ABSTRACT BOOK

4th Scientific Symposium on Niemann-Pick Type C: The Expanding Universe of NP-C
The European Accreditation Committee in CNS has designated this satellite symposium for a maximum of X CME credits. Those interested in obtaining these CME credits will be required to fill in a special on-line feedback rating form on the EACIC website: www.eacic.eu
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We are pleased to welcome you to the 4th Scientific Symposium on Niemann-Pick Type C (NP-C): The Expanding Universe of NP-C. During this conference, leading experts will present new research and clinical progress in this exciting field which spans paediatrics, biochemical genetics, neurology and psychiatry.

Interest in NP-C continues to grow year-on-year, with new discoveries advancing our knowledge of the disease and its pathophysiology. These in turn have led to improved understanding of NP-C, which has allowed us to better define at-risk patient groups, as well as providing new opportunities for earlier and more accurate diagnosis in both the clinic and laboratory. As a consequence, more patients are being diagnosed in adult phases of the disease, screening tools have been developed, new biomarkers are being prepared for clinical application, and the potential role of NP-C genotype in other diseases is starting to be investigated.

We encourage you to get involved in all aspects of the meeting and look forward to an exciting and stimulating conference here in Athens.

Marc Patterson (Rochester, MN, USA)  
Mark Walterfang (Melbourne, Australia)
**Faculty**

**Larry Abel**  
Department of Optometry & Vision Sciences, University of Melbourne, Melbourne, Australia

Dr. Larry Abel is a Senior Lecturer at the University of Melbourne since 2004 and leads the Eye Movement Laboratory. In 1976, he received his PhD in electrical engineering and bioengineering from the Carnegie Mellon University in Pittsburgh, USA. After completion of a 2-year post-doctoral training, he was Associate Professor at three different universities from 1986 to 2004. In 2010 he was awarded the Silver Fellowship from the Association for Research in Vision and Ophthalmology. Some of the research areas of the Eye Movement Laboratory include eye movements in neurodegenerative diseases, ageing and cognition.

**Generoso Andria**  
Department of Paediatrics, Federico II University, Naples, Italy

Prof. Generoso Andria is Director of the Department of Paediatrics and Head of the Unit for Paediatric Genetic and Metabolic Disease at the Federico II University of Naples, Italy. He has coordinated several research projects on genetic disorders, including a European Consortium on Lysosomal Storage Disease (EUCLYD) and an Italian multicentre clinical trial with miglustat in patients with Niemann-Pick type C. His main research interests are in the fields of inborn errors of metabolism, genetic syndromes and rare diseases.

**Mathieu Anheim**  
Department of Genetics, Pitié Salpêtrière Hospital, Paris, and Referral Centre of Neurogenetic Diseases, Paris, France

Dr. Mathieu Anheim, a trained neurologist, is a practitioner in the Department of Genetics at the Pitié Salpêtrière Hospital and at the Referral Centre of Neurogenetic Diseases in Paris. Dr. Anheim is member of the Movement Disorders Society, of several national networks (including “Genetics of Parkinson’s Disease” and “Fragile X Syndrome and Fragile X Ataxia Tremor Syndrome”), and of the international network SPATAX (ataxia and spastic paraplegia). In addition, he is involved in several hospital programmes for clinical research (spinocerebellar degeneration, Parkinson’s disease) and clinical trials (Friedreich’s disease, ataxia with oculomotor apraxia type 1, Parkinson’s disease).
Peter Bauer  
Department of Medical Genetics, University of Tübingen, Tübingen, Germany

Dr Peter Bauer graduated in medicine in 1997. He completed his thesis in cardiology at the Charité Berlin and the German Heart Institute, Berlin, and started his clinical career in 1997 in the Department of Neurology, University of Rostock, Germany. In 2001, Dr Bauer moved to Tübingen, Germany, where he became a research scientist in the Department of Medical Genetics. After receiving his board certification in human genetics, he became Assistant Medical Director and Head of Molecular Genetics in 2007. His research interests are in the genetics of neurodegenerative diseases.

Bruno Bembi  
Regional Co-ordination Centre for Rare Disorders of the Friuli-Venezia Giulia Region, 
University Hospital Santa Maria della Misericordia, Udine, Italy

Dr Bruno Bembi is Director of the Regional Co-ordination Centre for Rare Disorders of the Friuli-Venezia Giulia Region at the University Hospital Santa Maria della Misericordia, Udine, Italy. He is the regional representative at the State-Regions Permanent Technical Conference on Rare Diseases and at the Inter-Regional Network Group for Rare Diseases in North-Eastern Italy. Dr Bembi is involved in several multicentre trials and is responsible for research projects aimed at finding therapeutic approaches for treatment of lysosomal disorders.

Olivier Bonnot  
Child and Adolescent Department and Reference Centre for Rare Disease with Psychiatric Expression, 
Groupe Hospitalier Pitié Salpêtrière, Paris, France

Dr Olivier Bonnot works as child and adolescent psychiatrist at the Groupe Hospitalier Pitié Salpêtrière in Paris. He is Co-Head of the National Reference Centre for Rare Diseases Associated with Psychiatric Symptoms. His major fields of interest are early-onset schizophrenia and learning disorders. Within this area, Dr Bonnot actively researches psychopharmacology and its tolerance and efficiency in the paediatric population. He also leads research in organic psychoses, in particular those that develop from inborn errors of metabolism or auto-immune diseases, and in the cognitive processes underlying time perception and developmental dyspraxia.
**Alessandro Burlina**  
Neurological Unit, San Bassiano Hospital, Bassano del Grappa, Italy

Dr Alessandro Burlina is Director of the Neurological Unit at the San Bassiano Hospital, Bassano del Grappa, and Adult Neurologist Consultant at the Inherited Metabolic Disease Unit of the University Hospital of Padua, Italy. Since 1995, he has held positions at the Centre for Neurochemistry (Nathan S. Kline Institute for Psychiatric Research, New York University), the Department of Neurology (Yale University School of Medicine) and the Department of Biophysical Chemistry (Biocentre of the University of Basel). He is interested in the clinical and neurochemical aspects of leukodystrophies, lysosomal disorders and inherited neurometabolic diseases in adulthood. He has published many peer-reviewed publications and book chapters on inherited metabolic diseases.

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**Chris Hendriksz**  
Clinical Inherited Metabolic Disorders, Birmingham Children’s Hospital NHS Foundation Trust, Birmingham, UK

Dr Chris Hendriksz is Director for Lysosomal Storage Disorders (LSD) at the Birmingham Children’s Hospital, UK. Dr Hendriksz moved to Birmingham in 2004 to join the expanding metabolic service at the Birmingham Children’s Hospital. In 2007, he established the LSD Service at the hospital, as a nationally designated centre for these metabolic disorders. Since then, he has been involved in the daily management of patients with inborn errors of metabolism with a specific interest in LSD. Dr Hendriksz is actively involved in multiple research projects, mainly focusing on LSD.

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**Bénédicte Héron**  
Department of Paediatric Neurology, Trousseau Hospital, Paris, and Jean Verdier Hospital, Bondy (Seine-Saint-Denis), France

Dr Bénédicte Héron is a medical expert at the Referral Centre for Lysosomal Diseases. She is member of several associations including the French Society of Paediatric Neurology, the French Society of Inborn Errors of Metabolism, and the Scientific and Medical Council of the Association “Overcoming Lysosomal diseases”. In addition, she is member of the Evaluation Committee for the treatment of Lysosomal Diseases and Niemann-Pick Disease, and President of the Evaluation Committee for the treatment of mucopolysaccharidoses. Dr Héron is member of the French Scientific Committee Niemann-Pick type C (Actelion).
Ya Hui Hung
Oxidation Biology Laboratory, Mental Health Research Institute, University of Melbourne, Melbourne, Australia

Dr Ya Hui Hung is a senior scientist at the Oxidation Biology Laboratory, Department of Neuroscience in Mental Health, University of Melbourne, Australia. She completed her PhD studies on copper metabolism at the University of Melbourne. Her interest in Niemann-Pick type C (NP-C) disease evolved from her investigations of the interplay between copper and cholesterol metabolism in the development of neurodegeneration and Alzheimer’s disease. Her current research focuses on understanding the role of NPC1 in metal metabolism and metal-targeting therapeutic approaches for the treatment of NP-C.

Hans-Hermann Klünemann
Department of Psychiatry, University of Regensburg School of Medicine, Regensburg, Germany

Dr Hans Klünemann is Director of the Memory Disorders Clinic at the University of Regensburg School of Medicine, Regensburg, Germany. He studied medicine at the Medical School in Freiburg, Germany, and at the Albert Einstein College of Medicine, New York, USA. Dr Klünemann performed his Neurology Residency at the University of Vermont, USA, where he was promoted to Chief Resident and awarded a Clinical Neurophysiology Fellowship. He is actively involved in research in neurological diseases, including Niemann-Pick type C disease, and has authored numerous publications in this field.

Charles M. Lourenço
Neurogenetics Unit, Medical Genetics Division, University of Sao Paulo, Ribeirão Preto, Brazil

Dr Charles M. Lourenço is a consultant physician in neurometabolics at the Neurogenetics Clinic of the Hospital of Ribeirão Preto, Brazil. Member of the Lysosomal Unit at the Hospital of Ribeirao Preto, Dr Lourenço is in charge of the infusion centre and takes care of patients with lysosomal storage disorders. Dr Lourenço’s interests include the clinical and molecular aspects of leukodystrophies, hereditary spastic parapareses, hereditary spinocerebellar ataxias, lysosomal disorders of the brain (neurolipidoses) and inborn errors of metabolism with adult presentation. Dr Lourenço is currently pursuing a PhD in neurogenetics, with emphasis on spinocerebellar ataxias of early onset.
Dr Eugen Mengel studied medicine at the Phillips-University, Marburg and the Goethe-University, Frankfurt. He later trained in paediatrics at the Children’s Hospital, University of Mainz, as well as in paediatric metabolic medicine and haematology. In 1994, he researched Niemann-Pick and Gaucher diseases with Dr Michael Beck. Since 2001, Dr Mengel has been a consultant in paediatric inborn errors of metabolism. He has been a principal investigator in international clinical trials concerning Niemann-Pick, Pompe and Gaucher diseases; and has participated in trials of enzyme replacement therapy for Fabry disease, Pompe disease and mucopolysaccharidoses I, II and VI.

Dr Daniel Ory graduated from Harvard College and Harvard Medical School, before training at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology, USA. Dr Ory joined the faculty at Washington University in 1995 and began studying cholesterol biology and Niemann-Pick type C (NP-C) disease. He is now Director of the Washington University Metabolomics Facility and has served as Chair of the Scientific Advisory Board of the National Niemann-Pick Disease Foundation in the USA. Dr Ory currently leads SOAR-NPC, an international collaborative group aiming at identifying biomarkers and develop new therapies for NP-C.

Dr Alasdair Parker trained in paediatric neurology in London. He is now a consultant paediatric neurologist at Addenbrooke’s Hospital, Cambridge, UK, where he leads the Paediatric Neurology Service. He has recently developed movement disorder and neuromuscular services within his team, and continues to have a great interest in the efficient investigation of children presenting with neurological disorders, with particular reference to metabolic conditions. He holds an associate lectureship at the University of Cambridge and is interested in training undergraduates and junior doctors within the field of paediatric neurology. Dr Parker’s main research interests include the identification of genetic disorders and intractable epilepsies.
Marc Patterson  
Mayo Clinic Neurology, Paediatric and Adolescent Medicine, Rochester, MN, USA

Prof. Marc Patterson is currently Professor of Neurology, Paediatrics and Medical Genetics, Chair of the Division of Child and Adolescent Neurology and Director of the Child Neurology Training Program at Mayo Clinic, USA. He was trained in Neurology in Australia and moved to the US in 1988 to complete further training at the Mayo Graduate School of Medicine and the National Institutes of Health. He was Professor and Director of Paediatric Neurology at Columbia University, New York from 2001 to 2007. His research focuses on neurometabolic disorders, with special interests in lysosomal diseases and congenital disorders of glycosylation, areas in which he has published and spoken widely.

Mercedes Pineda  
Department of Neuropaediatrics, Hospital Sant Joan de Déu and University of Barcelona, Barcelona, Spain

Prof. Mercé Pineda is a Medical Associate at the Department of Neuropaediatrics at Sant Joan de Déu Hospital and Professor of Paediatrics in the Department of Paediatrics at the University of Barcelona. Prof. Pineda received her medical education at the University of Barcelona and has worked as a practicing physician ever since. She has studied lysosomal storage and other metabolic diseases, in particular Niemann-Pick type C disease and Gaucher disease. She is interested in the elucidation of neuropathological mechanisms of metabolic disorders and in their specific genotype–phenotype associations.

Frances Platt  
Department of Pharmacology, University of Oxford, Oxford, UK

Prof. Frances Platt obtained her PhD from the University of Bath, UK, and was a post-doctoral fellow at Washington University Medical School in St. Louis, USA. She was a Lister Institute Senior Research Fellow and a Reader at the University of Oxford. Prof. Platt’s main research interests include the biology and pathobiology of glycosphingolipids. Her research facilitated development of miglustat for the treatment of glycosphingolipid storage diseases. In 1999, Prof. Platt was awarded the Alan Gordon Memorial Award and the Horst Bickel Award for advances in metabolic disease therapy. Recently she was awarded a fellowship in The Academy of Medical Sciences.
Dr Frédéric Sedel is a neurologist working at the Pitié-Salpêtrière Hospital. After completing his PhD at the Ecole Normale Supérieure in Paris, he studied Inborn Errors of Metabolism (IEM) with Prof. Saudubray at the Necker Children’s Hospital, Paris. Dr Sedel now co-ordinates the Neurometabolic Department dedicated to treating adults with IEM. His main interests include diagnosis of late onset neurological forms of IEM and identification of new neurometabolic diseases in adults. Dr Sedel is part of the Reference Centre for Lysosomal Diseases, is Vice President of the French Society for IEM, and co-ordinates the SSIEM Adult Metabolic Group.

Frédéric Sedel  
Neurometabolic Department, Pitié-Salpêtrière Hospital, Paris, France

Dr Anja Schneider heads the Memory Clinic at the University Medicine in Göttingen and coordinates the Clinical Science Platform of the German Center for Neurodegenerative Disorders (DZNE) in Göttingen. She studied medicine and received her doctoral degree on the pathomechanisms of tau phosphorylation in Alzheimer’s disease, in Germany. During her postdoctoral training at the Max-Planck Institute for Experimental Medicine in Göttingen she focused on the cell biology of amyloid beta generation in Alzheimer’s disease. She was the principal investigator of numerous international trials in Alzheimer’s disease. Her research interests are the pathological function of exosomes/microvesicles in neurodegenerative dementia including their potential use as disease biomarkers.

Anja Schneider  
Memory Clinic, Department of Psychiatry, University Medicine Göttingen, Germany and Clinical Science Platform, German Center for Neurodegenerative Disorders, DZNE Göttingen, Germany

Dr Heiko Runz is a Group Leader and Faculty Member of the Molecular Medicine Partnership Unit and Group Leader of the Institute of Human Genetics in Heidelberg. He is a candidate for a tenured professorship in Human Molecular Genetics at the University of Heidelberg. His fields of interest include the cell biology of cholesterol metabolism and associated diseases; functional analysis of lysosomal storage disorders by advanced light-microscopy technology; and the identification of modifier genes for monogenetic lipid metabolic disorders.

Heiko Runz  
Medical Faculty of the University of Heidelberg, Heidelberg, Germany
Marie T. Vanier  
National Institute of Health and Medical Research (INSERM), and Hôpitaux de Lyon, Lyon, France

Dr Marie Vanier received her university degrees and medical training in Lyon, France, and Gothenburg, Sweden. Alongside her position as Director of Research at INSERM, Dr Vanier was, until 2009, the Head of a University Hospital laboratory offering diagnostic services for neurolipidoses. Her work on Niemann-Pick type C (NP-C) disease has contributed to the delineation and description of NP-C2, a better understanding of glycosphingolipid storage, and recognition of less common clinical forms. Dr Vanier has also made important contributions to the development of current laboratory diagnostic tests and the establishment of genotype–phenotype correlations.

Mark Walterfang  
Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, Australia

Dr Mark Walterfang completed specialist training in psychiatry in 2000 and is a consultant neuropsychiatrist and Research Fellow at the Royal Melbourne Hospital, Australia. Since joining the Royal Melbourne Hospital, he has developed an interest in the neuropsychiatry of Niemann-Pick type C disease, which frequently presents with psychiatric disorders. He is an author of over 50 journal publications and book chapters in neuropsychiatry, and recently contributed a chapter to the best-selling textbook, Kaplan and Sadock’s Comprehensive Psychiatry. Dr Walterfang is completing his PhD on magnetic resonance imaging of white matter changes in psychiatric disorders.

Frits Wijburg  
Department for Inborn Errors of Metabolism, Academic Medical Centre, Amsterdam, Netherlands

Frits Wijburg is Professor of Metabolic Diseases and Head of the Department for Inborn Errors of Metabolism (IEM) at the Academic Medical Centre, Amsterdam. He studied medicine at the University of Amsterdam and is certified in paediatrics, paediatric gastroenterology and paediatric IEM. Prof. Wijburg’s department has long-standing experience in the diagnosis, management and therapy of patients with IEM. His research interests include the timing and efficacy of treatment in lysosomal storage disorders. Author of numerous papers on IEM, Prof. Wijburg is a key member of many local, national, and international societies and groups for IEM.
An introduction to NP-C

Frances Platt
Department of Pharmacology, University of Oxford,
Oxford, UK

Niemann-Pick type C (NP-C) disease is an autosomal recessive, neurodegenerative lysosomal storage disorder. The clinical features can include hepatosplenomegaly in infants, eye movement abnormalities, dysphagia, dysarthria, ataxia and cognitive decline leading to dementia. NP-C can present at any age, although paediatric presentation is most common. It occurs at an estimated frequency of 1:120,000 live births but is probably under-diagnosed, particularly in adults.

There are many unusual features of NP-C disease, not least of which is that it can be caused by mutations in either of two genes \( \text{NPC1} \) or \( \text{NPC2} \). Mutations in the \( \text{NPC1} \) gene are the most common and account for approximately 95% of cases. The disease is indistinguishable both clinically and in terms of cell biology irrespective of which gene is defective, suggesting that the NPC1 and NPC2 proteins cooperate in a common cell biological pathway. The cellular pathology of NP-C is also complex. This involves the storage of multiple classes of lipids and a block in the late endosome/lysosome fusion. Both NPC1 and NPC2 can bind cholesterol but their interplay remains poorly understood.

In this presentation, a brief history of the disease will be presented along with the current understandings of NPC1 and NPC2 functions. The therapeutic implications of the complex pathogenic cascade in NP-C disease will also be discussed.
**Niemann-Pick type C disease**

- Caused by mutations in NPC1 (95% cases) or NPC2 genes
- Storage of cholesterol, multiple GSLs, sphingosine and SM
- Defective late endosome/lysosome fusion unique to NP-C
- If the block in the endocytic pathway could be overcome, the disease would be treatable
- Clinical manifestations include progressive neurodegeneration, cerebellar atrophy, ataxia, dementia, neuroinflammation, premature death

**NPC1 protein**

- 12 transmembrane helices
- Protein localized outer late endosome/lysosome membrane
- Contains a sterol sensing domain homologous to similar regions in SCAP, HMG-CoA reductase and Pahched
- NPC1 protein has highest homology to RND permeases and bacterial transporters

**NPC2 protein**

- NPC2 (HE1) is a soluble lysosomal cholesterol binding protein
- M6P targeted (BMT an option)
- Relationship with NPC1?
- Mutations in NPC1 or NPC2 genes result in the same cellular and clinical phenotypes

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**Notes:**

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Updates from the NP-C registry and Spanish cohorts

Mercedes Pineda
Department of Neuropaediatrics, Hospital Sant Joan de Déu and University of Barcelona, Barcelona, Spain

Updates from the NP-C registry

As of 19 August 2011, the International Registry for NP-C disease included 121 patients (median [range] age 16.9 [0.9–56.6] years), the median (range) age at onset of neurological manifestations was 8.2 (0–48.0) years, and the median (range) age at diagnosis was 11.8 (0.1–53.9) years. Eighty-eight patients (73%) received miglustat at enrolment. Mean (SD) exposure among 86 patients with available data was 1.69 (1.85) years.

Neonatal jaundice was observed in 4/4 (100%) patients with early-infantile disease onset (<1 to <2 years of age), 6/21 (29%) with late-infantile onset (2 to <6 years), 6/21 (29%) with juvenile onset (6 to <15 years), and 3/20 (15%) with adolescent/adult onset (≥15 years).

Frequency and type of symptoms in NP-C patients are reported in the table.

Patients’ disability status was assessed based on a disability scale evaluating language, manipulation, ambulation and swallowing, which were impaired in 94/110 (85%), 88/109 (81%), 87/110 (89%), 87/110 (89%), 72/110 (65%) patients, respectively. The median (range) composite disability scores (0=normal; 1=worst) were: 0.0 (0.0–0.94) in early infantile-onset (n=7), 0.29 (0.0–1.0) in late infantile-onset (n=28), 0.41 (0.15–0.88) in juvenile-onset (n=28), and 0.29 (0.06–0.81) in adolescent/adult-onset patients (n=26).

These data are in line with previous findings indicating different clinical manifestations according to age at onset of neurological disease.

Updates from the Spanish cohorts

There is consensus that, currently, stabilisation of neurological disease is the best attainable therapeutic goal in patients with NP-C presenting with neurological manifestations that reflect underlying and irreversible neuronal damage.

We started miglustat treatment in 2004, applying a protocol to evaluate clinical follow-up. Currently, 22 out of the 33 patients with NP-C are being treated with miglustat. Earlier age at diagnosis influenced response to treatment and clinical benefit. Furthermore, slowing of disease progression was equally seen in early, more advanced, infantile forms of NP-C.

Diagnosis must be established as early as possible, and treatment started as soon as neurological symptoms appear to prevent further irreversible damages. We should question the benefit of treating patients at the end stage of the disease.
NP-C registry: Symptoms at enrolment

Systemic symptoms: Patient's n (%)
- History of nevus flammeus 297/87 (32)
- History of nevus flammeus by age at neurological onset
  - Early-onset onset 4/4 (100)
  - Late-onset onset 19/1 (98)
  - Juvenile onset 19/1 (98)
  - Adolescent/adult onset 3/0/6 (100)
  - Hypertelorism and/or synophthalmia during infancy 48/80 (60)

Neurological manifestations:
- Ataxia 22/34 (63)
- Vertical gaze palsy 27/84 (69)
- Dysarthria 32/84 (62)
- Cognitive impairment 26/84 (62)
- Dysphagia 38/84 (45)
- Ophthalmoplegia 38/84 (45)
- Epilepsy 22/84 (26)
- Cerebellar 22/84 (26)

Psychiatric manifestations:
- Depression 26/87 (30)

* Patients could have >1 neurological manifestation. ** Cases present either at or before enrolment. || Psychiatric manifestations were more frequent in patients with a blinks-onset neuro-oncology vs. n = number of cases; n = number of patients with available data.

Spanish cohort: Chronology of neurological symptoms

- 2–4 years
  - Cerebellar ataxia and dysmetria
  - Brain stem disease
  - Dysarthria
- 1–2 years
  - Vertical ophthalmoplegia
  - Complete ophthalmoplegia
- 2–4 years
  - Dysphagia
  - Nasogastric feeding / gastric button
- 2–4 years
  - DEATH

Spanish cohort: Modified disability scale

1. Ambulation
   - Cerebral palsy
   - Autonomic ataxic gait
   - Outdoor assisted ambulation
   - Indoor assisted ambulation
   - Non-ambulation
   - Scores
2. Sensation
   - Visual deficits
   - Hearing deficits
   - Scores
3. Speech
   - Able to communicate
   - Scores
4. Swallowing
   - Swallowing difficulties
   - Scores
5. Motor
   - Lower limb spasticity
   - Scores

Disability Score

- Late infantile patients
- Juvenile patients

Notes:

Ferriero N et al. Mol Genet Metab. 2015;99:258–66
The French paediatric cohort

Bénédicte Héron
Department of Paediatric Neurology, Trousseau Hospital, Paris, and Jean Verdier Hospital, Bondy (Seine-Saint-Denis), France

Niemann-Pick type C (NP-C) disease is a neurovisceral lysosomal lipid storage disease characterised by progressive neurological deterioration. Different clinical forms have been described based on age at onset of neurological manifestations.1, 2 We compiled data on all paediatric NP-C patients treated with miglustat in France between October 2006 and December 2010. Pre-treatment and follow-up assessments were conducted according to a standardised protocol including disease-specific disability scale scores3 and brain imaging analyses.

Twenty children, 19 with NPC1 and one with NPC2 gene mutations, were included. Among NPC1 patients, eight were classified in the early-infantile onset group, eight in the late-infantile and three in the juvenile onset group. A history of hepatomegaly, splenomegaly and/or neonatal cholestasis was recorded in all early-infantile onset patients and in only 4/11 late-infantile and juvenile patients. The median (range) duration of miglustat therapy was 16 (8–27) months in early-infantile and 1 (0.6–5.0) year in late-infantile and juvenile onset patients. NP-C disability scale scores indicated stabilisation or improvement of neurological manifestations in 1/8 early-infantile patient and in 7/11 late-infantile and juvenile onset patients. Magnetic resonance imaging (MRI) indicated white matter abnormalities in most NPC1 patients in all subgroups. There were no apparent correlations between MR spectroscopy findings and clinical disease course.4 Most adverse events were mild or moderate in severity, except in three cases where persistent gastrointestinal adverse events led to discontinuation of miglustat therapy.

Miglustat can stabilise or improve neurological disease manifestations in paediatric patients with NP-C, particularly in those with the late-infantile or juvenile-onset forms. More clinical experience in early-infantile onset patients treated at the very beginning of their neurological disease is required to assess the therapeutic effects of miglustat in this group.

References
1. Vanier MT et al. Orphanet J Rare Dis. 2010;5:16
Key age milestones of the French NPC1 paediatric patients

Disease evolution during miglustat therapy in early infantile-onset patients

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<th>Patient</th>
<th>Age at onset of neurological manifestations</th>
<th>Age at start of miglustat therapy</th>
<th>Age at last visit on miglustat</th>
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<tr>
<td>1</td>
<td>6 months</td>
<td>9 months</td>
<td>2 years 3/12</td>
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<td>2</td>
<td>6 months</td>
<td>2 years 2/12</td>
<td>3 years 7/12</td>
<td>Worsened</td>
</tr>
<tr>
<td>3</td>
<td>7 months</td>
<td>2 years 3/12</td>
<td>4 years 7/12</td>
<td>Worsened</td>
</tr>
<tr>
<td>4</td>
<td>9 months</td>
<td>20 months</td>
<td>2 years 9/12</td>
<td>Worsened</td>
</tr>
<tr>
<td>5</td>
<td>9 months</td>
<td>3 years 7/12</td>
<td>5 years 1/12</td>
<td>Stabilised</td>
</tr>
<tr>
<td>6</td>
<td>10 months</td>
<td>2 years 2/12</td>
<td>3 years 2/12</td>
<td>Worsened</td>
</tr>
<tr>
<td>7</td>
<td>12 months</td>
<td>2 years</td>
<td>3 years</td>
<td>Worsened</td>
</tr>
<tr>
<td>8</td>
<td>12 months</td>
<td>2 years</td>
<td>2 years 9/12</td>
<td>Worsened</td>
</tr>
</tbody>
</table>

There is limited experience with the use of miglustat in patients with Niemann-Pick type C disease under the age of 4 years.

Conclusions

- Miglustat improved or stabilised neurological disease in 64% of the late-infantile and juvenile-onset patients.
- There is limited experience with the use of miglustat in patients with NP-C under the age of 4 years. No apparent correlations were found between MRS findings and clinical disease course during miglustat therapy.
- Miglustat is not indicated for the treatment of visceral disease in NP-C.
- When diagnosis of NP-C is established on neonatal choristosis or visceromegaly, a strict follow-up is mandatory to detect early neurological troubles and allow early miglustat treatment.

Notes:

- Miglustat was administered to patients in the early and late infantile stages.
- Improved or stabilised disease outcomes were recorded in a significant percentage of patients.
- Further studies are necessary to determine the optimal treatment duration and dosage of miglustat.

There is limited experience with the use of miglustat in patients with Niemann-Pick type C disease under the age of 4 years.
Monitoring the benefits of miglustat on the swallowing function in children with NP-C

Generoso Andria
Department of Paediatrics, Federico II University, Naples, Italy

Niemann-Pick type C (NP-C) disease is a rare autosomal recessive lysosomal storage disorder characterised by a wide spectrum of manifestations with progressive visceral and neurological involvement, including dysphagia. Swallowing impairment is a frequent cause of morbidity and disability in patients with NP-C, and progressive dysphagia may be considered a marker of neurological progression.

Substrate reduction therapy with miglustat has been approved for the treatment of NP-C. We report the results of an observational study on the long-term use of miglustat in four pediatric patients with NP-C, as well as its long-term effect after 3 years. We used a videofluoroscopic analysis of liquid barium swallowing to provide additional information on patterns of impairment of the swallowing mechanism and to detect aspiration. In three patients showing dysphagia and aspiration, miglustat treatment led to an improvement of the swallowing function and the sustained absence of barium aspiration in the airways. The patient with normal swallowing function at baseline did not show any deterioration upon miglustat treatment.

Based on these findings, we suggest that the videofluoroscopic study of swallowing should be routinely used to monitor the effects of treatment on swallowing ability in patients with NP-C.
Videofluoroscopic swallowing study in 4 paediatric NP-C patients

- Progressive dysphagia may be considered a marker of neurological progression in NP-C patients.
- The videofluoroscopic swallowing study (VFSS) is the gold standard test for determining the nature and the extent of swallowing disorders.
- It provides a dynamic view of all stages of swallowing (oral preparatory, oral, pharyngeal, and upper oesophageal phases).
- An observational study was performed on long-term use of miglustat in four paediatric patients with NP-C to show the benefits of the treatment on dysphagia.

Evolution of swallowing function

<table>
<thead>
<tr>
<th>Patients</th>
<th>NP-C Disability Score at baseline</th>
<th>MONTHS OF TREATMENT WITH MIGLUSTAT</th>
<th>NP-C disability Score at last swallowing evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>3 6 9 12 18 24 30 36 48</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>3 6 9 12 18 24 30 36 48</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>3 6 9 12 18 24 30 36 48</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>3 6 9 12 18 24 30 36 48</td>
<td>6</td>
</tr>
</tbody>
</table>

NP-C Disability score is the sum of rating scores for aspiration, naso-sinus, oral and swallowing function. See reference for details.

Biochemical and molecular analysis, demographics and phenotype classification

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical classification</td>
<td>Classical</td>
<td>Classical</td>
<td>Classical</td>
<td>Not performed*</td>
</tr>
<tr>
<td>Molecular analysis</td>
<td>NPC1</td>
<td>HE1</td>
<td>NPC2</td>
<td>p.E200X/E200X</td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td>Juvenile</td>
<td>Juvenile</td>
<td>Late infantile</td>
<td>Severe infantile</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>11</td>
<td>9</td>
<td>11.25</td>
<td>11.06</td>
</tr>
<tr>
<td>Age at start of treatment with miglustat (yrs)</td>
<td>12</td>
<td>9.6</td>
<td>9.6</td>
<td>9</td>
</tr>
</tbody>
</table>

* In an older affected brother the biopsy staining was compatible with a variant form of NPC.

Notes:

- Videofluoroscopic swallowing study (VFSS) is a gold standard test for determining the nature and the extent of swallowing disorders.
- Progression of dysphagia may indicate neurological progression in NP-C patients.
- Miglustat has shown benefits in reducing dysphagia over time in paediatric patients with NP-C.
- The evolution of swallowing function can be monitored using the NP-C Disability score.
- Biochemical and molecular analysis, including NPC1 and HE1 gene analysis, can provide insights into the phenotype.
- Demographics such as age and gender can influence the presentation and treatment approach in NP-C.

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Long-term effects of miglustat: A meta-analysis

Mark Walterfang
Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, Australia

Treatment to modify illnesses is not available for the majority of neurodegenerative disorders. In addition to slowing progression, increasing quality of life and delaying loss of function, illness-modifying treatment may also improve long-term outcome. Data from neurodegenerative disorders in which dysphagia is prevalent suggest that dysphagia drives aspiration, resultant pneumonia and death, and that improving dysphagia can affect mortality. Bronchopneumonia is the most frequent cause of death in Niemann-Pick type C (NP-C) disease, and dysphagia is known to be highly prevalent in NP-C. We examined indirect evidence that miglustat may affect life span. Data from patients with NP-C suggest that miglustat improves swallowing function. Survival evaluation, controlled for the confounding effects of age, in patients with NP-C treated with miglustat suggests that miglustat affects life span, most likely through improving swallowing function.

References
Cause of death in NP-C

- Data collected from 62 patients across 7 studies
- Respiratory failure or bronchopneumonia are the most frequently reported causes of death
- Unclear what proportion results from aspiration pneumonia

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Country</th>
<th>Study Design</th>
<th>n</th>
<th>Number of deaths</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burak et al. (2019)</td>
<td>Germany</td>
<td>Case Study</td>
<td>2</td>
<td>2</td>
<td>Respiratory failure (2)</td>
</tr>
<tr>
<td>Harris et al. (2018)</td>
<td>Canada</td>
<td>Case Study</td>
<td>2</td>
<td>2</td>
<td>Failure (1)</td>
</tr>
<tr>
<td>Jeantet et al. (2018)</td>
<td>France</td>
<td>Case Study</td>
<td>20</td>
<td>2</td>
<td>50% (10) aged 20-76 yrs, 50% (10) aged &gt;76 yrs</td>
</tr>
<tr>
<td>Knaus et al. (2015)</td>
<td>Germany</td>
<td>Case Study</td>
<td>1</td>
<td>1</td>
<td>Stroke and dysphagia leading to death</td>
</tr>
<tr>
<td>Kelly et al. (2015)</td>
<td>Unpublished</td>
<td></td>
<td>40</td>
<td>8</td>
<td>Major causes of death were bronchopneumonia or airway infections (n=6)</td>
</tr>
<tr>
<td>London et al. (2008)</td>
<td>Unpublished</td>
<td></td>
<td>1</td>
<td>1</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Sene et al. (2005)</td>
<td>France</td>
<td>Case Study</td>
<td>13</td>
<td>5</td>
<td>Esophageal (1), bronchopneumonia (1), hemorrhage (1) no cause specified (2)</td>
</tr>
</tbody>
</table>

Impact of dysphagia on mortality in NP-C

- Exploratory study with 94 patients from the UK known to NP-C clinical nurse specialists
  - n=36 had neurological symptoms at birth
  - n=58 after birth
- More patients with swallowing problems had died at follow-up (p=0.0001)

<table>
<thead>
<tr>
<th>Swallowing problem</th>
<th>Proportion of deceased patients (%)</th>
<th>Problem (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No swallowing problem</td>
<td>31 (33.3)</td>
<td>22 (23.0)</td>
</tr>
<tr>
<td>Swallowing problem</td>
<td>37 (29.4)</td>
<td>62 (32.0)</td>
</tr>
</tbody>
</table>

Aspiration pneumonia in other neurological disorders

- 53 out of 623 articles in March 2011
- Overall, 27.7% of patients with neurodegenerative disorders have dysphagia
- Highest rates in NP-C and HD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent with Dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>27.7%</td>
</tr>
<tr>
<td>NM-C</td>
<td>36%</td>
</tr>
<tr>
<td>ALS</td>
<td>34%</td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>33%</td>
</tr>
<tr>
<td>MS</td>
<td>26%</td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td>31%</td>
</tr>
<tr>
<td>Mixed population</td>
<td>31%</td>
</tr>
</tbody>
</table>

Notes:

- Please provide additional context or details here.

Modifying dysphagia in NP-C: OGT918-007

- Various interventions and therapies aimed at improving dysphagia in NP-C patients.
- Results indicate significant improvements in swallowing and quality of life for patients who received modified care plans.
NP-C treatment guidelines update

Marc Patterson
Mayo Clinic Neurology, Paediatric and Adolescent Medicine, Rochester, MN, USA

Niemann-Pick disease type C (NP-C) is a lysosomal storage disease caused by mutations in one of two genes, NPC1 and NPC2, leading to accumulation of cholesterol and glycosphingolipids in late endosomes and lysosomes causing progressive neurodegeneration and premature death. Increasing awareness of the disease has resulted in a growing research literature, meriting re-evaluation of the diagnosis and management guidelines published by the NP-C Guidelines Working Group in 2009.

The new guidelines represent the consensus of the Group, derived from the best available published data in late 2011. We note that manifestations of cerebellar and brainstem dysfunction are frequent at all ages; visceral disease is of most clinical relevance in early life, whereas cortical findings—psychiatric symptoms and dementia—often present in adolescence and adulthood. The insidious progression of this disease makes early diagnosis difficult; a clinical suspicion index has been developed to aid the clinician in identifying cases of NP-C. We emphasise the complementary roles and limitations of filipin staining of cultured fibroblasts and gene sequencing in making the diagnosis. We also discuss the potential of oxysterol measurement to simplify and accelerate the diagnosis of NP-C. We emphasise the importance of early diagnosis for genetic counseling and intervention. Symptomatic therapies should be implemented, and may provide substantial benefit in reduced morbidity, and perhaps even in mortality. The use of miglustat in managing the neurologic manifestations of NP-C is also discussed.
NPC treatment guidelines update

- NP-C Guidelines Working Group – 2011
- Diagnosis and management
- Literature review and expert consensus

Clinical

- Presentations across the lifespan
- Visceral manifestations dominates in infancy
- Progressive neurodegeneration after infancy
- Cerebellar, brainstem and basal ganglia findings: childhood
- Cortical manifestations: adolescents and adults
- NP-C Suspicion Index

Diagnosis

- Specific
  - Endosomal/lysosomal cholesterol accumulation: filipin staining
  - NPC1 and NPC2 sequencing
  - Oxysterol assays
- Non-specific

Notes:
Parallel Case-Study Workshops

Clinical cases in the paediatric setting

**Charles M. Lourenço**  
Neurogenetics Unit, Medical Genetics Division, University of Sao Paulo, Ribeirão Preto, Brazil

Presentation of Niemann-Pick type C (NP-C) disease in early life is usually non-specific and may be overlooked. Foetal ascites, early hypotonia, delayed milestones with visceromegaly and severe neonatal liver disease with jaundice can be presenting features in the newborn and toddlers. In older children, NP-C may present with neurological signs and symptoms with only minimal visceral disease. In this workshop, delegates will have the opportunity to review case studies from paediatric patients with NP-C. Cases will focus on the more common presentations, differential diagnosis and approaches towards diagnosis.

**Frits Wijburg**  
Department for Inborn Errors of Metabolism, Academic Medical Centre, Amsterdam, Netherlands

Clinical cases in the adult setting

**Alessandro Burlina**  
Neurological Unit, San Bassiano Hospital, Bassano del Grappa, Italy

Early diagnosis of Niemann-Pick type C (NP-C) disease is crucial for the effective management of the disease. The clinical picture of the disease is complex and the accurate detection of clinical signs is essential. This workshop will focus on clinical aspects related to the diagnosis and treatment of adult patients with NP-C. The workshop is designed to discuss, with the delegates, the diagnostic signs and symptoms that should raise suspicion of the disease. The presentation of clinical cases will help delegates identify the “red flag” symptomatology associated with NP-C.

**Hans-Hermann Klünemann**  
Department of Psychiatry, University of Regensburg School of Medicine, Regensburg, Germany

Identifying atypical symptoms in psychosis

**Mark Walterfang**  
Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, Australia

This workshop aims to provide psychiatrists and other physicians with skills in recognising when the symptoms of a psychotic presentation may be atypical, thus potentially indicating a secondary or organic psychosis. Using filmed interviews and a problem-based learning format, the workshop utilises clinical and case material with the aim of highlighting both typical and atypical features of psychosis, and methodology for assessing organicity in psychotic patients.
Metabolic disorders: Paediatric focus

Alasdair Parker
Child Development Centre, Addenbrooke’s Hospital, Cambridge, UK

The investigation of developmental and psychiatric disorders in childhood has become more complex in the last decade. With the advent of genetic, biochemical and neuroimaging techniques, the clinician is given many different opportunities to investigate children. However, are all these needed? If so, are the results easily interpreted? What are the false-positive/negative rates?
In parallel, there has been an explosion in the identification of neurodegenerative diseases, their testing and treatments. Every country and health care system is now faced with challenges on when and how to investigate these children, and the clinician is anxious not to miss a treatable diagnosis. In this workshop we will review the evidence on when and how children should be investigated for metabolic disorders, using video footage of normal/abnormal examination. The workshop will help the clinician gain confidence in an evidence-based approach. There will not be a “one size fits all”, instead strategies that allow the development of protocols and investigation that is appropriate to the participant’s country/region and speciality will be identified.

Metabolic disorders: Neurological aspects of NP-C in the context of treatable inborn error of metabolism

Frédéric Sedel
Neurometabolic Department, Pitié-Salpêtrière Hospital, Paris, France

Inborn errors of metabolism (IEMs) represent a subgroup of genetic disorders characterised by dysfunction of an enzyme or other proteins involved in cellular metabolism. With around 350 different diseases identified to date, IEMs represent about one third of genetic diseases. The first clinical symptoms usually manifest in infancy or childhood, but in a proportion of cases they appear in adolescence or adulthood, usually with neurological or psychiatric disorders. Many IEMs are amenable to specific therapeutic strategies. In all cases, treatments are more efficient if given at early stages, before the occurrence of irreversible neurological lesions. Focusing on treatable diseases constitutes a necessary and pragmatic approach to the complex field of metabolic diseases. This workshop is aimed at presenting clinical approaches to treatable IEMs in adult neurology. Neurological signs of Niemann Pick type C disease will be discussed in this context.

Notes:
Psychiatric symptoms in NP-C

Olivier Bonnot

Child and Adolescent Department and Reference Centre for Rare Disease with Psychiatric Expression, Groupe Hospitalier Pitié Salpêtrière, Paris, France

Searching for organic conditions, including inborn errors of metabolism (IEMs), in every patient with psychiatric symptoms is part of the healthcare programme in France. Given the prevalence of schizophrenia, occurring in around 1% of the general population, searching for organic schizophrenia is an important concern in psychiatry as various disorders may be associated with it.

The range of IEMs with involvement of psychiatric disturbances will be introduced, with particular emphasis on those where disease-specific treatment is available, including Niemann-Pick type C (NP-C) disease. A review of the literature on psychiatric symptoms (mainly schizophrenia-like) in NP-C will be provided. A simple diagnostic algorithm helping psychiatrists and caregivers in this field will also be presented. The key objectives are to: (i) know when schizophrenic symptoms may be atypical and draw attention to organic disease and NP-C; and, (ii) learn which physical and neurological signs may trigger the suspicion of specific IEMs, including NP-C.

The incidence of IEMs is underestimated, and patients showing early psychotic signs and intellectual regression may be a population at risk. NP-C, like other IEMs, is a rare disease with interesting features: (i) many patients can present with schizophrenia-like symptoms; (ii) treatment is more efficient when started at onset of neurological manifestations; and, (iii) most psychiatrists have no specific knowledge about NP-C or IEMs.

Looking for atypical signs of psychosis or minor physical signs may be extremely useful in such rare cases of treatable disease and may lead to diagnosis and early treatment.
Schizophrenic disorders associated with NP-C

- Rare but increasingly recognised
- Few case reports
- In all cases, there was a long delay before diagnosis

Main association between schizophrenia and organic conditions

Atypical features

**First order**
1. Visual hallucinations
2. Mental confusion
3. Catatonia
4. Fluctuating symptoms
5. Progressive cognitive decline
6. Unusual treatment response

**Second order**

Considered atypical if associated with first order features

- A. Acute or early onset
- B. Treatment ineffectiveness
- C. Intellectual disability
Saccadic eye movement disorders in NP-C

Larry Abel
Department of Optometry & Vision Sciences, University of Melbourne,
Melbourne, Australia

Niemann-Pick type C (NP-C) disease can present with a wide range of symptoms, but one of the most consistent is vertical gaze palsy, which is particularly marked in downgaze. However, horizontal saccades are also affected, and a parameter based on their asymptotic peak velocity has been used as one of the outcome measures in the miglustat clinical trial for NP-C treatment. The presence of NP-C pathology outside the brainstem, which also affected cortical structures, prompted us to assess a wider range of saccadic measures in nine adult patients with NP-C. In addition to peak velocity, reflexive saccade gain was often impaired in these patients, while latency varied between abnormally short to prolonged. The antisaccade task, dependent upon prefrontal cortex for suppression of unwanted reflexive saccades, was not adequately performed by any of the patients, whereas self-paced saccades, a frontally-mediated measure of the ability to initiate a volitional saccade, were normal in some patients whilst deficient in others. Correlations between illness severity and years of neurological symptoms, as well as with a range of magnetic resonance imaging (MRI)-based brain volumetric measures, were significant for most of the ocular motor parameters. Assessment of a wider range of saccadic eye movement measures may provide additional ways to evaluate the progression of NP-C disease and the effects of treatment.
The present study

- Horizontal saccades were assessed, and the range of parameters examined was extended to draw upon both brainstem and cortical mechanisms
  - Reflective saccade latency
  - Reflective saccade gain
  - Asymptotic peak velocity (\( V_{\text{max}} \))
  - Slope of peak duration vs amplitude plot (alpha)
  - Auto-saccade % error rate
  - Self-paced saccade count per 30 sec

- Eye movements recorded with infrared limbus tracker, digitised at 1kHz and analysed interactively offline with Matlab. Results compared to those from a group of 10 age-matched normal controls

### Patients:
P1: 32 y/o female
P2: 30 y/o male
P3: 18 y/o male
P4: 23 y/o male
P5: 31 y/o male
P6: 33 y/o female
P7: 43 y/o male
P8: 49 y/o male
P9: 34 y/o female

### Similar correlations were seen with years of neurological illness

- Self-paced saccade count per 30 sec

- Correlations were also seen between MRI-based measures of brain structures and ocular motor measures

### Notes:

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How to differentiate NP-C from other autosomal recessive cerebellar ataxia

Mathieu Anheim

Department of Genetics, Pitié Salpêtrière Hospital, Paris, and Referral Centre of Neurogenetic Diseases, Paris, France

Niemann-Pick type C (NP-C) disease belongs to the large group of autosomal recessive cerebellar ataxias (ARCAs). Therefore, algorithms for the aetiological diagnosis of ARCAs may be helpful in clinical practice.

They may include:

- Assessment of the natural history of the disease, including age at onset and progression of the disease
  - Heterogeneous from neonatal onset with rapid fatal progression to adult onset variant in NP-C
  - Precocious and severe in ataxia telangiectasia (AT)
  - Precocious and slowly progressive in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and ARCA2
  - Late-onset with slow progression in ARCA1

- Clinical delineation, including oculomotor examination, to detect
  - Supranuclear ophthalmoplegia in NP-C
  - Square waves-jerks in Friedreich’s ataxia (FRDA)
  - Oculocephalic dissociation in AT and ataxia with oculomotor apraxia type 1 (AOA1) and 2 (AOA2)

- Movement disorders
  - Chorea-dystonia in AT, AOA1, AOA2 and NP-C
  - Head tremor in ataxia with vitamin E deficiency (AVED) and NP-C
  - Myoclonus in sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO), ARCA2 and NP-C

Furthermore, ARCAs may be divided into three groups:
1. Cerebellar ataxia with pure sensory neuropathy, including FRDA, AVED and SANDO
2. Cerebellar ataxia with sensorimotor axonal neuropathy, including AT, AOA1, AOA2, ARSACS and cerebrotendinous xanthomatosis (CTX)
3. Cerebellar ataxia without neuropathy, including NP-C, ARCA1, ARCA2, ARCA3 and Wilson’s disease (WD)

Electroneuromyography can therefore help with the classification and aetiological diagnosis of ARCAs. Similarly, brain magnetic resonance imaging provides essential information on the presence (AT, AOA1, AOA2, ARCA1, ARCA2, ARSACS) or absence (FRDA, AVED, abetalipoproteinemia (ABL)) of clear cerebellar atrophy. Patients with NP-C may present with cortical atrophy and/or cerebellar atrophy. The most frequent ARCAs, especially FRDA, and treatable ARCAs, such as FRDA, AVED, ABL, CTX, WD, RD and NP-C should not be overlooked during diagnosis.
Autosomal recessive cerebellar ataxias

- Rare, heterogeneous and complex
- Inherited neurodegenerative disorders
- Involvement of cerebellum and/or
  - Posterior column of the spinal cord
  - Peripheral nerves
- Dominated by cerebellar signs and other neurological and/or extra-neurological signs
- Onset mostly before the age of 30
- Major disability after 10 years of disease progression

### Severity of disease progression

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Cerebellar Syndrome</td>
<td>SYNE1</td>
<td>SYNE1</td>
</tr>
<tr>
<td>ARCA1</td>
<td>ABCK3</td>
<td>ABCK3</td>
</tr>
<tr>
<td>ARCA2</td>
<td>ABCK3</td>
<td>ABCK3</td>
</tr>
<tr>
<td>ARCA3</td>
<td>ABCK2</td>
<td>ABCK2</td>
</tr>
<tr>
<td>NPC1</td>
<td>NPC1</td>
<td>NPC1</td>
</tr>
<tr>
<td>NPC2</td>
<td>NPC1</td>
<td>NPC1</td>
</tr>
<tr>
<td>NPC1/NPC2</td>
<td>NPC1</td>
<td>NPC1</td>
</tr>
<tr>
<td>Cerebellar syndrome with sensory neuropathy</td>
<td>FXN</td>
<td>Ftx</td>
</tr>
<tr>
<td>SANDO</td>
<td>POLG</td>
<td>POLG</td>
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<tr>
<td>SANDO</td>
<td>Twinkle</td>
<td>Twinkle</td>
</tr>
<tr>
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<td>ATP7</td>
<td>ATP7</td>
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ARCA: autosomal recessive ataxia (pure cerebellar syndrome), ARSACS: autosomal recessive spastic ataxia of Charlevoix-Smirnoff, VLANCA: very late-onset Friedreich ataxia.
NP-C symptoms: Understanding their pathophysiological basis

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Niemann-Pick type C (NP-C) disease is a proteiform disorder. Although visceral signs of the disease can be present from birth, neurological signs appear months to decades after. Some neurological signs, such as vertical supranuclear gaze palsy and gelastic cataplexy, are highly suggestive of NP-C. Others, including movement disorders, cerebellar ataxia, progressive dementia, epilepsy, hearing loss and atypical psychosis, are far less specific. Experiments using conditional mutant mice have clearly shown that impaired NPC1 or NPC2 arising in neurons, but not in astrocytes, is the determining factor in the development of NP-C neuropathology. Therefore, white matter changes that have been observed through imaging or spectroscopic studies are most likely secondary to primary neuronal and axonal damage. Biochemically, intracellular storage of GM2 and GM3 gangliosides is conspicuous in Purkinje cells, large pyramidal neurons, and neurons in the lateral thalamus, hippocampus and brainstem. In humans, the formation of neurofibrillary tangles in the basal ganglia, brainstem, cerebral cortex and hippocampus (particularly CA1 and CA2), may also contribute to neurodegeneration. Post-mortem studies and animal models, as well as imaging studies, have demonstrated a typical spatial and temporal pattern of neuronal degeneration that accounts for specific neurological signs. The characteristic vertical supranuclear ophthalmoplegia and cataplexy are reflected in early midbrain and diencephalic lesions. Ataxia is caused by the specific vulnerability of cerebellar Purkinje cells. Dystonia and other movement disorders relate to striatal changes. The significant verbal working memory deficits are consistent with the strong bilateral reduction in hippocampal volume.
The NP-C suspicion index: Further studies

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Department for Inborn Errors of Metabolism, Academic Medical Centre, Amsterdam, Netherlands

A Suspicion Index (SI) was developed to identify suspected patients with Niemann-Pick type C (NP-C) disease by ranking symptoms in visceral, neurological and psychiatric domains. To further examine the discriminatory power of the SI, the same retrospective patient data were re-analysed by age using logistic regression and by leading symptoms using descriptive statistics.

NP-C positive cases, suspected NP-C cases and non-cases were split into three age groups: <4 years (y); 4 to 16y; and >16y. When NP-C positives are compared to controls, i.e. suspected and non-cases combined, the discriminatory power of prediction score remains very strong for the two older groups (>4y). With these patients (>4y), the total and neurological symptoms prediction scores were excellent with AUC=0.97 and 0.93, respectively, and the visceral and psychiatric symptoms prediction scores were considered good with AUC=0.76 and 0.78, respectively. This is likely to be a consequence of the greater reliability in identifying neurological and psychiatric symptoms in older patients due to the progressive nature of NP C.

In patients >4y, the following leading symptoms were identified: vertical supranuclear gaze palsy, ataxia, dysarthria/dysphagia and cognitive decline. Ataxia was frequently seen with dystonia, dysarthria/dysphagia and cognitive decline. There was a close link between psychotic symptoms and dysarthria, and psychotic symptoms mostly co-occurred with cognitive decline and treatment-resistant psychiatric symptoms. Cognitive decline increased with disease severity. Overall, a high consistency of similar clinical picture was found across all patient sub-types.

Having a better understanding of the co-occurrence of symptoms in different domains based on leading symptoms can facilitate identifying patients with NP-C. The SI tool is not suitable for infants (<4y), but has a strong discriminatory power above age of 4y.

References
Paediatric screening studies for Niemann-Pick type C

Chris Hendriksz
Clinical Inherited Metabolic Disorders, Birmingham Children’s Hospital NHS Foundation Trust, Birmingham, UK

Rare, lysosomal storage disorders can present as neonatal cholestasis, acute liver failure, foetal hydrops, intrauterine growth restriction (IUGR), foetal ascites or isolated splenomegaly. Antenatal ultrasound imaging can detect foetal ascites, IUGR and hepatosplenomegaly. The true incidence of persistent familial intrahepatic cholestasis, Niemann-Pick type C (NP-C) disease and citrin deficiency is unknown, owing to its rarity and the cost of genetic testing. Accurate and timely diagnosis is essential for making clinical decisions, as some of these conditions have specific treatments and surveillance programmes.

The use of resequencing arrays permits analysis of multiple genes at the same time at reduced cost and with a potential turnaround time of just 5 working days, and with new 2nd generation technologies now decreasing in price genetic testing may become the first-line diagnostic investigation in the not too distant future.

To enhance current understanding of NP-C and identify disease-specific features, a microarray screening project in high-risk children has started in December 2011 as a prospective, multi-national study. The first 300 children identified under the age of 2 years with either of the following inclusion criteria have been included in the study: conjugated hyperbilirubinaemia defined as conjugated fraction >30% (conjugated bilirubin >20 μM/L or >1.2 mg/dL); or unexplained neonatal liver failure (prothrombin time of twice the upper limit of normal for age in a neonate under the age of 30 days at presentation); and, isolated splenomegaly or hepatosplenomegaly on physical examination or ultrasound scan. The first provisional interim data of this study will be presented with specific focus on NP-C.

New technologies such as resequencing arrays have the potential to dramatically increase the diagnostic yield for rare disorders and all healthcare professionals should be aware that specialist centres are developing these technologies.

Further reading
Kelly DA et al. J Pediatr. 1993;123;242–47
Vanier MT. Orphanet J Rare Dis. 2010;5;16
Neonatal screening studies

- Neonatal presentation of NP-C is diverse
- Overlap with many common conditions
- Diagnosis can be challenging
- Incidence of NP-C is 1/120,000
- NP-C affects about 8% of patients with neonatal cholestasis
- 10% of all patients with NP-C present with acute liver failure
- Incomplete data on many patients

Notes:


Neonatal presentation

- Neonatal cholestasis
- Acute liver failure
- Isolated splenomegaly
- Neonatal respiratory disease
- Thrombocytopenia
- Intrauterine growth restriction (IUGR)
- Foetal hydrops or ascites

Gene chip study in Birmingham

- Prospective multi-national study
- Included the first 300 eligible infants identified since study start from UK, Canada, Brazil, France, Germany, Australia, Greece
- Run BRUM Resequencing array chip, oysterols (where possible) and simple data collection
- Supported by direct sequencing and other 2nd generation molecular technologies
- Provisional data from this study will be presented
Adult screening: Lessons from the ZOOM study

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Late-onset cases courses of Niemann-Pick type C (NP-C) disease are being recognised with increasing frequency. The clinical diagnosis may be difficult to establish because symptoms do not necessarily resemble the classical infantile or juvenile picture. Psychiatric manifestations are prevalent, both as presenting symptoms and in the context of complex neuropsychiatric phenotypes. Therefore, the ZOOM study included primarily patients with such disturbances (psychosis, early-onset dementia) and symptoms of neurodegeneration (such as dystonia or ataxia) or visceral symptoms.

This screening study was designed to address the frequency and phenotypes of NP-C in adults with neurological and psychiatric signs. The diagnosis was established by genetic sequencing (NPC1 and NPC2 genes) and filipin staining when available. Plasma oxysterol levels are also being investigated as potential biomarkers of NP-C disease.

A total of 267 patients were enrolled in 47 centres, and NPC1 and NPC2 sequencing was completed. Filipin staining and oxysterol testing are in progress. Preliminary results highlight two key observations: two patients had known causal mutations in both NPC1 alleles thus establishing a genetic diagnosis. Another 15 patients displayed only one mutant NPC allele, giving a carrier frequency ~5%, more than 5-times higher than in the general population. This enrichment could point towards either a lack of sensitivity for NPC mutation detection in non-coding parts of either gene, or a possible phenotypic effect of heterozygous NPC mutations in our study population.

The combination of genetic analyses, oxysterol measurements, filipin staining (when available) and the clinical picture will ultimately improve understanding of the frequency of adult patients with NP-C showing neuropsychiatric signs.
Notes:
NP-C genetics and genomics

Heiko Runz
Medical Faculty of the University of Heidelberg, Heidelberg, Germany

The clinical manifestation and course of Niemann-Pick type C (NP-C) disease may vary considerably. Although most patients present with visceral signs and a rapidly fatal neurodegenerative course during childhood, some patients succumb to hepatic failure as neonates. In addition, NP-C is increasingly being diagnosed in juveniles and adults with psychiatric symptoms and/or a slowly progressive neurological decline. Several hundred rare NPC1 and NPC2 gene sequence variants have been identified in patients with NP-C (see NPC-db: http://npc.fzk.de), suggesting that the phenotypic variation of NP-C is, at least in part, attributable to genetics. For instance, the position of a variant within particular functional domains of the NPC1 protein has been shown to correlate with disease symptoms and clinical course. Moreover, most patients with NP-C show compound-heterozygosity for two different NPC1 mutations that are likely to differentially impair protein function and thus disease severity. However, as most NPC1 variants occur only in single families, functional evidence for the relevance of novel DNA-sequence variants on the disease phenotype is typically missing. Furthermore, in a considerable fraction of patients, current diagnostic strategies fail to secure or exclude NP-C with certainty. Here I will discuss latest strategies to better assess genetic variation in NP-C and to determine the relevance of genetic findings on cellular and clinical NP-C phenotypes.
NP-C genetics and genomics

NP-C1  Niemann-Pick C1 protein  18q11-q12  ~90% of cases

NP-C2  Epithelial secretary protein E1  14q24.3  ~5% of cases

Notes:

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Niemann-Pick type C (NP-C) disease: A tauopathy

Ashley Ian Bush and Ya Hui Hung
Oxidation Biology Laboratory, Mental Health Research Institute, University of Melbourne, Melbourne, Australia

Tauopathy describes a group of neurodegenerative disorders, including Alzheimer’s disease (AD) and frontotemporal dementia, with a brain pathological signature of neurofibrillary tangles (NFTs) composed of abnormally hyperphosphorylated tau protein aggregates. Post-mortem analysis of human Niemann-Pick type C (NP-C) disease brains revealed AD-like NFTs localised predominantly in the hippocampus, hypothalamus and brainstem. A positive correlation between NFTs and free cholesterol levels in AD and NP-C neurons suggests that cholesterol may influence NFT formation. Cholesterol metabolism can be affected by genetic variations and environmental factors.

Emerging evidence suggests that metals, in particular, copper, iron and zinc, have a multifactorial impact on NFT formation via modulation of expression, hyperphosphorylation and aggregation of tau. Consistent with these reports, we recently found a significant increase in zinc levels in post-mortem NP-C cerebellum, which may contribute to tau hyperphosphorylation and generation of NFTs. Similarly to patients with AD, there is a significant increase in the total levels of tau in the cerebrospinal fluid (CSF) of patients with juvenile-onset NP-C, but unlike patients with AD, no increases in the levels of pTau (T181) are observed. The longitudinal observation of a pair of identical twin patients with NP-C treated with miglustat plus cyclodextrin over 29 months revealed a decrease in the CSF tau, copper and zinc level, and an increase in the iron level, as compared to baseline values. We are exploring potential interactions between tau and metals that are influenced by changes in brain cholesterol and/or glycosphingolipids. Future investigations focusing on unravelling this relationship may allow identification of new therapeutic targets for NP-C and other tauopathies.

References
Experimental treatments for Niemann-Pick type C disease

Frances Platt
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The cell biology of Niemann-Pick type C disease (NP-C) is multi-faceted, involving defects in both lipid (cholesterol and sphingolipids) and acidic-store calcium homeostasis. The identity of the offending metabolite(s) in NP-C remains the subject of debate, as does the function of the pathway in which the NPC1 and NPC2 proteins operate. However, despite our incomplete knowledge of the disease pathway, advances in our understanding of NP-C disease have been made over the past few years. These advances have led to the proposal of new treatment strategies for NP-C. Indeed, the complexity of this disease offers an unprecedented number of potential clinical intervention points that can potentially be targeted with small molecules.

Several of these new treatment strategies have been tested using tissue culture and animal model systems, with some progressing to clinical studies in patients. These treatments utilise small molecule drugs that target unique steps in the pathogenic cascade. There is also considerable evidence indicating a role for combination therapy in NP-C disease, including combinations that utilise miglustat.* The idea of combination treatment is to use multiple drugs that target different steps in the pathogenic cascade to maximise clinical benefit. An additive or synergistic benefit may be predicted, and this has been shown in several animal model studies to date.# The current status of experimental treatments for NP-C disease will be presented and their proposed mechanisms of action discussed.

*Miglustat is not approved for combination therapy. #No data available in humans.
Pathogenic cascade in NP-C disease cells

- NPC1 mutation/ inactivation
- Increased Sphingosine
- Depleted Lub/lys Ca^{2+}
- Detergent endocytic transport
- Simultaneous storage of cholesterol and GSLs
- Neurodegeneration

Inflammation in CNS in LSDs, including NP-C, is a potential therapeutic target

Microglial activation in degenerating NPC1 mouse cerebellum: A useful readout in therapeutic trials in animal models

Red, Purkinje cells
Green, activated microglia

Notes:
Oxysterols biomarkers for NP-C type 1 disease

Daniel S. Ory
Diabetic Cardiovascular Disease Center, Washington University, St. Louis, USA

Recent efforts in the Niemann-Pick type C (NP-C) disease field have been directed towards identification of disease-specific biomarkers, using biochemical, proteomic and mass spectrometry-based assays. Our studies have focused on the possibility that non-enzymatic formation of cholesterol oxidation products (i.e. oxysterols), as a result of increased oxidative stress and cholesterol accumulation, could serve as disease biomarkers.

Metabolomic analyses of plasma samples from patients with mutated NPC1 led to the discovery that oxysterol species are markedly elevated in nearly all human patients with NP-C type 1 disease. It also delineates an oxysterol profile specific for this disease, and correlates with both the age of disease onset and disease severity.

A simple, non-invasive, biochemical assay has been developed that has a sensitivity and specificity of >97% and 100%, respectively, for diagnosis of NP-C type 1 disease. This has been adapted for high-throughput quantification of the oxysterol markers in clinical samples. This assay, which has many advantages over the filipin staining protocol, is being implemented in the USA, Europe and Brazil. On-going studies are examining the performance of the assay in populations enriched for NPC1 patients. The oxysterol biomarkers are also being employed as outcome measures in an upcoming clinical trial.
Barriers to the development of effective treatment for NP-C disease

- Biology of the NPC1 protein and neurodegenerative phenotype
- Rare disease status
- Difficulty in diagnosis of NP-C disease
- Lack of outcome measures to evaluate efficacy in clinical trials

Biomarker discovery for NP-C disease

- Biomarker discovery performed in conjunction with NP-C Observational Study at the National Institutes of Health
- Recent efforts to identify disease-specific markers using biochemical and mass spectrometry-based approaches
  - Lysosomal morphometry
  - Plasma and CSF proteomics
  - Plasma lipidomics
  - Plasma and CSF sterols

Oxysterols as biomarkers for NP-C disease

- Circulating oxysterols are highly sensitive and specific biomarkers for NP-C type 1 disease
- Developed a clinical assay that provides a more rapid and sensitive method for NP-C diagnosis
- Oxysterols may be useful to follow disease progression or efficacy of therapy
- Potential for translation of oxysterol assay to newborn screening

Notes:
Exosomal cholesterol as a potential biomarker for NP-C

Anja Schneider

Memory Clinic, Department of Psychiatry, University Medicine Göttingen, Germany and Clinical Science Platform, German Center for Neurodegenerative Disorders, DZNE Göttingen, Germany

Niemann-Pick type C (NP-C) disease is an autosomal recessive disorder, characterised by cholesterol accumulation in late endosomes. The diagnosis, especially of adults, is difficult because of the variable and unspecific neurological symptoms and because hepatosplenomegaly is often absent in adult patients. Therefore, NP-C diagnosis is often missed or delayed by years in children and adults.\(^1,2\)

Here, we propose a novel, non-invasive and fast urine screening test for NP-C that is based on recent findings that exosome secretion, especially exosomal cholesterol, is up-regulated in NP-C cell models, including patient fibroblasts.

Exosomes are small vesicles that are secreted by a variety of cell types. They are generated by inward budding of the late endosomal membrane giving rise to intraluminal vesicles (ILVs). After accumulation of ILVs, these compartments are termed multivesicular bodies (MVBs). MVBs can either be routed to lysosomes for degradation or fuse with the plasma membrane to discharge their intraluminal vesicles as exosomes in the extracellular space. As exosomes can be enriched in cholesterol, we investigated whether exosomes contribute to the regulation of cellular cholesterol homeostasis by exosomal egress of cholesterol from the cell.

In different cell types, we showed increased exosomal cholesterol secretion in cells challenged with cholesterol or U18666A, a drug leading to cholesterol accumulation in late endosomes. Up-regulation of exosomal cholesterol release was also observed after knock-down of NPC1 and was rescued by transfection of wild-type NPC but not by transfection of the NPC1 mutant. In summary, we found, in cell culture assays, including fibroblasts derived from patients with NP-C, that the cholesterol trafficking defect in NP-C is partially bypassed by up regulation of exosomal cholesterol release.\(^3\)

We developed an assay to quantify exosomal cholesterol levels in urine and will present preliminary data on NP-C patients.

References
1. Sevin M et al. Brain 2007;130:120–33
Biogenesis of exosomes

Quantification of exosome release

Exosomal cholesterol release as a bypass mechanism in NP-C

Notes:
Next generation sequencing for treatable neurodegenerative metabolic disorders

Frits Wijburg
Department for Inborn Errors of Metabolism, Academic Medical Centre, Amsterdam, Netherlands

Early diagnosis is important in metabolic diseases with progressive neurological symptoms for which disease-modifying treatment is available, since preventing neurological damage is the best case scenario for treatment. However, diagnosis of rare, genetic, neurodegenerative diseases, such as Niemann-Pick type C (NP-C) disease, is often significantly delayed due to non-specific and varying presentation as well as low awareness among physicians. When diseases are rare to such a degree that most specialists are unlikely to come across these diseases during their professional career, it becomes unrealistic to require in depth knowledge of the symptoms and diagnostics involved. As patients most often initially present in non-specialist clinics, a diagnostic tool that would help non-specialists to exclude relevant genetic neurodegenerative disorders without full awareness of many or most of them could significantly improve early diagnosis and thereby prognosis of these conditions.

We developed a sequence capture array, capturing 62 genes for 52 treatable different metabolic disorders, all characterised by progressive neurological disease, or delay in mental or motor skills plus other signs and symptoms. Capture of all 62 genes is followed by full exome sequencing on the Roche 454 pyrosequencing platform. Data analysis will allow for identification of pathogenic and novel missense mutations. Algorithms for subsequent metabolic studies are being designed to confirm the metabolic consequences of the detected genetic changes.

This whole exome sequencing screening strategy for a subset of 52 treatable neurodegenerative metabolic disorders should facilitate easy and early diagnostics therefore allowing timely initiation of treatment.
Rationale

- Early diagnosis and treatment of metabolic diseases with progressive neurological symptoms may prevent neurological damages
- However, awareness of symptoms and diagnosis of rare genetic diseases, such as NP-C, is difficult to achieve among specialists and general practitioners
- Developing a gene chip for the 52 treatable metabolic disorders with progressive neurological decline should improve diagnosis and treatment of these diseases

Pathogenic cascade in NP-C disease cells

APCCT mutation / inactivation

Sphingosine

Depleted Lys/Cytosolic Ca²⁺

Defective endocytic transport

Simultaneous storage of cholesterol and GSLs

Neurodegeneration


Notes:
Zavesca® (miglustat)

Abbreviated Prescribing Information (PI). For further prescribing information, please refer to the Zavesca Summary of Product Characteristics (SmPC).

Presentation
Miglustat 50 mg hard capsules. Four blister strips with 21 capsules per strip and 84 capsules per pack. MHL Number: BU 000218/001.

Indications / Use
The oral treatment of mild to moderate type 1 Gaucher disease for adult patients in whom enzyme replacement therapy is unsatisfactory.

Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.

Dosage and Administration
Therapy should be conducted under the supervision of a physician. Zavesca can be taken with or without food.

Dosage in type 1 Gaucher disease
The recommended starting dose is 100 mg three times a day. Temporary dose adjustments for some patients because of diarrhoea (see interaction with the use of Zavesca in patients with type 1 Gaucher disease under the age of 18). The use of Zavesca is therefore not recommended in children or adolescents with type 1 Gaucher disease. There is no experience of the use of Zavesca in patients over the age of 70.

Dosage in Niemann-Pick type C disease
The recommended dose for the treatment of adult and adolescent patients with Niemann-Pick type C disease is 200 mg three times a day. Dosing in patients under the age of 12 should be adjusted on the basis of body surface area. Temporary dose reduction may be necessary in some patients because of diarrhoea. The benefit of the patient to the treatment with Zavesca should be evaluated on a regular basis (see Warnings and Precautions). There is limited experience with the use of Zavesca in Niemann-Pick type C disease patients under the age of 4 years.

Contraindications
Hypersensitivity to miglustat or any of the excipients.

Warnings and Precautions
Serious consideration of Zavesca has not been specifically evaluated in patients with severe type 1 Gaucher disease.

In clinical trials, approximately 37% of patients with type 1 Gaucher disease, and 56% of patients with Niemann-Pick type C disease reported tremor on treatment. Dose reduction may ameliorate the tremor but cessation of treatment may be required. Patients with cronic diarrhoea or other persistent gastrointestinal disorders that do not respond to individualised diet modification, to taking Zavesca between meals and/or anti-diarrhoeal medicinal products such as loperamide, should be investigated according to clinical practice.

Zavesca has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.

Zavesca should not be used during pregnancy or during breastfeeding.

Most patients should maintain reliable contraception methods while taking Zavesca. Before seeking to conceive, male patients should use condoms and women should be advised to continue contraception for at least 1 month.

Hepatic impairment
Zavesca has not been evaluated in patients with hepatic impairment.

Renal impairment
Due to limited experience Zavesca should be used with caution in patients with renal impairment. Use in patients with severe renal disease is not recommended.

Type 1 Gaucher disease
Regular monitoring of vitamin B12 level is recommended because of the high prevalence of vitamin B12 deficiency in patients with type 1 Gaucher disease. Cases of peripheral neuropathy have been reported in patients treated with Zavesca with or without concurrent conditions such as vitamins B12 deficiency and oxidative anaemia. Peripheral neuropathy seems to be more common in patients with type 1 Gaucher disease compared to the general population. All patients should undergo biannual and repeated neural evaluation.

In patients with type 1 Gaucher disease, monitoring of platelet counts is recommended. Mild reductions in platelet counts without association with bleeding were observed in patients with type 1 Gaucher disease who were switched from Enzyme Replacement Therapy (ERT) to Zavesca.

Niemann-Pick type C disease
The benefit of treatment with Zavesca for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g., every 6 months. Continuation of therapy should be re-appraised after at least 1 year of treatment with Zavesca.

Reduced growth has been reported in some paediatric patients with Niemann-Pick type C disease. Growth should be monitored in paediatric and adolescent patients during treatment with Zavesca. If the benefit-risk balance should be re-assessed on an individual basis for continuation of therapy.

Mild reductions in platelet counts without association with bleeding were observed in some patients with Niemann-Pick type C disease treated with Zavesca. In patients included in a clinical trial, 40%–50% of patients had platelet counts below the lower limit of normal at baseline. Monitoring of platelet counts is recommended in these patients.

Interactions
When Zavesca is combined with Cerezyme, limited data suggest reduced exposure to miglustat (14% reduction in AUC) and limited or no effects on Cerezyme.

When Zavesca is combined with Cerezyme, limited data suggest decreased exposure to miglustat (14% reduction in AUC) and limited or no effects on Cerezyme.

Interactions
When Zavesca is combined with Cerezyme, limited data suggest decreased exposure to miglustat (14% reduction in AUC) and limited or no effects on Cerezyme.

Overdosage
Patients suffering from dizziness should not drive or operate machinery.

Zavesca has been used in studies where certain events reported as adverse drug reactions, such as neurological and neuropsychological symptoms/signs, cognitive dysfunction and thrombocytopenia, could also be due to the underlying condition.

Adverse reactions reported in post-marketing use were not different from those reported in clinical trials.

Effects on Availability to Drive and Use Machines
Patients suffering from dizziness should not drive or operate machinery.

Niemann-Pick type C disease
The benefit of treatment with Zavesca has been evaluated in adult patients with Niemann-Pick type C disease in a 12-month non-comparative study. In 22 patients who had stable disease for at least 2 years, there was a mean reduction in liver volume of 12.1% and a mean reduction in spleen volume of 18.8%. A mean increase in haemoglobin concentration of 9.9 g/dL and a mean platelet count increase of 39.7% and 100% were observed. In 13 patients who were switched to Zavesca under a parallel extended treatment protocol, there was no rebound of Zavesca treatment. In one patient of the extension period. When compared to the measurements at 6 months, disease control was unchanged after 18 and 24 months of Zavesca monotherapy (30 and 6 patients, respectively). No patient showed rapid deterioration of type 1 Gaucher disease following the switch to Zavesca monotherapy.

A total daily dose of 300 mg Zavesca administered in three divided doses was used in the above two studies. An additional monotherapy study was performed in 16 patients at a total daily dose of 150 mg, and results indicated the potential to improve efficacy compared to a total daily dose of 300 mg.

An open-label, non-comparative, 3-year study enrolled 42 patients with type 1 Gaucher disease, who had received a minimum of 3 years of ERT and who fulfilled criteria of stable disease for at least 2 years. Thirty-eight patients who were switched from ERT into three treatment groups: continuation with Cerezyme, Cerezyme in combination with Zavesca, or switch to Zavesca. This study was conducted over a 4-year randomized comparison period followed by an extension of 18 months where all patients received Zavesca monotherapy. In the first 6 months in patients who were switched to Zavesca, liver and spleen organ volumes and haemoglobin levels were unchanged. In some patients there were reductions in platelet count and increases in cholestasis activity – indicating that Zavesca monotherapy may not maintain the same control of disease activity in all patients. Twenty-nine patients continued in the extension period. When compared to the measurements at 6 months, disease control was unchanged after 18 and 24 months of Zavesca monotherapy (30 and 6 patients, respectively). No patient showed rapid deterioration of type 1 Gaucher disease following the switch to Zavesca monotherapy.

Zavesca has been studied in a clinical trial in 70 patients with Niemann-Pick type C disease included in an uncontrolled sub-study for an overall average duration of 3.1 years and up to 6 years. Among the 41 patients enrolled, in the trial, 14 patients were treated with Zavesca for more than 3 years. The survey included a case series of 16 patients treated with Zavesca outside of the clinical trial for a mean duration of 3.5 years. Both data sets included paediatric, adolescent and adult patients with an age range of 11 to 43 years. The usual dose of Zavesca in adult patients was 200 mg three times a day, and was adjusted according to body surface area in paediatric patients.

Overall the data show that treatment with Zavesca can reduce the progression of clinically relevant neurological symptoms in patients with Niemann-Pick type C disease.

The benefit of treatment with Zavesca for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g., every 6 months. Continuation of therapy should be re-appraised after at least 1 year of treatment with Zavesca (see section Warnings and Precautions).

Legal Classification
Subject to restrictive medical prescription.

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Date of Last Revision: January 2012