Fabry Disease

Deborah Elstein · Gheona Altarescu · Michael Beck
Editors

Fabry Disease

Springer

Editors
Deborah Elstein
Gaucher Clinic
Shaare Zedek Medical Center
Bayit Street 12
91034 Jerusalem
Israel
elstein@szmc.org.il

Gheona Altarescu
Genetics Unit
Shaare Zedek Medical Center
Bayit Street 12
91031 Jerusalem
Israel
gheona@szmc.org.il

Michael Beck
Children's Hospital
University of Mainz
Langenbeckstrasse 1
55131 Mainz
Germany
Dr.M.Beck@t-online.de

ISBN 978-90-481-9032-4 e-ISBN 978-90-481-9033-1
DOI 10.1007/978-90-481-9033-1
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2010930427

There is no medicine like hope, no incentive so great, and no tonic so powerful as expectation of something better tomorrow.

(Orison Swett Marden)

This is the first textbook dedicated solely to Fabry disease. Fabry disease unfortunately is a multi-system disease that is incompletely treated by the currently available enzyme replacement therapies. The often significant lag in achieving the correct diagnosis, the myriad of symptoms and signs, the suffering that the patient experiences on so very many levels, and the social ramifications for family and friends, all underscore the complexity of this disease and the inherent need for a better understanding of the pathological mechanisms underlying its expression.

The section on pre-clinical studies highlights the various directions that have been undertaken to improve diagnosis and identification of disease-specific features. The clinical chapters represent the most current evaluations by experts that should allow the uninitiated as well as the treating physician to appreciate the spectrum of disease-specific manifestations. And finally, the chapters assessing the various aspects of treatment are of importance for physician and patient alike.

We have had the good fortune to include chapters by many of the most prominent clinicians and researchers in the field, men and women who have been involved with Fabry disease for many decades and whose dedication has been unstinting. It is to the patients and those concerned with their welfare that this book is dedicated in the hope that the near future will provide insight into the disease and thereby improved treatment of its symptoms.

Contents

Contributors

Johannes M.F.G. Aerts Department of Medical Biochemistry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, j.m.aerts@amc.uva.nl

Francisco Allegue Department of Dermatology, University Hospital of Vigo, Vigo, Spain, francisco.allegue.rodriguez@sergas.es

Gheona Altarescu Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel, gheona@szmc.org.il

Maryam Banikazemi Columbia University School of Medicine, New York, NY, USA, mb3186@columbia.edu

Soraya Barrera Department of Pathology and Neuropathology, University Hospital of Vigo, Vigo, Spain, sbarcab@yahoo.es

Michael Beck Children's Hospital, University of Mainz, Mainz, Germany, Dr.M.Beck@t-online.de

Robin L. Bennett Division of Medical Genetics, Department of Medicine, UWMC Medical Genetics Clinic, University of Washington Medical Center, Seattle, WA, USA, robinb@u.washington.edu

Roscoe O. Brady National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA, bradyr@ninds.nih.gov

Tobias Böttcher Medical Faculty, Albrecht-Kossel-Institute for Neuroregeneration, University of Rostock, Rostock, Germany, tobias.boettcher@med.uni-rostock.de

T. Andrew Burrow Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA, Thomas.Burrow@cchmc.org

Joe T.R. Clarke Department of Pediatrics, Division of Clinical and Metabolic Genetics, Hospital for Sick Children and University of Toronto, Toronto, ON,

Canada; Service de génétique, Département de pédiatrie, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, QC, Canada, jtrc@sickkids.ca

Ales Dudesek Department of Neurology, University of Rostock, Rostock, Germany, alesdudesek@gmx.de

Milan Elleder First Faculty of Medicine, Institute of Inherited Metabolic Disorders, Charles University, Prague, Czech Republic, melleder@cesnet.cz

Carmen Fachal Department of Pathology and Neuropathology, University Hospital of Vigo, Vigo, Spain, Carmen.Fachal.Bermudez@sergas.es

Jian-Qiang Fan Pfantastic Medical Research Institute, Cresskill, NJ, USA, jfan@pfantastic.com

Jose M. Fernandez Department of Clinical Neurophysiology, University Hospital of Vigo, Vigo, Spain, Jose.Maria.Fernandez.Rodriguez@sergas.es

Manuela Födinger Institute of Laboratory Medicine, Sozialmedizinisches Zentrum Süd, Vienna, Austria, manuela.foedinger@wienkav.at

Andreas Gal Institut für Humangenetik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, gal@uke.de

Scott C. Garman Department of Chemistry, University of Massachusetts, Amherst, MA, USA; Department of Biochemistry & Molecular Biology, University of Massachusetts, Amherst, MA, USA, garman@biochem.umass.edu

Dominique P. Germain Medical Genetics, Centre de référence de la maladie de Fabry et des maladies héréditaires du tissu conjonctif, U.F. de Génétique Médicale, Hôpital Raymond Poincaré (AP-HP), Garches, France; University of Versailles – St Quentin en Yvelines (UVSQ), Versailles, France, dominique.germain@rpc.aphp.fr

Ehud Goldin Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA, goldine@mail.nih.gov

Gregory A. Grabowski Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA, greg.grabowski@cchmc.org

Abigail I. Guce Department of Chemistry, University of Massachusetts Amherst, Amherst, MA, USA, aguce@chem.umass.edu

C.E.M. Hollak Department of Internal Medicine/Endocrinology and Metabolism, Academic Medical Center, AZ Amsterdam, The Netherlands, c.e.hollak@amc.uva.nl

Robert J. Hopkin Division of Human Genetics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA, rob.hopkin@cchmc.org

Martin Hřebíček First Faculty of Medicine, Institute of Inherited Metabolic Disorders, Charles University, Prague and General University Hospital, Prague, Czech Republic, martin.hrebicek@lf1.cuni.cz

D.A. Hughes Lysosomal Storage Disorders Unit, Department of Academic Haematology, Royal Free Hospital and University College Medical School, London, UK, d.hughes@medsch.ucl.ac.uk

Satoshi Ishii Faculty of Medicine, Oita University, Oita, Japan, ishiists@hotmail.com

Christoph Kampmann University Medicine, Johannes Gutenberg University Mainz, Mainz, Germany, kampmann@uni-mainz.de

Jana Ledvinová First Faculty of Medicine, Institute of Inherited Metabolic Disorders, Charles University, Prague and General University Hospital, Prague, Czech Republic, jana.ledvinova@lf1.cuni.cz

Aleš Linhart Department of Internal Medicine, Carl's University, Prague, Czech Republic, ales.linhart@lf1.cuni.cz

G.E. Linthorst Department of Internal Medicine/Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands, g.e.linthorst@amc.nl

Jan Lukas Medical Faculty, Albrecht-Kossel-Institute for Neuroregeneration, University of Rostock, Rostock, Germany, jan.lukas@med.uni-rostock.de

Atul Mehta Department of Haematology, Royal Free Hospital, University College London, School of Medicine, London, UK, atul.mehta@royalfree.nhs.uk

Beatriz San Millan Department of Pathology and Neuropathology, University Hospital of Vigo, Vigo, Spain, Beatriz.San.Millan.Tejado@sergas.es

Omid Motabar Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA, motabaro@mail.nih.gov

Carmen Navarro Department of Pathology and Neuropathology, University Hospital of Vigo, Vigo, Spain, c.navarro.fb@gmail.com; cnavfer@sergas.es

João Paulo Oliveira Departments of Pathology, Medicine and Human Genetics, Faculty of Medicine, Hospital São João, Porto, Portugal, oliveira@med.up.pt

Catherine H. Orteu Department of Dermatology, Royal Free Hospital, London, UK, Cate.orteu@royalfree.nhs.uk; kateorteu@hotmail.com

Saida Ortolano Department of Pathology and Neuropathology, University Hospital of Vigo, Vigo, Spain, saida.ortolano@sergas.es

Gregory M. Pastores Departments of Neurology and Pediatrics, New York University School of Medicine, New York, NY, USA, gregory.pastores@nyumc.org

Carlos E. Prada Division of Human Genetics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA, carlos.prada@cchmc.org

Annick Raas-Rothschild Department of Human Genetics and Metabolic Diseases, Hadassah Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel, annik@hadassah.org.il

Julian A.J. Raiman Division of Clinical and Metabolic Genetics, Hospital for Sick Children, Toronto, ON, Canada, julian.raiman@sickkids.ca

Uma Ramaswami Department of Paediatrics, Addenbrooke's Hospital, Cambridge, UK, uma.ramaswami@addenbrookes.nhs.uk

Arndt Rolfs Medical Faculty, Albrecht-Kossel-Institute for Neuroregeneration, University of Rostock, Rostock, Germany, arndt.rolfs@med.uni-rostock.de

Perri Segal Department of Human Genetics and Metabolic Diseases, Hadassah Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel, perri.segal@mail.huji.ac.il

James A. Shayman Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA, jshayman@umich.edu

Ellen Sidransky Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA, sidranse@mail.nih.gov

Andrea Sodi Eye Clinic, University of Florence, Florence, Italy, andrea.sodi@unifi.it

Gere Sunder-Plassmann Division of Nephrology and Dialysis, Department of Medicine III, Medical University Vienna, Vienna, Austria, gere.sunder-plassmann@meduniwien.ac.at

Susana Teijeira Department of Pathology and Neuropathology, University Hospital of Vigo, Vigo, Spain, susana.teijeira.bautista@sergas.es

Carmen Valbuena Departments of Pathology, Medicine and Human Genetics, Faculty of Medicine, Hospital São João, Porto, Portugal, valbuena@med.up.pt

David G. Warnock Division of Nephrology, Department of Medicine, University of Alabama, Birmingham, AL, USA, dwarnock@uab.edu

Michael West Department of Medicine, Dalhousie University, Halifax, Canada, michael.west@cdha.nshealth.ca

Catharina Whybra-Trümpler Universitätskinderklinik der Johannes Gutenberg Universität Mainz, Langenbeckstr. 1, Mainz, Germany, c.whybra@web.de

Bryan Winchester Biochemistry Research Group, UCL Institute of Child Health at Great Ormond Street Hospital, University College London, London, UK, b.winchester@ich.ucl.ac.uk

Elisabeth Young Biochemistry Research Group, UCL Institute of Child Health at Great Ormond Street Hospital, University College London, London, UK, lissy@younglis.freeserve.co.uk

Wei Zheng NIH Chemical Genomics Center, NHGRI, NIH, Bethesda, MD, USA, wzheng@mail.nih.gov

Fabry Disease – An Overview

Roscoe O. Brady

Major Signs and Symptoms

Fabry disease is an X-linked hereditary metabolic storage disorder. It is a multisystem condition characterized by reddish-purple maculopapular lesions on the skin (angiokeratoma corporis diffusum), corneal opacities (cornea verticillata), hypohidrosis, gastroenteritis, chronic airflow obstruction, reduced kidney function leading to end-stage renal disease, left ventricular hypertrophy, premature myocardial infarctions and early-onset of strokes. The occurrence of these abnormalities varies in their extent and frequency in males with this condition. They are generally less prevalent in females with the disorder, but there are notable exceptions.

Pathological Biochemistry

Fabry disease is caused by the accumulation of excessive quantities of members of the class of lipids called sphingolipids that have the long chain aminoalcohol sphingosine as their common structural moiety (Fig. 1a). A long chain fatty acid is bound to the nitrogen atom on carbon atom two of sphingosine forming the structure called ceramide. Linked to carbon atom one of the sphingosine portion of ceramide are varying numbers of sugars forming glycosphingolipids. The most prevalent accumulating material in patients with Fabry disease is globotriaosylceramide (Gb3) that was previously called ceramidetrihexoside (Fig. 1b) [1]. Additional accumulating substances are digalactosylceramide that is especially present in kidneys (Fig. 1c) and globotriaosylsphingosine (lyso-Gb3) (Fig. 1d) [2]. Based on the discoveries of the enzymatic defects in Gaucher disease [3] and in Niemann-Pick disease [4], it was predicted that the metabolic defect in Fabry disease was due to insufficient activity of an enzyme that catalyzes the hydrolytic cleavage of the terminal galactose from

R.O. Brady (✉)
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
e-mail: bradyr@ninds.nih.gov

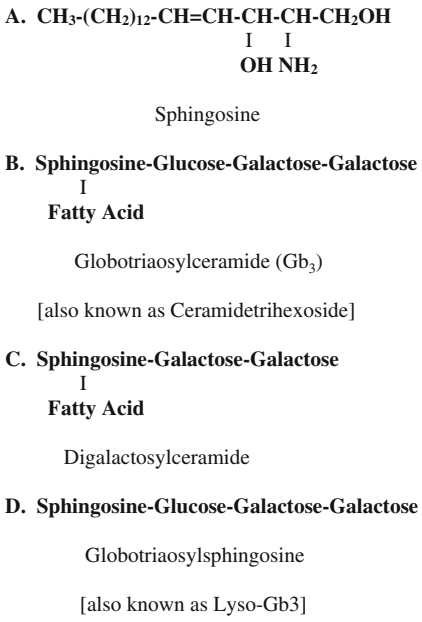

Fig. 1 Accumulating glycosphingolipids in patients with Fabry disease. The core component is the long chain amino alcohol sphingosine

Gb3 [5]. Because the chemical synthesis of Gb3 had not been accomplished at that time, the entire Gb3 molecule was labeled with ^{3}H using a technique what was known as the Wilzbach procedure [6]. The compound to be labeled is exposed to a high level of ^{3}H in a sealed ampoule under increased pressure for 7 days. The uniformly labeled radioactive product was purified extensively until background radioactivity was sufficiently low that it could be used as a substrate to detect an enzyme that might be involved in its catabolism. A survey of rat tissues revealed that the small intestine contained the highest level of specific catabolic activity [7]. That source was therefore used for the purification of the enzyme ceramidetrihexosidase that catalyzes the cleavage of the terminal molecule of galactose from Gb3. The cause of the accumulation of pathological quantities of Gb3 was quickly shown to be due to insufficient activity of ceramidetrihexosidase [8] (Fig. 2). Because the bond between the two molecules of galactose in Gb3 is in the α-anomeric configuration, ceramidetrihexosidase was subsequently termed α-galactosidase A. Since patients with both Gaucher disease and Niemann-Pick disease showed some detectable residual glucocerebrosidase and sphingomyelianse activity, it was somewhat surprising to find that the activity of ceramidetrihexosidase in the intestinal biopsies from the two Fabry patients that were examined was undetectable. This situation was later seen in approximately 45% of the hemizygous Fabry males examined in my Branch at the National Institutes of Health. Although the catabolism of digalactosylceramide and lyso-Gb3 catalyzed by α-galactosidase A appears not to have been specifically examined, the elevated levels of these substances in patients with reduced or absent α-galactosidase A activity implies that they are catabolized

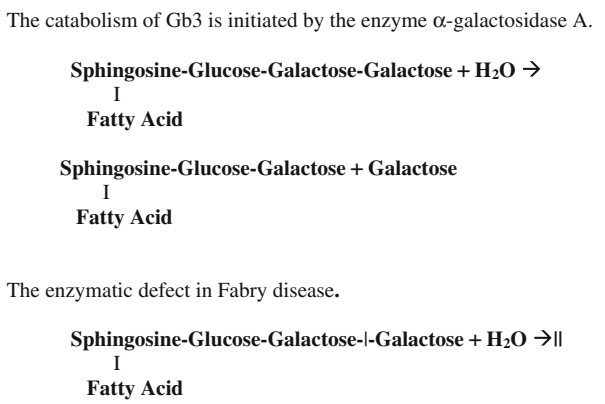

Fig. 2 The catabolism of Gb3 is initiated by the enzyme α-galactosidase A

by this enzyme. Based on very slow rate of hydrolysis of glucosylsphingosine catalyzed by gluocerebrosidase compared with glucocerebroside [9], one might deduce that the enzymatic cleavage of the terminal molecule of galactose from lyso-Gb3 might be much slower than that of Gb3. Because galactosylsphingosine (lyso-galactocerebroside) [10] and glucosylsphingosine (lyso-glucocerebroside) [11] have been shown to by highly cytotoxic, the toxicity of lyso-Gb3 may be anticipated to be considerably greater than Gb3.

Pathophysiology

Glycosphingolipids are found in the plasma cell membranes of most of the cells in the body. However, the turnover of red blood cells has emerged as a major contributor to the pathophysiology of Fabry disease. Except for persons with the pk and p red blood cell groups, the principal glycosphingolipid in erythrocyte stroma is globotetraosylcermide (Gb4), frequently referred to as globoside (Fig. 3). When red blood cells become senescent, they are removed from the circulation by tissue macrophages such as the Kupffer cells in the liver. All of the membranous components of the phagocytized cells are degraded enzymatically in subcellular organelles called lysosomes. Lysosomes contain a series of consecutively acting

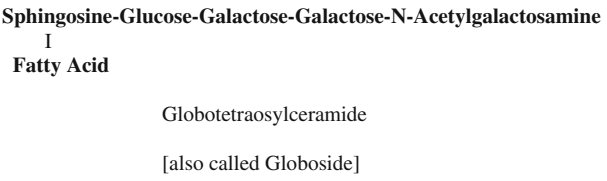

Fig. 3 Structure of the most prevalent glycosphingolipid in human red blood cell stroma

enzymes that biodegrade ingested membrane components as well as an acidic mileu at which these catalysts are maximally active. The catabolism of the major red blood cell membrane globotetroasylceramide (globoside) is initiated by the enzyme hexosaminidase B forming globotriaosylceramide (Gb3). Because of insufficient α-galactosidase A activity, pathological quantities of Gb3 accumulate throughout the body of patients with Fabry disease. The importance of a constant source of sphingoglycolipids originating from the stroma of senescent red blood cells was substantiated in experiments with a mouse model of Fabry disease. A significant accumulation of Gb3 occurs in the organs and tissues of mice when α-galactosidase A activity is eliminated [12]. However, the mice had a normal life span and showed no major manifestations of Fabry disease such as strokes, myocardial infarctions or renal disease. The reason for the absence of the typical Fabry phenotype was soon discovered [13]. Red blood cells in the C57BL/6 × 129/Svj hybrid strain of mice used for knocking out α-galactosidase A do not contain a detectable quantity of either Gb4 (globoside) or Gb3. They therefore have some resemblance to human blood group p that do not contain Gb3 or Gb4 in their red blood cells due to absence of Gb3 synthase that catalyzes the addition of galactose from UDP-galactose to ceramidelactoside [14]. If the findings in the α-galactosidase A –/– mouse models of Fabry disease can be extrapolated to humans, it would seem unlikely that a reduction or lack of α-galactosidase A activity in blood group p humans would cause the array of pathological manifestations conventionally associated with Fabry disease.

Therapy

Enzyme Replacement

Since many of the salient aspects of Fabry disease are discussed in detail in various chapters in this book, I should like to restrict my further remarks to a consideration of strategies for the treatment for patients with this disorder. Because of the extraordinarily beneficial effects of enzyme replacement therapy (ERT) in patients with Gaucher disease [15–17], this stratagem was high on the list of approaches to try to improve the lives of patients with Fabry disease. Even before ERT was undertaken in patients with Gaucher disease, an investigation along this line was carried out in patients with Fabry disease. In an effort to maximally reduce the possibility of sensitizing patients to the exogenous protein, a human source of ceramidetrihexosidase (α-galactosidase A) was considered desirable. An examination of fresh human placental tissue revealed that it contained this enzyme and was therefore used as the source [18]. When this enzyme was infused into two patients with Fabry disease, a rapid reduction of Gb3 in the circulation occurred [19]. The level of Gb3 returned to the pre-infusion value by 48 h following the administration of the enzyme. Additional preliminary ERT trials were carried out with α-galactosidase A preparations obtained from human spleen and plasma [20]. Variations in enzyme

kinetics and the extent of reduction of plasma Gb3 levels that were observed with the two isoforms were attributed to differences in sialylation and phosphorylation of these enzymes that are glycoproteins.

It was apparent that only limited quantities of α-galactosidase A could be obtained from sources such as these. Two biotechnology corporations began to prepare α-galactosidase A recombinantly. One of these was Transkaryotic Therapies, Inc., Cambridge MA, which subsequently became Shire Human Genetic Therapies, Inc. α-Galactosidase A was initially produced in a cultured human skin fibroblast cell line using a proprietary gene-activation technique. Intravenous administration of this preparation of α-galactosidase A to patients with Fabry disease caused a mean decrease of 31% of hepatic Gb3 and 38% decrease of urinary Gb3 [21]. Encouraged by these findings, larger quantities of α-galactosidase A were produced in a genetically engineered continuous human cell line. A randomized controlled trial with this preparation was conducted with 26 male patients with Fabry disease [22]. Recipients of the enzyme experienced a decrease in the severity of neuropathic pain and an increase of the quality of life. The recipients also had an approximately 50% reduction of plasma Gb3; a decrease of inulin clearance; an increase of creatinine clearance; improvement of cardiac conduction and gain of body weight. There was also a particularly striking increase in the number of normal kidney glomeruli and a reduction of the number of glomeruli with mesangial widening in the recipients. This preparation of α-galactosidase A is called Replagal. It is also known as agalsidase alfa (see Chapter 25 by Pastores). The dose used in patients is 0.2 mg/kg of body weight intravenously every 2 weeks.

The Genzyme Corporation, Cambridge, MA, used transduced Chinese hamster ovary cells to produce recombinant α-galactosidase A. This preparation is called agalsidase beta (Fabrazyme) (see Chapter 26 by Hopkin). It is administered at a dose of 1 mg/kg of body weight every other week. The initial trial with agalsidase beta revealed clearance of Gb3 from microvascular endothelial deposits in the kidney, skin and heart and reduction of plasma and urinary Gb3. Although seroconversion was observed in 88% of the recipients, it was concluded that it did not affect efficacy end points [23].

Based on these observations, agalsidase alfa and agalsidase beta were approved for the treatment of patients with Fabry disease in Europe and a number of other countries. However, only agalsidase beta was approved in the United States. Despite more than 8 years of availability of this therapy, complete restoration of health in patients with Fabry disease remains to be achieved. An encouraging possibility concerning the ultimate benefit of enzyme therapy for patients with Fabry disease might be derived from the finding that increasing the frequency of administration of α-galactosidase A from bi-weekly to weekly may slow the decline of renal function [24]. This observation, coupled with delay of onset of renal insufficiency in patients with mild mutations in the α-galactosidase A gene, prompted the deduction that there may be a need for a continuous presence of α-galactosidase A in cells [25]. Perhaps the most obvious approach to achieving this condition is gene therapy that is commented on later.

Molecular Chaperone Therapy

The discovery that certain small molecule inhibitors of α-galactosidase A can increase the catalytic activity of some of the mutated forms of this enzyme [26–30] has prompted a major investment into the identification and assessment of such agents that may be therapeutically useful (see Chapter 29 by Fan). Although this approach appears to be reasonable, the large proportion (∼45%) of nonsense mutations in the α-galactosidase A gene in patients with Fabry disease results in no detectable residual enzyme (vs. and 31). This situation precludes a large number of patients with Fabry disease from benefiting from this treatment. In order to identify patients who might be helped by molecular chaperone therapy, a rapid procedure was developed to assess the degree of enhancement of α-galactosidase A catalytic activity by a molecular chaperone [32]. Application of this technique should assist in deciding who might benefit from chaperone therapy.

Substrate Reduction Therapy

Substrate reduction therapy (SRT) is accomplished by blocking a specific enzymatic step in the biosynthesis of an accumulating substance. Partially blocking the addition of glucose to ceramide to form glucocerebroside has been shown to provide benefit to some patients with Gaucher disease [33]. It is an approved therapy for certain patients with this disorder. More recently an improved inhibitor of glucocerebroside biosynthesis has been produced and is in clinical trial [34]. It was considered to be of interest in Fabry disease to examine the effect of blocking the addition of glucose to ceramide that would result in reducing the formation of Gb3. Therefore, the effect of a strong inhibitor of glucocerebroside biosynthesis was examined in Fabry mice [35]. A reduction of Gb3 of approximately 50% was observed in the kidneys, liver and heart following 8 weeks of intra-peritoneal administration of the inhibitor. The precise mechanism of clearance of Gb3 from the organs of mice lacking α-galactosidase A has not been established. Nevertheless, further examination of SRT appears warranted in patients with Fabry disease.

Gene Therapy

The availability of α-galactosidase A–/– knock-out mice [12] made it possible to undertake a number of critical experiments in regard to eventual gene therapy in patients with Fabry disease [36]. Pertinent findings in these investigations include significant reductions of accumulated Gb3 following a single injection of a recombinant adeno-associated viral vector containing a modified chicken α-actin promoter. At 6-months after administration of the vector, the elevated Gb3 in the liver and spleen were found to be normal levels. There was an 85% reduction in the heart and a 66% reduction in the lung [37]. Kidneys showed an 82% reduction at 2 months.

However, at 6 months, the amount of Gb3 in this organ had returned to 60% of the pre-treatment level. Gene therapy for Fabry disease and many other metabolic storage disorders has been significantly delayed by the occurrence of insertional mutagenesis following the use of a retroviral vector that caused leukemia in several human recipients [38–40]. Hopefully, the use of self-inactivating lentival vectors in stem cell-derived erythroid cells [41–43] may reduce oncogenic hazards associated with gene therapy and successful treatment for patients with Fabry disease will be realized.

The Future

I should like to touch on two additional potential approaches to treat patients with Fabry disease and other hereditary metabolic disorders. The first is the use of reagents to induce exon skipping in the considerable number of patients with Fabry disease who have nonsense mutations that disrupt the open-reading frame for α-galactosidase A causing a lack of enzyme. Aminoglycosides have been tried to induce exon skipping in a number of instances, particularly with regard to the treatment of Duchenne muscular dystrophy. However, the near-toxic levels required of these agents has limited their use. Recently, an examination of antisense oligonucleotides and several derivatives has been undertaken [44] as well as studies with viral vectors containing small nuclear RNAs [45] to induce exon skipping. Whether this approach is feasible for patients with Fabry disease remains to be determined.

An additional possibility that has yet to be shown to be clinically effective is homologous recombination. There are a number of potential advantages if this technique becomes useful [46]. This approach is under extensive consideration for the treatment of hemoglobinopathies [47]. Successful application of this strategy to treat a hereditary metabolic storage disorder remains to be demonstrated.

References

1. Sweeley CC, Klionsky B (1963) Fabry's disease: classification as a sphingolipidosis and partial characterization of a novel glycolipid. J Biol Chem 238:3148–3150
2. Aerts JM, Groener JE, Kuiper S et al (2008) Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci USA 105:2812–2817
3. Brady RO, Kanfer JN, Shapiro D (1965) Metabolism of glucocerebrosides. II. Evidence of an enzymatic deficiency in Gaucher's disease. Biochem Biophys Res Commun 18:221–225
4. Brady RO, Kanfer JN, Mock MB, Fredrickson DS (1966) The metabolism of sphingomyelin. II. Evidence of an enzymatic deficiency in Niemann-Pick disease. Proc Natl Acad Sci USA 55:366–369
5. Brady RO (1966) Sphingolipidoses. N Engl J Med 275:312–318
6. Wilzbach KE (1956) Tritium-labeling by exposure of organic compounds to tritium gas. J Am Chem Soc 79:1013
7. Brady RO, Gal AE, Bradley RM, Martensson E (1967) The metabolism of ceramidetrihexosides. I. Purification and properties of an enzyme which cleaves the terminal galactose molecule of galactosylgalactosylglucosylceramide. J Biol Chem 242:1021–1026

8. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L (1967) Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficency. N Engl J Med 276:1163–1167
9. Pentchev PG, Brady RO, Hibbert SR, Gal AE, Shapiro D (1973) Isolation and characterization of glucocerebrosidase from human placental tissue. J Biol Chem 248:5256–5261
10. Suzuki K (1998) Twenty-five years of the "psychosine hypothesis". A personal perspective of its history and present status. Neurochem Res 23:251–259
11. Schueler U, Kolter T, Kaneski CR, Blusztajn JK, Herkenham M, Sandhoff K, Brady RO (2003) Toxicity of glucosylsphingosine (glucopsychosine) to cultured neuronal cells: a model system for assessing neuronal damage in Gaucher disease Type 2 and 3. Neurobiol Disease 14:595–601
12. Ohshima T, Murray GJ, Swain WD et al (1997) α-Galactosidase A deficient mice: a model of Fabry disease. Proc Natl Acad Sci USA 94:2540–2544
13. Ohshima T, Schiffmann R, Murray GJ et al (1999) Aging accentuates and bone marrow transplantation ameliorates metabolic defects in Fabry disease mice. Proc Natl Acad Sci USA 96:6423–6427
14. Furukawa K, Iwamura K, Uchikawa M et al (2000) Molecular basis for the p phenotype. J Biol Chem 275:37752–37756
15. Barton NW, Brady RO, Dambrosia JM et al (1991) Replacement therapy for inherited enzyme deficiency – macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 324:1464–1470
16. Grabowski GA, Barton NW, Pastores G et al (1995) Enzyme therapy in Gaucher disease Type 1: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Ann Int Med 122:33–39
17. Brady RO (2006) Enzyme replacement therapy for lysosomal diseases. Ann Rev Medicine 57:283–296
18. Johnson WG, Brady RO (1972) Ceramidetrihexosidase from human placenta. Methods Enzymol XXVIII:849–856
19. Brady RO, Tallman JF, Johnson WG et al (1973) Replacement therapy for inherited enzyme deficiency: use of purified ceramidetrihexosidase in Fabry's disease. N Engl J Med 289:9–14
20. Desnick RJ, Dean KJ, Grabowski G, Bishop DF, Sweeley CC (1979) Enzyme therapy in Fabry disease. Differential in vivo plasma clearance and metabolic effectiveness of plasma and splenic a-galactosidase A isozymes. Proc Natl Acad Sci USA 76:5326–5330
21. Schiffmann R, Murray GJ, Treco D et al (2000) Infusion of α-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. Proc Natl Acad Sci USA 97:365–370
22. Schiffmann R, Kopp JB, Austin HA et al (2001) Enzyme replacement therapy in Fabry disease. A randomized controlled trial. JAMA 285:2743–2749
23. Eng CM, Guffon N, Wilcox WR et al (2001) Safety and efficacy of recombinant human a-galactosidase A replacement theapy in Fabry's disease. N Engl J Med 345:9–16
24. Schiffmann R, Askari H, Timmons M et al (2007) Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. J Am Soc Nephrol 18:1576–1583
25. Schiffmann R (2009) Fabry disease. Pharmacol Ther 122:65–77
26. Fan J-Q, Ishii S, Asano N, Suzuki Y (1999) Accelerated transport and maturation of lysosomal a-galactosidase A in Fabry lymphoblasts by an enzyme inhibitor. Nat Med 5:112–115
27. Yam GH-F, Bosshard N, Zuber C, Steinmnn B, Roth J (2006) Pharmacological chaperone corrects lysosomal storage in Fabry disease caused by trafficking-incompetent variants. Am J Physiol Cell Physiol 290:C1076–C1082
28. Shin S-H, Murray GJ, Kluepfel-Stahl S et al (2007) Screening for pharmacological chaperones in Fabry disease. Biochem Biophys Res Commun 359:168–173
29. Sugawara K, Tajima Y, Kawashima I et al (2009) Molecular interaction of imino sugars with human a-galactosidase: insight into the mechanism of complex formation and pharmacological chaperone action in Fabry disease. Mol Genet Metabol 96:233–238

30. Benjamin ER, Flanagan JJ, Schillinig A et al (2009) The pharmacological chaperone 1-deoxygalactonojirimycin increases alpha-galactosidase A levels in Fabry patient cell lines. J Inherit Metab Dis 32:424–440
31. Desnick RJ, Ioannou YA, Eng CM (2001) α-Galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS Valle D (eds) The metabolic and molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, pp 3733–3774
32. Shin SH, Kluepfel-Stahl S, Cooney AM et al (2008) Prediction of response of mutated α-galactosidase A to a pharmacological chaperone. Pharmacogenet Genomics 18:773–780
33. Cox T, Lachmann R, Hollak C et al (2000) Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate diosynthesis. Lancet 355:1481–1485
34. McEachern KA, Fung J, Komarnitsky S et al (2007) A specific and potent inhibitor of glucosylceramide synthase for substrate inhibition therapy of Gaucher disease. Mol Genet Metabol 91:259–267
35. Abe A, Gregory S, Lee L et al (2000) Reduction of globotriaosylceramide in Fabry disease mice by substrate deprivation. J Clin Invest 105:1563–1571
36. Jung S-C, Han IP, Limaye A et al (2001) Adeno-associated viral vector-mediated gene transfer results in long-term enzymatic and functional correction in multiple organs of Fabry mice. Proc Nat Acad Sci USA 98:2676–2681
37. Park J, Murray GJ, Limaye A et al (2003) Long-term correction of globotriaosylceramide storage in Fabry mice by recombinant adeno-associated virus-mediated gene transfer. Proc Nat Acad Sci USA 100:3450–3454
38. Hacein-Bey-Abina S, Garrigue A, Wang GP et al (2008) Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest 118:3132–3142
39. Howe SJ, Mansour MR, Schwarzwaelder K et al (2008) Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-XI patients. J Clin Invest 118:3143–3150
40. Kohn DB, Sadelain M, Glorioso JC (2003) Occurrence of leukaemia following gene therapy of X-linked SCID. Nat Rev 3:477–488
41. Moreau-Gaudry F, Xia P, Jiang G et al (2001) High-level erythroid-specific gene expression in primary human and murine hematopoietic cells with self-inactivating lentiviral vectors. Blood 98:2664–2672
42. Chang AH, Stephan MT, Sadelain M (2006) Stem cell-derived erythroid cells mediate long-term systemic protein delivery. Nature Biotechnology 24:1017–1021
43. Enquist IB, Nilsson E, Mansson J–E et al (2009) Successful low-risk hematopoietic cell therapy in a mouse model of Type 1 Gaucher disease. Stem Cells 27:736–744
44. Heemskerk HA, de Winter CL, de Kimpe SJ et al (2009) In vivo comparison of 2'-O-methyl phosphorothioate and morpholino antisense oligonucleotides for Duchenne muscular dystrophy exon skipping. J Gene Med 11:257–266
45. Goyenvalle A, Babbs A, van Ommen GJ, Garcia L, Davies KE (2009) Enhanced exon-skipping induced by U7 snRNA carrying a splicer silencer sequence: promising tool for DMD therapy. Mol Ther 17:1234–1240
46. Porteus M (2007) Using homologous recombination to manipulate the genome of human somatic cells. Biotechnol Genet Eng Rev 24:195–212
47. Sadelain M, Boulad F, Lisowki L, Moi P, Riviere I (2008) Stem cell engineering for the treatment of severe hemoglobinopathies. Curr Mol Med 8:690–697

Fabry Disease – A Patient Perspective

Jack Johnson

The weekend has arrived that I had designated for myself to begin writing about Fabry disease. I apologize, but do not feel well enough to do this right now.

Several days have passed and I can now continue. Things not going as planned is just one aspect of living with Fabry disease. It can be very difficult to make plans of any kind at times. Even feeling well enough to keep scheduled doctor appointments can be difficult for some, but enough about that for now.

I would like to disclose that unlike other distinguished authors in this book I have no formal medical training. What degree of expertise I may kindly be attributed with comes from personal experience as patient with a Fabry disease and many years of contact with numerous individuals in the Fabry community, including patients, care givers and members of the medical community.

Fabry disease is known as a rare disease and meeting others that suffer from the condition certainly can be a very unusual occurrence. This not withstanding that Fabry disease is not so rare when it affects you or your family. Some individuals may be the only person affected in a family, while others may have parents, children, aunts, uncles and additional extended family members with the disease. One thread that runs throughout this varied community is a feeling of loneliness.

So many patients suffer for years or even decades not knowing what is wrong. They may feel isolated because no one understands what they are going through. Patients go from doctor to doctor. They receive some diagnosis or another thinking an answer has been found. The treatment regimen that is begun does not provide the improved health as expected. Instead frustration replaces the hope that was previously conveyed. This cycle of disappointments for some patients is too much and they retreat from the medical community denying that their problems still persist.

Many patients who suffer don't recognize that the medical establishment is not geared to train each physician to recognize every condition. Nor has the medical establishment done a very good job at having its members reveal this lack of pertinent information to patients.

Some patients are ultimately rewarded by being persistent enough to keep seeking answers until the puzzle pieces are in place. Other patients eventually develop

---

This title is edited by Michael J. Russo

significant organ involvement which points a specialist in the right direction, too frequently via a biopsy. A very few patients actually manage to be directed to a physician knowledgeable about Fabry disease at a point early enough in the progression of the disease to impact symptoms and possibly alter the disease course. Whatever the specific route, receiving that correct diagnosis is the pivotal point that leads to another universal thread: diagnosed patients finally have a name for what has been plaguing them and that small bit of data provides some level of relief.

Once the initial diagnosis has been made, it can lead to a domino affect as additional family members are diagnosed. While some sense of relief may be felt learning the name of what is causing their myriad symptoms, initially it can also be quite frightening. With this information newly-diagnosed patients may look at older relatives and worry that they too will follow the same path. Patients may be afraid of the future after learning about the impact Fabry disease can have on one's health.

Denial is another regrettable possibility that may develop after being diagnosed or even after a relative's diagnosis. Too many patients have stories about a relative who says his/her health problems have nothing to do with Fabry disease although s/he may have already been diagnosed or are at genetic risk for the condition. These individuals may say that they don't need to worry about Fabry disease because they have been getting along well enough so far (Nothing went wrong yesterday so there is no reason to think it will be worse tomorrow). Other individuals may not be able to accept the probability that s/he may have passed a serious disease like Fabry disease on to their children.

For most patients, the first symptoms of Fabry disease occur during childhood or adolescence. Children continue to play and run like they have on so many other days, but then comes the time when intense pain surges through their feet. They crumple to the ground crying just wanting the pain to go away. This pain is unlike anything they have ever experienced and may disappear within a few minutes. Perhaps, their first symptom is complaint of a fever. The youngster's mother is not able to stop the fiery burning pain in her child's hands and feet.

The emergency room physician, pediatrician, or family doctor finds nothing unusual during an examination and chalks the complaints up to growing pains, some other common aliment, or suggests that perhaps the child just doesn't want to be in physical education class anymore and is making all this up.

After a number of episodes at school, classmates often stop believing that these spells of distress are genuine. A child may even be called a 'crybaby' by his teacher. Lack of understanding from parents or siblings also takes its toll. Some patients may conclude that the best way to cope with this is to stop talking about their symptoms all together. Even if it is acknowledged that a child has Fabry disease, these issues may be impossible to control or avoid.

The intensity of pain that Fabry disease can inflict on the body may be incredibly difficult to convey to others. This pain can vary from person to person and the types of pain experienced by a single individual may vary greatly during any given day. Oftentimes, one particular day or perhaps several consecutive days, remain clearly fixed in the patient's mind.. . . not because of the pain, but rather because for that

brief period, absolutely no Fabry pain was present. These occasions are few and far between.

At first it may not be obvious what precipitating event is responsible for the onset of pain, but in time it frequently becomes clearer, especially with the onset of the more severe episodes. Common factors include: over-exertion, getting too hot, or stress to the body from temperature changes, hot or cold. Fevers are frequent triggers and some patients have recurring fevers with no apparent cause. Changes in the weather can cause increased pain. This may be associated with seasonal changes such as the onset of spring, or pain may be brought on by a strong weather front passing through. The stresses of daily living may also cause an episode of pain.

Another common complaint is a degree of 'background pain'; this is so prevalent and chronic that when asked about the presence of discomfort or pain, the patient may take a moment to realize that there is a level of pain that is always there. This pain may be uniquely present in the hands, feet, or certain joints, or may be generalized to the entire body or large portion of the body. It seems an odd thing to believe someone can suffer pain and not readily know it, but don't we often believe we are sitting in a quiet room only to realize that this is not the case once the air-conditioning stops and the fan noise ceases.

Background pain is often mild, but can also be severe in some individuals. It may have a diurnal rhythm where the pain worsens during the afternoon or perhaps makes restful sleep difficult at night. Traditionally, anti-convulsion medications have been effective in reducing or controlling this type of pain, but they are insufficient for more acute pain.

Periodic episodes of severe pain and burning may also occur. This pain may last from minutes to hours but also may seem like endless days or even weeks. This pain can be extremely intense and completely debilitating. Eating and drinking may not only be difficult, but it may even be avoided because it leads to needing to frequent the bathroom, which in turn causes increased pain because of bowel movements. The burning sensation accompanying hand and foot pain can feel as if the extremities are in a steam-cooker. Pain may radiate up the arms and legs and may feel as if it has settled in the bones. Avoiding what causes the onset of these painful episodes may help, but unfortunately this is not always possible.

While relief may be gained from prescription pain medications, at times the extreme pain of Fabry disease goes beyond the ability even of powerful narcotic drugs. Patients continue to suffer in agony until the right medication or combination of medications is found.

Experiencing pain crises leaves patients in a weakened state that may take days and even months to achieve some degree of recovery. For many patients, these episodes of pain are more frequent in adolescence and early adulthood, but this is by no means true of all patients. Some patients may believe that they are getting better because the occurrence of these pain crises has diminished, only to develop renal, cardiac or cerebral vascular events later in life.

To complicate matters associated with the sensitivity to temperature change, fever, and physical exertion, Fabry patients often suffer anhidrosis or hypohidrosis, although in some hyperhidrosis may also be a complaint. Because of this inability

to perspire adequately (or at all), family and teachers should be made aware that dangerous overheating can occur. Children commonly become very red in the face, and the hands and feet may begin to burn. This can frequently cause young patients with Fabry disease to fall behind their peers specifically in warm weather or when required to engage in physically demanding activities. Providing shade and keeping water nearby can be crucial. Wetting the hands, arms, face and feet to accelerate cooling can provide much needed relief.

Fortunately, air-conditioning is available in many homes and cars to provide comfortable temperatures during the hot summer months. When participating in activities outside, learning to stay cool can be helpful. There are a number of products on the market to help, from small fans with a mist of water to cooling vests. Simple things like eating ice chips, dressing in layers, wearing light-colored clothes or avoiding direct exposure to the sun are other measures one can take.

For those who are able to perspire adequately and handle warm temperatures, or when temperatures are cooler, patients may still have difficulty with physical exertion. Exercise intolerance can leave patients short of breath and exhausted well before healthy people in similar situations. This may become obvious in school-aged children as they try to keep up with peers in physical education class or in extracurricular sport activities. Even social events such as a school dance can pose difficulties because of the necessity for more frequent rest breaks. Making sure the school staff is aware of these limitations can be important. It may be best to let the child set his/her own pace. In some cases a medical exemption from physical education class may be necessary.

Independent of exercise intolerance, a state of generalized fatigue or tiredness may develop in both adolescents and adults. Although it is usually not debilitating, this symptom can have a detrimental impact on quality of life and be difficult for others to understand or appreciate.

Gastrointestinal involvement can be a severe problem affecting many patients' lives. As with extremity pain, bouts of diarrhea, constipation, stomach pain and vomiting can be episodic or chronic. Care should be taken so Fabry-associated abdominal pain is not confused with more common ailments and *vice versa*. Diarrhea and stomach cramping are prevalent and debilitating gastrointestinal symptoms. Those who suffer from abdominal symptoms are often forced to plan their day around the location of the nearest restroom. Gastrointestinal symptoms frequently strike within 30–60 min after meals making social involvement with friends and family difficult. Episodes of diarrhea and vomiting resulting in 10–30 trips to the toilet per day are not only embarrassing, they can be physically exhausting and make regular school/work attendance impossible. Dietary factors can play a role, but unfortunately there is great variability between patients making a recommended diet complicated at best.

Many patients report that pain and gastrointestinal involvement are the two greatest factors impairing quality of life. These complications may cause patients to undergo numerous expensive and difficult tests in the search for the etiology. Some patients give up of finding an answer, resigning to the notion that this is just how life is. In fact, some young suffers may believe this is how it is for most people and

wonder why they can't cope as well as their friends or unaffected family members. These very young patients may be very surprised to find out that the rest of the world does not share the same (gastrointestinal) difficulties.

You mean your hands and feet don't hurt and burn like they are on fire every time you run a temperature?

How can you stand to walk bare foot on this sidewalk? It burns my feet right through the soles of my shoes.

Why don't you get all sweaty like the rest of us? I don't know. I get so hot I just can't stand it, but my socks don't even get damp. I don't need to use antiperspirant either.

How can you eat that? It makes me sick every time I have some.

Most symptoms experienced by Fabry patients are also common to the general population, and thus are relatively non-specific. This contributes to a fairly high incidence of misdiagnosis, which causes delays in receiving proper treatment.

Misdiagnosis and delay can be an even bigger problem for females who inherit the mutated gene. Since Fabry is an X-linked disease, many in the medical community assume this is equalent to a recessive genetic trait. This has been a long-held view, believing females with Fabry disease were just 'carriers' and rarely affected. Recent research has largely dispelled this view by showing that the impact of Fabry disease can be just as severe among females as among males.

In general, females who inherit the mutated Fabry gene have a wider degree of variability of symptoms and often have a slightly later onset. Females may range from asymptomatic to exhibiting full-blown symptoms as well as random degrees of involvement. Symptoms expressed by all patients should be taken seriously regardless of gender. Females heterozygous for Fabry disease should be thought of as Fabry patients and treated likewise. Use of the term 'carrier' should be discontinued.

Outward signs of Fabry may not be pronounced, but when noticed can be telling. Angiokeratomas are the most readily visible, but due to their frequent 'bathing suit' distribution from the waist to groin, may not be noticed during a normal examination. This particular skin abnormality is not exclusive to Fabry disease sufferers, but, when brought to the attention of a dermatologist, may lead to a correct diagnosis. In most instances, angiokeratomas do not cause any significant problems; sometimes they can be removed with argon laser treatment. However, these small red to blue-black lesions have been known to be rather embarrassing for young men because of their rash-like appearance and location. In some instances, angiokeratomas may produce larger wart-like lesions. They can result in bleeding on towels, bedding and clothing, although this is usually minor. As with other signs and symptoms, not all Fabry sufferers have angiokeratomas.

The other visible signs of Fabry disease are normally seen only by an optometrist or ophthalmologist. The characteristic corneal opacity that forms on the surface of the eye can be seen during a slit-lamp examination. Fabry disease is one of a short list of causes for this finding, so, like dermatologists, optometrists are relatively good at referring potential Fabry patients for diagnosis. Other eye findings may result from the vascular involvement associated with Fabry such as torturous blood

vessels in the retina. While Fabry may not result in noted vision problems, it may be possible in some cases.

Nephrology is another medical specialty that can help confirm a Fabry diagnosis. Excess levels of urinary protein and other signs of kidney disease are prominent features of Fabry disease. Even though Fabry may not be readily apparent as the cause for declining kidney function, a renal biopsy will often clarify the matter. If left untreated, most male patients with what is viewed as 'classic' Fabry will eventually progress to end-stage renal disease and kidney failure. Recent research has also brought to light the impact of renal involvement in the female patient population which is greater than previously believed (Fabry RADAR 2007: The Fabry Registry Aggregate Data Annual Report: Genzyme Corporation; 2007).

Kidney failure is a great and looming fear for many Fabry patients. The requirement for dialysis can place an enormous burden on the patient and family. Fortunately, many patients are able to receive a kidney transplant either via cadaver or live donor such as a family member. Uniformly, receiving a kidney transplant has been expressed by patients as a positive step even if the procedure itself may be viewed with apprehension.

Cardiac involvement can be a particularly troubling aspect for both males and females with Fabry disease. While the associated clinical findings may paint a particular picture, the realities of daily life can be frustrating in trying to adequately convey symptoms to a physician.

The transient nature of cardiac conductive abnormalities can be alarming, and in some cases very difficult to document. Spells of palpitations may be short-lived and can occur with atrial or ventricular tachycardia or other arrhythmias. Patients may be aware of these abnormal heart rhythms. They may be of brief duration or extend for hours before conversion back to a normal heart rhythm. Seeking medical attention for these arrhythmias can be a frustrating process since symptoms may resolve before reaching medical care.

Cardiac symptoms may occur in conjunction with a slowed heart rate resulting in shortness of breath, light-headedness, dizziness, and fainting. Eventually, implantation of a cardiac pacemaker or pacemaker-cardioverter defibrillator combination may be necessary. Left ventricular hypertrophy with reduced cardiac efficiency may also contribute to these symptoms. Mitral valve prolapse and additional complications of cardiac disease such as congestive heart failure can contribute to cause further impact. For patients who develop significant cardiac complications, the possibility of a heart attack is a significant concern.

Neurological events are another aspect of Fabry disease that can take a toll on the patient. They can be as simple and non-specific as frequent headaches to Transient Ischemic Attacks (TIAs), or strokes, the latter of which can of course be very alarming and serious events for patients and their families. While these cerebrovascular events are not normally associated with younger patients, they present another potentially debilitating aspect that can strike without warning. Anti-coagulant medications are helpful in attempting to prevent blood clots, which can be of significant concern for a condition that is known to cause narrowing of blood vessels due to glycosphingolipid accumulation in endothelial cells lining the vascular system.

Patients may also suffer complications resulting from peripheral neuropathy commonly seen in Fabry disease. Extremity pain is probably the most frequently experienced result, but patients may also develop some degree of temperature sensitivity. In particular cold temperatures may become especially difficult to tolerate and quite painful, but sensitivity to heat may also occur. In time, patients may also experience a loss in temperature and vibration sensation. In these instances, care may be needed to prevent burns or frost bite to the feet and hands.

Auditory involvement is noted in many Fabry sufferers. Tinnitus and high-frequency hearing loss are relatively common. In some instances, greater degrees of gradual bilateral hearing loss may occur. The development of reduced hearing may first be noticed by family members. Hearing aid use is helpful in compensating for the impact of reduced hearing.

Spells of dizziness, vertigo and nausea may also occur as the vestibular system can be affected in conjunction with hearing impairment. Episodes of extreme dizziness may range in duration from minutes to hours with repeated bouts of vomiting. These episodes can be extremely difficult for the patient to endure. In more severe cases of hearing impairment, the use of cochlear implants has proven successful with marked improvement in the patient's ability to hear. Instances of sudden deafness in one ear have also occurred in association with TIA.

Patients may develop pulmonary symptoms. A nagging cough may develop with a frequent and irritating need to clear the throat. A cough from seasonal allergies or a simple cold may take months to clear up. Some patients may progress to chronic bronchitis. Airway obstructions may also occur resulting in wheezing and shortness of breath. In some instances supplemental oxygen may be needed. These symptoms also contribute to fatigue and reduced general health.

Owing to the nature of vascular involvement associated with Fabry disease, sexual dysfunction may become an additional complication. This imposes yet another physical and emotional burden on patients.

The progressive and chronic nature of Fabry disease can significantly impact all aspects of a patient's life. The burden this condition may place on an individual's life should not be underestimated. Whether due to the condition itself or the associated disease burden, depression can present a considerable hurdle for any patients. Treatment and education about depression should be considered wherever appropriate. Many patients do not appreciate the impact depression can have on their health. Counseling and treatment may provide substantial benefit.

Potential contributors to depression are the psychosocial aspects of living with Fabry disease. This impact often starts in childhood. Not being able to keep up with one's peers may cause a young patient to feel set apart and not able to fit in or participate as desired. This could be at school or other activities. There seems to be no link between Fabry and any impaired academic ability, although sports and other physical activities certainly can be impacted. Some students may not be able to attend school regularly due to episodes of pain or gastrointestinal involvement.

Participation in school, social or family activities, and work can be hindered, leading to lowered self esteem. Isolation or withdraw can occur due to such factors as pain, diarrhea or vomiting shortly after meals, hearing impairment, heat

intolerance, fatigue or even the fear of Fabry associated symptoms. These and other symptoms may contribute to a patient feeling alone. They may believe no one else suffers like this or can understand what they are going through. The rarity of Fabry disease and the current insufficient number of medical professionals that know of the condition may also contribute to feelings of isolation.

Feelings of guilt may be a substantial burden for some patients. An individual may feel guilty for passing Fabry disease on to a child or children. These feelings may weigh heavily on the parent-patient and can be long-lasting. Feelings of guilt may be true for both males and females, but seems to be a more difficult for female patients.

In an attempt to cope with symptoms of Fabry, some patients may look outside the normal realm of traditional medical intervention. The consumption of alcohol to ease pain may lead to the additional burden of alcohol addiction. The use of (medicinal) cannabis may be sought to moderate gastrointestinal problems, pain and other symptoms. These and other recreational drugs may contribute further to complicate factors affecting the medical management of the disease.

As may be expected, the impact of Fabry disease on all aspects of quality of life measures can be enormous. There are those fortunate enough to have very little impact on their daily functioning, but it may also range to moderate or severe impairment. Disability and dependency on government provided healthcare and disability income programs is a reality for many Fabry sufferers.

To help manage the burden of disease, an emotional support system can prove extremely important for a patient's well being and daily functioning. Understanding family or friends can help to meet this need. Educating the members of the support team about Fabry disease can prove crucial. People may be afraid of what they don't understand so encourage steps to get beyond this potential barrier. Providing educational materials or directing patients, care givers and family members to sources of these materials and additional support may help enhance care outcomes and assist in quality of life issues.

Fabry disease has had a long history where no specific treatment was available to address the underlying condition. Fortunately, that changed in 2001 for many countries in Europe and elsewhere in the world with the regulatory approval of the Enzyme Replacement Therapy (ERT) drugs Fabrazyme® and Replagal®. In 2003 the Food and Drug Administration granted approval for Fabrazyme® allowing United States physicians to join their foreign counterparts in treating Fabry disease patients with ERT. Now, as in the past, treatment requires the appropriate standard of care measures for all aspects of Fabry disease, along with ERT.

The complexity of Fabry disease often requires the involvement of many medical specialists. Communication between these specialist and involvement of the patient or care giver all working together as a health care team provides the most optimal environment for positive patient care.

While research has provided much information about this rare condition, Fabry is anything but a simple disease. To date no set rules have been developed to predict disease impact or patient outcome. There is great variability in signs and symptoms,

which require each patient to be evaluated and treated on an individual bases to ensure optimal care.

A discussion of treatment for Fabry disease is not complete without the mention of drug cost. Enzyme replacement therapy is currently among the most expense drug treatment options in the world. Without a reimbursement mechanism in place the vast majority of patients will not be able to receive treatment for the underlying disease. Dealing with reimbursement issues places a further level of burden on the disease community.

Fabry disease is a complex condition that requires a multi-disciplinary approach to treat. The future for patients and their families is looking brighter as new challenges are being addressed. The goal of all parties involved should be targeted toward the best possible outcome for the Fabry disease patient.