IN HUNTER SYNDROME

GAG buildup never stops, so neither will I.[1-3]

For patients with Hunter syndrome, or mucopolysaccharidosis type 2 (MPS II), there is an unmet need for addressing CNS symptoms and normalizing GAGs in both the brain and the body.[3-6]

With scientific advancements on the horizon for Hunter syndrome, read on to learn more and stay prepared.

CNS=central nervous system; GAG=glycosaminoglycan.

Why GAG normalization in the brain matters for all patients with Hunter syndrome[7-9]

While severe Hunter syndrome is characterized by GAG accumulation in the brain and neurocognitive decline, patients with attenuated Hunter syndrome **may also experience behavioral issues, inattentiveness, and hyperactivity**.[7-9]

GAG levels are elevated in the brain of patients with severe or attenuated Hunter syndrome[7]

	CSF GAG level (ng/mL)
Children without Hunter syndrome (n=201)	<37-202
Adults without Hunter syndrome (n=31)	<37-95
Children with attenuated Hunter syndrome (n=2)	357-373
Adults with attenuated Hunter syndrome (n=4)	382-1181
Children with severe Hunter syndrome (n=19)	424-3427

Data based on an analysis from 4 studies of GAG levels in the CSF in 257 individuals, including 25 with Hunter syndrome. These 4 studies included a phase 1-2, multicenter, randomized, open-label, interventional study of Hunter syndrome patients with cognitive manifestations; a multicenter study of pediatric and adult Hunter syndrome patients; a single-center study of healthy adult volunteers; and analysis of samples from children without Hunter syndrome.[7]

In a study that included 51 patients with non-neuronopathic Hunter syndrome, 65% (n=33/51) reported neurologic symptoms by age 10 and 33% (n=17/51) after age 10.[8,a]

[a]Clinical manifestations classified in this study were recorded using predefined fields from the HOS database.[8]
CSF=cerebrospinal fluid; HOS=Hunter Outcome Survey.

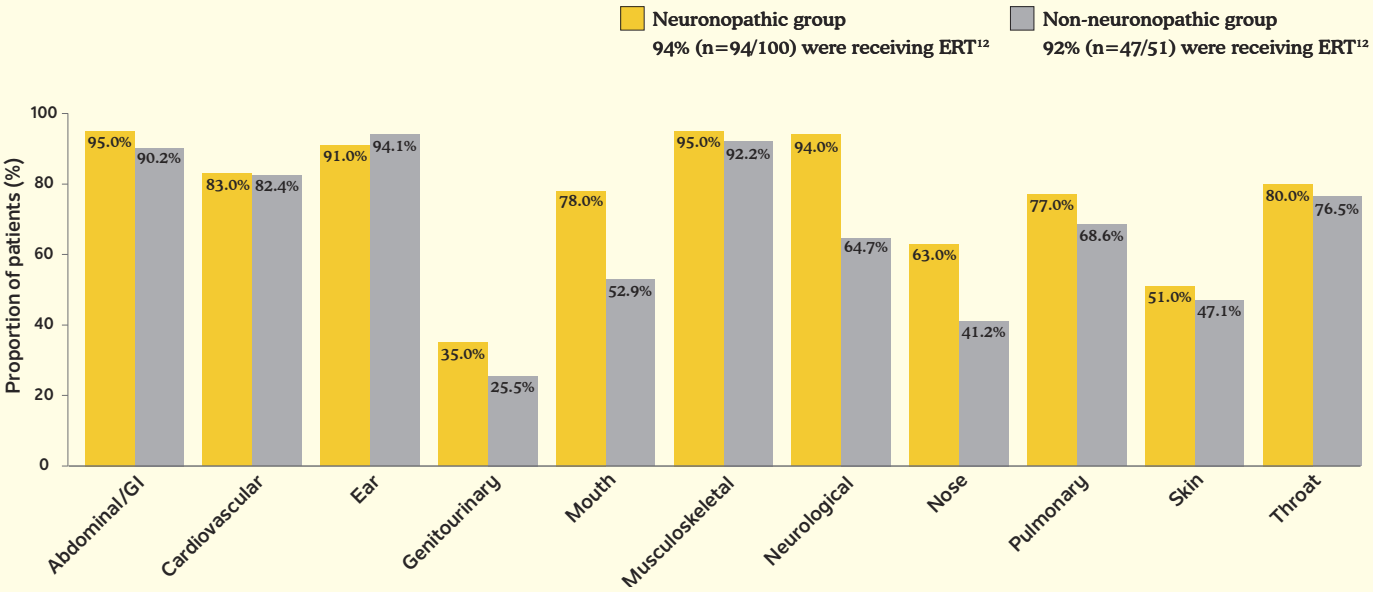
GAG accumulation continues in the brain and body due to insufficient clearance[2,3,6]

Despite current treatment, prolonged exposure to elevated GAG levels can contribute to a range of multisystem symptoms that worsen over time.[8,10,11]

- Both severe and attenuated Hunter syndrome patients experience varying degrees of somatic manifestations. Incomplete GAG reduction over time can contribute to joint pain, hearing loss, carpal tunnel syndrome, and—most importantly—respiratory and cardiac issues, which have been shown to be the primary cause of mortality[12-18]
- For many patients across the disease spectrum, neurologic issues such as cognitive decline and behavioral challenges emerge as part of the disease's manifestations[8]

Incomplete GAG reduction contributes to the continued development of disease manifestations[8]

Somatic and neurologic manifestations in patients in the Hunter Outcome Survey[8,b]



Adapted from Lau H, Harmatz P, Botha J, Audi J, Link B. Clinical characteristics and somatic burden of patients with mucopolysaccharidosis II with or without neurological involvement: an analysis from the Hunter Outcome Survey. *Mol Genet Metab Rep.* 2023;37:101005. © 2023 The Authors. Published by Elsevier Inc.

The impact of GAG accumulation should be considered for all patients. Individuals across the disease spectrum eventually develop clinically significant symptoms.[8,18]

[b]Data presented are disease manifestations in Hunter syndrome patients by age 10.[8]
ERT=enzyme replacement therapy; GI=gastrointestinal.

Emerging CNS biomarkers may provide additional promising information[6,19-22]

The use of CNS biomarkers in Hunter syndrome continues to evolve and may have utility in the future to support disease management.[6]

In Hunter syndrome, heparan sulfate (HS) is one major GAG that accumulates in the brain.[6,23]

Measurement of CSF HS can reflect GAG accumulation in the brain, but clinical utility may be limited due to the invasiveness of sample collection.[21]

NfL, a structural protein in brain neurons, is released into the bloodstream during neuronal degeneration or damage and has been linked to cognitive decline in other neurodegenerative conditions.[24-28,c]

Serum NfL provides a less invasive alternative for monitoring neurodegeneration, with studies showing a correlation between elevated NfL levels and CSF HS concentrations.[6,29]

Sign up to stay up-to-date on information and advancements in Hunter syndrome. Scan the QR code or visit **KnowHunterSyndrome.com** to learn more.

[c]Huntington's disease and Parkinson's disease.[26,28]
NfL=neurofilament light.

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