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Brain MRI and MR Spectroscopy in Pediatric Mucopolysaccharidoses: Diagnostic Utility, Biomarkers, and Correlation with Neurodevelopment

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ABSTRACT

***Background*:** Pediatric mucopolysaccharidoses (MPS) encompass a group of lysosomal storage disorders characterized by deficient degradation of glycosaminoglycans, leading to progressive multisystem and central nervous system (CNS) involvement. Brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have emerged as critical tools for identifying and quantifying CNS pathology, which underlies the neurodevelopmental decline seen in neuronopathic MPS subtypes such as MPS I Hurler, MPS II severe Hunter, and MPS III Sanfilippo syndrome. Structural MRI provides detailed visualization of white matter abnormalities, cortical and subcortical atrophy, ventricular enlargement, and perivascular space dilation—findings that parallel disease severity and progression. Meanwhile, advanced MRI modalities including volumetrics, diffusion tensor imaging (DTI), and quantitative susceptibility mapping are increasingly recognized for their sensitivity to microstructural changes, often preceding overt clinical deterioration.

Magnetic resonance spectroscopy offers a complementary metabolic perspective by detecting alterations in neuronal and glial markers. Decreased N-acetylaspartate (NAA) and elevated myo-inositol (mIns) and choline (Cho) levels reflect neuronal loss, gliosis, and neuroinflammation—pathologic hallmarks of MPS-associated neurodegeneration. These metabolic abnormalities correlate with neurodevelopmental outcomes and may serve as early indicators of CNS involvement before structural MRI changes become apparent. As emerging therapies such as intrathecal enzyme replacement, gene therapy, and substrate reduction strategies increasingly target CNS pathology, sensitive and reliable imaging biomarkers are urgently needed to monitor treatment response.

Despite substantial progress, challenges remain in standardizing imaging protocols, establishing pediatric normative ranges, and correlating imaging findings with clinical outcomes. Variability in sedation requirements, disease severity, and voxel placement complicates longitudinal assessment. Nevertheless, growing evidence supports the integration of MRI, MRS, and developmental testing into a multimodal framework capable of capturing the complexity of CNS involvement in MPS.

This review synthesizes current knowledge on the diagnostic utility of MRI and MRS in pediatric MPS, highlights validated and emerging imaging biomarkers, and explores their correlation with neurodevelopmental function. By consolidating structural, microstructural, and metabolic imaging insights, this review aims to guide clinicians and researchers toward improved diagnosis, monitoring, and therapeutic evaluation in children with neuronopathic MPS.

Keywords: Brain MRI and MR Spectroscopy, Mucopolysaccharidoses

INTRODUCTION

Central nervous system (CNS) involvement represents one of the most challenging aspects of pediatric mucopolysaccharidoses

(MPS), particularly in neuronopathic forms such as MPS I Hurler, MPS II severe Hunter, and all subtypes of MPS III. Progressive accumulation of glycosaminoglycans (GAGs) in neurons, glia, and meningeal tissues leads to neuroinflammation, white matter injury, and neuronal loss. Clinically, these processes manifest as developmental delay, behavioral dysregulation, cognitive decline, and loss of adaptive functioning. As therapeutic strategies increasingly target CNS pathology through intrathecal enzyme delivery, gene therapy, and substrate modulation, there is an urgent need for accurate, sensitive biomarkers to detect early brain involvement and monitor disease progression. Brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have therefore become central tools for evaluating the neurobiological underpinnings of neurodevelopmental deterioration in MPS [1–4].

MRI provides structural and microstructural insight into disease burden, revealing characteristic abnormalities including white matter hyperintensities, cortical and cerebellar atrophy, ventriculomegaly, hippocampal atrophy, and enlarged perivascular spaces. Studies demonstrate significant correlations between MRI abnormalities and neurodevelopmental decline, making imaging a valuable surrogate for clinical assessment, especially in children whose cognitive testing is limited by severe impairment or behavioral challenges. Quantitative modalities—such as volumetric analysis and diffusion tensor imaging (DTI)—offer even greater sensitivity by identifying microstructural changes before overt atrophy appears on conventional imaging. However, variability in MRI protocols and timing across clinical centers continues to limit widespread standardization of imaging biomarkers [5–8].

Magnetic resonance spectroscopy complements MRI by detecting metabolic disturbances that provide direct information on neuronal integrity and glial activation. Reduced N-acetylaspartate (NAA), elevated myo-inositol (mIns), and alterations in choline-containing compounds have been repeatedly observed in MPS I, II, and III, reflecting neuronal injury, demyelination, and gliosis. Importantly, metabolic abnormalities may precede structural MRI changes, making MRS a promising tool for early detection of CNS involvement and for monitoring therapeutic responses. As novel therapies aim to restore neuronal health and reduce neuroinflammation, MRS-derived biomarkers are increasingly incorporated into clinical trials as objective indicators of treatment efficacy [9–11].

Despite these advances, several challenges persist, including limited normative pediatric databases, variability in voxel placement, and the need for harmonized acquisition protocols across studies. A major research gap remains in defining robust correlations between imaging metrics and neurodevelopmental outcomes across diverse MPS phenotypes and treatment backgrounds. This review aims to synthesize current knowledge on the diagnostic utility of MRI and MRS in pediatric MPS, describe emerging neuroimaging biomarkers, and clarify the relationships between imaging findings and neurodevelopmental trajectories. By integrating structural, microstructural, and metabolic perspectives, this review seeks to inform both clinical practice and research directions in the evolving landscape of CNS-directed therapies for MPS [12–14].

Structural Brain MRI Findings in Pediatric MPS

Structural brain MRI plays a central role in characterizing CNS involvement in pediatric mucopolysaccharidoses, providing detailed visualization of abnormalities that correspond to disease burden and neurodevelopmental impairment. One of the most consistently reported findings across neuronopathic MPS types is **white matter hyperintensity** on T2-weighted sequences, reflecting delayed myelination, demyelination, gliosis, or edema secondary to glycosaminoglycan (GAG) accumulation and neuroinflammation. These white matter changes often begin in periventricular regions and expand centrifugally with disease progression. In children with MPS I Hurler and severe MPS II, the extent of white matter abnormality correlates with cognitive decline, adaptive dysfunction, and disease severity, underscoring MRI's ability to act as a surrogate biomarker when neurodevelopmental testing becomes unreliable in advanced stages [15–17].

Ventriculomegaly and **cortical and subcortical atrophy** are additional hallmark features observed on structural MRI in MPS. Enlargement of lateral ventricles is believed to arise from impaired CSF absorption or secondary white matter loss, while progressive cortical thinning reflects underlying neuronal death. In MPS III, cortical atrophy is often severe and accompanied by hippocampal volume loss, a finding that corresponds to early deficits in memory, language, and adaptive function. Several studies have identified that ventricular enlargement and corpus callosum thinning are associated with more rapid neurodevelopmental decline, suggesting that structural measurements may serve as quantifiable biomarkers in natural history studies and therapeutic monitoring. These changes become increasingly pronounced with advancing disease and are often detectable before overt neurological regression becomes clinically apparent [18–20].

Another distinctive feature in MPS is the presence of **dilated perivascular spaces**, which appear as round or linear CSF-like signal intensities within the basal ganglia, thalami, and subcortical white matter. These enlarged spaces reflect abnormal storage material within vascular and perivascular tissues and are particularly prominent in MPS I and III. While historically considered incidental, emerging evidence suggests that increased perivascular space burden correlates with neuroinflammation and cognitive impairment. Their presence may also assist in differentiating MPS from other leukodystrophies in neuroimaging-based diagnostics. Additional MRI findings—such as brainstem volume reduction, cerebellar atrophy, and signal abnormalities in the dentate nuclei—are variably reported and may reflect subtype-specific patterns of storage and degeneration. Collectively, these structural features highlight the broad diagnostic utility of MRI in evaluating disease progression and its neurological impact [21–22].

Advanced MRI Techniques: Diffusion, Volumetric, and Quantitative Imaging Biomarkers

Diffusion tensor imaging (DTI) has emerged as one of the most sensitive MRI modalities for detecting early microstructural changes in pediatric MPS, particularly within white matter tracts. Reductions in fractional anisotropy (FA) and increases in mean diffusivity (MD) have been consistently reported in MPS I, II, and III, indicating compromised axonal integrity and myelination. Notably, DTI abnormalities often appear **years before conventional T2 hyperintensities**, making them an important candidate biomarker for early CNS involvement. In Sanfilippo syndrome (MPS III), DTI changes in the corpus callosum, internal capsule, and frontal white matter correlate strongly with early declines in cognitive and adaptive functioning, suggesting that diffusion metrics may serve as predictive markers for neurodevelopmental deterioration. The sensitivity of DTI to subtle white matter injury makes it a valuable tool for monitoring response to emerging CNS-directed therapies, particularly gene therapy and intrathecal enzyme approaches [23–25].

Volumetric MRI provides additional insight into the structural consequences of GAG accumulation and neurodegeneration in MPS. Automated or semi-automated segmentation techniques have demonstrated progressive reductions in total brain volume, cortical thickness, hippocampal volume, and cerebellar volume across neuronopathic MPS types. In MPS III, hippocampal atrophy is particularly prominent and precedes measurable deficits in memory and language functions, highlighting its potential role as a structural biomarker. Similarly, reductions in corpus callosum thickness and white matter volume have been linked with cognitive decline in MPS I and II. Quantitative volumetric techniques allow for more objective and reproducible assessment of progression compared with qualitative radiologic interpretations, but challenges remain in standardizing normative pediatric datasets and harmonizing multicenter acquisition protocols [26–28].

Emerging quantitative imaging modalities, including quantitative susceptibility mapping (QSM), magnetization transfer imaging (MTI), and T1/T2 relaxometry, are expanding the imaging toolkit available for assessing CNS involvement in MPS. QSM has shown promise in detecting microglial activation and iron deposition—processes increasingly recognized in the neuroinflammatory cascade of MPS III. MTI has demonstrated early myelin abnormalities not visible on standard sequences, providing complementary information to DTI regarding white matter integrity. Quantitative relaxometry may help capture subtle changes in tissue composition associated with GAG accumulation, gliosis, and demyelination. While these advanced techniques are not yet routinely used clinically, early research suggests they may offer highly sensitive biomarkers for therapeutic monitoring and could become essential tools in future clinical trials targeting CNS disease in MPS [29–30].

Magnetic Resonance Spectroscopy (MRS): Metabolic Signatures of Neuronal and Glial Pathology

Magnetic resonance spectroscopy (MRS) provides crucial metabolic insights into the CNS manifestations of mucopolysaccharidoses, detecting early biochemical disturbances that often precede structural changes visible on MRI. One of the most characteristic findings is **reduced N-acetylaspartate (NAA)**, a marker of neuronal integrity and viability. Studies across MPS I, II, and III consistently demonstrate lowered NAA or reduced NAA/creatine (NAA/Cr) ratios, reflecting neuronal loss, axonal injury, or impaired mitochondrial metabolism. These reductions often correlate with cognitive decline, adaptive impairments, and worsening behavioral symptoms, underscoring the diagnostic value of NAA as an early biomarker of neurodegeneration. Importantly, diminished NAA can be detected even in young children prior to overt neurodevelopmental regression, making MRS a sensitive tool for early CNS surveillance [31–33].

In addition to neuronal loss, MRS captures signatures of **glial activation and neuroinflammation**, most notably through elevated **myo-inositol (mIns)** and, in some cases, increased **choline (Cho)** levels. Myo-inositol elevation, representing astrocytosis, has been repeatedly documented in MPS III and correlates with behavioral disturbances such as hyperactivity,

irritability, and sleep disruption. Increased Cho or Cho/Cr ratios may indicate altered membrane turnover, demyelination, or gliosis resulting from ongoing inflammatory processes triggered by GAG accumulation. Emerging studies also suggest abnormalities in glutamate–glutamine (Glx) peaks, potentially reflecting excitotoxicity, though these findings are less consistent. Together, these metabolic shifts provide a multifaceted picture of neuronal compromise, glial dysfunction, and inflammatory activity that is not obtainable through structural imaging alone [34–36].

A major advantage of MRS is its utility as a **biomarker for therapeutic monitoring**, particularly for emerging CNS-directed treatments such as intrathecal enzyme replacement, AAV-mediated gene therapy, and substrate reduction therapy. Early-phase trials in neuronopathic MPS II and III have demonstrated stabilization or partial improvement in NAA/Cr ratios following treatment, suggesting improvements in neuronal metabolism even when structural MRI remains unchanged. These metabolic responses may appear earlier than clinical improvement, highlighting MRS as a potential surrogate outcome measure in clinical trials. However, challenges remain—including voxel-placement consistency, scanner variability, and the need for pediatric normative datasets—to optimize the reliability of MRS as a longitudinal biomarker. Despite these limitations, MRS continues to gain prominence as a critical tool for evaluating CNS involvement and therapeutic response in pediatric MPS [37–38].

Correlating MRI and MRS Findings With Neurodevelopmental Outcomes

Correlating neuroimaging findings with neurodevelopmental outcomes is essential for understanding the trajectory of CNS involvement in pediatric MPS and for guiding clinical decision-making. Numerous studies have demonstrated that **white matter abnormalities**, ventricular enlargement, and cortical atrophy on MRI correlate with reduced cognitive scores, delayed language acquisition, and declining adaptive functioning. In MPS I and II, greater T2-weighted white matter hyperintensity burden is associated with poorer performance on developmental scales such as the Bayley Scales and Wechsler tests, indicating that demyelination and gliosis have direct clinical relevance. In MPS III, hippocampal and cortical atrophy strongly predicts early regression in communication, memory, and social behaviors. These associations underscore MRI's utility as an objective surrogate for cognitive decline, especially when standardized cognitive testing is limited by severe impairment or behavioral dysregulation [39–41].

Magnetic resonance spectroscopy provides a metabolic dimension to these structural–clinical correlations. Declines in **N-acetylaspartate (NAA)**, representing neuronal dysfunction and loss, strongly correlate with decreasing developmental quotient (DQ) or IQ scores in MPS I, II, and III. Elevated **myo-inositol (mIns)**, reflecting gliosis, has been linked with behavioral disturbances—particularly hyperactivity, anxiety, and sleep disruption—in Sanfilippo syndrome. These metabolic signatures often appear earlier than structural abnormalities, making MRS particularly valuable for predicting impending neurodevelopmental regression. In longitudinal studies, decreasing NAA/Cr ratios precede worsening Vineland Adaptive Behavior Scales scores, supporting MRS as an early indicator of neurocognitive decline. This temporal sensitivity positions MRS as a crucial tool for monitoring disease burden and treatment response [42–44].

As CNS-directed therapies advance, integrating MRI and MRS with neurodevelopmental assessments is increasingly necessary for comprehensive monitoring. Imaging biomarkers can detect subtle structural or metabolic stabilization that may not immediately translate into measurable cognitive gains on standardized tests, particularly in children already near developmental floor levels. Early clinical trials of intrathecal enzyme replacement and gene therapy have shown promising signals, such as stabilization of hippocampal volume or improved NAA levels, even when cognitive outcomes are less clear in short-term follow-up. Multimodal models combining imaging metrics with clinical scores offer more robust predictive power than either modality alone, helping identify responders to therapy and refine prognostic models. Continued refinement of these integrated frameworks will be critical for designing effective outcome measures in future therapeutic trials [45–47].

Diagnostic Utility of MRI and MRS in Pediatric Mucopolysaccharidoses

Brain MRI often provides the first objective evidence of CNS involvement in children with suspected mucopolysaccharidoses and can raise diagnostic suspicion even before a metabolic or genetic diagnosis is confirmed. The combination of **diffuse or periventricular white matter hyperintensities**, **dilated perivascular spaces**, **ventriculomegaly**, and **cortical or cerebellar atrophy** is highly suggestive of MPS in the appropriate clinical context of coarse facial features, organomegaly, and skeletal abnormalities. In some cases, neuroimaging is obtained for developmental delay or seizures, and the characteristic pattern of enlarged perivascular spaces and white matter changes prompts targeted metabolic testing, leading to earlier diagnosis. While MRI is not specific for MPS, recognition of these imaging patterns helps distinguish MPS from other leukodystrophies, hypoxic–

ischemic injury, or congenital malformations, thereby narrowing the diagnostic workup and accelerating appropriate biochemical confirmation [48–50].

MRS contributes additional **diagnostic specificity** by revealing metabolic disturbances compatible with lysosomal storage–related neurodegeneration. The combination of **reduced NAA** and **elevated myo-inositol** in cortex or deep gray matter structures supports a pattern of neuronal loss with gliosis, which, in the setting of systemic signs of MPS, strengthens the suspicion of CNS involvement. In Sanfilippo syndrome, for example, markedly reduced NAA/Cr in frontal and temporal regions is frequently observed, even at relatively early clinical stages. Though MRS findings are not pathognomonic for MPS, their presence in conjunction with typical MRI abnormalities can help differentiate MPS from primarily hypomyelinating disorders, in which NAA is often preserved. Furthermore, demonstrating such metabolic abnormalities at baseline offers a reference point for future monitoring once the diagnosis is confirmed and treatment initiated [51–53].

Beyond supporting diagnosis, MRI findings can be used to **stratify disease severity and inform prognosis** at the time of initial evaluation. More extensive white matter involvement, advanced cortical atrophy, and significant hippocampal volume loss are associated with a higher likelihood of rapid neurocognitive decline and earlier functional loss. In MPS I Hurler and severe MPS II, children who already exhibit marked ventriculomegaly and diffuse white matter signal changes at diagnosis are less likely to achieve age-appropriate developmental milestones even with prompt treatment. This prognostic information helps guide discussions with families regarding therapeutic options, realistic expectations, and the urgency of CNS-directed interventions. Thus, early MRI and, where feasible, MRS should be considered integral components of the diagnostic and baseline evaluation of children with suspected neuronopathic MPS [54–55].

MRI and MRS as Biomarkers in Therapeutic Monitoring and Clinical Trials

As CNS-directed therapies for mucopolysaccharidoses continue to advance, brain MRI has become a key component of **therapeutic monitoring** and clinical trial design. For intrathecal enzyme replacement therapy in neuronopathic MPS II, serial MRI has been used to track ventricular size, white matter hyperintensities, and cortical atrophy over time alongside neurocognitive measures. Long-term extension studies of intrathecal idursulfase have reported generally stable or slowly progressive structural changes in some treated patients, suggesting a potential attenuation of neurodegenerative progression compared with historical natural history cohorts, even though full prevention of CNS disease is not yet achieved [56–58]. Similarly, MRI is increasingly incorporated into trials of blood–brain barrier–crossing fusion enzymes and other biologics to document stabilization or slowing of brain volume loss and white matter injury in treated children with MPS I and II [59].

MRS has emerged as a complementary **pharmacodynamic biomarker** in early-phase CNS-targeted trials, offering a window into changes in neuronal and glial metabolism that may precede detectable clinical improvement. In pilot intrathecal enzyme replacement studies for MPS II, stabilization or modest improvement in NAA/Cr ratios and reduction in elevated myo-inositol peaks have been reported in some patients, suggesting partial amelioration of neuronal dysfunction and gliosis after treatment [37,56]. Likewise, preclinical and early human gene therapy work for neuronopathic MPS has highlighted the potential for MRS to demonstrate normalization of neuronal metabolites as a correlate of improved synaptic and network function, even before volumetric MRI changes are apparent [57,60–61]. These observations support the use of MRS as a sensitive tool for detecting early CNS responses and for differentiating biological activity from placebo effects in small pediatric cohorts.

The broader field of **gene and cell therapy for lysosomal storage disorders** has also driven the development of standardized neuroimaging frameworks that integrate MRI, MRS, and diffusion imaging as composite outcome measures. Consensus guidelines now emphasize the importance of prespecifying imaging endpoints, harmonizing acquisition protocols, and linking imaging changes with clinically meaningful outcomes such as stabilized developmental quotient or preserved adaptive skills [12,57,62]. Advanced analytic approaches, including automated volumetrics and quantitative susceptibility mapping, are being explored to enhance reproducibility and reduce observer variability in multicenter trials. As more CNS-directed therapies progress to late-stage development, regulatory agencies increasingly expect robust imaging data to support claims of neuroprotection. In this context, MRI and MRS are transitioning from purely descriptive tools to **central biomarkers** that underpin efficacy evaluation and long-term follow-up in pediatric MPS.

CONCLUSION

Brain MRI and magnetic resonance spectroscopy (MRS) have become indispensable tools for understanding the central nervous system involvement in pediatric mucopolysaccharidoses. Together, these modalities provide a comprehensive view of the

structural, microstructural, and metabolic abnormalities that underlie the neurodevelopmental deterioration characteristic of neuronopathic MPS subtypes. Structural MRI reliably demonstrates hallmark features such as white matter hyperintensities, cortical and hippocampal atrophy, ventriculomegaly, and enlarged perivascular spaces, each reflecting key aspects of disease pathology. Advanced MRI techniques—including diffusion tensor imaging and quantitative volumetric analyses—offer heightened sensitivity to early tissue injury, often detecting changes before clinical symptoms emerge. These imaging findings correlate strongly with cognitive, behavioral, and adaptive outcomes, reinforcing their relevance for diagnosis, prognostication, and longitudinal monitoring.

MRS adds a critical metabolic dimension by quantifying neuronal loss and glial activation through biomarkers such as decreased N-acetylaspartate and elevated myo-inositol. Because metabolic disturbances often precede visible structural alterations, MRS provides early insight into evolving CNS disease, enabling clinicians to monitor neurodegenerative processes at a stage when interventions may be most effective. As CNS-targeted treatments, including intrathecal enzyme replacement and gene therapy, progress through clinical development, MRS is emerging as a key pharmacodynamic marker capable of detecting early metabolic stabilization or improvement even in the absence of immediate neurocognitive gains.

Despite substantial advancements, challenges remain in standardizing MRI/MRS protocols, harmonizing multicenter imaging data, and establishing robust correlations across heterogeneous patient populations. The development of integrated neuroimaging frameworks that combine structural, diffusion, volumetric, and metabolic data will be essential to improving diagnostic accuracy and assessing therapeutic efficacy. As the field moves toward earlier detection and more effective CNS-directed therapies, MRI and MRS will continue to play central roles—not only as diagnostic and monitoring tools but also as validated biomarkers that shape clinical trial design, regulatory approval, and long-term care strategies.

Ultimately, the incorporation of multimodal neuroimaging into routine clinical management offers an opportunity to refine prognosis, guide personalized treatment plans, and improve neurodevelopmental outcomes for children affected by these devastating lysosomal storage disorders.

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