Vertical supranuclear gaze palsy?
Gelastic cataplexy?

Have you considered Niemann–Pick type C disease?

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

Sponsored by Actelion Pharmaceuticals Ltd
Date of preparation: March 2012
Job number: ZAV 228
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, but in up to a third of cases, symptoms may not present until adolescence or adulthood.

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. However, an early diagnosis is important as patients are able to access support and also start appropriate treatment, when it is likely to be most effective.

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.

Patients presenting with NP-C in early infancy, within the first year of life, commonly experience the most aggressive form of the disease, which often leads to death in early childhood. Patients diagnosed later in life, sometimes into late adulthood, often experience a slower rate of disease progression and associated clinical symptoms.

Symptoms of NP-C can be grouped into visceral, neurological, or psychiatric categories. One of the strongest indicators of NP-C is when a patient presents with symptoms in more than one of these categories.

Diagnosis of NP-C

Neurologists can play a fundamental role in diagnosing NP-C patients, as the disease may not be as rare as currently thought. It is vital that neurologists are aware of the disease and are able to recognize the signs and symptoms that could be indicating NP-C.

Dr Frédéric Sedel, MD, PhD
Coordinator of Neurometabolic Unit, Reference Center for Lysosomal Diseases, Pitié-Salpêtrière Hospital, Paris

How to use this guide

The aim of this guide is to help neurologists increase their awareness of how NP-C might present in childhood, adolescence and adulthood; 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.
**Have you considered NP-C?**

<table>
<thead>
<tr>
<th>Patients with NP-C may present with progressive neurological or visceral symptoms, starting at any age from infancy to adulthood²⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If one of the following symptoms is present, the patient should be considered for further follow-up, including discussion with a specialist NP-C center. For more information visit <a href="http://www.npc-si.com">www.npc-si.com</a>.</strong></td>
</tr>
<tr>
<td><strong>The following neurological symptoms are less specific on their own. However, they are frequent and, in combination with the specific signs to the left, could prompt referral of the patient to a specialist NP-C center.</strong></td>
</tr>
</tbody>
</table>

**Vertical supranuclear gaze palsy (VSGP)**

One of the earliest neurological signs of NP-C and present in almost all cases.

VSGP initially affects the vertical gaze, in particular downward gaze. This can advance to impaired vertical and horizontal eye movements, making activities like reading and going downstairs difficult.³ Initial eye movement abnormalities are most commonly seen from late infancy, but VSGP may not present until late adolescence or adulthood. VSGP should be checked by asking the patient to voluntarily look up and down; patients are unable to look voluntarily down or do it very slowly. In contrast, slow eye pursuit is often well preserved.

**Gelastic cataplexy**

Although present in a minority of children and adults with NP-C, gelastic cataplexy is a characteristic feature of NP-C. Patients may experience sudden loss of muscle tone (without loss of consciousness), which is typically triggered by an emotional stimulus, for example laughter. Loss of tone may involve the legs, neck or jaw. Therefore, cataplexy may manifest as sudden falls, sudden head drop or jaw drop, triggered by laughing.

**Isolated splenomegaly or hepatosplenomegaly**

Isolated splenomegaly or hepatomegaly is another hallmark sign of NP-C. It is present in nearly all patients in all age categories. It varies in intensity¹ and may be particularly difficult to recognize in adults, where an abdominal ultrasound is required.

**Cerebellar ataxia**

Patients may present with poorly coordinated movements affecting walking or manipulation.³ Ataxia may start at any age from late childhood to adulthood and can be progressive.

**Cognitive decline**

Patients may present a progressive fronto-temporal dementia together with progressive memory loss. This type of presentation is frequent in adults who experience disease onset after 25 years of age.

**Dystonia and movement disorders**

Patients may demonstrate abnormal dystonic postures in hands, feet or face. Combination of dystonic postures with cerebellar ataxia is suggestive of NP-C.⁴⁵ Other movement disorders such as action myoclonus, myoclonic tremor and Parkinsonism have been observed in a few patients.

**Dysphagia**

Dysphagia may be present early in the disease course and may manifest as difficulty swallowing liquids. During disease progression, severe dysphagia can lead to aspiration and malnutrition.

**Dysarthria**

Dysarthria is a consequence of a combination of cerebellar and dystonic syndromes. It is characterized by poor articulation and slurred speech.

**Seizures**

Partial and/or generalized seizures are frequently observed in the juvenile form of the disease but are rare in the adult form.

**Hearing loss**

Progressive hearing loss may be a presenting feature of NP-C and may be present in at least 10% of patients.
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.

In combination with other signs of the disease, these symptoms could prompt referral of the patient to a specialist NP-C center.

**Early-onset psychosis**
Patients may experience paranoid delusions, hallucinations, delusional ideation, disturbance with aggression, self-mutilation or social isolation.5

**Prominent visual hallucinations**
Patients may experience prominent visual hallucinations in addition to other psychotic symptoms.5,6

**Incomplete response to treatment**
Despite treatment for psychiatric symptoms, for example neuroleptics and mood stabilizers, patients may still experience significant residual positive psychotic symptoms, which are resistant to treatment.5

It is important that neurologists link together the visceral, neurological and psychiatric symptoms that a patient might present with, in order to reach a fast and differential diagnosis of NP-C.

Patients may also present with the following psychiatric symptoms in adulthood

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset psychosis</td>
</tr>
<tr>
<td>Prominent visual hallucinations</td>
</tr>
<tr>
<td>Incomplete response to treatment</td>
</tr>
</tbody>
</table>

Prominent visual hallucinations could prompt referral of the patient to a specialist NP-C center.

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
5. Sevin M, Lesca G, Baumann N et al. The adult form of Niemann–Pick disease type C. Brain. 2007; 130: 120–133