

Report on WORLD Symposium 2011 February 16-18, 2011

The seventh annual World Symposium, co-presented by the Lysosomal Disease Network and the National Institutes of Health, was held in Las Vegas, Nevada, February 16-18, 2011. It included 72 presentations over the course of three days, in addition to poster presentations. There were five presentations specifically about Niemann Pick Disease – four on NPC and one on ASMD (Types A, B, and A/B).

Intrathecal Cyclodextrin Therapy of Feline Niemann-Pick Disease Type C

Presented By Charles Vite, University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania, USA

Authors: Charles Vite, Elizabeth Mauldin, Sarah Ward, Veronika Stein, Maria Prociuk, Mar E. Haskins, Rick Strattan, Mark Kao, Caniel Ory, Steven U. Walkley, Marie T. Vanier

Objective -- To rigorously evaluate the issues related to the use of 2-hydroxypropyl- β -cyclodextrin utilizing the spontaneous feline NPC model with a mutation in NPC 1 orthologous to the most common mutation in juvenile onset patients. This feline model has clinical, neuropathological and biochemical abnormalities similar to those present in juvenile onset patients. The untreated cats die at 24 weeks of age.

Two routes of administration studied - intrathecal and subcutaneous

Intrathecal injection of cyclodextrin was done every 2 weeks and was started prior to the cats showing any symptoms of the disease (cats were genotyped at birth). At 24 weeks of age these cats showed no motor impairment. The intrathecal injection of cyclodextrin had no effect on hepatic disease. Brain cholesterol, gangliosides and sphingosine were normalized in the treated cats. There was, however, a dose-related toxic effect on hearing function - cats lose their hearing.

Subcutaneous injection of cyclodextrin was effective in normalizing liver function, but required high doses to substantially affect neurological disease (8000mg/kg) and this dose was associated with early death due to pulmonary toxicity.

Changes in Neuropsychological Functioning in Three Pediatric Patients with Niemann-Pick Disease Type C (NPC) Following Treatment with Miglustat

Presented By Eva Mamak, Hospital for Sick Children, Toronto, Ontario, Canada

Neuropsychological functioning of three children with NPC assessed prior to initiation of miglustat therapy and one year later. Baseline results indicated variable neuropsychological impairments with marked difficulties in behavioural regulation, fine motor skill and expressive language. On reassessment one year later, a pattern of stabilized visual/motor skill and cognitive abilities was noted with gains in language.

Overall changes in functioning following treatment with miglustat seem most prominent in communication skills. Limitations of the study are the small sample size and the difficulty in testing.

A Phase 1 Trial of Recombinant Human Acid Sphingomyelinase (rhASM) Enzyme Replacement Therapy in Adults with Non -Neuronopathic ASM deficiency (ASMD; Niemann-Pick Disease Type B)

Presented by Margaret McGovern, Stony Brook University School of Medicine, Stony Brook, New York, USA

Authors: Margaret McGovern, Melissa Wasserstein, Brian Kirmse, Lane Duvall, Thomas Schiano, Beth Thurberg, Susan Richards, Gerald Cox

The objectives of this phase 1 trial were to evaluate the safety and pharmacokinetics of rhASM (enzyme replacement) in non -neuronopathic ASMD. Eleven adult patients meeting the entry criteria were administered single ascending doses of intravenous rhASM in 5 dose groups. No clinically significant cardiovascular changes occurred. At doses equal or greater than 0.3mg/kg, 4 of 5 patients experienced a total of 23 drug related adverse events. Dose-related rises in ceramide, bilirubin, C-reactive protein, cytokines and other acute phase reactants peaked at 24-48 hours post dose and resolved by days 3-14. The major safety findings were dose related hyperbilirubinemias, acute phase response and constitutional symptoms occurring 1-3 days post dose. The maximum tolerated starting dose was 0.6mg/kg. Within-patient dose escalation may be an option for higher repeat doses of rhASM.

Baseline Data from a Prospective International Disease Registry for Niemann-Pick Disease Type C

Presented by Marc Patterson, Mayo Clinic, Rochester, Minnesota, USA

Authors: Marc Patterson, Eugen Mengel, Ed Wraith, Frits Wijburg, Marie Vanier, Barbara Schwierin, Audrey Muller, Mariabeth Silkey, Ruben Giorgino, Mercedes Pineda

A prospective disease registry was started in Europe in September 2009 to evaluate the long-term course of Niemann-Pick disease type C in clinical setting. All patients with a diagnosis of NPC are eligible for inclusion, irrespective of treatment. Demographics, disease characteristics and treatment data are collected. Patients are monitored using a disability scale assessing ambulation, manipulation, language and swallowing (rating from 0 (best) to 1(worst)). 30 patients, with a median age of 14.4 years, were enrolled by June 7, 2010 - 24 were confirmed as receiving miglustat therapy. 83% of patients had neurological manifestations at enrollment. Low numbers of patients had normal ambulation (24%) language (20%) and manipulation (23%) at enrollment.

Most of the data has come from Europe. Miglustat is approved for NPC in Europe, Brazil and Canada. The registry is a web based electronic data capture system that captures demographics, diagnostic information, treatment history and relevant disease specific data.

This registry will provide valuable information on the long-term progression of functional neurological impairments and treatment outcomes in NP-C

Treating Niemann-Pick Type C in Brazil: follow up of 28 patients

Presented by Charles Lourenco, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil

Authors: Charles Lourenco, Vanessa Van der Linden, Mara Santos, Erlane Ribeiro, Regina Albuquerque, Raquel Boy, Fernanda Souza, Roberto Biublani, Wilson Marques Jr

Objective was to report on the follow up of a cohort of Brazilian NPC patients treated with substrate reduction therapy (SRT) (miglustat) for a period of 3 years. 28 patients with a clinical, biochemical and/or molecular diagnosis of NPC were evaluated with a clinical protocol/physical exam and complementary exams (abdominal ultrasound, MRI brain, EEG, EMG) during 3 years of treatment with miglustat. All but two of the patients had started miglustat after the onset of the neurological symptoms. Most of the patients had the classical childhood presentations of NPC but there were 4 patients with perinatal presentation. Stabilization of mental deterioration was seen in 18 patients with neurological symptoms. Although in the remaining 8 patients miglustat appeared to slow the progressions of the disease, further neurological deterioration could be seen. Miglustat was discontinued in 1 patient due to worsening tremor and in 1 patient due to difficulty managing diarrhea episodes.

Conclusion: SRT (miglustat) seems to be a reasonable and safe approach to treat NPC patients. Nevertheless, there are patients that seem to have a poor response, regardless of the age of starting the treatment, so it is necessary to develop better biomarkers to follow treatment responses in NPC patients

WORLD Symposium 2011 - Poster Presentations

Clinical follow-up of Niemann-Pick Disease Type C patients, Natural History and the Importance of the Disability Scale Assessing Neurological Disease Progression

Ramses Badilla-Porras, Maha Saleh, Don Mahuran, Brigitte Rigat, JTR Clarke, Margaret Mackrell, Julian Raiman - The Hospital for Sick Children, Toronto, Ontario, Canada

This is an observational retrospective study including 15 patients (10 with an identifiable NPC1 mutation, 3 with an NPC 2 mutation). The results indicate severe phenotype in patients with NPC2 mutations and a higher progression rate in the infantile types among the NPC 1 patients.

Cholesterol Esterification and Filipin Staining in Non-Classical Forms of Niemann Pick Type C

Gisele Bentz Pino, Susonne Ursin, Daniel Kraft, Brian Dawson, Dietrich Matern, Kimiyo Raymond

Mayo Clinic, Rochester, Minnesota; Louisiana State University School of Medicine; USA

Two siblings assessed by filipin staining and cholesterol esterification were interpreted as not consistent with classical NPC. Subsequent DNA analysis was positive for a known pathological mutation as well as a mutation previously reported in a specific ethnic group. These cases suggest that results of cholesterol esterification and filipin staining in some individuals with clinical features consistent with NPC may have a broader variability than previously thought. Accordingly molecular genetic analysis should be considered when the clinical presentation is suspicious or the family history is positive for NPC.

ZOOM - Observational Genetic Screening Study of Niemann-Pick Disease Type C in Adults with Neurological and Psychiatric Signs

Marc Patterson, Peter Bauer, Hans Klunemann, Frederic Sedel, David Linden, Ed Wraith, Mercedes Pineda, Josef Priller, Audrey Muller, Harbajan Chandha-Boreham, Christine Rey, David Balding

A gene sequencing analysis recently found an NPC prevalence of 6.4% among undiagnosed adolescent and adult psychiatric patients. To investigate further the extent to which adult psychiatric patients might be affected by NPC, an international genetic screening study has been designed to investigate NPC in patients with psychosis or early onset dementia. This screening study will provide valuable data on the prevalence of latent NPC among adults with neurological/psychiatric signs and will strengthen the knowledge of the clinical manifestations of adult NPC.

Longitudinal Study of Cognition in Niemann- Pick Disease, Type C

Marc Patterson, Tanya Brown, Michael Zaccariello, Rebecca Vaurio, Forbes Porter
NIH, Mayo Clinic, USA

There is no approved disease modifying therapy for NPC in the US, but several interventions have shown promise in vitro and in animal models, and in three human trials. The design and execution of clinical trials in NPC has been hindered by the lack of prospectively gathered natural history data or validated biomarkers. Progressive cognitive decline is typical of NPC; it is hypothesized that patients with NPC will show a characteristic pattern or cognitive impairment prior to the onset of other neurologic symptoms or signs and that there will be a steady progression of cognitive impairment over time. Subjects are being recruited from two studies of NPC currently in progress at the NIH and Mayo Clinic. All have a biochemical proven diagnosis of NPC and will be administered a set of developmentally appropriate psychometric instruments at annual intervals.

Quantification of the Intensity of Filipin Fluorescence as a Diagnostic test for Niemann-Pick Disease Type C

Brigitte Rigat, Christopher Fladd, Julian Raiman, Joe Clarke, John Calahan, Don Mahuran

The Hospital for Sick Children, Toronto, Ontario, Canada

Quantification of the Intensity of Filipin Fluorescence (QIFF) as evaluated as a more rapid and reliable clinical test versus the classical, manual and qualitative evaluation of the intensity of filipin staining. The QIFF assay is a simple, rapid and reliable tool to generate accurate diagnosis for NPC disease that could be easily set up in most hospital laboratories. Additionally, this assay could represent a valuable tool to search for novel therapeutic compounds and/or for monitoring therapeutic molecules.

**Respectfully submitted by Sandra Cowie, OT
Director-at-Large for the National Niemann-Pick Disease Foundation
Adult with Niemann-Pick Disease Type B (ASMD)**