THINK MPS IIIA

If your patient is experiencing developmental delay, think MPS IIIA

Mucopolysaccharidosis type IIIA (MPS IIIA), also known as Sanfilippo syndrome type A, is a rare, nearly universally fatal neurodegenerative disorder that results in severe and progressive cognitive, language, and motor decline.[1,2]

Early diagnosis and management are critical to slow disease progression and maximize quality of life for children and their families.[3]

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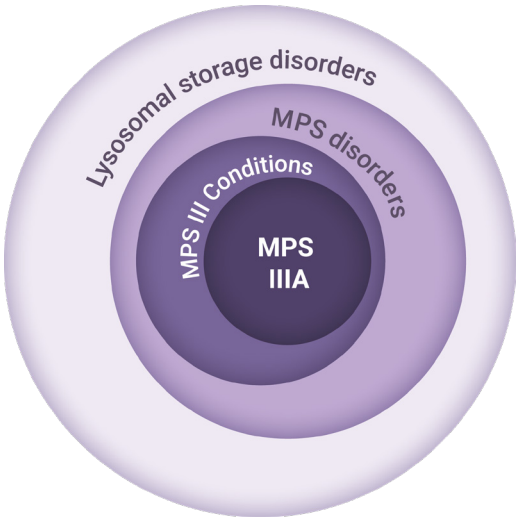
MPS IIIA is a rare lysosomal storage disorder that leads to toxic accumulation of heparan sulfate[1,4]

MPS IIIA is a lysosomal storage disorder caused by a deficiency in the enzyme sulfamidase due to pathogenic variants of the *SGSH* gene.[1,5]

This deficiency leads to the toxic accumulation of heparan sulfate—a disease-causing biomarker—resulting in cellular dysfunction and the clinical symptoms of MPS IIIA.[1,6]



Pathophysiology of MPS IIIA[1,6]

Unaffected Form of *SGSH*

The unaffected form of *SGSH* carries instructions for cells to create sufficient sulfamidase

Sulfamidase metabolizes heparan sulfate

Variant Form of *SGSH*

The variant form of *SGSH* in children with MPS IIIA leads to an absent or dysfunctional sulfamidase

Deficiency in functional sulfamidase leads to toxic accumulation of heparan sulfate within cells, causing eventual cell damage

Sulfamidase | Heparan sulfate | Dysfunctional sulfamidase

Children with MPS IIIA face rapid and progressive decline, leading to premature death[1,2]

Children with MPS IIIA appear healthy at birth and develop normally until around 2 years of age, when developmental delays and behavioral problems begin to emerge.[7,8]

Following a developmental plateau, children with MPS IIIA experience severe and progressive neurodegeneration, leading to a decline in cognitive, verbal, and motor skills.[1,9] Premature death, often due to respiratory, neurologic, or gastrointestinal complications, typically occurs by 20 years of age.[2,10]

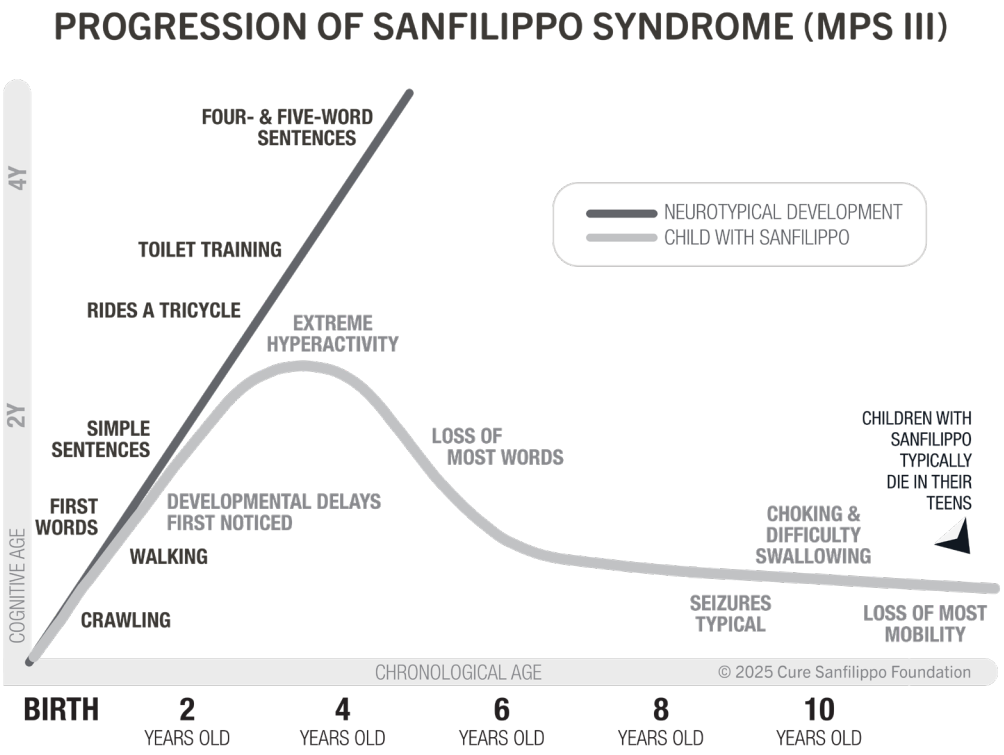


Figure represents studies of disease impact in rapidly-progressing forms of Sanfilippo Syndrome
Figure created by and used with permission of Cure Sanfilippo Foundation.

Early diagnosis is critical for the management of MPS IIIA, yet families commonly face diagnostic delays[3]

In a study of children with MPS III, the median diagnostic delay* was **~3 years** and the median age at diagnosis was **~5 years**[12]

*Defined as the time between the first medical specialist visit and final diagnosis of MPS III.[12]

Early symptom recognition and screening are key to shortening the diagnostic journey[3]

Symptoms of MPS IIIA overlap with other developmental disorders, including autism spectrum disorder and attention-deficit/hyperactivity disorder (ADHD), complicating the clinical picture.[13]

Common Behavioral Symptoms[1,14-16]

Children may experience hyperactivity that does not respond to medication, impulsive and aggressive behavior, lack of danger awareness, and autistic-like social and emotional behaviors

Common Sleep Disturbances[1,17]

Common manifestations include difficulty falling asleep, frequent nighttime waking, disruptive nighttime behavior (eg, singing, laughing), early morning waking, daytime somnolence

Children with MPS IIIA exhibit a physical appearance that is common across all MPS III subtypes[1]

- Dolichocephaly or macrocephaly[1]
- Coarse facial features (eg, thick alae nasi, lips, and ear helices or lobules, macroglossia)[1]
- Hirsutism and synophrys[1]
- Dry, coarse, thick hair[1]
- Oral abnormalities (eg, gingival hyperplasia, misshapen teeth, enamel defects, open bite)[18]
- Tough, thick skin[1]
- Protuberant abdomen[19]

Images from left to right: From Baldini 2020,[20] Escolar 2020,[13] Escolar 2020,[13] Galimberti 2018.[21]

In many cases, these features are mild and may go unnoticed early in the disease course[22,23]

MPS IIIA can impact nearly all body systems[1]

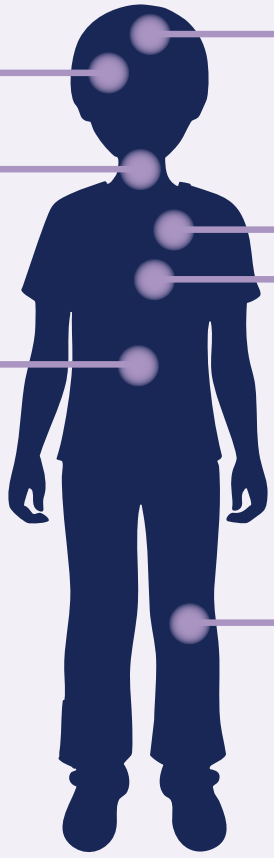
Although cognitive, neurologic, and behavioral issues are the hallmarks of MPS IIIA, nearly all body systems can be affected through the progressive course of the disease, with variability across individual children.[1]

Multisystemic manifestations of MPS IIIA[24]

Ophthalmologic
Vision problems
Retinal damage

Ear, nose, and throat
Otitis media
Hearing loss
Recurrent sinusitis
Tonsils and adenoid hypertrophy
Tracheomalacia
Sleep apnea
Dysphagia

Gastrointestinal
Hepatosplenomegaly
Diarrhea and/or constipation
Umbilical and inguinal hernias



Other neurological manifestations
Hydrocephalus
Loss of language

Cardiovascular
Mild valvular problems

Respiratory
Reduced lung function
Frequent coughs and colds

Musculoskeletal
Joint stiffness, pain, deformities or dislocation
Scoliosis
Early osteoporosis
Clinodactyly
Difficulty fully extending arms
Knock knees
Tight Achilles tendon
Loss of mobility

Diagnosing MPS IIIA

Urinary glycosaminoglycan (GAG) analysis can screen for MPS IIIA but diagnosis is confirmed using genetic testing and/or enzyme activity assay[3]

SCREENING[3,25]

Urinary GAG screening[3,25]

- Cannot rule out diagnosis due to poor sensitivity and high rates of false negatives
- Abnormal/negative results with clinical suspicion of MPS are confirmed via genetic testing and/or enzyme activity assay

DIAGNOSIS[1,3]

Genetic testing

- Identifies pathogenic variants in *SGSH*[1,3]

AND/OR

Enzyme activity assay[1]

- Measures the activity of all 4 enzymes associated with MPS III
- Very low or absent activity of sulfamidase, with normal activity of the other 3 MPS III enzymes, confirms an MPS IIIA diagnosis

Recognizing MPS IIIA: a case study

A 7-year-old male was referred to neurology with hyperactivity, speech delay, and behavioral problems that had developed since the age of 3 years.[23]

Developmental history

- Walked at 2 years
- Spoke first words at 3 years
- Slowing of psychomotor development with restlessness, impulsivity, and hyperactivity, which prompted referral to pediatric psychiatrist
- Diagnosed with ADHD and started on risperidone with no improvements in neurologic status after 6 months

Past medical history

- Born at term, uncomplicated delivery
- No family history of speech delay or intellectual disability
- History of recurrent upper respiratory tract infections

Physical exam

- Mild coarse facial features, slightly depressed nasal bridge, frontal bossing, and stocky hands with short fingers (Figure A)
- Appeared anxious with mild speech impairment

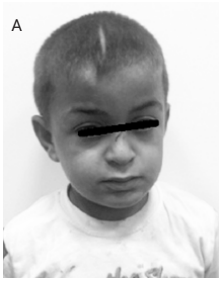


Figure A: Facial dysmorphism (reproduced with permission).[23]

Screening

- Negative urinary GAG screening
- MRI of the brain showed thinning of the corpus callosum, dilated perivascular spaces within the body of the corpus callosum, J-shaped sella turcica, enlarged subarachnoid area, and cysts within the body of the corpus callosum (Figure B)

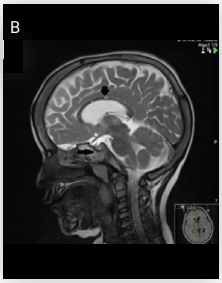


Figure B: MRI of the brain (reproduced with permission).[23]

DIAGNOSIS

Given clinical suspicion for an MPS disorder, enzyme analysis was performed and showed null activity of sulfamidase, confirming an MPS IIIA diagnosis.

Is your patient experiencing developmental delay?

THINK MPS IIIA

- MPS IIIA results in toxic accumulation of heparan sulfate[4]
- Children with MPS IIIA experience progressive neurocognitive decline and multisystemic consequences, leading to premature death[1,2]
- Early symptom recognition and screening can shorten the diagnostic journey[3]
- MPS IIIA management is supportive and focused on treating symptoms and preventing complications[3]

To learn more about MPS IIIA, visit thinkmpsiiiahcp.com

MPS, mucopolysaccharidoses; MRI, magnetic resonance imaging.

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