Niemann-Pick Type C Disease

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Niemann-Pick Type C Disease

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Objectives

- Discuss ways to **reduce time** needed for Niemann-Pick Type C (NPC) diagnosis

- Identify classic **NPC symptoms in children**

- Describe methods of **multispecialty collaboration** when NPC is suspected

- Discuss **current management and treatment options** for NPC
Introduction to Niemann-Pick Disease
Niemann-Pick Disease

• Inherited condition involving abnormal lipid metabolism

• Harmful amounts of lipids accumulate in the spleen, liver, lungs, bone marrow, and brain

• Autosomal recessive pattern of inheritance (two copies of the gene must be present)

• Four variants: A, B, C1, and C2
Niemann-Pick Disease

Two distinct entities

Types A and B: mutated SMPD1 gene
- **SMPD** gene carries instructions for cells to produce sphingomyelinase, which processes lipids
- Mutations lead to deficiency of sphingomyelinase and accumulation of cholesterol and lipids

Types C1 and C2: mutated NPC1 or NPC2 gene
- **NPC1** gene encodes a protein that plays a critical role in regulation of intracellular cholesterol trafficking
- NPC2 gene encodes a protein that binds and transports cholesterol (this is not fully understood)

Niemann-Pick Disease Type C
Niemann-Pick Type C (NPC) is a Fatal, Progressive, Neurodegenerative Disorder

- NPC occurs with a minimal incidence of 1:120,000 live births\(^1\)
  - This number is based on 63 cases diagnosed in French hospitals between 2000-2009 versus the number of total births during this period
  - The prevalence is higher (1:104,000) when including prenatal cases from terminated pregnancies
- This is considered an under-estimate of the true prevalence of NPC, as atypical phenotypes may be not be clinically suspected\(^1\)
- There are reports that the prevalence of NPC is approximately 500 patients worldwide and 200 patients in the United States\(^2,3\)

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In Most Cases, NPC is Caused by Mutations in Two Genes: *NPC1* (95% of Cases) or *NPC2* (5% of Cases)

- The Niemann-Pick type C1 (*NPC1*) gene is responsible for most (~95%) cases of NPC disease\(^1\)
  - *NPC1* is located on chromosome 18 at cytogenetic band 18q11-12\(^2,3\)
  - *NPC2* is mapped at chromosome 14q24.3

- The *NPC1* gene encodes a small soluble lysosomal protein involved in cholesterol binding\(^3\)

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Both NPC1 and NPC2 have identical biochemical patterns, suggesting that the two proteins function together in cellular transport of cholesterol, glycolipids, etc. Their precise functions and relationship remain unclear and are currently the subject of intense investigation.

NPC mutations result in intracellular lipid accumulation in various tissues, including the brain, liver, and spleen. In most cases, NPC is caused by mutations in two genes: NPC1 (95% of cases) or NPC2 (5% of cases).


Figure reproduced from Vanier MT, Millat G. *Clin Genet* 2003;64(4):269-81.
Pathophysiology
In NPC Disease, the Central Biochemical Defect is Impaired Intracellular Lipid Trafficking

- NPC1 is a transmembrane protein located on the LE/L compartments where it regulates cholesterol efflux.
- The cholesterol trafficking defect occurs when endocytosed LDL-cholesterol becomes sequestered in lysosomes around the cell nucleus.
- Transport from these perinuclear lysosomes is delayed, resulting in excess accumulation of unesterified cholesterol.
- This accumulation may result in a deficiency in cell membrane cholesterol with subsequent membrane dysfunction/a triggering of apoptosis.

LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LE, late endosomes; L, lysosomes.

The *NPC1* Deletion (NPC1\(^{-/-}\)) Mouse Model Demonstrates Accumulation of Cholesterol Within Tissues\(^{1,2}\)

- Loss-of-function mutation in either *NPC1* or *NPC2* results in disruption of cholesterol transport out of the LE/L, causing accumulation of cholesterol.
- Cholesterol accumulation was ~7-fold greater in NPC1\(^{-/-}\) mice compared with control animals, due to daily sequestration of 67 mg cholesterol per kg in various organs\(^{2}\).
- LDL uptake from the circulation was not altered in NPC1\(^{-/-}\) mice, and cholesterol absorption was not increased\(^{2}\).
- Furthermore, administration of a sterol-binding agent to NPC1\(^{-/-}\) mice increased cholesterol movement out of the LE/L in the liver from near 0 to 233 mg/day/kg\(^{3}\).
- This suggests that *NPC1* deletion causes accumulation of cholesterol by disrupting cholesterol transport out of the LE/L.

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LE, late endosomes; L, lysosomes
### Animal and Organ Weights, Cholesterol Pool Sizes, and Rates of Dietary Cholesterol Absorption in NPC1⁻/⁻ Mice

<table>
<thead>
<tr>
<th></th>
<th>NPC⁺⁺/⁺⁺ LDLR⁺⁺/⁺⁺</th>
<th>NPC⁻⁻/⁻⁻ LDLR⁺⁺/⁺⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of whole animal, g</td>
<td>21.3 ± 0.3</td>
<td>17.4 ± 0.3ₐ</td>
</tr>
<tr>
<td>Weight of liver, g</td>
<td>1.20 ± 0.03</td>
<td>1.33 ± 0.037ₐ</td>
</tr>
<tr>
<td>Weight of brain, g</td>
<td>0.44 ± 0.01</td>
<td>0.38 ± 0.03ₐ</td>
</tr>
<tr>
<td>Cholesterol pool at day 1, mg/kg</td>
<td>1725 ± 22</td>
<td>2453 ± 35ₐ</td>
</tr>
<tr>
<td>Cholesterol pool at 7 weeks, mg/kg</td>
<td>2165 ± 47</td>
<td>5669 ± 173ₐ</td>
</tr>
<tr>
<td>Cholesterol sequestration, mg/day per kg</td>
<td>9.2</td>
<td>67.0</td>
</tr>
<tr>
<td>Cholesterol absorption, mg/day per kg</td>
<td>14 ± 2</td>
<td>8 ± 2ₐ</td>
</tr>
</tbody>
</table>

A mouse model (NPC1nmf164) of a point mutation in *NPC1* has been described, which causes a single amino acid change in a region of the NPC1 protein where ~1/3 of mutations in patients with NPC are found. NPC1nmf164 mutant mice demonstrate cholesterol accumulation in the liver, spleen and brain.

Cholesterol accumulation was also evident in a mouse model of the most common *NPC1* mutation found in patients with NPC (p.I1061T)

- A broad range of lipids including unesterified cholesterol accumulated in the liver

- Cholesterol storage was observed throughout all layers of the neocortex

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Figure reproduced from Reid PC et al. *J Lipid Res.* 2004;45(3):582-91.
Clinical Presentation
Average Age at **Diagnosis** is 10 Years; Average Age at **Death** is 16 Years

NPC Disease US Database: **Delayed Diagnosis**
- It can take **up to 10 years** for a diagnosis
- **50%** of patients are diagnosed before age **6.9 years**
- Average age at diagnosis is **10.4 years**

NPC Disease US Database: **Poor prognosis**
- **50%** of patients die before age **12.5 years** in most cases
- Death occurs between **8 and 25 years** in most cases
- Average age at death is **16.2 years**

NPC is Often Categorized by the Age of Onset of the First Neurological Symptoms (Early Infantile, Late Infantile, Juvenile, and Adult)

- In NPC, cholesterol accumulation in the CNS results in progressive and irreversible neuronal degradation and neurological manifestations.
- Early onset of neurological symptoms is directly linked to severity of NPC.

Schematic of the main forms of NPC, with emphasis on type and age of onset of first neurological symptoms.
The Clinical Presentation of NPC is Heterogenous and Nonspecific, Rendering Diagnosis Challenging

- NPC has a **variable presentation**, including visceral, neurological, and psychiatric signs and symptoms and can present at any age\(^1,2\)
  - Younger patients tend to present predominantly with **visceral manifestations**
  - Neurological and psychiatric symptoms become more common with increasing age

- **Visceral**
  - Isolated unexplained splenomegaly
  - Hepatomegaly/splenomegaly
  - Prolonged neonatal cholestatic jaundice
  - Hydrops fetalis or fetal ascites
  - Pneumopathologies (aspiration pneumonia, alveolar lipidosis, interstitial lung involvement)
  - Mild thrombocytopenia

- **Neurological**
  - Vertical supranuclear gaze palsy
  - Gelastic cataplexy
  - Ataxia
  - Dystonia
  - Dysarthria
  - Dysphagia
  - Delayed developmental milestones
  - Seizures
  - Hearing loss

- **Psychiatric**
  - Developmental delay
  - Pre-senile cognitive decline
  - Organic psychosis
  - Disruptive/aggressive behavior
  - Progressive development of treatment-resistant symptoms

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Progressive neurodegeneration results in disabling neurological and psychological symptoms like ataxia, dystonia, hypotonia, vertical supranuclear gaze palsy, gelastic cataplexy, dysarthria, dysphagia, cognitive decline, pre-senile cognitive decline/dementia and psychosis.

Mortality usually results from the neurological manifestations of the disease, most commonly dysphagia (and consequent aspiration pneumonia), and is exacerbated by the delays in diagnosis.

Diagnostic Delay Exacerbates Morbidity and Mortality

- **Dysphagia** is a common neurological symptom in NPC patients (prevalence ~55%)\(^1\)

- The risk of **aspiration pneumonia** is significantly increased in patients with dysphagia,\(^2\) and the most common reported cause of death in patients with NPC is **bronchopneumonia**\(^2,3\)

- The **average delay in diagnosis** from onset of neurological manifestations is **4.1 years**\(^4\)

## Age at Neurological Onset and Age at Diagnosis for Patients With Neurological Manifestations From NPC

SD, standard deviation.
Table reproduced from Patterson MC, et al. Orphanet J Rare Dis. 2013,8:12.

<table>
<thead>
<tr>
<th>Age at neurological onset, years</th>
<th>Age at diagnosis, years</th>
<th>Mean difference, years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Patients with neurological manifestations</td>
<td>145</td>
<td>10.9 (9.8)</td>
</tr>
<tr>
<td>Early infantile (&lt;2 years)</td>
<td>16</td>
<td>0.8 (0.6)</td>
</tr>
<tr>
<td>Late infantile (2 to &lt;6 years)</td>
<td>45</td>
<td>4.2 (1.3)</td>
</tr>
<tr>
<td>Juvenile (6 to &lt;15 years)</td>
<td>45</td>
<td>9.7 (2.8)</td>
</tr>
<tr>
<td>Adolescent/adult (≥15 years)</td>
<td>39</td>
<td>24.0 (8.9)</td>
</tr>
</tbody>
</table>
Neurological involvement defines the disease severity in most patients but is typically preceded by systemic signs (cholestatic jaundice in the neonatal period or isolated spleno- or hepatosplenomegaly in infancy or childhood)\textsuperscript{1,2}

Progressive Hepatosplenomegaly is Present in $\sim$50% of Patients, With Variable Intensity

- Overall neonatal jaundice during infancy (49/126; 39%)
- Overall hepatomegaly during infancy (50/127; 39%); splenomegaly (69/127; 54%)

Clinical Diagnosis
Highly Variable Clinical Presentation Leads to a Lack of Detection and Diagnosis

- Low disease awareness and heterogeneous clinical presentation impedes diagnosis, often resulting in misdiagnosis and/or delay in therapy initiation

Symptom progression from onset of disease and common misdiagnoses of NPC

Figure reproduced from Klunemann H, et al. Eur Neuro Rev. 2011;12-15.
Diagnosis of NPC is Often Delayed, and NPC is Often Confused With Other Diseases

- Time to diagnosis is limited by the symptomology exhibited by patients and speed of recognition by healthcare professionals

- Greater awareness of the disease and its manifestations among healthcare professionals may expedite referral to specialist centers

Average time to diagnosis from symptom onset:

<table>
<thead>
<tr>
<th>Visceral symptoms</th>
<th>Developmental delay</th>
<th>Psychiatric symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months</td>
<td>6 years</td>
<td>Up to 19 years</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Clumsiness</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Ataxia</td>
<td>Aggressive behaviour</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Declining academic performance</td>
<td>Paranoia (often in teens)</td>
</tr>
</tbody>
</table>

Average Delay in NPC Diagnosis of 4-6 Years

Diagnosis of NPC is Often by Clinical Exclusion and Confirmatory Biomarker Testing in Addition to Important Genetic Evaluation

- Laboratory tests include biochemical testing of intracellular cholesterol homeostasis, DNA tests for NPC gene mutations, and skin biopsy.

- A key diagnostic test is demonstration of impaired intracellular cholesterol transport by filipin staining of fibroblasts cultured from patient skin biopsies\(^1,2\):
  - NPC+ cells show up as strongly fluorescent cholesterol-filled perinuclear vesicles under fluorescence microscopic examination\(^1,2\).
  - This is the classical cholesterol storage pattern, demonstrated in >80% of cases\(^3\).
  - Other patients show a variant biochemical phenotype with less pronounced and more variable cholesterol storage\(^1-3\).

- DNA tests for NPC1/NPC2 mutation should be performed in parallel with filipin staining\(^1\):
  - Although significant advances have been made in genetic sequencing of NPC1/NPC2, filipin staining remains the primary diagnostic test.

Visualization of unesterified cholesterol by filipin staining of fibroblasts from a typical patient with NPC1 mutations (A) and a typical patient with NPC2 mutations (B)

Figure reproduced from Vanier MT, Latour P. Method Cell Biol 2015;126:357-75

Biomarkers could potentially substantially reduce diagnostic delays and may also prove useful in establishing disease severity and monitoring disease progression and response to therapeutic interventions¹.

Recently, biomarkers have been developed to diagnose NPC that are less invasive, cost-effective, and easier to perform than conventional NPC diagnostic methods¹.

### Minimally Invasive Biomarkers Investigated in NPC

- **Cholestane-3β,5α,6β-triol**²,³
- **24(S)-hydroxycholesterol**³
- **Lysosphingomyelin**⁴
- **Bile acids**⁵
- **Lysobisphosphatidic acid**⁶

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Experts recommend initiating specific therapy at the first appearance of neurological symptoms.

Given the heterogeneous presentation of NPC, international experts developed a simple and reliable screening tool which aims to:

- Identify patients who should undergo testing for NPC
- Raise awareness of the key signs and symptoms of NPC
- Exclude patients unlikely to have NPC
- In patients >4 years, prominent leading manifestation–associations were ataxia with dystonia, dysarthria/dysphagia, and cognitive decline. Psychosis was associated with dysarthria/dysphagia but also with cognitive decline and treatment-resistant psychiatric symptoms.

Making a Diagnosis in Pediatric Patients
Patients May See Numerous Specialists Prior to Receiving a Diagnosis of NPC

- Absence of a symptom checklist for identifying metabolic disease often means a lengthy wait before patients receive a diagnosis.

Pediatricians Have a Fundamental Role Linking Symptoms Together to Facilitate a Fast Differential Diagnosis 1-3

**Presentation**

- History of prolonged neonatal cholestasis, hepatomegaly, and presence of splenomegaly in combination with clumsiness, frequent falls, or developmental delay could indicate NPC
- Symptoms might present at different times; some symptoms may appear to have been resolved
- Patient medical histories can often reveal unexplained cholestatic jaundice
- Although vertical supranuclear gaze palsy is a characteristic symptom of NPC and is present in nearly all cases, it is often missed, especially among younger patients

**Differential Diagnosis**

- Hepatosplenomegaly? +
- Ataxia? +
- Developmental delay? +
- Eye movement abnormalities? =

Consider NPC

### In Some Cases, the Disease May Never be Detected or May be Misdiagnosed

(Adapted from Alobaudy H. Int J Ped. 2015;1-10)

<table>
<thead>
<tr>
<th>Age</th>
<th>Presenting symptoms</th>
<th>Common differential diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-/perinatal period &lt;3m</strong></td>
<td><strong>Fetal hydrops</strong></td>
<td>Chromosomal disorders, Congenital heart malformations</td>
</tr>
<tr>
<td></td>
<td><strong>Prolonged neonatal cholestatic jaundice</strong></td>
<td>Idiopathic hepatitis, Biliary atresia, Galactosemia, Alpha 1 antitrypsin deficiency, Bile acid synthesis disorders</td>
</tr>
<tr>
<td><strong>Early infantile (3m-2y) + Late infantile period (2-6y)</strong></td>
<td><strong>Isolated splenomegaly or hepatosplenomegaly</strong></td>
<td>Mucopolysaccharidosis, Oligosaccharidosis, Sphingolipidosis (Gaucher, Niemann-Pick A and B)</td>
</tr>
<tr>
<td><strong>Late infantile + Juvenile period (6-15y)</strong></td>
<td><strong>Dystonia</strong></td>
<td>Respiratory chain disorders, Pyruvate dehydrogenase deficiency, Vitamin E deficiency, Glucose transporter 1 deficiency</td>
</tr>
<tr>
<td></td>
<td><strong>Ataxia</strong></td>
<td>Vitamin E deficiency, Autosomal recessive cerebellar ataxia (ARCA)</td>
</tr>
<tr>
<td></td>
<td><strong>Vertical supranuclear gaze palsy (usually downgaze first)</strong></td>
<td>Progressive supranuclear palsy, Multiple system atrophy, Dementia with Lewy bodies, Spinocerebellar ataxia, Tay-Sachs, Thyroid disorders (usually up gaze first)</td>
</tr>
<tr>
<td></td>
<td><strong>Gelastic cataplexy</strong></td>
<td>Gelastic seizures</td>
</tr>
<tr>
<td><strong>Juvenile period (6-15y)</strong></td>
<td><strong>Psychosis</strong></td>
<td>Hysteria, schizophrenia, Wilson disease, Acute intermittent porphyria, Cerebrotendinous xanthomatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homocystinuria, Wilson disease, Urea cycle defects, Organic aciduria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitochondrial disorders, Friedreich’s ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wernicke encephalopathy, Sporadic Creutzfeldt-Jakob, Huntington’s, Wilson, Vitamin B12 deficiency, Kernicterus, Whipple disease (3 months to 81 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narcoleptic pentad</td>
</tr>
</tbody>
</table>
Clinical Management
There is Currently No Cure for NPC

- Supportive therapies are variably effective for the alleviation of numerous clinical problems associated with the disease\textsuperscript{1}
- Current therapeutic approaches focus on health-related quality of life, via multidisciplinary control of symptoms and their onset \textsuperscript{2}

Management strategies include non-specific, symptomatic treatments and NPC-specific therapies\textsuperscript{1,3}

<table>
<thead>
<tr>
<th>Symptomatic therapies</th>
<th>aim to improve a patient's quality of life. However, they have no impact on disease progression or long-term outcomes\textsuperscript{1}</th>
</tr>
</thead>
</table>

Recent advances in the understanding of NPC pathophysiology have led to the development of an NPC-specific treatment, Miglustat, that can slow down the progression of the disease\textsuperscript{1,4}

Early diagnosis of NPC means that patients can access treatment and is crucial for timely intervention\textsuperscript{1}

Current Approaches Target Symptoms and Focus on Health-related Quality of Life

- Symptomatic management includes gastrostomy to maintain caloric intake, antiepilepsy drugs to prevent seizures, tricyclic antidepressants to control cataplexy, and anticholinergic drugs to treat dystonia and tremors

- Most treatments for NPC focus on symptomatic management to improve patient’s quality of life

## Current Approaches Target Symptoms and Focus on Health-related Quality of Life, cont.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological manifestations</strong></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>• Antiepileptic drugs</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>• Tricyclic antidepressants or CNS stimulants</td>
</tr>
<tr>
<td>Dystonia and tremor</td>
<td>• Anticholinergic drugs</td>
</tr>
<tr>
<td></td>
<td>• Other drugs that can be effective: trihexyphenidyl, benzodiazepines, botulin toxin (selected cases), gamma-aminobutyric acid derivatives (advanced dystonia)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>• Softening or thickening of food</td>
</tr>
<tr>
<td></td>
<td>• Gastrostomy</td>
</tr>
<tr>
<td>Drooling</td>
<td>• Oral atropine, parotid/submandibular injections of botulin toxin, hydrosyne patches, or glycopyrronium bromide</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>• Melatonin or positive airway pressure</td>
</tr>
<tr>
<td></td>
<td>• Support services</td>
</tr>
<tr>
<td></td>
<td>• Miglustat may stabilize cognitive decline</td>
</tr>
<tr>
<td>Psychosis</td>
<td>• Atypical antipsychotics and regular neurological monitoring to minimize aggravation of preexisting dystonia</td>
</tr>
<tr>
<td><strong>Psychiatric illness</strong></td>
<td></td>
</tr>
<tr>
<td>Catatonia</td>
<td>• Electroconvulsive therapy</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>• Mood stabilizers (eg, sodium valproate)</td>
</tr>
<tr>
<td>Depression</td>
<td>• Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td><strong>Systemic manifestations</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
<td>• Antipropulsive agents (eg, loperamide) for diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Bowel monitoring to prevent constipation in affected patients</td>
</tr>
<tr>
<td>Primary lung involvement</td>
<td>• Aggressive bronchodilation and, in some cases, chest physical therapy</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
There Are Currently **No Treatments** For NPC That Directly Address The Pathophysiology Of Disease

- In the United States, Miglustat was approved only for the treatment of mild to moderate Type I Gaucher disease in adults who cannot use enzyme replacement¹
- Outside the United States, Miglustat is approved for the treatment of NPC. Miglustat has demonstrated limited efficacy in stopping or delaying the progression of NPC in the majority of patients

- Miglustat is an iminosugar that reversibly inhibits the enzyme glucosylceramide synthase, the first committed step in glycosphingolipid synthesis²
- Although not approved in the United States for NPC,³ Miglustat is approved in Europe and other countries for the treatment of progressive neurological manifestations in adult and pediatric patients with NPC⁴
- Miglustat was approved in Europe based on the results from a small randomized controlled trial and its long-term extension studies, as well as a retrospective observational cohort study³

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VTS-270 Re-Establishes the Cell’s Ability to Transport and Regulate Cholesterol

Preliminary results from a Phase I/IIa study showed that administration of VTS-270 slowed and changed the course of disease progression.

Phase II/III Study of VTS-270 (2-hydroxypropyl-β-cyclodextrin) to Treat Niemann-Pick Type C1 (NPC1) Disease (NCT02534844)

- **Efficacy and safety of VTS-270 in patients (aged 4-21 years) with neurologic manifestations of NPC disease**
  - Onset of neurological symptoms prior to 15 years of age and confirmed diagnosis of NPC1 determined by either:
    - 2 NPC1 mutations
    - Positive filipin staining and ≥1 NPC1 mutation
    - Vertical supranuclear gaze palsy plus either: one NPC1 mutation, OR positive filipin staining or oxysterol levels consistent with NPC disease and no NPC2 disease mutations
  - Approximately two-thirds of patients will receive VTS-270 and the remaining study participants will receive sham control
  - Aim to enroll 51 patients, estimated completion date: March 2018

Primary outcome measure (52 weeks)
- NPC Clinical severity score

Secondary outcome measures (52 weeks)
- Clinician and Caregiver Global Impression of Change
- Time to get up and go test
- 9-hole peg test
- Percentage of patients with clinical worsening
- European quality of life score

Other outcome measures (52 weeks)
- CSF biomarkers
- Plasma protein biomarkers

Currently, therapies are targeted at one or more pathologic features of NPC, and combinations of these small-molecule drugs have shown enhanced clinical benefit.

Individual treatments aim to:

- (1) reduce the accumulation of offending metabolites
- (2) bypass defective metabolic pathways
- (3-5) enhance a cell’s resistance to disease
- (6) increase/rescue function of existing NPC proteins
- Molecular chaperone therapy only works with certain mutations: Gaucher’s disease, Fabry disease, Pompe disease and Late-onset Tay-Sachs disease.
- (7-8) correct the primary metabolic defects
- (9) improve lysosomal function

HPBCD, 2-hydroxypropyl-beta-cyclodextrin.
Case Presentation
Patient Presentation


Patient History

- 14-year-old female
- Hepatomegaly occurred at approximately age 6 years
- Developed dyspraxia, which manifested as slow running at the age of 8 years
- Bilateral dystonia was observed at age 10 years
- Scholastic achievement began to decline at age 12 years

Patient Presentation

- Recent unexplained frequent falls and seizures reported by parents
- Coupled with neurological regression
- Hypotonia
- Facial dyskinesia
How would you manage the patient at this point?

1. Referral for a neurological assessment
2. Referral for further testing (ie, MRI, laboratory analysis, genetic analysis)
3. Follow-up within 3 to 6 months
4. Consider a differential diagnosis
5. Other
How would you manage the patient at this point?

1. Referral for a neurological assessment
2. Referral for further testing (ie, MRI, laboratory analysis, genetic analysis)
3. Follow-up within 3-6 months
4. Consider a differential diagnosis
5. Other

ANSWER

MRI, magnetic resonance imaging.
Diffuse cerebral and cerebellar atrophy was observed
Serum chitotriosidase levels were above normal limits
Bone marrow biopsy showed sea-blue histiocytes and foamy cells
Skin fibroblast culture was atypical

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal brain MRI</td>
<td>+</td>
</tr>
<tr>
<td>High chitotriosidase level</td>
<td>+</td>
</tr>
<tr>
<td><strong>Sea-blue histiocytes at bone marrow</strong></td>
<td>+</td>
</tr>
<tr>
<td>Foamy cells at bone marrow</td>
<td>+</td>
</tr>
<tr>
<td>Filipin staining</td>
<td>+</td>
</tr>
</tbody>
</table>

Bone marrow biopsy showing sea blue histiocytes with May-Grumwalld-Giemsa staining or Niemann-Pick cells

What would your differential diagnosis be?

1. Gaucher’s disease
2. Niemann-Pick disease Type C
3. Multiple sclerosis
4. Other
What would your differential diagnosis be?

1. Gaucher’s disease
2. Niemann-Pick disease Type C
3. Multiple sclerosis
4. Other
Genetic testing revealed compound heterozygotic mutations in the \textit{NPC1} gene on alleles 1 and 2 (A764V and A1035V, respectively).

\begin{itemize}
\item \textit{NPC1} gene
\end{itemize}

\textbf{Suspected NPC}

\begin{itemize}
\item Early treatment in the disease course is associated with improved responses, highlighting the need for rapid diagnosis.
\end{itemize}

Summary

- Early diagnosis is strongly influenced by symptoms presentation and speed of symptoms recognition.
- There is a low awareness about the metabolic storage diseases, such as NPC.
- There is a need for improved education among healthcare professionals so that they can recognize the link between the symptoms that will lead to the diagnosis of NPC.
- There is a need for a greater focus on raising awareness of the classic symptoms in infants and for proactive testing of newborns with splenomegaly and/or hepatomegaly and severe jaundice before the symptoms subside.
- For those patients whose first symptoms are learning and behavioral difficulties, pediatricians need to recognize and link symptoms together and think of a wider picture to allow multispecialty collaboration.
- Unexplained “Hepatosplenomegaly + Ataxia + Developmental delay + Eye movement abnormalities consider NPC”
Currently, there are no treatments for NPC that directly address the pathophysiology of disease; current management approaches of NPC have shown limited efficacy and focus on symptomatic treatment strategies.

VTS-270 re-establishes cholesterol homeostasis by bypassing the NPC1/NPC2 pathway.
Resources


• Vanier TM. Niemann-Pick Disease Type C. Orphanet J Rare Dis. 2010;5:6. Available at: http://www.ojrd.com/content/5/1/16.


NORD Member Organizations

• National Niemann-Pick Disease Foundation, Inc.
  Email: nnpdf@nnpdf.org
  Website: http://www.nnpdf.org

Other Organizations

• CLIMB (Children Living with Inherited Metabolic Diseases)
  Email: enquiries@climb.org.uk
  Website: http://www.CLIMB.org.uk

• Genetic and Rare Diseases (GARD) Information Center
  Website: http://rarediseases.info.nih.gov/GARD/

• GOLD, Global Organisation For Lysosomal Diseases
  Email: enquiries@goldinfo.org
  Website: http://www.goldinfo.org
Questions?
Thank you