp.org
www.mpsesp.org/
Tel: 617 080 198

**Morbus Fabry Selbsthilfegruppe e.V.**
Ditmar Basalla
Guilleaumestr. 13
51065 Köln
Germany
info@fabry-selbsthilfegruppe.de
www.fabry-selbsthilfegruppe.de
Tel.: +49 (0) 221 - 222 73 93

**National Fabry Disease Foundation**
4301 Connecticut Ave. N.W.
Suite 404
Washington, DC 20008-2369
Tel: 800-651-9131
Fax: 800-651-9135
info@TheNFDF.org
www.thenfdf.org
Tel: 800-651-9131

**National Organization for Rare Disorders (NORD)**
P.O. Box 1968
(55 Kenosia Avenue)
Danbury, CT 06813-1968
orphan@rarediseases.org
http://www.rarediseases.org
Tel: 203-744-0100 Voice Mail 800-999-NORD (6673)
Fax: 203-798-2291
National Tay-Sachs and Allied Diseases Association
2001 Beacon Street
Suite 204
Brighton, MA 02135
info@ntsad.org
http://www.ntsad.org
Tel: 617-277-4463 800-90-NTSAD (906-8723)
Fax: 617-277-0134

New England Fabry Support Group
www.nefsg.org

Nordic Fabry
Christina Graef Christensen,
Ravnstrupvej 9
4684 Holmegaard
Denmark
formand@fabry.dk
www.fabry.dk
Tel: 5556 2212

VML – Vaincre les Maladies Lysosomales
2 Ter Avenue De France
91300 MASSY
France
www.vml-asso.org
Tel: 01 69 75 40 30
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