



**WORLD
Symposium
2005**

Presented by
**Lysosomal Disease
Network**

May 22nd
Phoenix, Arizona USA

WORLD

Symposium

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**Lysosomal Disease
Network**

May 22, 2005

Wigwam Resort & Golf Club
Phoenix, Arizona, USA

May 22, 2005

Dear Colleagues,

Welcome to the 2005 WORLD (**W**orld **O**rganization for **R**esearch on **L**ysosomal **D**iseases) Scientific Symposium presented by the Lysosomal Disease Network. This is the second annual symposium, the first was held in Minneapolis, Minnesota in 2004.

This year's meeting will emphasize neurological aspects of lysosomal diseases, including potential treatments for many of the lysosomal diseases with central nervous system effects that are not yet in place, and exploration of CNS effects in currently treatable diseases. We are excited to have you join us for this important event!

We have assembled an outstanding program, which has been organized into four (4) sessions: Current Laboratory Approaches to Understanding and Treating Lysosomal Diseases, Promising Clinical Approaches in CNS Diseases, Innovative Therapies - Promising Clinical Approaches in CNS Diseases-Gene Therapy, and Longitudinal and Outcome Studies in CNS Diseases. Concurrent disease-specific lectures on the afternoon of May 22, designed specifically for patients and patient advocates will include educational presentations, and round table discussions.

We look forward to welcoming you to the WORLD Scientific Symposium and to your participation in this exciting and important meeting.

Sincerely,

The **WORLD** Symposium Organizing Committee
Lysosomal Disease Network

SYMPOSIUM PURPOSE

This symposium is a multidisciplinary forum to present and discuss basic and clinical research discoveries in Lysosomal diseases, and related treatment, and quality of life issues. Specific aims are to: 1) foster interdisciplinary collaboration with the overall goal of improving knowledge of basic discoveries and clinical manifestations of these diseases; 2) identify and discuss the latest findings in the natural history of Lysosomal Diseases, diagnostic testing and screening, and treatment; and 3) identify areas requiring additional basic/clinical research public policy and regulatory attention.

SYMPOSIUM AUDIENCE

Clinicians, geneticists and genetic counselors, neurologists and neuropsychologists, researchers, health care professionals, patients and families, patient/family support organizations and industry professionals.

2005 SYMPOSIUM SPEAKERS

Lorne A. Clarke, MDCM, FRCPC, FCCMG

Associate Professor, Department of Medical Genetics and Director of
Medical Genetics

*Children's and Women's Hospital University of British Columbia,
Vancouver, British Columbia, Canada*

Lawrence Charnas, MD, PhD

Assistant Professor of Pediatrics

University of Minnesota, Minneapolis, Minnesota

Ronald G. Crystal, MD

Professor and Chairman, Department of Genetic Medicine

Weill Medical College, Cornell University, New York, New York

Maria Luisa Escolar, MD

Assistant Professor of Pediatrics

University of North Carolina, Chapel Hill, North Carolina

Robert Giguere

*Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec,
Canada*

Gregory Grabowski, MD

Professor and Director

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Priya S. Kishnani, MD

Associate Professor in Pediatrics

Duke University Medical Center, Chapel Hill, North Carolina

Paul Harmatz, MD

Children's Hospital of Oakland, Oakland, California

Don J. Mahuran, PhD

Professor

*University of Toronto, Hospital for Sick Children, Toronto, Ontario,
Canada*

Pramod Mistry, MD, PhD
Associate Professor, Internal Medicine
Yale School of Medicine, New Haven, Connecticut

Margaret M. McGovern, MD, PhD
Professor of Human Genetics
Mount Sinai School of Medicine of New York University, New York, New York

Joseph Muenzer, PhD, MD
Associate Professor, Department of Pediatrics and Genetics
University of North Carolina, Chapel Hill, North Carolina

Paul Orchard, MD
Assistant Professor, Department of Pediatrics
University of Minnesota, Minneapolis, Minnesota

Gail Ouellette, PhD
Genetic Counselor
Sherbrooke University Hospital Centre, Sherbrooke, Quebec, Canada

Marco A. Passini, PhD
Senior Scientist
Genzyme Corporation, Cambridge, Massachusetts

Gregory M. Pastores, MD
Associate Professor
New York University School of Medicine, New York, New York

Marc C. Patterson, MD, FRACP
Professor and Head, Division of Pediatric Neurology, Director of
Pediatric Neurology
*Columbia University Medical Center, Morgan Stanley Children's Hospital
of New York Presbyterian and Neurological Institute of New York, New
York, New York*

Raphael Schiffmann, MD, PhD
Lead Investigator, Staff Clinician
*Developmental and Metabolic Branch, National Institute of Neurological
Disorders and Stroke, National Institutes of Health, Bethesda, Maryland*

Elsa G. Shapiro, PhD

Professor, Departments of Pediatrics and Neurology
University of Minnesota, Minneapolis, Minnesota

Robert Steiner, MD

Associate Professor, Department of Pediatrics, Head, Division of
Metabolism
Oregon Health Sciences University, Portland, Oregon
Doernbecher Children's Hospital, Portland, Oregon

Neal J. Weinreb, MD, FACP

*University Research Foundation for Lysosomal Diseases, International
Collaborative Gaucher Group, Hollywood, Florida*

Chester B. Whitley, PhD, MD

Professor, Department of Pediatrics
University of Minnesota, Minneapolis, Minnesota

William Wilcox, MD, PhD

Associate Professor of Pediatrics, UCLA
*Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles,
California*

DISEASE FOCUS

- Mucopolysaccharidoses

 - Hurler syndrome (I),
 - Hunter syndrome (II),
 - Sanfilippo syndrome (III),
 - Morquio syndrome (IV),
 - Maroteaux-Lamy syndrome (VI),
 - Sly syndrome (VII)

- Fabry disease

- Gaucher disease

- Globoid cell leukodystrophy (Krabbe disease)

- Pompe disease

- Tay-Sachs disease

- Neuronal ceroid lipofuscinosis (Batten disease)

- Niemann-Pick disease

- Metachromatic leukodystrophy (MLD)

EXHIBITS

Exhibits will be open to all participants throughout the symposium

DISCLOSURE POLICY

It is the policy of the Lysosomal Disease Network to ensure balance, independence, objectivity and scientific rigor in all of its sponsored educational activities. All speakers participating in sponsored programs are expected to disclose to the program audience any real or apparent conflict of interest related to the content of their presentation.

REGISTRATION FEES

The fees listed on the Registration Form includes: records processing, conference materials, continental breakfast, lunch, dinner and refreshment breaks.

WORLD NETWORK WEB SITE

WWW.WORLD.UMN.EDU – Additional information on this symposium and general information on WORLD (World Organization for Research on Lysosomal Diseases) Symposium, presented by the Lysosomal Disease Network.

Sponsors

The organizers and members of the Lysosomal Disease Network thank these sponsors for their generous support of the WORLD Symposium 2005 (Phoenix, AZ, May 22, 2005).

PLATINUM

National Institutes of Health (1R13NS053341-01)
National Institute of Neurological Disorders and Stroke (NINDS)
Office of Rare Diseases (ORD), Office of the Director

GOLD

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In addition to cash contributions to this meeting, we thank Genzyme Corporation for allowing co-localization of the WORLD Symposium following the LSD Registries meetings.

TKT (Transkaryotic Therapies, Inc.)

Zebraic

PROGRAM

Sunday, May 22, 2005

- 7:00 a.m. **Registration & Continental Breakfast**
- 7:45 a.m. **Welcome and Opening Remarks** *Chester Whitley*
- 8:00 a.m. **Session I - Current Laboratory Approaches to Understanding and Treating Lysosomal Diseases**
Moderator: Chester Whitley
- 8:00 a.m. A New Murine Model for Gaucher Disease *Lorne Clarke*
- 8:20 a.m. Biomarkers of Lysosomal Storage Disease *Pramod Mistry*
- 8:40 a.m. Differential Gene Expression in Mouse and Human Variants of Gaucher Disease *Gregory Grabowski*
- 9:00 a.m. Screening (Mass and High-risk) and Diagnosis of Lysosomal Storage Diseases *Robert Giguère*

- 9:20 a.m. **Session II - Promising Clinical Approaches in
CNS Diseases-Innovative Therapies**
Moderator: Robert Steiner
- 9:20 a.m. Long Term Experience with Recombinant Human *Priya Kishnani*
Acid Alpha Glucosidase Enzyme Replacement
Therapy for Infantile Pompe Disease
- 9:40 a.m. Modifier Genes and the Vasculopathy of Fabry *Raphael Schiffmann*
Disease
- 10:00 a.m. **Morning Refreshment Break, Exhibits**
- 10:20 a.m. Pharmacological Chaperones: Unraveling the *Donald Mahuran*
Mutational Knot in Adult Tay-Sachs Disease.
- 10:40 a.m. **Panel Discussion** Neurological Response to *Lawrence Charnas*
Therapy: Stabilization, Slow Decline or
Improvement?

- 11:10 a.m. **Session III - Promising Clinical Approaches in
CNS Diseases-Gene Therapy Approaches**
Moderator: Gregory Grabowski
- 11:10 a.m. AAV-Mediated Gene Therapy of Niemann-Pick Type *Marco Passini*
 A Disease
- 11:30 a.m. AAV Gene Therapy for Hunter Syndrome and *Joseph Muenzer*
 Sanfilippo Syndrome Type B
- 11:50 a.m. Lentivirus Gene Therapy for Hurler Syndrome *Chester Whitley*
- 12:10 a.m. Gene Therapy for Batten Disease *Ronald Crystal*
- 12:30 p.m. **Lunch**
- 1:45 pm
to
5:00 pm *Concurrent Patient-Oriented Breakout Panels*
 (see separate schedule)

- 2:00 p.m. **Session IV - Longitudinal and Outcome Studies
In CNS Diseases**
Moderator: William Wilcox
- 2:00 p.m. Spectrum of Neurologic Disease Manifestations in *Margaret McGovern*
Type B Niemann-Pick Disease
- 2:20 p.m. Clinical Studies of Niemann-Pick Disease Type C *Marc Patterson*
- 2:40 p.m. Late-Onset Tay-Sachs Disease: Assessment of *Gregory Pastores*
Functional Disease Severity
- 3:20 p.m. **Afternoon Refreshment Break, Exhibits**
Moderator: Gregory Pastores
- 3:30 p.m. Neurodevelopmental Outcomes of Umbilical Cord *Maria Escolar*
Blood Transplantation for Infantile Krabbe Disease
- 3:50 p.m. Longitudinal Outcomes of Early- and Late-Onset *Elsa Shapiro*
Metachromatic Leukodystrophy after Hematopoietic
Stem Cell Transplantation
- 4:10 p.m. Challenges in Treating Neuronopathic Gaucher *Neal Weinreb*
Disease: A Report From the Gaucher Registry
- 4:30 p.m. Discussion and Closing Remarks
- 4:45 p.m. **ADJOURN**

**CONCURRENT PATIENT-ORIENTED BREAKOUT PANELS
PROGRAM**

- 1:45 p.m. **Panel I – Mucopolysaccharidoses (MPS) and Glycoproteinosis (ML) Diseases**
Moderator: Robert Steiner
- A Difficult Journey But a Happy Outcome for an Orphan Disease Patient *Gail Ouellette*
- An Overview: Successes and Challenges for Treatment Of MPS and ML Disorders Enzyme Replacement for Mucopolysaccharidosis Diseases *Joseph Muenzer*
- 2:30 p.m. **Panel II – Hematopoietic Stem Cell Transplantation**
Moderator: Lorne Clarke
- Outcomes of Umbilical Cord Transplantation *Maria Escolar*
- 25 Years of Hematopoietic Stem Cell Transplantation *Paul Orchard*
- 3:15p.m. **Panel III – Fabry Disease**
Moderator: Christine Eng
- Exercise Testing in Fabry Disease *William Wilcox*
- The Central Nervous System in Fabry Disease *Raphael Schiffmann*
- Lessons from the Fabry Registry *Christine Eng*
- 4:00 p.m. **Panel IV – New Therapies on the Horizon**
Moderator: Lawrence Charnas
- Substrate Inhibition Therapy *Gregory Pastores*
- Pharmacological Chaperones *Donald Mahuran*
- Gene Therapy of Niemann-Pick Disease Type A *Marco Passini*
- Gene Therapy for Batten Diseases *Ronald Crystal*
- 4:45 p.m. **ADJOURN**

EVENING PROGRAM

6:00 p.m. **Reception (Cash Bar)**

6:30 p.m. **Dinner and Lysosomal Disease Network business meeting**

Ali Garba, Guest Speaker

Lysosomal Disease Network - Business Meeting

ABSTRACTS

A New Murine Model for Gaucher Disease

Lorne Clark, MDCM, FRCPC, FCCMG, Children's and Women's Hospital,
University of British Columbia, Vancouver, British Columbia, Canada

Biomarkers of Lysosomal Storage Disorders

Pramod K Mistry, MD, PhD, Yale School of Medicine, New Haven, CT

Lysosomal storage disorders (LSDs) are characterized by vast clinical spectrum and complex multi-systemic phenotypes. In the past, ascertainment of disease severity relied on clinical indicators of disease activity as exemplified by the development of severity score index (SSI) for Gaucher disease(GD). However, clinical ascertainment of disease severity is of limited value for longitudinal follow-up for disease progression before development of irreversible complications or for monitoring response and fine-tuning of enzyme replacement therapy (ERT). Development of reliable biomarkers overcomes these limitations and has the potential to provide pathophysiologic insights. The desired properties of a biomarker for LSD include specificity to the disease, correlation with disease burden, its ability to reflect disease remission on therapy and conversely relapse of disease activity on sub-optimal therapy. In addition the biomarker should be applicable to the majority of patients and there should be reliable assays as well as easy access to testing.

Accumulation of substrate in serum and/or urine is an attractive biomarker but it represents only a trivial fraction of substrate accumulation, the majority being confined intracellularly within storage cells and it correlates poorly with clinical indicators of disease severity. Therefore, attention has turned to monitoring secretory products of storage cells triggered by the accumulating substrate, in the expectation that these biomarkers will represent total body burden of storage cells as well as their state of activation. These efforts are in the most advanced stage of development for GD.

The Gaucher phenotype results from accumulation of glucosylceramide-laden lysosomes in mononuclear phagocytes and systemic macrophage activation, thereof. These cellular responses to accumulating substrate are reflected in elevated serum levels of angiotensin converting enzyme (ACE), tartrate-resistant acid phosphatase (TRAP), chitotriosidase, several lysosomal enzymes, several cytokines and a chemokine, CCL18. In addition, serum ferritin is elevated and there is a reduction of serum lipoproteins, both phenomena reflecting systemic macrophage activation. This presentation will review latest data on commonly utilized biomarkers of GD activity. Several case studies will be presented to illustrate how biomarker monitoring provides invaluable insights into the extent of disease activity in ‘difficult-to-quantify’ disease compartments such as the marrow and lungs, that are associated with high level of morbidity. It is expected that in the future, the treating clinician will have access to several new biomarkers of GD activity that will facilitate fine-tuning of ERT and may even provide prognostic as well as pathophysiologic insights.

Planned LSDN initiative under the auspices of WORLD will provide an invaluable platform for biomarker discovery and routine clinical monitoring in the context of patient-oriented research studies. Therefore it is recommended that the topic of biomarkers becomes an important component of the planned WORLD/LSDN initiative to link nationwide efforts in lysosomal storage diseases.

Differential Gene Expression in Mouse and Human Variants of Gaucher Disease

Gregory A. Grabowski, Ying Sun, and You-Hai Xu, The Division and Program in Human Genetics, Cincinnati Children's Hospital Research Foundation, Cincinnati, OH

Gaucher disease is a common lysosomal storage disease due to defects in the activity of the enzyme acid β -glucosidase (GCase). There are over 200 mutations that have been identified in patients with Gaucher disease at this particular locus (GBA) and some degree of genotype/phenotype correlation exists. Enzyme therapy has been available for the treatment of Gaucher disease for a decade, but the ability to monitor biochemically the progress of the disease or the effects of therapy have been hampered by the inability to create viable mouse models of Gaucher disease. Recently, we created several point mutations in the *gba* locus in mice that lead to differential phenotypic manifestations of Gaucher disease including mild (4L/4L) and more severe (9V/null) mice with varying degrees of Gaucher cell and a glucosylceramide accumulation in the liver, spleen, and lungs. To explore the pathophysiologic effects of these mutations, microarray analyses were undertaken of the major visceral tissues, liver, spleen and lung, in an effort to identify potential “signature pathways” related to the disease pathophysiology with correlations to the histopathologic and biochemical abnormalities. For these studies mRNA from strain and age matched affected and wild-type mice was harvested from the above tissues, subjected to microarray analyses of mRNA expression using the Affymatrix chips. For these studies, pooled samples in duplicate from three mice at several different ages of development were analyzed. RNA quality was verified by a variety of QA/QC studies and included analysis by individual tissue and group tissue by median/quantile normalization as well as by ANOVA and student t-tests followed by false discovery rate analyses ($q < 0.05$) and, finally, cluster and pathway analyses for the identification of specific genes and changes. The human sample was from a 45-year-old Gaucher type 1 patient who underwent splenectomy for severe thrombocytopenia and visceral bleeding to prevent developing blindness. The control sample for this spleen was from publicly available databases. The presentation will deal with principally the pro-inflammatory pathways in each of the major visceral organs and their changes with different point mutations as well as progress through time. In particular, the pathways modulated by interferon- α and interleukin-4 representing the classical and alternatively activated macrophage pathways will be presented. Comparisons of the genes involved in the classical and alternatively activated macrophages will be discussed in-depth with comparisons to the human spleen RNA expression. These will be correlated with histopathologic and biochemical (lipid) abnormalities within the tissues. The emphasis will be on the pro-inflammatory pathway and the development of a potential “course” for predication of disease status.

Screening (Mass and High-risk) and Diagnosis of Lysosomal Storage Diseases

Giguère, R., Auray-Blais, C., Drouin, R., Lemieux, B.

Centre Hospitalier Universitaire de Sherbrooke, Service of Medical Genetics, Sherbrooke, Quebec, Canada

A major limitation for effective treatment of individuals with lysosomal storage diseases (LSDs) has been the relatively late diagnosis which is based on the clinical recognition of symptoms, some of which are not remedial, e.g., permanent skeletal abnormalities, irreversible brain damage, fibrotic cardiac changes.

Interest in pre-symptomatic identification by screening newborn or high-risk populations, has been driven by the increasing availability of systemic therapy, and the need for earlier, pre-symptomatic treatment. It was hypothesised that testing the urine of young children might facilitate such early diagnosis and treatment.

In Quebec, a Provincial Mass Urinary Screening Program was instigated in 1971 for the detection of hereditary metabolic disorders in newborn babies. Parents voluntarily collect the urine of their babies at 3 weeks of age on a filter paper. The cooperation of the parents is good at 90%. From 1989-1994, we participated in a NIH pilot project for the screening of neuroblastoma by using urine filter paper samples collected at 3 weeks and 6 months of age, that are still kept in storage at -20°C. Also, a Provincial High-Risk Screening Laboratory has been established 20 years ago for the diagnosis of inborn errors of metabolism by semi and quantitative methods.

In 1980, we performed the Berry spot test for the detection of mucopolysaccharidoses (MPS) on 5,000 urine filter paper samples of newborn babies at 3 weeks of age. We found no positive cases with this procedure, due to its very low sensitivity. During the last fifteen years, we have been using a two-step approach for the high-risk screening of MPS and oligosaccharidoses: first, a total quantification of glycosaminoglycans (GAG) by the dimethylmethylene blue (DMB) coloration and secondly, when positive, we perform a paper chromatography for the sulphate identification. Oligosaccharides are analysed by thin-layer chromatography using the orcinol coloration. After analysing nearly 500 samples from all the hospitals in Quebec for metabolic evaluation, we detected 2 cases of Hurler disease, 1 case of fucosidosis, 1 case of mannosidosis and 1 case of Sandoff disease. The two patients with Hurler syndrome are on enzyme replacement therapy (ERT) and doing well. Recently, we have started a research project for the identification and quantification of LSD biomarkers by liquid chromatography tandem mass spectrometry (LC-MS/MS) in newborn and high-risk populations.

Based on our experience, we have concluded that high-risk screening and detection of abnormal pre-symptomatic LSD patients is very important to assure their efficient clinical treatment and monitoring. We thus emphasise the need for early detection of LSD patients.

Long Term Experience with Recombinant Human Acid Alpha Glucosidase Enzyme Replacement Therapy for Infantile Pompe Disease

Priya S. Kishnani, Duke University Medical Center, Durham, NC

Background: Pompe disease, also referred to as glycogen storage disease type II and acid maltase deficiency, is a genetic muscle disorder caused by a deficiency of the lysosomal enzyme acid α -glucosidase (GAA, also referred to as acid maltase). The enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, with cardiac, skeletal, and smooth muscle cells being the most seriously affected.

Clinically, Pompe disease encompasses a range of phenotypes. Infantile-onset Pompe disease is uniformly lethal. Affected infants present in the first few months of life with hypotonia, generalized muscle weakness and a hypertrophic cardiomyopathy followed by death from cardiorespiratory failure usually by 1 year of age. (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Van den Hout, 2003, *Pediatrics*). To date, clinical trials with recombinant human acid alpha glucosidase (rhGAA) have focused largely on the demonstration of efficacy of ERT in patients with the infantile-onset form of the disease as these patients represent the greatest unmet medical need.

With enzyme replacement therapy likely to become available in the near future for Pompe disease, an understanding of complications and natural history of the infantile form of the disease is of paramount importance. A team approach to care is necessary due to the multi-systemic nature of the disease.

Methods: Experiences from the Duke University Medical Center with the management of different aspects of Pompe disease (anesthesia, cardiac, pulmonary, gastrointestinal, orthopedics) and other long term complications not previously recognized will be presented. Several ERT trials with rhGAA are currently underway and data from these recent trials will be presented.

Results: In the infantile-onset patients, rhGAA markedly extended survival and prevented or delayed time to ventilator dependence as compared to available data from untreated historical cohorts. ERT with rhGAA also reversed indices of cardiomyopathy, and prevented or reversed failure to thrive in the vast majority of patients treated. Consistent gains in motor function were observed in approximately two thirds of the patients, with a subset of these patients achieving independent ambulation. Together these findings, which contrast sharply to the severe and unremitting clinical deterioration observed in virtually all untreated patients with infantile-onset Pompe disease, support the efficacy of ERT. There is also a general trend indicating that ERT success improves with early start of treatment.

Conclusions: Because Pompe disease, particularly the infantile onset form, has such a rapid progression to respiratory failure and death, it is essential that clinicians recognize, diagnose and treat Pompe disease patients as rapidly as possible. Long term complications of the disease also need to be understood to better guide management.

Modifier Genes and the Vasculopathy of Fabry Disease

Raphael Schiffmann, M.D., National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, MD

The alpha-galactosidase A deficiency of Fabry disease leads to a systemic vasculopathy manifesting as skin angiokeratomas, cerebrovascular strokes and dolichoectasia, renal insufficiency and cardiac disease. The mechanism and pathogenesis of this disease is poorly understood. We hypothesized that the Fabry vasculopathy is associated with abnormalities of blood components, blood flow and vascular wall (Virchow's Triad) leading to a vascular dysfunction. If so, these vascular abnormalities should improve with specific therapy and serve as surrogate indicator of reduction in the rate of these complications. The finding of increased soluble sICAM-1, sVCAM-1, P-selectin, PAI, and decreased thrombomodulin combined with increased monocyte CD11b expression confirmed a prothrombotic state in Fabry disease. We then found significant cerebral hyper-perfusion in Fabry disease compared to controls using three independent methods (positron emission tomography, arterial spin-tagging MRI and transcranial Doppler). We subsequently demonstrated that this hyperperfusion is a vascular phenomenon and is not caused by neuronal overactivity. Cerebrovascular hyper-reactivity to acetazolamide infusion indicated abnormal cerebral regulation in Fabry patients. This cerebral hyper-perfusion was associated with calcifications (end-organ damage) in the cerebral white matter and in the posterior thalamic regions. We also found increased endothelium-dependent vascular reactivity to acetylcholine in the forearm vascular bed that was still present with a competitive inhibitor of arginine indicating an altered function of non-nitric oxide pathways. These findings led us to test the hypothesis that the vascular dysfunction in Fabry disease is due increased release of reactive oxygen species leading to increased oxidative stress. We found support for this theory with the increased staining for 3-nitrotyrosine in dermal and cerebral blood vessels and in the increased nitrotyrosine and myeloperoxidase in blood of patients with Fabry disease compared to controls.

More recently we found an altered reactivity of the cerebral vasculature to ascorbate infusion coupled with low blood levels of ascorbate in Fabry patients. Elevated myeloperoxidase in blood may be related to our recent observation that the Fabry disease process accelerates atherosclerosis. Indeed, we increasingly observe premature fixed coronary artery and cerebral artery disease in Fabry patients. The cerebral blood flow pattern and dermal vascular 3-nitrotyrosine staining significantly improved with enzyme replacement therapy. However, thus far we have not observed any reduction in the incidence of strokes in treated adult Fabry patients. Finally, In a prospective observational study we evaluated 57 consecutive Fabry hemizygous male patients for brain FLAIR MRI lesions and for 174 G/C of IL6 polymorphism of interleukin 6 (IL-6), the G894T polymorphism of endothelial nitric oxide synthase (eNOS), the factor V G1691A mutation, the prothrombin G20210A variant, the methylenetetrahydrofolate reductase (MTHFR) C677T, as well as the G79A and the A-13G polymorphisms of protein Z. Each locus was looked at independently using logistic regression with age as covariate and corrected for type 1 error using the false discovery rate correction of Benjamini & Yekutieli. The age range of the NIH Fabry cohort was 12 to 64 years with a mean age of 36 years. Four patients were Hispanic in origin and the others were Caucasians. Thirty patients had no FLAIR lesions on MRI. IL-6 (genotype=GC, p=0.011), IL-6 (genotype=CC, p=0.038), factor V (genotype=GA, p=0.011), protein Z polymorphisms G79A (genotype=GA, p=0.034) and A-13G (genotype=AG, p=0.036) and eNOS (genotype=GT, p=0.035) were significantly associated with cerebral lesions but not prothrombin and MTHFR. We therefore found a clear relationship between a number of pro-thrombotic gene polymorphisms and the presumptive ischemic small-vessel cerebral lesions in Fabry disease. This finding suggests that these proteins modulate Fabry cerebral vasculopathy and may allow the prospective identification of patients who are most at risk for developing these complications. We conclude that Fabry disease has all the features of a classic vasculopathy and is likely associated with increased oxidative stress and accelerated atherosclerosis especially in susceptible individuals. Another group recently confirmed the above results using an animal model. These findings have implications for the pathogenesis and treatment of Fabry disease as well as for the monitoring of the response to specific therapies.

Pharmacological Chaperones: Unraveling the Mutational Knot in Adult Tay-Sachs Disease

Michael B. Tropak¹, Brigitte Rigat¹, Eric Brown², Stephen G. Withers³ and Don Mahuran^{1*}.¹ The Hospital For Sick Children and University of Toronto, Toronto, Ontario Canada, ² McMaster Highthroughput Screening Laboratory, McMaster University, Hamilton, Ontario Canada, ³ University of British Columbia, Vancouver, British Columbia, Canada

*Corresponding and presenting author

For lysosomal storage diseases such as Tay-Sachs, intralysosomal accumulation of the substrate results when lysosomal levels of beta-N-acetyl hexosaminidase A are reduced below a critical threshold of about 10% of normal. The residual activity of mutant hexosaminidase A in fibroblasts from patients with the chronic form of Tay-Sachs disease can be enhanced above this critical threshold using compounds which specifically bind to the active site of the protein i.e. enzyme inhibitors such as N-acetyl glucosamine-thiazoline (NGT). These compounds represent potential therapeutics for the treatment of late-onset Tay-Sachs disease. It is believed that enzyme inhibitors in general can stabilize the active, folded conformation of their associated enzyme (mutant or wild type) after biosynthesis, allowing more of the enzyme to escape the quality control system of the cell's endoplasmic reticulum and be transported to the lysosome. Classic competitive inhibitors resemble the substrate or reaction intermediate of the target enzyme and are thus, often predictable. Using hexosaminidase as a model system and NGT as a positive control, we examined the idea that non-classical compounds also exist that can function as specific enzyme inhibitors, and that they could be identified using a high throughput screening strategy. Furthermore, if these compounds did act as competitive inhibitors, they would also serve as pharmacological chaperones. Thus, we developed a method to screen the Maybridge library of 50,000 drug-like compounds for novel competitive inhibitors of hexosaminidase. All inhibitors examined in detail also functioned as pharmacological chaperones, since like NGT, they enhanced hexosaminidase activity in fibroblast cell line derived from a chronic Tay-Sachs patient. We believe that this approach can be adapted to any lysosomal enzyme for which a methylumbelliferone-based substrate is available.

(This work was funded by grants from CIHR Canada, PENCE Canada and the Uger Estate)

Panel Discussion

Neurological Response to Therapy: Stabilization, Slow Decline or Improvement

Lawrence Charnas, Chair

AAV-Mediated Gene Therapy of Niemann-Pick Type A Disease

Marco A. Passini, Genzyme Corporation, Framingham, MA

Type A Niemann-Pick disease (NPA) is a neurometabolic disorder caused by a genetic deficiency of acid sphingomyelinase (ASM). The lack of functional ASM results in sphingomyelin, cholesterol and ganglioside accumulation within the lysosomes of cells throughout the brain, leading to progressive neurodegeneration and death in early childhood. We investigated the efficacy of using AAV gene therapy as a form of ASM enzyme replacement to correct brain pathology in a ASM knockout (ASMKO) mouse model of NPA. In the first study we injected adeno-associated virus serotype 2 that encoded for human ASM (AAV2-hASM) into the adult ASMKO hippocampus of one hemisphere. This resulted in human ASM mRNA and protein expression in all major cell layers of the ipsilateral (injected) hippocampus for up to 15 weeks post-injection. Translation of virally-encoded message occurred in a pattern consistent with targeting of hASM protein to the lysosomal/endosomal compartment. Beyond the hippocampal injection site, hASM mRNA- and protein-positive cells were abundantly present in the entorhinal cortex, medial septum, mammillary body, and the contralateral hippocampus. The transduction of these distal sites matches the pattern of known major afferent projections to the hippocampus, and demonstrates that the hASM can be delivered to multiple regions of the brain by retrograde axonal transport of AAV2. Sections through the brain showed a substantial reduction of distended lysosomes and cholesterol in all structures that were targeted by the viral vector. In our next study, we determined if a different AAV serotype provides better therapeutic outcome in the NPA brain. An AAV serotype-1 vector (AAV1-hASM) was generated and injected unilaterally into the striatum, hippocampus, and cerebellum of 6 week-old ASMKO mice and sacrificed 14 weeks later (20 week-old). Biweekly testing on the rotorod showed preservation of motor function that was comparable to wild type controls ($p < 0.001$). Consistent with these behavioral changes, calbindin immuno-positive were present in the cerebellum of treated mice, demonstrating that AAV1-ASM prevented Purkinje cell death. Human ASM immuno-positive cells were found surrounding the injection sites and in distant brain regions including the contralateral hemisphere receiving efferent projects. This distribution pattern was consistent with local viral diffusion as well as anterograde axonal transport of ASM protein leading to cross-correction of distal structures. Levels of sphingomyelin, cholesterol and gangliosides were significantly reduced in all samples taken bilaterally across the entire rostrocaudal axis of the brain. The overall therapeutic benefits were better with AAV1-hASM compared to parallel experiments done with AAV2-hASM, demonstrating that AAV1 is superior to AAV2 for correcting pathology and achieving behavioral recovery. In conclusion, AAV-mediated human ASM enzyme replacement therapy leads to long-lasting, reversal of brain pathology in a mouse model of NPA. We also show that widespread distribution of virus and/or protein can occur via axonal transport in projection neurons. This suggests that brain circuits may be exploited to achieve global distribution of therapeutics, which may be employed as a general strategy to treat a variety of lysosomal storage disorders that affect the brain.

AAV Gene Therapy for Hunter Syndrome and Sanfilippo Syndrome III B

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Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders with a wide range of clinical disease with progressive tissue and organ dysfunction, and premature death in the severe forms. A majority of MPS patients have central nervous system (CNS) involvement. No definite treatment is available for patients with Hunter syndrome (MPS II) or Sanfilippo syndrome (MPS III). Clinical trials of peripheral administration of recombinant enzyme in MPS II patients are in progress, but CNS disease is not expected to be improved. MPS II is an X-linked disease due to the deficiency of the lysosomal enzyme iduronate sulfatase (Id-S) with both somatic and CNS involvement. MPS IIIB is due to the deficiency of α -N-acetylglucosaminidase (NaGlu) which results in only severe neurological involvement. A critical factor impacting therapeutic development for MPS II and MPS IIIB is how to efficiently deliver the therapeutic materials into the CNS to correct the global neurological pathology, which is the cause of high mortality and premature death in most MPS patients. The therapeutic effects of AAV gene delivery on the CNS disease in adult MPS II and MPS IIIB “knockout” mice were studied using combined intravenous (IV) and intracisternal (IC) injections after pretreatment with mannitol. An AAV serotype 2 vector was used, containing either the human Id-S cDNA or the human NaGlu cDNA driven by a cytomegalovirus promoter (CMV). AAV2 vector was delivered into adult (4-6 week old) MPS “knockout” mice by tail vein injection 10 minutes after an IV infusion of mannitol (1-2 mg/gm of body weight). The IV administered AAV vector was followed by AAV2 vector delivered directly into the posterior cistern. Complete correction of glycosaminoglycan accumulation in the liver of MPS II mice was achieved ($P < 0.01$) and partial correction in spleen, heart, muscle, and lung was observed ($P < 0.05$). Id-S enzyme activity was detected in the treated MPS II mouse liver (50%-100% of normal mouse liver). Decreased CNS lysosomal storage was shown by histopathology in Purkinje cells and also in the neurons of the hippocampus, thalamus and cerebral cortex after AAV-mediated gene transfer in both MPS II and MPS IIIB mice. The life spans of the MPS II and MPS IIIB mice after the AAV gene therapy were prolonged compared with the life span of the non-treated mice. Our results suggest that IV injection combined with an IC injection of AAV2 vector following mannitol pretreatment is a promising approach for treating both somatic and CNS disease in lysosomal storage disorders.

Lentivirus Gene Therapy for Hurler Syndrome

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Background. Treatment of neurologic lysosomal disorders of the central nervous system are limited by the associated toxicities (i.e., hematopoietic stem cell transplantation) or lack of efficacy in the nervous system tissue (i.e., enzyme replacement therapy).

Hypothesis. Gene therapy may offer the potential to achieve metabolic correction in the central nervous system without systemic myeloablation, graft-versus-host disease.

Results of Murine Studies. In studies of the murine model of Hurler syndrome (mucopolysaccharidosis type IH) we have found that a single intravenous injection of lentiviral vector is dramatically efficacious, and appears to be safe.

Interpretation. If these experiments are predictive, such treatment would be curative of the disease in infants, and toxicities would be essentially inconsequential (i.e., negligible adverse reactions to infusion, and low risk of germ line mutation).

Speculation. These observations lead to the design of a future clinical trial to be described as: “A Phase I-II, double-blind, cross-over, dose-escalation, clinical trial of intravenous iduvec gene therapy for Hurler syndrome”. Outcome measures that would be proposed to the FDA and NIH RAC would include the identification of any toxicities, as well as specific measures of efficacy: (1) decrease in urine GAG/creatinine; (2) increase in circulating alpha-L-iduronidase enzyme activity; (3) preservation or changes in brain structure as observed by cranial MRI; and (4) neurocognitive measurements of language acquisition and DQ/IQ currently used to assess children with Hurler syndrome.

Gene Therapy for Batten Disease

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Late infantile neuronal ceroid lipofuscinosis (LINCL), a pediatric autosomal recessive lysosomal-storage disorder, manifests with blindness, progressive neurodegeneration, and death by age 8 to-12. The disease results from mutations in the CLN2 gene and deficiency in its product tripeptidyl-peptidase (TPPNI), resulting in progressive loss of pigmented retinal epithelium and neurons. We-have demonstrated that direct central nervous system gene transfer of AAV2ÚhCLN2 (asero-type-2, adenoassociated gene transfer expressing the human CLN2 cDNA) in rats and nonÑhuman-primates mediates long term TPPNI expression in the brain. On the basis of this efficacy data we-carried out preÑclinical toxicology assessment of AAV2ÚhCLN2. Clinical grade AAV2Úvector was administered to the CNS of rats and nonÑhuman primates at doses scalable to humans.-In Fischer 344 rats and in African green monkeys there were no biologically significant-differences between control and vector groups for all toxicology parameters. Taken together, the-long term gene expression following gene transfer and the safety data in multiple animal models-supported the initiation of clinical trials to assess the safety of AAV2ÚhCLN2 administration to-the CNS of children with LINCL. When completed, the clinical studies, now ongoing, will-include 5 children with severe manifestations of LINCL, and 6 with a moderate phenotype.-Following administration with 3.6×10^9 particle units of the AAV2ÚhCLN2 vector to the brain at-12 locations through 6 burr holes, the children are being followed with a LINCL neurologic-ratingscale and CNS nuclear magnetic resonance and magnetic resonance spectroscopy.

Spectrum of Neurologic Manifestations in Type B Niemann-Pick Disease

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Niemann-Pick disease due to acid sphingomyelinase deficiency is a multisystemic lysosomal storage disease resulting from the accumulation of sphingomyelin within cells of the monocyte-macrophage system. Classically, patients with ASM deficiency are categorized into two allelic subtypes, a severe neurodegenerative form leading to death in by three years (Type A Niemann-Pick disease, or NPD-A) and a milder phenotype characterized by hepatosplenomegaly, hyperlipidemia, and pulmonary involvement, with most patients living into adulthood (Type B Niemann-Pick disease, or NPD-B). In addition, several reports have described an intermediate subtype in patients who survive early childhood and have the somatic findings of NPD-B, but who also have evidence for clinically significant neurological involvement. Over the past decade we have conducted detailed clinical evaluations of over 100 patients with ASM deficiency in order to delineate the natural history of the disease, including detailed neurologic assessments. These studies have permitted the identification of the spectrum of neurologic deficits in acid sphingomyelinase deficiency. This presentation will describe the natural history of the neurologic disease in patients with the Type A phenotype and describe the frequency of neurologic abnormalities in a series of patients with NPD-B, including detailed clinical and molecular data for five patients with an atypical presentation of NPD-B characterized by hepatosplenomegaly, retinal changes, and progressive neurologic manifestations.

Clinical Studies of Niemann-Pick Disease Type C

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Niemann-Pick Disease Type C (NPC) is a progressive neurodegenerative disease associated with excess lysosomal storage of multiple lipids and mutations in two genes, designated NPC1 and NPC 2. The basic defect is not an enzyme deficiency, but impaired intracellular endosomal-lysosomal trafficking. The diagnosis is technically challenging, and is available in only a few centers. Mutational analysis is available, but is also difficult owing to the size of the major gene, NPC1, and large number of mutations (>150) that have been recognized. The clinical manifestations of NPC affect the nervous system, liver, spleen and lungs to highly variable degrees. A number of case reports, small series and retrospective reviews are available describing the phenotype. Characteristic presentations include:

- Perinatal hepatic failure with or without pulmonary infiltration, associated with high infant mortality.
- Hypotonia and delay in infancy, with subsequent regression and death in childhood.
- Childhood presentations with vertical supranuclear gaze palsy, ataxia, action dystonia, seizures, gelastic cataplexy and progressive dementia.
- Adolescent and adult presentations with attenuated and fragmentary phenotypes, particularly psychiatric disturbances and atypical dementia.

A trial of cholesterol lowering agents in NPC was published in 1993, but there have been no further systematic therapeutic studies published to date. Currently, a therapeutic trial of miglustat for glycosphingolipid substrate inhibition in NPC is in progress, and is gathering longitudinal clinical and laboratory data in treated and untreated study participants. The primary outcome measure in this study is rate of change of horizontal saccadic velocity; secondary outcome measures include quality of life, organ volumes, swallowing ability and psychometrics. Findings to date will be reviewed.

Late-Onset Tay-Sachs Disease (LOTS): Assessment of Disease Severity

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Late-onset Tay-Sachs disease (chronic G_{M2}-gangliosidosis) is a progressive neurodegenerative disorder, due to mutations of the α -subunit of the Hexosaminidase A gene that result in residual enzyme activity. The latter partly explains the delayed onset of symptoms (in our cohort of 21 patients; mean age at diagnosis was 18.1 years) and protracted disease course (current mean age 40.4 years; 71% remain ambulatory, with or without the use of an assistive device).

Assessment of disease severity and its impact on health-related quality of life are important in establishing ‘disease burden’, and the rating scale which is developed may also potentially be useful in determination of the disease-modifying effects of treatment (i.e., effect size in outcomes research).

From investigations of the natural history of LOTS, we have identified several domains of assessment: mental status, speech and communication, manual dexterity, muscle strength, gait and coordination. The challenges inherent in development of a disease severity score for a predominantly neurologic phenotype associated with heterogeneity in clinical expression will be discussed. A disease-specific instrument is being developed, to complement generic tools found useful in neurorehabilitation care. A clinician-based assessment of functional ability is proposed, with supplemental information drawn from instrumental measurements. The presentation will focus on two single item-categories (specifically, the assessment and scoring of muscle strength and gait).

Neurodevelopmental Outcomes of Umbilical Cord Blood Transplantation for Infantile Krabbe Disease

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Background: Infantile Krabbe disease produces progressive neurological deterioration and death in early childhood. We hypothesized that unrelated donor umbilical cord blood transplantation before development of symptoms, would favorably alter the natural history of disease among newborns diagnosed because of a family history. We compared the outcomes of these newborns with those of infants who were transplanted after the development of symptoms and with an untreated cohort of affected children.

Methods: 11 asymptomatic newborns (ages 12-44 days) and 14 symptomatic infants with infantile Krabbe disease (ages 142-352 days) were treated with unrelated donor umbilical cord blood transplantation after myeloablative chemotherapy. Engraftment, survival and neurodevelopmental function were evaluated longitudinally for 4 months to 6 years.

Results: The rates of donor cell engraftment and survival were 100 percent in the newborns (median follow-up 3 years) and 43 percent in the symptomatic group (median follow-up 3.4 years). Surviving patients demonstrated durable engraftment of donor-derived hematopoietic cells with restoration of normal blood galactocerebrosidase levels. Infants transplanted before the development of symptoms demonstrated progressive central myelination and continued gains in developmental skills with most having age appropriate cognitive function and receptive language skills, but mild to moderate delays in expressive language and gross motor function. Children transplanted after onset of symptoms experienced minimal neurological improvement.

Conclusions: Unrelated umbilical cord blood transplantation in newborns with infantile Krabbe Disease favorably alters the natural history of the disease. The procedure may extend life in a subset of symptomatic patients but does not result in significant neurological improvement.

Longitudinal Outcomes of Early and Late-Onset Metachromatic Leukodystrophy after Hematopoietic Stem Cell Transplantation

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Metachromatic Leukodystrophy is a lysosomal storage disease that affects the central nervous system and can present during the entire life span. It is caused by the deficiency of the enzyme arylsulfatase A (gene locus 22q13.31). The accumulation of sulfatide leads to progressive demyelination, dementia, and death. The age of onset is generally concordant within families. We examined the natural history of MLD in 42 patients seen at the University of Minnesota by age category and by treatment response.

Early onset MLD (under the age of 6) is characterized by rapid peripheral and somewhat slower central demyelination. Motor symptoms are followed by memory, perceptual and language decline relatively rapidly over several years. While transplant halts the central demyelination, peripheral disease progresses and these children quickly become wheelchair bound. Quality of life outcomes are poor due to severe motor handicap. .

Later onset MLD with onset in childhood, adolescence or adulthood has a behavioral presentation that is consistent with frontal lobe demyelination (also seen on MRI). MRI scores (amount of increased signal) correlate with neuropsychological functions such as memory, visual spatial ability, and ability to do mental calculations. However, the course is slow and insidious, and patients are almost universally thought to have a psychiatric disorder before the diagnosis is made. The mean number of years to from psychiatric to MLD diagnosis is seven years. These subjects have been shown to have symptoms progressing from ADHD to conduct problems to more serious psychiatric disturbances.

HSCT has been shown to halt the progression of disease in later onset MLD. Peripheral disease is less severe than in early onset MLD. Central disease is halted but usually after serious loss of function. Quality of life outcomes are poor due to severe mental handicap. Better outcomes can be had only if the diagnosis can be made early in the course of the disease. It is rare that diagnosis is made early unless it is through a sibling diagnosis. Earlier diagnosis must occur through either improved clinician sensitivity or through early screening.

A pattern of onset of attention and psychiatric symptoms in a previously healthy individual together with deficits in memory, attention, and spatial perception signals the need for a thorough medical investigation in a patient considered to have a psychiatric disorder.

HSCT is an imperfect treatment for MLD. Although enzyme replacement is being worked on, substrate reduction may hold the most promise for alleviating symptoms of this disease.

Challenges in Treating Neuronopathic Gaucher Disease: A Report from the Gaucher Registry

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Gaucher disease, an inherited, autosomal recessive lysosomal storage disorder that encompasses a number of heterogeneous clinical phenotypes, is caused by deficient glucocerebrosidase activity. Consequently, glycolipids accumulate most prominently within the lysosomes of macrophages, particularly those in the spleen, liver, bone marrow, and lung. Systemic manifestations found to a variable degree in most patients with Gaucher disease include anemia, thrombocytopenia, hepatosplenomegaly, and skeletal pathology including chronic bone pain, periodic bone crises, growth retardation, and osteopenia.

Approximately 90% of all patients with Gaucher disease have no clinical evidence of primary central nervous system pathology. These patients, many of whom carry at least one, allegedly “neuro-protective” N370S allele are commonly designated as non-neuronopathic or GD Type 1. However, some do suffer secondary neurological complications from thrombocytopenia-associated CNS bleeding or from vertebral compression fractures. Recently, attention has been directed at a number of apparent type 1 adult patients with relatively early onset of Parkinson’s disease that is resistant to pharmacotherapy. It is unclear to what, if any, extent, the glycolipid storage process contributes to the development of Parkinsonian neuropathology. Based on studies identifying an inordinate number of glucocerebrosidase mutations in post-mortem brain tissue from Parkinson patients and among patients in Parkinson’s disease clinics, it is hypothesized that a significant presence of abnormal glucocerebrosidase protein may itself contribute to a vulnerability to Parkinsonism.

Neuronopathic disease, which occurs with an estimated incidence of 1:200,000 to 1:500,000 in most Western populations, affects about 10% of all patients with Gaucher disease. As in type 1 disease, neuronopathic GD is often clinically heterogeneous within genotypes and even among siblings. Although two forms of neuronopathic disease (types 2 and 3) are classically defined, there may be no clear-cut pathophysiologic delineation between these types, and neuronopathic GD may be more appropriately depicted in terms of a disease spectrum. Therefore, prognostication and treatment decisions should be based on ongoing, methodical, comprehensive systemic and neurological assessments as discussed below rather than by assignment to an arbitrary disease type.

Features typically associated with type 2 (acute neuronopathic) GD include presentation in infants between 4 and 5 months of age, and death usually before 2 years of age. Characteristic clinical features include progressive bulbar involvement with stridor, swallowing difficulty, and squinting. Other findings such as head retroflexion, opisthotonos, spasticity and cognitive impairment may or may not be present.

The clinical manifestations associated with type 3 (sub-acute or chronic neuronopathic) GD are considerably more variable and may present in infancy, childhood, adolescence, or even in early adulthood. Usually, there is a combination of the systemic symptoms of type 1 and some of the neurological presentation of type 2 (oculomotor apraxia due to supranuclear ophthalmoplegia, extrapyramidal syndrome, myoclonic or generalized seizures, cerebellar involvement with ataxia, and intellectual regression, but the latter to a lesser extent). Early development of horizontal supranuclear gaze palsy is a major neurological sign of the illness. In some patients, findings may be initially restricted to subtle eye movement abnormalities, and progressive changes may occur slowly if at all. Some of these patients have been misidentified as having type 1 GD. As awareness of GD has increased world-wide, unique neuronopathic phenotypes have increasingly emerged.

Although there is no cure for GD, enzyme replacement therapy using Ceredase[®] (alglucerase) or Cerezyme[®] (imiglucerase), specific forms of glucocerebrosidase modified for uptake by macrophages halts and/or reverses the non-neurological, systemic manifestations. However, the impact on neurological manifestations is not well investigated and understood. There have been some reports of stabilization of neurological manifestations such as supranuclear gaze palsy and cognitive function after initiation of Cerezyme therapy. Decreased ataxia and decreased seizure activity has been observed by some investigators whereas others have noted no reversal in myoclonic encephalopathy. The general consensus is that the impact of Cerezyme on neuronopathic Gaucher disease is unclear.

The International Collaborative Gaucher Group (ICGG) Gaucher Registry is a large cooperative, observational registry on Gaucher disease, which was established in 1991 as a longitudinal database tracking outcomes of routine clinical practice. More than 4000 patients are currently enrolled, 261 with neuronopathic disease (33 Type 2, 228 Type 3). In my opinion, the current data supports the following conclusions:

- Of 33 children reported to have type 2 disease, 19 have died, 12 despite ERT. Median age at death is 1.2 years (0.2-4.9). For 14 patients (median age=2.5 years), outcome data is currently uncertain. 16 additional Type 2 children on ERT (but not enrolled in the Registry), have also died: Median age of death: 1.9 years (0.8-6.5). The mortality in type 2 Registry patients seems to be no different than that observed in the Pittsburgh Gaucher Registry (Lee RE, personal communication) reporting type 2 patients born 1952-94, none of whom had ERT: 43 dead (median age of death 1.0 year [0-2.8]), 6 status unreported. This data supports the European consensus that “with established acute neuronopathic disease, ERT has had little effect on the progressively downhill course. It has merely resulted in prolongation of pain and suffering.”

- In patients classified as having type 3 disease, ERT completely or partially ameliorates the hematologic, visceral, and bone manifestations associated with GD, and improves quality of life (Pastores G, presented at SSIEM, 2002)

- Of 228 patients reported to have type 3 disease, 21 (9.2%) have died, 19 of whom received ERT. In addition to ERT, one patient had bone marrow transplantation and one had HSCT. Median age at death is 9.8 years (1.5-38.9). The current status of 207 patients is uncertain, but at least one patient was alive at age 53. 15 additional type 3 patients on ERT (not enrolled in the Registry) have also died: Median age at death: 7.5 years (3.2-46.5). In the Pittsburgh Registry, of 25 Type 3 patients, 14 (56%) have died, none of whom had ERT. 18/25 underwent splenectomy. Median age at death: 11 years (1.0-33.0). Current status of 11 patients is uncertain, but no patient is conceivably older than 63 years.

It is therefore possible that ERT in Type 3 GD may confer some survival benefit, but the data is yet inconclusive, as most of the ICGG Registry patients are less than 15 years old. Furthermore, ICGG Registry data indicates that Type 3 patients at any age are at a substantially higher risk of dying than patients with type 1 disease in whom current life expectancy is essentially the same as the normal population.

Until recently, the ICGG Registry was not structured to collect the standardized data necessary to evaluate the extent of neurological impairment in type 3 GD, the longitudinal progress of neurological symptoms, nor the neurological response to treatment. For that

purpose, the Neurological Outcomes Sub-Registry to the ICGG Gaucher Registry was initiated in November 2003. The schedule of baseline and semi-annual assessments includes:

Neurological medical history and developmental milestones

Cranial nerve assessments (extra-ocular eye movements, speech, eating, stridor, head posture.

Motor assessments (presence or absence of myoclonus, fine and gross motor assessments

Seizure evaluation

Electroencephalogram, audiogram, brain stem auditory evoked potentials.

The current status of this Sub-Registry is described below. Follow-up data are very limited at this time,

As of March 2005, 51 patients (mean age 7.9 years) diagnosed with Type 3 Gaucher disease, have been enrolled. The mean age that neurological symptoms were first noted is 3.3 years. A majority of the patients have problems with eye movements (vertical and horizontal gazing). About a third show convergent squint or abnormal slow object tracking, while a minority show other abnormalities such as chewing and swallowing difficulties. Only 10-20% of the patients were reported to have motor abnormalities, such as myoclonus, weakness, spasticity, wide-based gait, and requiring assistance with walking, which in most cases started after the age of 10 years. Only 5 patients had experienced one or more different types of seizures on a daily or weekly basis.

Neurological tests were performed in only a few patients enrolled in the Gaucher Registry. Six of the 9 (66.7%) patients tested had abnormal electroencephalograms (EEGs) at a mean age of 9 years. Audiograms showed sensorineural and mixed abnormalities in both ears in 3 of the 4 (75.0%) patients tested at a mean age of 8.2 years.

All but two of the enrolled patients are receiving Cerezyme; the mean time between diagnosis and first infusion was about 3 years. Treatment started at a mean age of 6.4 years and, thus far, the patients have been treated for a period of 0.2 to 14 years.

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