Isolated unexplained splenomegaly?
Prolonged cholestatic neonatal jaundice?

Have you considered Niemann-Pick type C disease?

A guide to recognizing the clinical features of Niemann-Pick type C disease (NP-C) for pediatricians

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What is Niemann-Pick type C disease?

Niemann-Pick type C disease (NP-C) is a rare, progressive, autosomal recessive neurodegenerative disorder with an incidence of approximately one in 120,000 live births. In two thirds of cases, presentation occurs in infancy or childhood, with early symptoms generally affecting the liver and spleen, progressing into a number of highly variable neurological symptoms.

NP-C is commonly undetected or misdiagnosed due to its heterogeneous clinical presentation, characterized by a wide range of symptoms that are not specific to the disease. Therefore, the journey to diagnosis can often be long and frustrating for NP-C patients and their families. Age of onset ranges from the antenatal period until well into adulthood and the lifespan of patients varies between a few days to over 70 years of age, although most patients die between 10 and 25 years of age.

NP-C is marked by the development of a large variety of symptoms, including visceral, neurological and psychiatric symptoms. The strongest predictors of NP-C are: isolated unexplained splenomegaly, prolonged neonatal jaundice, vertical supranuclear gaze palsy, gelastic cataplexy, pre-senile cognitive decline and/or dementia, hallucinations and delusions and/or thought disorders (mainly presenting in adulthood).

Diagnosis of NP-C

Pediatricians play a fundamental role in making links between symptoms, which might present at different times in the child’s life and where symptoms may appear to have been resolved, in order to make a differential diagnosis of NP-C. If a pediatrician sees a patient with unexplained neonatal jaundice, splenomegaly or hepatomegaly and further neurological symptoms such as clumsiness and ataxia, NP-C should be considered. Patient medical histories can often reveal unexplained neonatal or infant hepatosplenomegaly. An early diagnosis is important for the patient as they are able to access support and also start appropriate treatment, when it is likely to be most effective.

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How to use this guide

The aim of this guide is to help pediatricians increase their awareness of how NP-C might present in childhood; when to suspect NP-C; which symptoms and features should prompt further investigation and when referral is recommended.

For more information

Please visit www.npc-info.com for further information on NP-C.

Please visit www.npc-si.com to access the NP-C Suspicion Index, a tool that has been developed to provide healthcare professionals unfamiliar with NP-C with a simple-to-use and interactive screening tool.
## Patients may present with the following symptoms during the pre-/ante-natal period (less than 3 months old)\(^6\)

### Visceral symptoms (precede onset of neurological symptoms):

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal ascites on ultrasound</td>
<td>Appears in first days or weeks of life and usually associated with progressive hepatosplenomegaly. Jaundice usually resolves spontaneously by 2 to 4 months of age.(^1)</td>
</tr>
<tr>
<td>Prolonged unexplained cholestatic jaundice</td>
<td>(Hepato) Splenomegaly Present in nearly 50% of NP-C patients but with varied intensity.(^1)</td>
</tr>
<tr>
<td></td>
<td>Respiratory failure More common in patients with the NPC2 gene mutation.(^1)</td>
</tr>
<tr>
<td></td>
<td>Impaired liver function</td>
</tr>
</tbody>
</table>

### Neurological symptoms are not usually recognized in children of this age.

## Patients may present with the following symptoms in early to late infancy (3 months to 6 years)\(^6\)

### Visceral symptoms:

- Isolated hepatosplenomegaly
- May stay isolated for many years.\(^1\)

### Organomegaly

### Neurological symptoms:

- Delayed developmental motor milestones
- One of the first neurological symptoms, which can become evident between the ages of 1 to 2 years.\(^1\)

- Central hypotonia
- One of the first neurological symptoms, which can become evident between the ages of 1 to 2 years.\(^1\)

- Hearing loss

- Gait problems, frequent falls and clumsiness
  - Between 3 and 5 years of age due to ataxia\(^4\) or visual disturbance.

- Seizures
  - (partial or generalized)

- Cataplexy
  - Patients may experience a sudden loss of muscle tone, often as a result of emotional stimulus.\(^1\) Initially, patients may only experience subtle head nodding.

- Vertical supranuclear gaze palsy (VSGP)
  - Usually present but may not be recognized at an early stage,\(^1\) as only upward gaze may be abnormal to begin with. VSGP should be checked by asking the patient to voluntarily look up and down, as slow eye pursuit is often well preserved.

- Progressive ataxia
  - (clumsiness), dystonia (prolonged muscle contraction), dysphagia (difficulty swallowing), dysarthria (speech disorder)
Early diagnosis is important as treatment can help reduce the progression of NP-C. Patients presenting with a combination of the features outlined within this guide should be considered for referral to a specialist center.

It is important that pediatricians link together both the visceral and neurological symptoms outlined in this guide that an infant or child may present with, in order to reach a fast and differential diagnosis of NP-C.

Patients may present with the following symptoms in the juvenile period (6 to 15 years)\(^6\)

<table>
<thead>
<tr>
<th>Visceral symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated organomegaly</td>
</tr>
<tr>
<td>Not always present in juvenile patients with NP-C but may have a history of hepatosplenomegaly.(^1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>School problems, learning disabilities</td>
</tr>
<tr>
<td>Can often lead to misdiagnosis.(^1)</td>
</tr>
<tr>
<td>Vertical supranuclear gaze palsy</td>
</tr>
<tr>
<td>Usually present and often the initial sign of NP-C.(^1) In the early stages, only upward gaze may be abnormal.</td>
</tr>
<tr>
<td>Behavioral problems</td>
</tr>
<tr>
<td>Frequent falls, clumsiness</td>
</tr>
<tr>
<td>Cataplexy</td>
</tr>
<tr>
<td>Typically laughter-induced.(^1)</td>
</tr>
<tr>
<td>Progressive ataxia, dystonia, dysphagia, dysarthria</td>
</tr>
<tr>
<td>Myoclonic jerks</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>(partial and/or generalized)</td>
</tr>
</tbody>
</table>

Please note that treatment information is country-specific and you are responsible for obtaining and adhering to your country-specific product information. This document is only to be used in countries where specific treatment has an approved indication for NP-C.

References:
1. Vanier M. Niemann-Pick disease type C. Orphanet Journal of Rare Diseases. 2010; 5(16)
3. Wijburg F, Sedel F, Pineda M et al. Suspicion Index to Aid Diagnosis of Niemann-Pick Type C (NP-C) Disease, an Autosomal Recessive Neurovisceral Disorder. Poster session presented at the Annual Symposium Society for the Study of Inborn Errors of Metabolism, 30 Aug-2 Sep 2011 in Geneva, Switzerland