Musculoskeletal manifestations of mucopolysaccharidoses

Kimberly Morishita1 and Ross E. Petty1

Abstract

The mucopolysaccharidoses (MPSs) are a heterogeneous group of inherited metabolic disorders caused by enzyme deficiencies that lead to progressive lysosomal storage of glycosaminoglycans. Musculoskeletal manifestations are common across all forms of MPS and are often apparent early in the disease course. Diagnostic delays occur frequently in these patients, especially those with more attenuated forms of disease. Treatments for many types of MPS are now available; however, they are most effective if started early before the development of irreversible damage. Some manifestations such as stiffness and joint contractures may mimic other conditions such as inflammatory arthritis, which may cause further delays. Rheumatologists and other specialists should be aware of the musculoskeletal manifestations of MPS so that diagnostic delays can be avoided and appropriate management initiated.

Key words: Mucopolysaccharidoses, Contractures, Musculoskeletal, MPS, Juvenile idiopathic arthritis, Rheumatology, Inflammation, Dysostosis multiplex.

Introduction

The mucopolysaccharidoses (MPSs) comprise a group of disorders characterized by progressive lysosomal accumulation of glycosaminoglycans (GAGs). The seven major types of MPS are categorized on the basis of the specific enzyme deficiency present, the major clinical manifestations or both [1]. Clinical features and severity of symptoms vary widely both among and within the seven major types of MPS; however, musculoskeletal involvement is a common feature in all types. Early in the disease course and in those with milder forms of disease patients with MPS may first seek medical attention because of musculoskeletal complaints. Their symptoms and signs may be confused with inflammatory arthritides such as polyarticular JIA [2].

Delays in diagnosis of MPS are common and many children and young adults will suffer for years with unrecognized MPS [3-6]. In a study of 13 patients with an intermediate form of MPS I (Scheie syndrome), all had prominent musculoskeletal involvement at the onset of their disease in childhood; however, diagnosis was delayed for 4–54 years [4]. In a recent survey of European and Canadian adult and paediatric rheumatologists, <20% recognized signs and symptoms of MPS type I (one of the more common types of MPS) [7]. In the absence of appropriate treatment, these conditions are chronic, progressive and often debilitating. With the advent of enzyme replacement therapy, some types of MPS are now treatable, and when initiated early, treatment may prevent damage and improve outcomes. Thus there is an important need for increased awareness about MPS among rheumatologists and other musculoskeletal specialists in order to facilitate timely diagnosis and appropriate management of these patients.

Case report

At the age of 4 years, the patient began developing subtle flexion contractures of his fingers and his mother noticed that he could not lift his arms above his head. He frequently asked for assistance with dressing and he tended to walk on his toes. He had bilateral inguinal and umbilical hernia repairs at ages 12 months and 2 years, respectively. At the age of 5 years, corneal clouding was detected on a routine ophthalmological assessment. The patient was referred to Genetics and was found to have elevated GAG levels in his urine. Subsequent enzyme analysis revealed reduced fibroblast α-L-iduronidase enzyme activity, and the diagnosis of Hurler–Scheie syndrome (attenuated MPS I) was made. He had otherwise been healthy with normal growth and development.

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When first evaluated at our hospital at the age of 6 years he had restricted, but pain-free movement of his hips, shoulders, wrists, elbows, ankles and knees. He had subtle flexion contractures of his DIP joints with a mild claw hand deformity (Fig. 1). Radiographs demonstrated dysostosis multiplex. He developed bilateral CTS at the age of 8 years presenting as night pain in the hands and thenar muscle wasting. His height crossed from the 25th percentile to <5th percentile in early adolescence. Since the age of 8 years he has been receiving enzyme replacement therapy.

Clinical manifestations

The accumulation of partially degraded GAGs in the lysosomes of connective tissue cells and chondrocytes is thought to be responsible for most of the musculoskeletal manifestations seen in the different types of MPS [8].

Similar musculoskeletal manifestations are seen in all types of MPS, and it is usually the other major clinical manifestations that distinguish one type of MPS from another. The more severe forms of MPS, for example, Hurler syndrome (severe form of MPS I), typically present in infancy or early childhood with severe somatic and neurological manifestations, whereas less severe forms such as Scheie syndrome (attenuated form of MPS I) present later in life, with normal intelligence and milder somatic manifestations [1]. It is the milder, more attenuated forms that are most likely to present to a rheumatologist or orthopaedic surgeon with musculoskeletal complaints [3, 4, 6] and are often diagnosed late or misdiagnosed as an inflammatory joint disease. The main musculoskeletal manifestations seen in MPS are discussed below and shown in Table 1.

Growth abnormalities

Short stature, thought to be caused by a disruption in the programmed maturation of the chondrocyte at the level of the growth plate [9], is a common feature in all types of MPS, although it may be mild or under-recognized in the attenuated forms. Axial growth is usually affected more than appendicular growth resulting in disproportionately short stature [10]. Severe forms of MPS may present with dwarfism or with significant growth failure after a period of normal early growth [11]. Final height in affected patients is frequently 3–6 S.D. below the mean height for age and gender [12]. However, patients with attenuated subtypes of MPS may have normal or near-normal linear growth. By comparison, patients with inflammatory arthritis are more likely to develop localized growth disturbances (e.g. micrognathia or leg-length discrepancies) or proportional short stature secondary to chronic active inflammation or long-term CS use, and such disturbances

<table>
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<th>Table 1 Major musculoskeletal manifestations of MPSs</th>
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<td><strong>Disorder</strong></td>
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<td>MPS I (severe)/Hurler syndrome</td>
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<td>MPS II/Hunter</td>
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Fig. 1 Mild flexion contractures of the fingers in Hurler–Scheie syndrome.
only occur in patients who develop disease before reaching skeletal maturity.

**Joint stiffness and contractures**

Joint stiffness and contractures can be found in all types of MPS, except for MPS IV (Morquio syndrome) and MPS IX [10]. These abnormalities are felt to arise secondary to infiltration by GAGs of the ligaments, tendons, joint capsules and other soft tissues in combination with epiphyseal and metaphyseal deformities owing to defective skeletal remodelling [8, 9]. The stiffness and contractures may mimic rheumatic conditions such as RA and JIA; however, there are several important differences [10]. Unlike the stiffness that is seen in inflammatory arthritis, the stiffness in MPS is not typically worse in the morning and is not exacerbated by rest or relieved by activity [10]. In addition, local signs of inflammation such as swelling, warmth and tenderness are absent, as are systemic signs of inflammation such as fever and/or elevated laboratory markers of inflammation (ESR and CRP) [7]. Some joints may have a swollen appearance due to underlying bony enlargement as opposed to the presence of synovial effusions. Furthermore, the articular abnormalities in patients with MPS do not respond to CSs or other anti-inflammatory treatment [7, 10].

Stiffness and contractures preferentially affect the phalangeal joints; however, all joints can be affected, especially in the more severe forms [3, 4]. When the IP joints of the hands are affected, the characteristic claw hand deformity develops, often resulting in impaired hand function (Fig. 1) [13]. In contrast to patients with inflammatory arthritis, patients with MPS are more likely to have DIP joint involvement rather thanPIP or MCP joint involvement [10, 14].

The phalangeal contractures observed in MPS may also mimic the contractures seen in camptodactyly and diabetic cheiroarthropathy. Camptodactyly, classically defined as flexion deformities of the PIP joints [15], is similar to inflammatory arthritis in that it preferentially affects the PIP and MCP joints rather than the DIP joints. The fifth finger is most commonly affected in camptodactyly, whereas MPS tends to affect all fingers in addition to other joints. Camptodactyly may occur as an isolated finding or as part of a syndrome, such as camptodactyly–arthropathy–coxa vara–periarteritis [16]; however, other features characteristic of MPS such as dysostosis multiplex are absent. Diabetic cheiroarthropathy, previously described as stiff-hand syndrome or pseudo-scleroderma [17], is a condition usually associated with type 1 diabetes, although it also occurs in type 2 diabetes. It was initially described in association with juvenile-onset diabetes [18]; however, it is now recognized as a frequent complication of adult-onset diabetes as well. Diabetic cheiroarthropathy commonly affects the PIP joints of the fourth and fifth fingers, although the other fingers and small joints of the hands often become affected over time [19]. Skin tightening and thickening accompany the contractures and resemble the skin changes of scleroderma.

When stiffness and contractures involve the ankles and Achilles tendons, patients may present with toe-walking [20, 21]. Other foot abnormalities such as pes cavus, metatarsus adductus and equinovarus deformities may also be present [20, 22]. The combination of joint contractures, foot abnormalities, hip joint abnormalities (discussed below) and frequently genu valgum (may be severe) can have a significant impact on gait and the ability to walk independently [20, 23, 24].

**CTS and trigger digits**

CTS is uncommon in childhood and its occurrence in a paediatric patient should prompt the physician to consider the possibility of an MPS, which accounts for more than one-half of the cases in this age group [25]. The median nerve compression occurs as a result of thickening of the flexor retinaculum and the tissues around the tendon sheaths [25]. The diagnosis may be delayed as the presentation is commonly atypical. Many patients do not complain of numbness or pain, particularly early in the course of disease when verbal or intellectual limitations may pose additional challenges to diagnosis [26, 27]. Other symptoms such as increased difficulty with fine motor tasks may be detected, however [28].

Trigger fingers in association with CTS are well recognized in patients with MPS [29–31]. Triggering occurs as a result of GAG deposits in the capsular tissues of the joints or flexor tendons [27]. In a study of 22 children with MPS by Van Heest et al. [27], 17 children were diagnosed with CTS by electromyographic/nerve conduction velocity testing and triggering was diagnosed clinically in 45 digits in 8 children. Trigger digits can also occur in association with inflammatory arthritis, mainly RA; however, in such cases the triggering is caused by inflammation of the tenosynovium and the resulting mismatch between the size of the flexor tendon sheath and the enclosing fibro-osseous canal [32]. The diagnosis of a trigger digit is usually made clinically; however, there may be role for high-resolution ultrasonography in determining the underlying cause for triggering [33, 34].

**Odontoid hypoplasia**

Patients with MPS have an increased incidence of hypoplasia of the odontoid process that predisposes them to atlanto-axial instability [35–37]. Spinal cord compression may occur as a result of atlanto-axial subluxation and lead to neurological complications, most commonly spastic tetraparesis; however, paraparesis and hemiparesis have also been reported [38]. Compression may also occur as a result of GAG deposition in the surrounding tissues, ligaments and dura mater [38, 39]. The risk of subluxation must be considered in all patients with MPS, but especially those who are scheduled to undergo surgery requiring general anaesthesia and those who choose to participate in sports activities such as the Special Olympics [40, 41]. Patients with Hurler syndrome (MPS I) and Morquio syndrome (MPS IV) appear to have the highest risk of developing odontoid hypoplasia, although
it can occur in other types as well [36, 41, 42]. Cervical instability can also be a feature of JIA, especially systemic or polyarticular types, or enthesitis-related arthritis. It is characterized by stiffness and painful limitation of cervical spine range (especially hyperextension). The odontoid may appear to be hypoplastic secondary to bony erosion. Neurological abnormalities, however, are rare in this group of inflammatory arthritides.

**Joint hypermobility**

Joint stiffness is characteristic of most types of MPS; however, joint hypermobility is seen in the majority of patients with Morquio syndrome (MPS IV) [43]. The hypermobility results from metaphyseal deformities, hypoplasia of the bones and degradation of connective tissues around the joint [43]. Most patients have significant joint hypermobility of the hands and wrists (distal joints) contrasting with proximal stiffness [44]. The distal hypermobility often results in a very weak grip and progressive difficulties with activities of daily living such as dressing and grooming [43]. The combination of joint hypermobility and odontoid hypoplasia in these patients is thought to be responsible for the very high incidence of atlanto-axial subluxation [45].

**Dysostosis multiplex**

Dysostosis multiplex is the term used to describe the constellation of radiographic changes characteristically seen in MPS. These skeletal abnormalities include flattened vertebral bodies (platyspondyly) with anterior beaking, odontoid hypoplasia, thoracolumbar kyphosis, oar-shaped ribs, short thickened clavicles, bullet-shaped phalanges (short and thick with proximal widening), a large skull with a thickened calvarium and J-shaped sella turcica [46, 47]. Changes in the lower extremities include dysplastic femoral heads, flattened acetabula, hypoplasia of the inferior portions of the iliac bones with flared iliac wings, coxa valga and genu valgum deformities [46, 47] (Fig. 2).

The basis for the skeletal abnormalities characteristic of the MPS disorders is not fully understood [40]. Studies in animal models suggest that GAG accumulation in articular cartilage promotes inflammation and chondrocyte apoptosis [48, 49]. The increased chondrocyte apoptosis leads to release of MMPs, which subsequently leads to progressive degenerative joint disease [48–50]. In addition, it is suggested that joint disease is further exacerbated by abnormal biomechanical forces that result from the underlying skeletal deformities [10, 49, 51]. Degenerative changes in joints may accompany long-standing inflammatory joint disease, but primary degenerative joint disease is rare in children, and occurs in geographically restricted populations in South Africa (Mseleni joint disease) [52], China (Kashin–Beck disease) [53] and India (Handigodu disease) [54].

In contrast to patients with MPS, patients with inflammatory arthritis may have radiographic changes such as erosive bone lesions, periarticular osteopenia, joint space narrowing, and joint effusions [7, 10] (Fig. 3). Changes in the shape or length of bones can occur at sites of chronic inflammation; however, the diffuse, symmetrical skeletal changes seen in MPS are not present.
Conclusion

The patient with an MPS may present to the rheumatologist because of discomfort or deformity in joints. Differentiation of these disorders from the inflammatory arthritides is essential in order to institute appropriate therapy as early as possible. Attention to the characteristics of the musculoskeletal disease and the presence of extra-skeletal abnormalities, together with radiographic investigation, will facilitate the timely diagnosis and appropriate management of these patients.

Rheumatology key messages

- Joint symptoms may prompt patients with undiagnosed MPS to consult a rheumatologist.
- Differentiation of MPSs from inflammatory arthritides is essential to ensure early initiation of therapy.

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Fig. 3 JIA. Periarticular osteopenia, joint space narrowing of the IP joints and intercarpal joints, erosive changes of the second and third PIP joints bilaterally.


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