Niemann-Pick disease Type C (NP-C): a clinically challenging disorder

A rare genetic, progressive and irreversible neurovisceral lysosomal lipid storage disease affecting patients at any age

Caused by mutations in two genes, NPC1 and NPC2, which results in intracellular lipid accumulation in various tissues, including the brain, liver and spleen

Affects approximately 1:10,000 neonates

Clinical manifestation varies with age

NP-C clinical diagnosis and prognosis

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

Early onset of neurological symptoms is directly linked to severity of NP-C

Irreversible progressive neurological symptoms result in premature death in most patients

Clinical experts recommend initiating specific therapy at the first appearance of neurological symptoms

References

1. Vanier MT. Niemann-Pick disease Type C. Orphanet J Rare Dis 2010;5:16.

Online tools and mobile applications

visit: [NPC-SI.com](http://NPC-SI.com)
or download the app for free in the online stores:


The NEW Niemann-Pick disease Type C (NP-C) Suspicion Index (SI): designed to improve NP-C screening in clinical practice

Making the connection

Identifying symptom combinations to improve detection of Niemann-Pick type C (NP-C)

Visit the NEW NPC-SI.com for practical guidance on diagnosing Niemann-Pick disease Type C

The NEW Ni-Pick Suspicion Index is...

- quick, convenient and easy-to-use
- to help physicians identify patients with clinical suspicion of NP-C
- by determining which patients to send for confirmatory testing²
- age-specific to ensure correct assessment of patients from all ages:
  - NP-C SI 0–4y for patients under 4 years old
  - NP-C SI >4y for patients over 4 years old
- superior at discriminating patients with NP-C from those without compared with the original NP-C SI
- the result of the collaboration of international experts in NP-C

References

1. Vanier MT. Niemann-Pick disease Type C. Orphanet J Rare Dis 2010;5:16.

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Facilitating the identification of NP-C in patients with an unclear diagnosis

The NEW Niemann-Pick Disease Type C Suspicion Index (NP-C SI) provides:

- New analyses of the original NP-C SI database, considering combinations of signs and symptoms
- Improved discriminatory performance versus the original NP-C SI in patients aged >4 years using the NP-C SI >4y
- A new infantile database of patients aged >4 years was used to produce a NP-C SI tool with improved discriminatory performance in this age group NP-C SI 0–4y
- Shown to detect more patients with NP-C versus the original NP-C SI in an additional patient cohort*1
- Shown to detect more patients with NP-C versus the original NP-C SI in a clinical setting, and in whom you suspect NP-C

The NEW NP-C SI allows a quick and easy assessment of your patients with unclear diagnosis, and in whom you suspect NP-C

Find out how to use the NP-C Suspicion Index in the following pages

The 7 key discriminatory signs and symptoms of NP-C in patients older than 4 years*2

- Prolonged, unexplained neonatal jaundice or cholestasis
- Isolated unexplained splenomegaly (historical and/or current) + hepatomegaly
- Pre-senile cognitive decline and/or dementia
- Vertical supranuclear gaze palsy (VSGP)
- Gelastic cataplexy
- Psychotic symptoms (hallucinations, paranoid delusions + thought disorder)
- Parent, sibling or cousin with NP-C

NP-C should be highly suspected when 2 or more of these 7 key discriminatory signs and symptoms, or VSGP alone, are present in your patient*2

If NP-C is suspected: the NP-C SI >4y should be used to confirm suspicion and to obtain additional clinical information

* Because only 7 signs and symptoms are assessed, this list does not reflect a comprehensive clinical picture of NP-C and should not be used as an isolated screening tool

Developed utilising the same patient cohort as the original NP-C SI, the benefit of symptom combinations in determining suspicion of NP-C was assessed*3
- All signs and symptoms contained within the original NP-C SI were reassessed
- Assessment of symptoms individually and in specific combinations provides superior predictive performance versus the original NP-C SI
- The 7 key discriminatory symptoms are integrated into the online NP-C SI >4y

Calculating a risk prediction score (RPS)

1. Select the age of your patient
2. Carefully assess the symptoms of your patient
3. Select the symptoms in the Suspicion Index
4. Calculate the score to assess the likelihood of NP-C

Due to the advanced calculation of the total RPS based on combinations of symptoms, the NEW NP-C SI >4y can only be used online or as an app.

The NEW Niemann-Pick Disease Type C Suspicion Index in patients aged up to 4 years

- Developed utilising a novel infantile cohort consisting of 200 patients to determine the key discriminatory signs and symptoms of NP-C in this age group
- Family history of NP-C and visceral symptoms are highly suggestive of NP-C in infantile patients
- Infantile specific discriminatory symptoms provide improved discriminatory performance versus the original NP-C SI tool

Calculating a risk prediction score

1. Work your way through the disease categories adding points as appropriate
2. Pay close attention to the co-occurrence of ataxia and/or mental regression with central nervous system (CNS) or splenic symptoms
3. Calculate the total RPS for your patient by adding the totals for each category
4. Refer your patient as appropriate

Calculating the total RPS for your patient by adding the totals for each category

- Referral to an NP-C centre for immediate testing
- Ensure other possible causes have been discounted
- Contact your nearest NP-C referral centre for further discussion

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Interpreting the results

Two outputs will be derived from the refined adult NP-C SI: a total RPS and a percentile score.

- Total RPS: sum of individual RPS for each contributing symptom and symptom combinations
- Percentile score compares the total RPS against all patients from the cohort database

<table>
<thead>
<tr>
<th>Total RPS</th>
<th>Percentile rank</th>
<th>Suspicion of NP-C</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>&gt;40</td>
<td>113%</td>
<td>High likelihood</td>
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</tr>
<tr>
<td>20–39</td>
<td>5–12%</td>
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Interpreting the results

The NP-C SI 0–4y is derived from an independent patient cohort; the total infantile RPS therefore cannot be directly compared with RPS derived from other NP-C SI tools

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Plots

- NPGSI.com
- CNS signs
- Splenomegaly
- Liver signs
- Hepatomegaly
- Abdominal pain
- Asymmetry
- Gastric sign
- CNS signs
- Spinal curvature

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