SPOTLIGHT ON

NIEMANN-PICK DISEASE TYPE C (NPC)

Overcoming Diagnostic Challenges to Help Improve Patient Outcomes

Walla Al-Hertani, MD, MSc, FRCPC, FCCMG, FACMG

Chief and Medical Director, Division of Metabolic Disorders
Clinical Geneticist and Biochemical Geneticist
Rady Children's Health

NPC at a Glance[1]

LOOK FOR SYMPTOMS	THINK NPC	CONFIRM DIAGNOSIS
If you see – Ataxia/clumsiness – Seizures – Vertical supranuclear gaze palsy – Hepatosplenomegaly	think **NPC** and	**Confirm diagnosis with** – Biomarker analysis of plasma oxysterols – Genetic testing for *NPC1* and *NPC2*

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NPC Is a Rare Lysosomal Storage Disorder That Is Underdiagnosed

NPC is a progressive and life-limiting genetic disorder that manifests with neurological and neurodegenerative symptoms.[1-3] Lysosomal storage disorders (LSDs), such as NPC, lead to abnormal cholesterol trafficking.[1] It is estimated that **approximately 1 in 100,000 infants are diagnosed**, highlighting NPC as an ultra-rare condition.[1] In late-onset forms, the approximate incidence ranges from **1 in 19,000 to 36,000 adults**.[4] The heterogenous presentation of the disease may contribute to underestimation of the incidence of NPC.[1] Furthermore, diagnosis is typically delayed, as symptom presentation may be subtle, progress at different rates, or be misattributed to numerous different diseases.[5] **In fact, the estimated diagnostic delay for patients with NPC is 4.1 years** from the first onset of neurological symptoms.[5] Misdiagnosis or delayed diagnosis may contribute to additional physical, psychological, and intellectual impairments, which can in turn limit the effectiveness of treatments and lead to irreversible damage.[1]

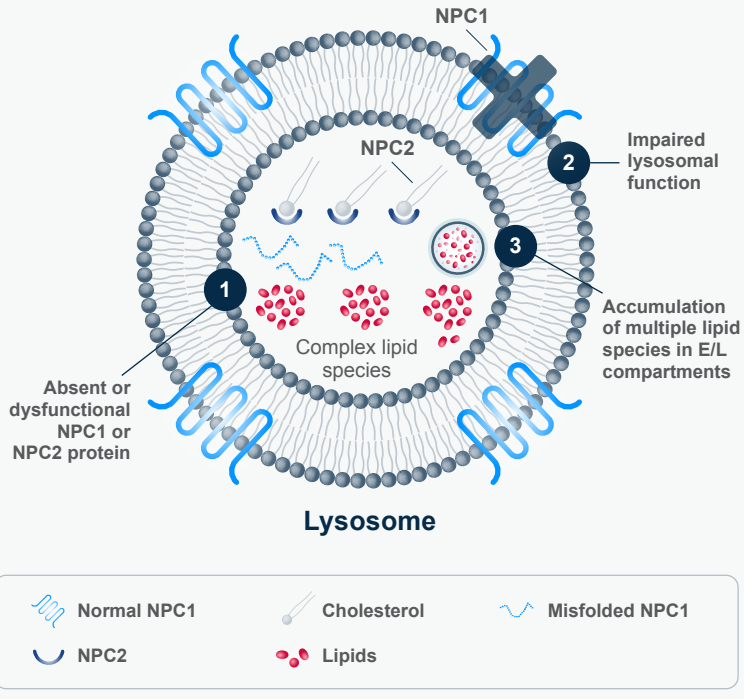
"NPC is so heterogenous that it can be challenging to identify. Some specialties may not have access to testing or know how to proceed which contributes to missed or delayed diagnoses."

— Walla Al-Hertani, MD, MSc, FRCPC, FCCMG, FACMG

NPC Is Caused by Genetic Mutations in *NPC1* or *NPC2*

NPC is caused by mutations in *NPC1* or *NPC2* genes, which are responsible for producing proteins that aid in the cellular export of cholesterol and lipids.[6] There are >486 *NPC1* and 27 *NPC2* pathogenic variants.[7] **In the absence of functional NPC1 or NPC2 protein *(step 1)*, lysosomal function is impaired *(step 2)* and multiple lipid species accumulate in the endosome/lysosome compartment *(step 3)*** (Figure 1).[8] This contributes to the neurological and neurodegenerative symptoms that patients with NPC experience.[1]

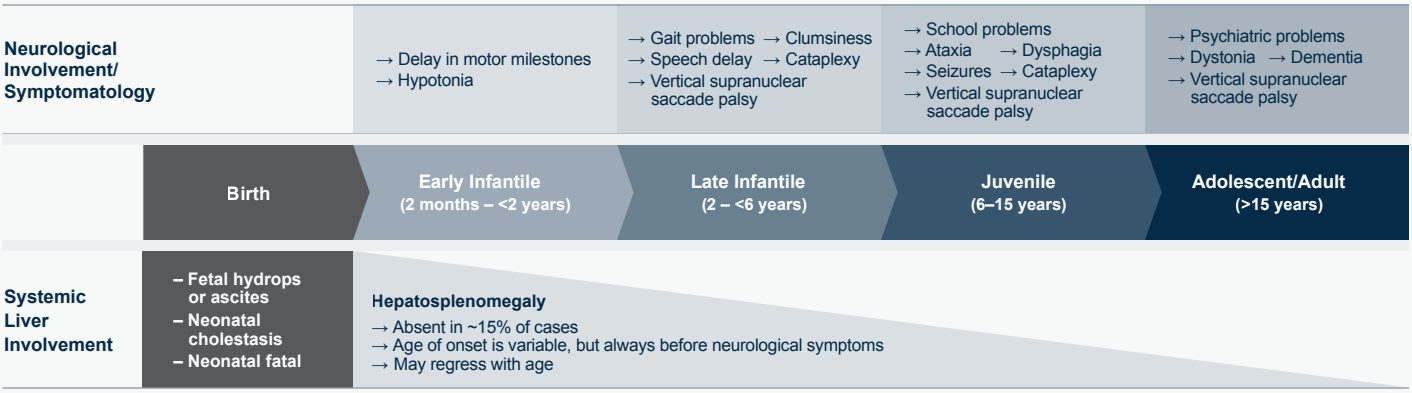
Figure 1. Overview of NPC Pathophysiology[8]



Symptom Recognition Is Key to Accurate and Timely Diagnosis

Recognizing the symptoms of NPC can be challenging, as **symptoms may manifest at any age and progress uniquely in each patient** (Figure 2).[1] Visceral manifestations, including those observed in the liver, spleen, and occasionally the lungs, typically occur in the neonatal or infantile stage.[6] Neonatal or infantile disease onset often leads to a more rapid and fatal disease course.[1] In comparison, adult-onset forms usually manifest as a slowly progressing neurodegenerative disease.[1] Symptoms occur across a broad spectrum and may include neurological symptoms (eg, aphasia, dysarthria, dystonia, dysphagia, ataxia, seizures, cataplexy), impaired eye movements, psychiatric symptoms (eg, early-onset cognitive decline, schizophrenia/psychosis [an atypical sign of NPC]), and cognitive impairments (eg, developmental delay).[1,6] **NPC should be considered a differential diagnosis**, and groups at risk for NPC diagnosis include those with movement disorders, such as ataxia, clumsiness, or dystonia, and those with cognitive disorders, such as intellectual disability, developmental delay, cognitive impairment, and early-onset decline or dementia.[4]

Figure 2. NPC Symptom Presentation Over Time[6]

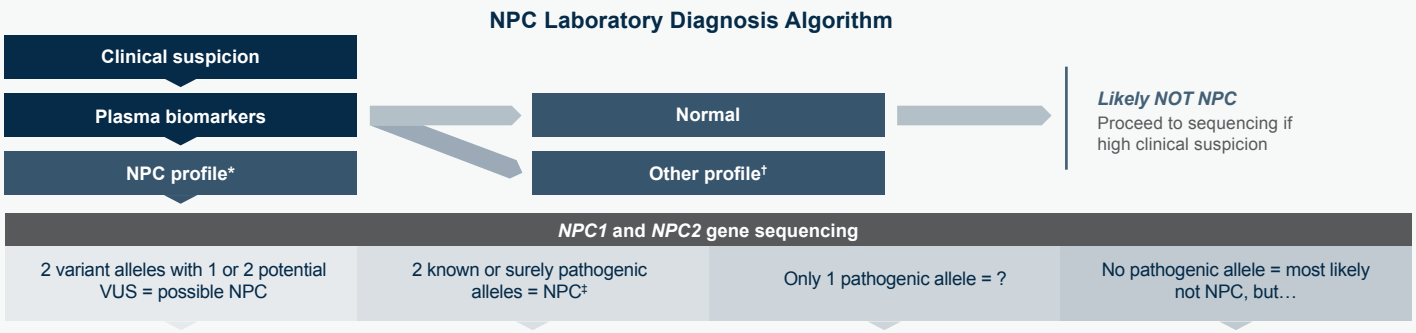


Genetic Testing Is Required to Confirm a Diagnosis of NPC

Biomarker and genetic testing are critical to diagnose patients with NPC (Figure 3).[1] Biomarker testing is recommended for patients with a strong clinical suspicion of NPC, those belonging to at-risk clinical groups, and patients exhibiting signs such as splenomegaly or hepatosplenomegaly, neurological or psychiatric symptoms, or for neonates and young infants presenting with cholestatic jaundice.[4] Biomarker classes to test for include plasma oxysterols.[4] Biomarker testing offers several advantages, as it is noninvasive, rapid, high throughput, and available at a lower cost.[4] **Although biomarker testing may be a first approach to quickly identify potential patients with NPC, genetic testing is required to confirm a NPC diagnosis**.[1] Both *NPC1* and *NPC2* genes should be sequenced, as mutation in either of these genes may cause similar symptom presentation.[1,9]

> *"Genetic testing may indicate a variant of uncertain significance (VUS) which may prompt physicians to stop pursuing a diagnosis, especially in ethnic minorities. If you see a VUS, test for plasma oxysterols to confirm NPC."*
>
> **— Walla Al-Hertani, MD, MSc, FRCPC, FCCMG, FACMG**

Figure 3. NPC Diagnostic Algorithm[1]



*Elevated cholestane-triol or bile acid derivative and/or lysoSM-509, with normal or slightly elevated lysoSM.
†Cholestane-triol also elevated in ASMD, acid lipase deficiency, cerebrotendinous xanthomatosis, and certain neonatal cholestasis conditions. All lysoSM analogues and bile acid derivatives are elevated in ASMD.
‡Check allele segregation by parental study or other test.

Timely Diagnosis and Treatment Initiation Are Associated With Improved Patient Outcomes

Early identification of NPC, and the appropriate use of symptomatic and disease-specific therapies, are critical to improve patient quality of life.[10] Studies have shown that there is a narrow window of opportunity for successful patient outcomes, and early diagnosis and treatment initiation are essential given the progressive nature of the disease course.[11] Patients started on therapy at younger ages display more developmental milestones, since treatment is initiated before disease progression worsens.[11] Therefore, patients who are diagnosed as a result of sibling screening should be monitored closely, and treatment should be considered at the first sign of neurological disease onset.[10] Guideline recommendations strongly encourage minimizing the time between the first neurological dysfunction symptom and further investigation or referral to expert centers.[10]

> *"Early diagnosis is so important for this condition because we now have treatments available to manage it."*
>
> **— Walla Al-Hertani, MD, MSc, FRCPC, FCCMG, FACMG**

Key Takeaways

- Staying vigilant and proactive in recognizing the symptoms of NPC is necessary, as they can emerge at different stages and progress uniquely in each patient[1]
- If you observe ataxia/clumsiness, seizures, vertical supranuclear gaze palsy, or hepatosplenomegaly in your patients, consider NPC[1]
- Reducing misdiagnosis, through genetic and biomarker testing, is vital to accelerate treatment initiation and improve patient outcomes[1,10]

Healthcare professionals play a pivotal role in identifying patients with NPC, ensuring early diagnosis to access treatment. Your expertise and attentiveness are vital in recognizing the signs and symptoms early.

Scan here to close the gap in NPC care and discover patients who may have been overlooked

Learn about a product for NPC

References:

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