Clinical and family burden across I-NPC severity groups

Niemann-Pick disease type C (NPC) is a rare, progressive, and fatal neurodegenerative disorder caused by impaired cholesterol trafficking.[1,2] Infantile-onset NPC (I-NPC; neurological symptom onset <6 years of age) is the most severe and rapidly progressing form of NPC.[1-3]

DISEASE BURDEN BY SEVERITY GROUP

The profiles below illustrate disease burden across severity groups in children with I-NPC, along with the associated caregiving burden.[4]
Participants with I-NPC from an Expanded Access Program (EAP) were grouped into four severity groups, Minimal (0–4), Mild (5–8), Moderate (9–12), and Severe (13–20), based on their baseline rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) scores.
The R4DNPCCSS is a 0–20 composite score of four domains: ambulation, fine motor, speech, and swallowing.[5]
See **METHODS** for more information on R4DNPCCSS domains and scoring.

	MINIMAL (0–4) A largely self-sufficient child with early neurological impairment	MILD (5–8) A child who needs support to move, speak, and learn	MODERATE (9–12) A child with advanced multi-domain neurodegeneration	SEVERE (13–20) A child with profound neurodegeneration and complete dependence
Ambulation	Clumsy gait with frequent falls when walking; stroller/ walker use for long distances	Impaired by ataxia; unsteady gait; posterior walker, ankle-foot orthotics or stroller for distance	Dependent on a walker or wheelchair; many cannot sit or stand unaided	All are non-ambulatory or wheelchair-dependent; spasticity, dystonia, and even scoliosis limit mobility
Fine motor	Largely self-sufficient; VSGP can be present but is not functionally limiting	Mild dysmetria/dystonia; still feeds themselves; VSGP is present in most	Marked tremor, dysmetria, and dystonia; many are dependent on daily activities	Fine motor function largely lost; fully dependent on self-care; prevalent dystonia
Speech	Mild dysarthria; typical classroom with individual plan	Severe dysarthria; single words or signs; special education is common	Reduced speech, relying on communication device; most are on PT/OT/speech therapy	Minimal or absent speech; communication device required
Swallow	Normal oral diet	Choking when eating; may require soft foods, but still feed orally	Marked dysphagia; G-tube feeding often required; issues with aspiration pneumonia	Severe dysphagia with aspiration; G- or GJ-tube feeding required
Family & Caregivers	**Coordinating** therapy visits, school advocacy, and monitoring; no mobility aids or in-home care; age-typical family and social activities	**Hands-on care**; coordinating multiple therapies and adaptive equipment; monitor mobility, feeding, and communication	**Assistance on most daily activities**; possible home nursing, tube feeding, and airway management; treatment competes with school activities	**Total, around-the-clock care**: feeding, airway management, and hygiene; home nursing and complex medical support; frequent hospitalizations, with school secondary to medical needs

As I-NPC progresses, increasing neurological impairment is accompanied by increasing caregiving demands. As the R4DNPCCSS score rises, caregiving shifts from coordinating therapies to hands-on assistance to total, around-the-clock nursing care.

METHODS

Representative profiles were synthesized from EAP investigator questionnaires and participant narratives.[4] Forty-three participants with I-NPC were mapped to baseline severity groups (Minimal, n=20; Mild, n=8; Moderate, n=7; Severe, n=8). These profiles describe typical presentations and do not represent an individual patient; features within a severity group may not apply to every child.

R4DNPCCSS BY DOMAIN (composite score is the sum of the 4 domains; 0–20)

The R4DNPCCSS is a modified version of the 5-domain NPC-CSS, which includes the domains most relevant to patients, caregivers, and clinicians: ambulation, swallowing, cognition, speech, and fine-motor skills.[5] The R4DNPCCSS eliminates the cognitive domain and adds an improved swallow scoring algorithm. Higher scores indicate greater impairment.

Score	Ambulation	Fine motor	Speech	Swallow
0	Normal	Normal	Normal	Normal
1	Clumsy, bangs into things	Slight dysmetria/dystonia (independent manipulation)	Mild dysarthria	Cough while eating
2	Ataxic unassisted gait	Mild dysmetria/dystonia (little assistance, feeds self)	Severe dysarthria	Intermittent dysphagia
3	—	—	Non-verbal / functional communication skills	Dysphagia
4	Assisted ambulation	Moderate dysmetria/dystonia (limited motor skills, difficulty feeding self)	—	NG/G tube for supplemental feeding
5	Wheelchair dependent	Severe dysmetria/dystonia (needs assistance)	Minimal communication	NG/G tube feeding only

The value of 3 is not an option for rating NPC-CSS ambulation and fine motor skills, and the value of 4 is not an option for rating NPC-CSS speech.

ABBREVIATIONS: EAP, Expanded Access Program; G, gastric; GJ, gastro-jejunal; I-NPC, infantile-onset NPC; NG, nasogastric; NPC, Niemann-Pick disease type C; NPC-CSS, NPC Clinical Severity Scale; OT, occupational therapy; PT, physical therapy; R4DNPCCSS, rescored 4-domain NPC Clinical Severity Scale; VSGP, vertical saccade gaze palsy.

REFERENCES: 1. Vanier MT. *Orphanet J Rare Dis*. 2010;5:16. **2.** Imrie J, et al. *BMC Neurol*. 2015;15:257. **3.** Bianconi SE, et al. *Mol Genet Metab*. 2019;126(4):466-469. **4.** Data on File. Beren Therapeutics P.B.C. **5.** Mengel E, et al. *Mol Genet Metab Rep*. 2025;43:101233.