Infantile-Onset Niemann-Pick Disease, Type C (I-NPC)

Disease-state backgrounder: severity, progression, and burden of I-NPC

> For a family, I-NPC most often begins not with a diagnosis but with a question: why is my child not reaching developmental milestones or losing skills they had just months ago? Niemann-Pick disease, type C (NPC) is a rare, inherited condition that progressively damages the brain and nervous system.[1,2] In infantile-onset NPC (I-NPC), the first neurological signs appear before a child's sixth birthday; a child who is still learning to walk, to speak, and to feed themselves, and these skills do not get better on their own. Behind every diagnosis is a family navigating a relentless, progressive illness: coordinating specialists, adapting the home, school accommodations, and managing feeding, movement, and seizures while holding on to ordinary childhood. This backgrounder explains what I-NPC is, how it progresses, how it affects families, and why an earlier diagnosis matters.

What is NPC?

NPC is an inherited lysosomal disorder that causes progressive neurodegeneration (loss of brain and nerve cells) and premature death, caused by variants (mutations) in the *NPC1* (~95% of cases) and *NPC2* genes.[1,2] These disease-causing variants disrupt the body's ability to properly move (or traffic) cholesterol and other lipids inside the cells. As a result, cholesterol accumulates and cannot be transported to where the cell needs it. This buildup affects every cell in the body but is most devastating in the brain and nervous system, driving progressive neurological decline and increased cell death in multiple organs and tissues.[2,3] More severe *NPC1* mutations cause faster cholesterol accumulation, earlier neurological onset, and more rapid progression.[4] Once neurological symptoms appear, the disease does not stabilize or reverse.[3]

NPC is inherited in an autosomal recessive manner, meaning both biological parents are typically carriers of variants in the same gene even when there is no family history.[2] Siblings may be affected before any symptoms appear and warrant evaluation at the time of a sibling's diagnosis.[3]

Severity and the NPC spectrum

All forms of NPC share the same underlying biology and are progressive and life-shortening; what differs is how early neurological symptoms appear and how fast they progress.[2] The 2025 international consensus guidelines classify NPC into subtypes based on age of neurological symptom onset (Table 1). Age at onset remains the strongest predictor of disease course and life expectancy.

Table 1. NPC age of neurological onset, diagnostic delay, and age at death[a]

NPC subtype	Age of neurological onset[2]	Mean diagnostic delay[5,b]	Mean age at death[6]
Early I-NPC	<2 years	2.5 years	5.6 years
Late I-NPC	2 to <6 years	4.3 years	13.4 years
Juvenile NPC	6 to 16 years	Over 6 years	25.9 years
Adult NPC	Over 16 years	Over 6 years	33.7 years

[a]Pre/perinatal NPC not included as this subtype is a visceral form of NPC (e.g., liver disease most commonly presenting with prolonged cholestatic jaundice and hepatosplenomegaly).[2]

[b]Mean delay between neurological symptom onset and confirmed diagnosis.[2,5]

Abbreviations: I-NPC, infantile-onset NPC; NPC, Niemann-Pick disease, type C.

The early and late subtypes (neurological onset before age 6) make up I-NPC, and account for about half of all NPC diagnoses.[2,7] I-NPC is associated with the most rapid neurodegeneration, accelerated clinical progression, and markedly increased risk of premature mortality.[1,6] Juvenile and adult NPC usually progress more slowly and carry longer life expectancies, but share the same eventual decline. Across the NPC spectrum, aspiration pneumonia from dysphagia (difficulty swallowing), respiratory complications, and seizures are the most common proximate causes of death.[1] While these figures in Table 1 are population averages, individual trajectories vary widely, and the disease course can differ even between siblings.[6,7]

I-NPC clinical presentation

In early I-NPC, hypotonia (low muscle tone), delayed motor milestones such as learning to walk, and speech delay are the defining signs; hepatosplenomegaly (enlarged liver and/or spleen) and/or prolonged neonatal jaundice (yellowing of the skin and eyes from impaired bile flow) are almost always present.[2] As the disease progresses, children may develop spasticity (muscle stiffness), dysphagia (difficulty swallowing), and vertical supranuclear gaze palsy (VSGP, loss of the ability to move the eyes up and down on command).[1,2]

Late I-NPC often begins with clumsiness, gait disturbance, fine-motor skill difficulty, loss of previously acquired developmental milestones, and speech delay; a history of neonatal cholestatic jaundice, seizures, lung disease, or hepatosplenomegaly may also be present.[2] As the disease advances, children develop progressive ataxia (loss of coordination), dysarthria (slurred speech), and dysphagia. Hallmark eye-movement signs are often present early but easily missed: vertical supranuclear saccadic palsy (VSSP, slowing of rapid up-and-down eye movements) typically appears first and progresses to VSGP.[2,3] Gelastic cataplexy (sudden loss of muscle tone triggered by laughter) or sensorineural hearing loss can be the first symptoms, and dystonia (sustained muscle contractions causing twisting) and worsening seizures develop later.

Living with I-NPC: the burden on families

I-NPC reshapes daily life for the whole family. As swallowing becomes unsafe, mealtimes turn into a medical task, with thickened foods, careful positioning, and often a feeding tube, alongside the constant worry of aspiration and pneumonia.[8,9] As coordination and muscle control decline, a child who once walked may need support, a wheelchair, and help with everyday movement, and the home may need ramps, lifts, or a hospital bed. Seizures bring emergency plans, rescue medications, and broken sleep. Behavior, attention, and communication change in ways that are hard to explain to others.

Much of the work is invisible: parents become full-time care coordinators, scheduling and chasing specialists (neurology, gastroenterology, ophthalmology, ENT, audiology, physical and occupational therapy, and more) while managing medications, equipment, insurance, and school. Education and social life require constant accommodation as abilities change.[8,9] The caregiving load is relentless and falls heaviest on parents and siblings, with real tolls on work, finances, mental health, and family relationships. In a survey of NPC families, most caregivers reported altering their daily behavior and taking on additional caregiving as the disease advanced, and more than half said their own quality of life was affected through sadness, anxiety, and worry, the strain of being constantly on alert, social isolation, and giving up work.[8] Families consistently rank eating and drinking, mobility, communication, and self-care among the daily abilities they most want to preserve.[8,9]

Diagnostic delay

NPC is rare, reported in roughly 1 in 100,000 births, but genetic data suggest the true number is higher (closer to 1 per 89,229 conceptions) and that most cases go undetected.[2,10] It is estimated that about two-thirds of individuals with NPC are never diagnosed under today's clinical-suspicion-driven pathway.[11,12] As shown in Table 1, families wait years between a child's first neurological symptoms and a confirmed diagnosis. In I-NPC, where mean age at death is 5 to 13 years, a delay of 2 to 4 years consumes a large fraction of a child's expected lifespan.[5,6]

For families, this delay means 2 things: a diagnostic odyssey that can stretch for years and missed early windows for therapies and supportive care. The path is often a series of pediatrician visits, inconclusive tests, and single-symptom referrals (to ENT, ophthalmology, audiology, neurology, and hepatology) before anyone connects the symptoms to a single genetic disease.[2] Time and again, it is the caregiver who pushes for the next evaluation when the pieces do not add up. In a survey of NPC families, about half of patients first received an incorrect diagnosis, among them were Lyme disease, attention deficit disorder (ADD), autism, and psychiatric conditions.[9]

Why an earlier diagnosis matters

I-NPC follows a stepwise downward course: developmental delay or loss of skills in the first years, progressive ataxia, slurred speech, swallowing difficulty in early-to-mid childhood, and a late phase of severe dystonia, swallowing failure, seizures, and loss of mobility.[1,2,7] Since neurological decline in

I-NPC begins while children are still learning basic skills like walking, talking, and feeding themselves, each year without a diagnosis means losing developmental time that can never be recovered.[2] Earlier diagnosis shapes outcomes that families and clinicians can influence: the opportunity to limit disease progression by using foundational therapies that treat the underlying biology of NPC; access to multidisciplinary supportive care for feeding, breathing, seizures, and mobility, as well as planning for educational, social, and home accommodations; enrollment in natural-history studies and clinical research; informed reproductive planning; and the capacity to plan around predictable disease milestones rather than react to them.[2,7]

A diagnosis is the beginning of the journey. I-NPC is managed over years by a changing team (neurology, gastroenterology, pulmonology, therapists, dietitians, and others), and families need sustained, coordinated support that evolves as the disease does.[2] An earlier diagnosis gives families the time, the information, and the standing to advocate for their child, connect with the NPC community, and reach the care and research their child needs, before more time is lost.

References

1. Vanier MT. Niemann-Pick disease type C. *Orphanet J Rare Dis.* 2010;5:16. doi:10.1186/1750-1172-5-16
2. Hiwot T, Porter FD, Bremova-Ertl T, et al. 2025 Consensus Clinical Management Guidelines for Niemann-Pick Disease Type C. *J Inherit Metab Dis.* 2026;49(3):e70185. doi:10.1002/jimd.70185
3. Patterson MC, Clayton P, Gissen P, et al. Recommendations for the detection and diagnosis of Niemann-Pick disease type C: An update. *Neurol Clin Pract.* 2017;7(6):499-511. doi:10.1212/CPJ.0000000000000399
4. Musalkova D, Majer F, Kuchar L, et al. Transcript, protein, metabolite and cellular studies in skin fibroblasts demonstrate variable pathogenic impacts of NPC1 mutations. *Orphanet J Rare Dis.* 2020;15(1):85. doi:10.1186/s13023-020-01360-5
5. Patterson MC, Mengel E, Vanier MT, Moneuse P, Rosenberg D, Pineda M. Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease Type C: a final report of the NPC Registry. *Orphanet J Rare Dis.* 2020;15(1):104. doi:10.1186/s13023-020-01363-2
6. Imrie J, Heptinstall L, Knight S, Strong K. Observational cohort study of the natural history of Niemann-Pick disease type C in the UK: a 5-year update from the UK clinical database. *BMC Neurol.* 2015;15:257. doi:10.1186/s12883-015-0511-1
7. Bolton SC, Soran V, Marfa MP, et al. Clinical disease characteristics of patients with Niemann-Pick Disease Type C: findings from the International Niemann-Pick Disease Registry (INPDR). *Orphanet J Rare Dis.* 2022;17(1):51. doi:10.1186/s13023-022-02200-4
8. Mengel E, Patterson MC, Chladek M, et al. Impacts and Burden of Niemann pick Type-C: a patient and caregiver perspective. *Orphanet J Rare Dis.* 2021;16(1):493. doi:10.1186/s13023-021-02105-8
9. Ara Parseghian Medical Research Fund, et al. Niemann-Pick Type C Patient and Caregiver Voices: Externally-led, Patient-Focused Drug Development Meeting. March 18, 2019; Hyattsville, MD. Published September 2019. Accessed June 4, 2026. https://niemannpickc-pfdd.com/wp-content/uploads/2020/05/NPC-PFDD-Voice-of-the-Patient-report-ver2-1.pdf
10. Wassif CA, Cross JL, Iben J, et al. High incidence of unrecognized visceral/neurological late-onset Niemann-Pick disease, type C1, predicted by analysis of massively parallel sequencing data sets. *Genet Med.* 2016;18(1):41-48. doi:10.1038/gim.2015.25
11. Burton BK, Ellis AG, Orr B, et al. Estimating the prevalence of Niemann-Pick disease type C (NPC) in the United States. *Mol Genet Metab.* 2021;134(1-2):182-187. doi:10.1016/j.ymgme.2021.06.011
12. Pineda M, Mengel E, Jahnová H, et al. A Suspicion Index to aid screening of early-onset Niemann-Pick disease Type C (NP-C). *BMC Pediatr.* 2016;16:107. doi:10.1186/s12887-016-0641-7