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Mucopolysaccharidosis and Its Orthopedic Manifestations – A Review

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KEYWORDS

Mucopolysaccharidosis, Calcium signalling, Orthopedic deformities, Skeletal abnormalities, Osteonecrosis .

ABSTRACT:

Mucopolysaccharidosis (MPS) represents a group of rare, inherited lysosomal storage disorders characterized by defective enzymatic degradation of glycosaminoglycans (GAGs). These sulphated carbohydrate polymers are integral to cellular architecture and signaling. In MPS, deficient or malfunctioning lysosomal enzymes lead to the accumulation of undegraded GAGs—such as heparan sulphate, dermatan sulphate, and keratan sulphate—within tissues, disrupting cellular homeostasis and triggering multisystemic manifestations. Clinically, patients exhibit a spectrum of features including coarse facies, cognitive impairment, hepatosplenomegaly, hernias, joint stiffness, and corneal clouding. The disease is classified into seven major subtypes (MPS I–IV, VI, VII, IX), each defined by a unique enzymatic defect and associated GAG profile, with variable severity and inheritance patterns. Among the most debilitating aspects of MPS are skeletal complications and these include thickened calvarium, malformed vertebrae, shortened long bones, and joint contractures, often resulting in restricted mobility, chronic pain, and orthopedic deformities. Musculoskeletal complications vary among the different subtype of MPS. This review synthesizes current knowledge on skeletal manifestations in MPS, drawing from literature published since 2000.

1.INTRODUCTION

Mucopolysaccharidosis (MPS) comprises a heterogeneous group of rare, inherited lysosomal storage disorders resulting from the deficiency or malfunction of specific enzymes responsible for breaking down glycosaminoglycans (GAGs). These long-chain sugar molecules, also known as mucopolysaccharides, play essential roles in cellular adhesion, proliferation, and intercellular signalling(Gaffke et al. 2021). MPS enzymes are involved in the sequential reduction of long-chain GAGs to monosaccharides, including heparan sulphate (HS), keratan sulphate (KS), and dermatan sulphate (DS)(Muenzer 2011). In individuals with MPS, the absence or reduced activity of these enzymes leads to the progressive accumulation of undegraded GAGs within lysosomes across various tissues and organs. This biochemical defect disrupts normal cellular function, triggering a cascade of clinical manifestations. Patients often present with coarse facial features, developmental delays or cognitive impairment, hepatosplenomegaly, umbilical or inguinal hernias, kyphoscoliosis, joint stiffness, and corneal clouding. The phenotypic spectrum of MPS is broad, encompassing several distinct subtypes (MPS I, II, III, IV, VI, VII, and IX), each defined by the deficiency of a

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unique enzyme and exhibiting variable severity and progression(Barone et al. 2018; Del Longo et al. 2018).

Among the most debilitating complications of MPS are those affecting the osteoarticular system. Skeletal abnormalities, collectively termed dysostosis multiplex, are hallmark features and include thickened calvarium, shortened and malformed long bones, abnormal vertebral bodies, and joint contractures. These changes often result in significant orthopedic challenges such as restricted mobility, chronic pain, and progressive deformities. Joint stiffness and limited range of motion are common, and in severe cases, patients may require surgical interventions to correct spinal instability or hip dysplasia (Borgo et al. 2018). Musculoskeletal involvement not only impairs physical function but also contributes to a reduced quality of life. Early diagnosis and multidisciplinary management—including enzyme replacement therapy (ERT), physical therapy, and orthopedic care—are crucial to mitigate disease progression and improve outcomes. Continued research into gene therapy and novel pharmacological approaches holds promise for more effective treatment strategies in the future.

The current review aims to summarise the current knowledge on the skeletal manifestation of MPS. To ensure comprehensive coverage, relevant literature was retrieved from databases including PubMed, Google Scholar, and others using the following search terms: “Mucopolysaccharidosis” OR “Mucopolysaccharidoses” [MeSH] OR “MPS” AND “Skeletal” OR “Orthopaedic” AND “Complication.” The search was limited to articles published in English from the year 2000 onward. Additional sources were identified through manual screening of reference lists from key publications. Studies focusing on pathophysiology, clinical presentation, diagnostic imaging, therapeutic interventions, and long-term orthopaedic outcomes were prioritized to provide a multidisciplinary perspective on skeletal involvement in MPS.

2.PATHOPHYSIOLOGY OF MPS

GAGs are a varied group of sulphated, linear carbohydrate polymers distributed widely across mammalian tissues. The GAGs are fundamental structural elements within the extracellular matrix and cell membranes, where they help maintain tissue hydration and provide biomechanical stability. Beyond their structural functions, GAGs are actively involved in intercellular signalling, influencing critical biological processes such as cell proliferation, adhesion, coagulation, and tissue regeneration. In the extracellular space, GAGs often act as co-receptors and reservoirs for signaling molecules, enhancing their local concentration and biological effectiveness(Raman et al. 2005).The catabolism of GAGs is tightly regulated by lysosomal enzymes, notably exoglycosidases and sulfatases. Exoglycosidases sequentially cleave sugar units from the termini of oligosaccharide chains, while sulfatases remove sulphate groups from specific sugar residues. These enzymatic steps follow a strict order, and any disruption, such as enzyme deficiency or dysfunction, can interrupt the degradation cascade, resulting in the pathological accumulation of partially degraded GAGs(Fecarotta et al. 2020).

MPS are a group of inherited metabolic disorders characterized by enzymatic failure leading to widespread clinical manifestations, including somatic, neurological, skeletal, hematologic, and ocular abnormalities. The pathological consequences extend beyond GAG accumulation and include secondary substrate storage, altered membrane lipid composition, defective vesicle trafficking, impaired autophagy, mitochondrial dysfunction, oxidative stress, and chronic inflammation. Additionally, disruptions in calcium signalling and homeostasis are frequently observed (Vitner et al. 2010; Platt et al. 2012).Alterations in GAG profiles such as elevated levels of heparan sulphate and reduced keratan sulphate, are commonly noted. Secondary metabolites like GM2 and GM3 gangliosides and lactosylceramide also accumulate. These stored compounds are chemically diverse, encompassing glycosphingolipids, phospholipids, and cholesterol, contributing to the heterogeneity of disease pathology. The different mechanisms involved in the pathophysiology of MPS is shown in Figure 1.

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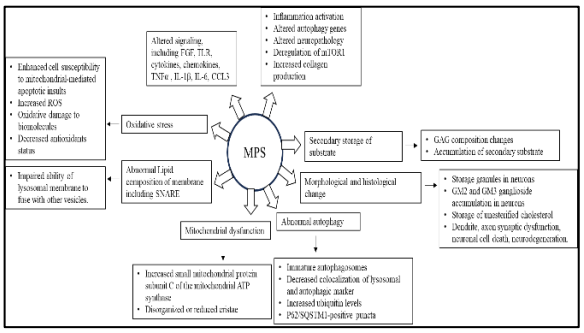

Figure 1: The pathophysiology of MPS.

3.CLASSIFICATIONOF MPS

MPS encompass a group of seven distinct lysosomal storage disorders, labeled MPS I through IX (except V and VIII), each defined by a specific enzymatic deficiency and the corresponding accumulation of GAGs. These disorders are differentiated based on the nature of the defective enzyme and the type of GAGs that build up in tissues as shown in Table 1.MPS I occurs in approximately 1 out of every 100,000 live births. MPS II, a rare X-linked condition, affects roughly 1 in 162,000 male newborns (Kabbassi et al. 2025; Hashmi et al., 2023). Historically, the Scheie variant was classified as MPS V, but due to overlapping clinical features, it has since been consolidated under MPS I (Fisher 2025). MPS III, commonly referred to as Sanfilippo syndrome, is subdivided into four autosomal recessive forms—types A, B, C, and D—each resulting from a deficiency in a distinct enzyme responsible for degrading heparan sulfate, a widely distributed GAG. The combined prevalence of these subtypes varies between 1 in 50,000 and 1 in 250,000, depending on the population studied. Among them, type A is the most frequently encountered worldwide. Types C and D are significantly rarer, with global incidence estimates of approximately 1 in 1.5 million and 1 in 1 million, respectively(Muschol et al. 2022a).MPS VI shows considerable variation in birth prevalence across populations, ranging from 0.0132 to 20 per 100,000 live births (D'Avanzo et al. 2021). In Asian populations, MPS II is the most prevalent subtype, accounting for 50–54% of diagnosed MPS cases. It is followed in frequency by MPS III, MPS I, MPS IV, and MPS VI (Zhou et al. 2020). MPS II is an X-linked disorder, while all other MPS classes are autosomal recessive.

Table 1: Classification of MPS.

MPS	Eponyms	Enzyme Deficient	Gene	Gene Locus	GAG	Clinical Severity
MPS I	Hurler	α-L-Iduronidase	IDUA	4p16.3	HS, DS	Severe
	Hurler-Scheie				DS	Intermediate
	Scheie				DS	Mild
MPS IIA	Hunter Type A	Iduronate -2-Sulfatase	IDS	Xq28	HS, DS	Severe
MPS IIB	Hunter Type B	Iduronate-2-Sulfatase	IDS	Xq28	HS, DS	Mild
MPS IIIA	Sanfilippo A	Heparan-N-Sulfatase	SGSH	17q25.3	HS	Variable in the severity
MPS IIIB	Sanfilippo B	α-N-Acetyl-Glucosaminidase	NAGLU	17q21.2	HS	Variable in the severity
MPS IIIC	Sanfilippo C	α-Glucosaminidase Acetyltransferase	HGSNAT	8p11.21	HS	Variable in the severity
MPS	Sanfilippo D	α-Acetylglucosamine6-	GNS	12q14.3	HS	Variable in the

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IIID		Sulfatase				severity
MPS IVA	Morquio A	α-Acetyl-Galactosamine-6-Sulfatase	GALNS	16q24.3	C6S, KS	Variable in the severity
MPS IVB	Morquio B	β-Galactosidase	GLB1	3p22.3	KS	Mild
MPS VI	Maroteaux Lamy	Nacetylgalactosamine 4-Sulfatase	ARSB	5q13	DS, C4S	Variable in the severity
MPS VII	Sly	β-Glucuronidase	GUSB	7q11.21	DS, HS, C4S,C6S	Variable in the severity
MPS IX	Hyaluronidase Deficient	Hyaluronidase 1	HYAL1	3p21.3	HA	Mild

HS: Heparan Sulfate, DS: Dermatan Sulfate, KS: Keratan Sulfate, C4S: Chondroitin-4-Sulfate, C6S: Chondroitin-6-Sulfate, HA: Hyaluronic Acid

4.ORTHOPEADIC COMPLICATIONS OF MPS I

Orthopaedic complications in individuals diagnosed with Hurler's syndromeare among the most debilitating and persistent clinical features of the condition. These musculoskeletal abnormalities primarily impact gait, independent mobility, and a wide array of skeletal structures, often manifesting early in life and progressing despite therapeutic interventions such as hematopoietic stem cell transplantation (HSCT). The burden of these complications significantly affects quality of life, functional independence, and long-term prognosis. Gait disturbances in Hurler's syndrome are multifactorial and evolve across developmental stages. In infancy and early childhood, individuals affected by this condition often experience delays in achieving motor milestones, particularly the initiation of independent walking. This delay is not merely a reflection of general developmental lag but is rooted in structural and functional impairments of the musculoskeletal system. As children grow, the quality of their gait remains compromised. Observations include reduced walking speed, shortened step length, and increased energy expenditure during ambulation. These inefficiencies in movement are often exacerbated by joint stiffness, muscle weakness, and skeletal deformities, making walking a physically demanding task even in the absence of overt neurological deficits.By late childhood and adolescence, mobility challenges become more pronounced. Many patients exhibit a decline in autonomous ambulation, with some requiring assistive devices or transitioning to partial or full wheelchair dependence. The progressive nature of these impairments underscores the importance of early intervention and ongoing physical therapy, although even with optimal care, deterioration is common due to the underlying pathophysiology of the disease.

Gross motor development in Hurler's syndrome is significantly hindered. Children often show marked delays in acquiring motor skills such as crawling, standing, and coordinated limb movements. This is compounded by joint contractures and limited range of motion, particularly in the upper extremities. Shoulder abduction, elbow extension, and wrist flexibility are frequently restricted, which not only affects mobility but also impairs fine motor tasks and self-care abilities. These limitations are attributed to the accumulation of GAGs within connective tissues, leading to thickening, fibrosis, and mechanical obstruction of joint function.One of the most critical and distinctive cervical spine abnormalities in Hurler's patients is odontoid dysplasia or hypoplasia. This condition involves incomplete ossification of the odontoid process, a bony projection of the second cervical vertebra (C2) that plays a vital role in stabilizing the atlantoaxial joint. When the odontoid fails to develop properly, it compromises the integrity of the cervical spine, increasing the risk of atlantoaxial instability and potential spinal cord compression. In addition to the bony defect, soft tissue deposits around the odontoid and hypertrophy of the longitudinal ligament further exacerbate cervical instability. These changes can be visualized through MRI and often

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necessitate surgical intervention to prevent neurological deterioration. Spinal deformities are another hallmark of Hurler's syndrome, with thoracolumbar kyphosis being particularly prevalent. This abnormal curvature of the spine, often presenting as a gibbus deformity at the L1-L2 vertebral level, results from anterior vertebral body wedging and growth plate dysfunction. The gibbus deformity is not only a diagnostic clue but also a source of mechanical pain and postural imbalance. Additional spinal anomalies include spondylolisthesis (forward slippage of one vertebra over another), thinning and elongation of the pedicles, hypoplasia of the facet joints, and scalloping of the posterior vertebral borders. These structural changes contribute to spinal instability, reduced flexibility, and increased susceptibility to compression injuries.

Hip abnormalities are also commonly reported in Hurler's syndrome and are primarily due to defective ossification processes during skeletal development. The acetabulum, which forms the socket of the hip joint, often fails to ossify properly, leading to acetabular dysplasia. This results in poor containment of the femoral head, causing lateral displacement, subluxation, or even complete dislocation in severe cases. These deformities impair weight-bearing capacity and contribute to gait abnormalities. Radiographic evaluations frequently reveal shallow acetabular roofs and irregular joint congruency, necessitating orthopedic monitoring and, in some cases, surgical reconstruction. Knee involvement typically manifests as progressive genu valgum, commonly referred to as "knock knees." This condition is characterized by an increased tibi ofemoral shaft angle, often exceeding 7°, with documented pre-operative averages around 17.9°. The deformity arises from irregular growth and ossification of the proximal tibial metaphysis, leading to angular misalignment of the lower limbs. Genu valgum not only affects the mechanical axis of the leg but also contributes to joint pain, instability, and difficulty in ambulation. Surgical correction, such as guided growth or osteotomy, may be considered in cases where conservative management fails to halt progression.The hands of individuals with Hurler's syndrome are frequently affected by carpal tunnel syndrome (CTS), a condition resulting from compression of the median nerve within the carpal tunnel of the wrist. In Hurler's patients, CTS is primarily caused by GAG deposition in the flexor retinaculum, which thickens and narrows the tunnel space. This is compounded by skeletal deformities such as bullet-shaped metacarpals and joint contractures, which further restrict hand function. Symptoms of CTS include numbness, tingling, and weakness in the hands, often impairing fine motor skills and daily activities. Diagnosis may be challenging due to communication barriers in young children, and electrophysiological studies are often required for confirmation. Surgical decompression is a common treatment, though recurrence is possible due to ongoing GAG accumulation.

Collectively, the orthopaedic manifestations of Hurler's syndrome represent a complex interplay of developmental, structural, and biochemical factors. Despite advances in systemic therapies such as enzyme replacement and stem cell transplantation, many skeletal abnormalities remain refractory to treatment. Regular imaging, multidisciplinary care, and individualized orthopedic interventions are essential to manage these complications and preserve functional capacity. The lifelong nature of these musculoskeletal challenges necessitates ongoing surveillance and adaptive strategies to support mobility, independence, and quality of life in affected individuals (Weisstein et al. 2004; Taylor et al. 2008; van der Linden et al. 2011).

5.ORTHOPEADIC COMPLICATIONS OF MPS II

In individuals diagnosed with MPS II/Hunter's disease, skeletal abnormalities are among the most prevalent clinical features. The majority of patients exhibit some form of musculoskeletal involvement, underscoring the systemic nature of the disorder. One of the more visible and functionally significant consequences is abnormal gait. Data from the Hunter Outcome Survey (HOS), a comprehensive registry tracking clinical outcomes in MPS II patients, has revealed a strong association between orthopedic manifestations and other systemic complications, particularly those involving the central nervous system (CNS) and pulmonary function. This correlation suggests that skeletal involvement may serve as a clinical marker for disease severity and progression.

Among the wide range of skeletal features observed in MPS II, five manifestations are consistently reported as the most common: coarse facial features, claw-shaped hands, kyphosis or gibbus deformity,

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scoliosis, and various foot deformities. Coarse facial features typically emerge early and are characterized by thickened skin, broad nasal bridge, and enlarged tongue, reflecting underlying GAG accumulation in connective tissues(Link et al. 2010).Claw hands, a hallmark of MPS II, result from shortened ligaments and widened bones in the fingers. This deformity not only alters the appearance of the hands but also contributes to functional impairment. The structural changes predispose patients to CTS and is often compounded by GAG deposition in the flexor retinaculum, further narrowing the carpal tunnel and exacerbating symptoms. As a result, fine motor control is significantly diminished, affecting tasks such as writing, grasping, and self-care.Restricted wrist movement is another common finding, particularly in terms of flexion and extension. This limitation likely contributes to reduced grip strength and overall hand function. Notably, the wrist is the joint most frequently affected by stiffness in MPS II patients. However, joint stiffness is not confined to the hands—it is also prevalent in the elbows, shoulders, knees, and ankles. In many cases, stiffness in the elbows and knees becomes apparent as children grow older, while involvement of the hips and ankles tends to follow.Spinal abnormalities, including kyphosis and scoliosis, typically develop later in the disease course. These deformities are accompanied by stiffness in the spine, which further restricts mobility and posture(Link et al. 2024). Both upper and lower body stiffness are common, with the median age of onset being approximately 4.2 years for the upper body and 5.3 years for the lower body. Joint ROM (JROM) assessments consistently show values below the normal range, indicating widespread joint involvement(Link et al. 2010).Contractures—permanent shortening of muscles or tendons leading to joint immobility—are a defining feature of MPS II. These affect nearly all major joints, including the elbows, wrists, shoulders, hips, and knees, and typically begin in early childhood. Among the various movements assessed, extension is the most severely restricted. This limitation has profound implications for posture and mobility. For instance, contractures in the hip (with extension deficits up to 55°), knee (up to 45°), and foot (up to 25°) collectively contribute to the abnormal gait observed in many patients. These mechanical constraints prevent individuals from standing fully erect and reduce their walking efficiency, as evidenced by poor performance in the six-minute walk test. Shoulder mobility is also markedly impaired, particularly in terms of flexion (restricted by up to 90°) and abduction (up to 105°). These deficits are believed to result from GAG accumulation in the soft tissues surrounding the shoulder joint, leading to inflammation, fibrosis, and structural damage. When combined with elbow flexion contractures (restricted by up to 51°), the overall range of arm motion is significantly compromised, affecting activities of daily living and overall independence(Link et al. 2010, 2024; Andrew 2022).

6.ORTHOPEADIC COMPLICATIONS OF MPS III

Sanfilippo syndrome/MPS III presents a range of musculoskeletal complications that can progressively worsen over time, particularly in individuals experiencing a significant decline in physical engagement. In advanced stages, this deterioration may lead to complete loss of mobility, rendering patients fully bedridden. The primary musculoskeletal issues associated with MPS III include in-toeing, toe walking, joint stiffness, osteonecrosis of the femoral head, and scoliosis. These complications can severely impact posture, gait, and overall functional independence. Despite these challenges, not all individuals with MPS III exhibit overt musculoskeletal symptoms in the early stages. As a result, initial orthopaedic assessments may be conducted by primary care clinicians. These evaluations typically involve a thorough musculoskeletal examination and baseline radiographic imaging of the hips and spine to detect subtle abnormalities and establish a reference for future monitoring (Muschol et al. 2022b).

Compared to other forms of mucopolysaccharidosis, the skeletal involvement in MPS III tends to be less severe. However, retrospective data from two clinical institutions have documented notable orthopaedic findings in affected patients. These include scoliosis with curvature ranging from 21 to 99 degrees, hypoplasia of the first lumbar vertebra (L1), and osteonecrosis of the femoral heads. Additionally, carpal tunnel release and trigger thumb release have been reported, indicating the presence of compressive neuropathies and tendon-related complications (White et al. 2011).Overall, while musculoskeletal manifestations in MPS III may vary in severity, early detection and ongoing orthopaedic surveillance are

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essential to manage progression and maintain quality of life.

7.ORTHOPEADIC COMPLICATIONS OF MPS IV

Musculoskeletal abnormalities are among the earliest and most prominent clinical features in patients with MPS IV. These manifestations typically include short stature, spinal deformities, hip dysplasia, genu valgum (also known as knock knees), joint laxity, and abnormal gait. Spinal involvement is particularly concerning, as it can lead to progressive instability, irreversible neurological damage, and, in severe cases, premature death. As the disease advances, lower limb involvement and increasing muscle weakness further impair mobility. Many patients eventually require walking aids, and a significant proportion become wheelchair-dependent during adolescence.Hand function is also notably affected. Patients often experience a gradual decline in grip strength, wrist stability, and fine motor coordination, which collectively contribute to substantial functional limitations in daily activities (White et al. 2014; Sawamoto et al. 2016).

The MorCAP study identified a comprehensive list of common musculoskeletal complications in Morquio patients, including short neck, kyphoscoliosis, odontoid dysplasia, lumbar lordosis, cervical spinal instability, spinal disc disease, pectus carinatum, joint stiffness, pain, contractures, subluxations, and abnormal gait.Radiographic findings consistent with dysostosis multiplex—a hallmark of Morquio A syndrome—include anterior breaking and posterior scalloping of vertebral bodies, platyspondyly, dens hypoplasia, thoracolumbar kyphosis, short and broad metacarpals with proximal rounding, irregular carpal bones, rounded iliac wings, acetabular dysplasia, coxa valga, ankle valgus, paddle-shaped ribs, and short, thick clavicles. However, not all features are present at diagnosis, and some may be overlooked by clinicians unfamiliar with the condition, emphasizing the need for specialized evaluation and imaging(Charrow et al. 2015; Hendriksz et al. 2015).

8.ORTHOPEADIC COMPLICATIONS OF MPS VI

Maroteaux-Lamy syndrome presents with musculoskeletal abnormalities that are common across many MPS subtypes. These include dysostosis multiplex—a constellation of skeletal anomalies—along with scoliosis, joint stiffness, contractures, and pectus carinatum. A distinctive feature of MPS VI is discordant short stature, often characterized by a disproportionately short trunk relative to limb length, particularly in patients with the rapidly progressing form of the disease.CTS is notably more prevalent in MPS VI than in other MPS types due to GAGs accumulation in the soft tissues surrounding the median nerve, leading to compression and functional impairment. In early infancy, radiographic signs such as femoral head deformity and lateral migration of the hip may already be evident. However, the timing and efficacy of early surgical intervention for these hip abnormalities remain uncertain.

Lower limb deformities, especially progressive genu valgum (knock knees), can become severe and may eventually require surgical correction to restore alignment and mobility. Spinal involvement is a major concern in MPS VI. Patients frequently develop multi-level cervical stenosis and atlantoaxial instability, which can result in spinal cord compression, myelopathy, and spastic quadriparesis. MRI studies have identified cervical cord compression in up to 75% of cases, with some diagnosed as early as two years of age.Angular thoracolumbar kyphosis, caused by vertebral wedge deformities, may lead to canal compromise and neurologic injury. Surgical intervention is typically considered when kyphotic angles exceed 40 degrees. Additionally, osteopenia is more commonly observed in MPS types VI and VII(White 2011).

9.ORTHOPEADIC COMPLICATIONS OF MPS VII

Musculoskeletal abnormalities in MPS VII closely resemble those observed in MPS I and MPS II. These manifestations are typically evident early in life and include dysostosis multiplex, disproportionate short stature, joint contractures, and significantly reduced range of motion. Affected individuals often present with odontoid hypoplasia and atlantoaxial instability, although the latter is less frequently observed than in MPS IV. Hip involvement is common, with acetabular dysplasia contributing to impaired mobility and postural imbalance. Pectus carinatum, a protrusion of the chest wall, is another frequent skeletal feature.Additional musculoskeletal findings include genu valgum (knock

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knees), claw hand deformity, and curved fingers, all of which contribute to functional limitations in ambulation and fine motor tasks. These deformities are often progressive and may require orthopedic intervention to preserve mobility and independence.

Spinal involvement is a prominent and concerning aspect of MPS VII. Patients frequently develop scoliosis, kyphosis, and thoracolumbar kyphosis, which tend to worsen with age. The progression of spinal and chest wall deformities is gradual but relentless, often accompanied by pain stemming from hip dysplasia and joint contractures. As the disease advances, these complications can severely restrict mobility, leading to wheelchair dependence in some individuals as early as 10 years of age. Early recognition and multidisciplinary management are essential to mitigate functional decline and improve quality of life in patients with MPS VII(Morishita and Petty 2011; Montaño et al. 2016).

10.ORTHOPEADIC COMPLICATIONS OF MPS IX

MPS IX, an exceptionally rare subtype of MPS, presents with musculoskeletal features that can mimic other joint disorders, particularly Juvenile Idiopathic Arthritis (JIA). The first documented case involved a patient with short stature and multiple periarticular soft-tissue masses, including popliteal cysts and joint effusions. Radiographic imaging revealed acetabular erosions, indicating early hip joint involvement. In contrast, three subsequent cases exhibited isolated joint disease without systemic features. These individuals developed polyarthropathy affecting large joints, and MRI scans revealed proliferative synovitis and joint effusions, although erosive changes were not present at the time of imaging.Initially, these patients were misdiagnosed with JIA due to the similarity in clinical presentation. However, the emergence of a familial pattern of joint disease prompted further investigation. MPS IX can be differentiated from JIA by several key features: its familial inheritance, poor response to conventional anti-inflammatory therapies, extensive synovial abnormalities visible on MRI, and distinctive findings on synovial biopsy. These diagnostic clues are critical, especially since MRI and biopsy are not routinely performed in standard JIA evaluations, raising the possibility that additional cases of MPS IX may remain undiagnosed.

Supporting its rarity, a subsequent screening study involving 108 Turkish patients previously diagnosed with JIA found no evidence of hyaluronidase deficiency, the enzymatic defect underlying MPS IX. This finding reinforces the notion that MPS IX is exceedingly uncommon and may be underrecognized due to its clinical overlap with more prevalent rheumatologic conditions. Early recognition and targeted diagnostic workup are essential for accurate identification(Imundo et al. 2011; Kiykim et al. 2015).

11.CONCLUSION

In conclusion, MPS represents a complex spectrum of lysosomal storage disorders rooted in enzymatic deficiencies that impair GAG degradation. The resulting accumulation of undegraded GAGs disrupts cellular homeostasis and manifests in a wide array of clinical symptoms, with skeletal complications being among the most debilitating. Dysostosis multiplex, characterized by profound osteoarticular abnormalities, significantly compromises mobility, physical function, and quality of life. The diversity of MPS subtypes—each defined by a unique enzymatic defect and GAG profile—further complicates diagnosis and management. Advances in molecular understanding have revealed that MPS pathophysiology extends beyond GAG storage, involving secondary metabolic disruptions, oxidative stress, and chronic inflammation. These insights pave the way for emerging therapeutic strategies, including gene therapy and targeted pharmacological approaches. By synthesizing literature from the past two decades, this review provides a comprehensive overview of skeletal involvement in MPS, highlighting the need for continued research and clinical vigilance. A deeper understanding of genotype-phenotype correlations and long-term orthopedic outcomes will be essential to improve patient care and develop more effective, personalized treatment modalities.

REFERENCES

1. Andrew L. Insights on Hunter’s Syndrome. J Metab Syndr. 2022;11:260.
2. Barone R, Pellico A, Pittalà A, Gasperini S. Neurobehavioral phenotypes of

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(5), 2387-2396 | ISSN:2251-6727

neuronopathic mucopolysaccharidoses. Ital J Pediatr. 2018 Nov 16;44(S2):121.
3. Borgo A, Cossio A, Gallone D, Vittoria F, Carbone M. Orthopaedic challenges for mucopolysaccharidoses. Ital J Pediatr. 2018 Nov 16;44(S2):123.
4. Charrow J, Alden TD, Breathnach CAR, Frawley GP, Hendriksz CJ, Link B, et al. Diagnostic evaluation, monitoring, and perioperative management of spinal cord compression in patients with Morquio syndrome. Mol Genet Metab. 2015 Jan;114(1):11–8.
5. D'Avanzo F, Zanetti A, De Filippis C, Tomanin R. Mucopolysaccharidosis Type VI, an Updated Overview of the Disease. Int J Mol Sci. 2021 Dec 15;22(24):13456.
6. Fecarotta S, Tarallo A, Damiano C, Minopoli N, Parenti G. Pathogenesis of Mucopolysaccharidoses, an Update. Int J Mol Sci. 2020 Apr 4;21(7):2515.
7. Fisher P. Mucopolysaccharidosis Types I, II, III, V, VI and VII. In: Anesthesia Care of Patients with Skeletal Dysplasia. Cham: Springer Nature Switzerland; 2025. p. 161–76.
8. Gaffke L, Pierzynowska K, Podlacha M, Brokowska J, Węgrzyn G. Changes in cellular processes occurring in mucopolysaccharidoses as underestimated pathomechanisms of these diseases. Cell Biol Int. 2021 Mar 10;45(3):498–506.
9. Hendriksz CJ, Berger KI, Giugliani R, Harmatz P, Kampmann C, Mackenzie WG, et al. International guidelines for the management and treatment of Morquio A syndrome. Am J Med Genet A. 2015 Jan 24;167(1):11–25.
10. Imundo L, LeDuc CA, Guha S, Brown M, Perino G, Gushulak L, et al. A complete deficiency of Hyaluronoglucosaminidase 1 (*HYAL1*) presenting as familial juvenile idiopathic arthritis. J Inherit Metab Dis. 2011 Oct 11;34(5):1013–22.
11. Kabbassi W, Hessissen H, Hammouti J. Hurler syndrome: Oral and radiographic findings of a rare clinical case. Medical Reports. 2025 Dec;14:100325.
12. Kiykim E, Barut K, Cansever MS, Zeybek CA, Zubarioglu T, Aydin A, et al. Screening Mucopolysaccharidosis Type IX in Patients with Juvenile Idiopathic Arthritis. In 2015. p. 21–4.
13. van der Linden MH, Kruyt MC, Sakkers RJB, de Koning TJ, Öner FC, Castelein RM. Orthopaedic management of Hurler's disease after hematopoietic stem cell transplantation: a systematic review. J Inherit Metab Dis. 2011 Jun 17;34(3):657–69.
14. Link B, Botha J, Giugliani R. Characterization of orthopedic manifestations in patients with mucopolysaccharidosis <scp>II</scp> using data from 15 years of the Hunter Outcome Survey. JIMD Rep. 2024 Jan 27;65(1):17–24.
15. Link B, Pinto LL de C, Giugliani R, Wraith JE, Guffon N, Eich E, et al. Orthopedic manifestations in patients with muco-polysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey. Orthopedic Review. 2010 Sep 23;2(2).
16. Del Longo A, Piozzi E, Schweizer F. Ocular features in mucopolysaccharidosis: diagnosis and treatment. Ital J Pediatr. 2018 Nov 16;44(S2):125.
17. Montaño AM, Lock-Hock N, Steiner RD, Graham BH, Szlago M, Greenstein R, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). J Med Genet. 2016 Jun;53(6):403–18.
18. Morishita K, Petty RE. Musculoskeletal manifestations of mucopolysaccharidoses. Rheumatology. 2011 Dec 1;50(suppl 5):v19–25.
19. Muenzer J. Overview of the mucopolysaccharidoses. Rheumatology. 2011 Dec 1;50(suppl 5):v4–12.
20. Muschol N, Giugliani R, Jones SA, Muenzer J, Smith NJC, Whitley CB, et al. Sanfilippo syndrome: consensus guidelines for clinical care. Orphanet J Rare Dis. 2022a Oct 27;17(1):391.
21. Platt FM, Boland B, van der Spoel AC. Lysosomal storage disorders: The cellular

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impact of lysosomal dysfunction. Journal of Cell Biology. 2012 Nov 26;199(5):723–34.

22. Raman R, Sasisekharan V, Sasisekharan R. Structural Insights into Biological Roles of Protein-Glycosaminoglycan Interactions. Chem Biol. 2005 Mar;12(3):267–77.
23. Sawamoto K, Suzuki Y, Mackenzie WG, Theroux MC, Pizarro C, Yabe H, et al. Current therapies for Morquio A syndrome and their clinical outcomes. Expert Opin Orphan Drugs. 2016 Sep 1;4(9):941–51.
24. Taylor C, Brady P, O'Meara A, Moore D, Dowling F, Fogarty E. Mobility in Hurler Syndrome. Journal of Pediatric Orthopaedics. 2008 Mar;28(2):163–8.
25. Vitner EB, Platt FM, Futerman AH. Common and Uncommon Pathogenic Cascades in Lysosomal Storage Diseases. Journal of Biological Chemistry. 2010 Jul;285(27):20423–7.
26. Weisstein JS, Delgado E, Steinbach LS, Hart K, Packman S. Musculoskeletal Manifestations of Hurler Syndrome. Journal of Pediatric Orthopaedics. 2004 Jan;97–101.
27. White KK. Orthopaedic aspects of mucopolysaccharidoses. Rheumatology. 2011 Dec 1;50(suppl 5):v26–33.
28. White KK, Jester A, Bache CE, Harmatz PR, Shediac R, Thacker MM, et al. Orthopedic management of the extremities in patients with Morquio A syndrome. J Child Orthop. 2014 Aug 1;8(4):295–304.
29. White KK, Karol LA, White DR, Hale S. Musculoskeletal Manifestations of Sanfilippo Syndrome (Mucopolysaccharidosis Type III). Journal of Pediatric Orthopaedics. 2011 Jul;31(5):594–8.
30. Zhou J, Lin J, Leung WT, Wang L. A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management. Intractable Rare Dis Res. 2020 Feb 29;9(1):1–9.