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Joint Problems in Patients with Mucopolysaccharidosis Type II

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Hunter syndrome or mucopolysaccharidosis type II (MPS-II) (OMIM 309900) is a rare lysosomal storage disorder caused by deficiency in the activity of the enzyme iduronate-2-sulfatase. This enzyme is responsible for the catabolism of the following two different glycosaminoglycans (GAGs): dermatan sulfate and heparan sulfate. The lysosomal accumulation of these GAG molecules results in cell, tissue, and organ dysfunction. Patients can be broadly classified as having one of the following two forms of MPS II: a severe form and an attenuated form. In the severe form of the disease, signs and symptoms (including neurological impairment) develop in early childhood, whereas in the attenuated form, signs and symptoms develop in adolescence or early adulthood, and patients do not experience significant cognitive impairment. The involvement of the skeletal–muscle system is because of essential accumulated GAGs in joints and connective tissue. MPS II has many clinical features and includes two recognized clinical entities (mild and severe) that represent two ends of a wide spectrum of clinical severities. However, enzyme replacement therapy is likely to have only a limited impact on bone and joint disease based on the results of MPS II studies. The aim of this study was to review the involvement of joints in MPS II.

Keywords: Hunter syndrome, Lysosomal storage disease, Mucolopysaccharidosis type II, Joint

Introduction

Mucopolysaccharidosis type II (MPS II), also called Hunter's syndrome according to the first description of two affected brothers by Charles Hunter[1] in 1917, is a rare lysosomal storage disorder caused by deficiency in the activity or insufficient activity of the iduronate-2-sulfatase (IDS) enzyme. This deficiency results in the accumulation of glycosaminoglycans (GAGs), previously called mucopolysaccharides or MPS, in various tissues and organs of the body[2,3]. Specific to MPS II, dermatan sulfate and heparan sulfate are the GAGs that are stored.

The gene that encodes the *IDS* enzyme is also called IDS and is located in Xq27.3-q28. To date, no precise genotype–phenotype correlation has been determined[2]. As it follows X-linked recessive inheritance, it is almost exclusively seen in males. Only few females have been diagnosed with MPS II, and most cases have involved an autosomal X-chromosomal translocation or non-random X-chromosomal inactivation[3-5]. There is a wide range of clinical features that occur in variable degrees, which have a chronic progressive course despite the age of symptom onset. The progression of the disease is characterized by multisystemic involvement with coarse facial features, an enlarged tongue, a short stature, hepatosplenomegaly, cardiac disease, dysostosis multiplex, joint stiffness, and sometimes neurological involvement[6-8]. Although the phenotypic expression of MPS II spans a wide spectrum of clinical severities, patients can be divided into the following two groups: severely affected patients with profound neurologic involvement leading to cognitive impairment and developmental regression and attenuated patients with normal intelligence[9,10]. In recent years, improvements in patient identification, care, and management have meant that patients with MPS II are living longer[11]. With the introduction of enzyme re-

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placement therapy (ERT), it is clear that we can expect additional benefits in terms of improvements in visceral manifestations and increased mobility[12]. Although there is some indication that joint contractures may be improved by ERT, both ERT and bone marrow transplantation are likely to have only a limited impact on bone and joint disease based on the results of studies in animal models[13,14]. The underlying causes of degenerative joint and bone disease are a lack of skeletal remodeling, disordered endochondral and intramembranous ossification, disruption of normal elastogenesis, and GAG infiltration into ligaments, tendons, joint capsules, and other tissue structures[15-17]. GAG storage in MPS induces a complex sequence of molecular abnormalities that leads to inflammation, apoptosis (cartilage), and hyperplasia (synovial membranes), resulting in poorly organized and metabolically abnormal connective tissue matrices[17-20]. The cartilage is the major area of pathology in mucopolysaccharidoses, leading to poor bone growth, poor joint mobility, and painful joints[17]. The study reviews previous literature on joint involvement in MPS II.

Diagnosis of MPS II

The most common screening test for MPS II is quantitative measurement of urinary GAGs; the test can discriminate between broad classes of MPS but cannot distinguish subgroups[2,3]. A definitive diagnosis is usually made by measuring *IDS* enzyme activity in the serum, white blood cells, or skin fibroblasts. Analysis of the *IDS* gene could be helpful in determining clinical severity in some cases, although genotype–phenotype correlations are not precise[2]. Prenatal diagnosis is also possible through the measurement of *IDS* activity in chorionic villous tissue or amniotic fluid[6]. An important characteristic of MPS II is the X-linked mode of inheritance, which could lead to wrong interpretations because it may cause mosaicism in heterozygous female cells with the normal or mutant *IDS* gene[6]. The incidence and estimated prevalence of MPS II varies between 1:76 000 and 1:162 000 among male live births[21]. In Great Britain, Young and Harper[8] mentioned an incidence of 1:171 132 in males and a prevalence of 1:79 million among males and females. A retrospective case study covering a period of 16 years was carried out to estimate the prevalence of lysosomal storage disorders in Australia. The studied revealed an incidence of 1:162 000 and a prevalence of 1:136 000[22]. Muenzer[3] reported that the incidence of the disease in the United States is unknown and that it is difficult to estimate the prevalence of MPS disorders because population-based studies and epidemiological data are scarce.

Joint Stiffness

Joint stiffness is present in patients with MPS II. The accumulation of GAGs from fetal life within bone, ligaments, synovial tissue, and skin leads to functional deficits, including progressive joint contractures, altered hand function, and a loss of fine motor skills[5]. The cartilage is the major area of pathology in mucopolysaccharidoses leading to poor bone growth, poor joint mobility, and painful joints[5,6,8]. Contractures cause significant loss of joint mobility and represent one of the earliest noteworthy indicators. All contractures are associated with widespread joint involvement, which can cause significant loss of function. The most involved joints are the elbows, with symptoms of reduced extension, pronation, and supination; the shoulders, with symptoms of limitations in flexion, abduction, and lateral rotation; and the wrists, with symptoms of restrictions of flexion and extension[23,24]. In the inferior limbs, there is restriction in the extension, abduction, and lateral rotation of the hips; great loss of knee extension in the severe form; and limited dorsal extension of the ankles. According to Neufeld and Muenzer[6], abnormal joint function probably results from a combination of metaphyseal deformities and thickened joint capsules secondary to GAG accumulation and fibrosis. Joint stiffness is also common in the elbow (59.7%), shoulder (54.8%), knee (42.7%), and ankle (33.9%)[24]. Joint stiffness appears in the hand at a median age of 4.4 years and in the shoulder at a median age of 4.6 years. Joint stiffness generally becomes apparent in the elbow and knee when children are slightly older (median onset: 5.1 years)[24]. The next two joints in which stiffness is reported to develop are the hip (median onset: 5.6 years) and ankle (median onset: 6.1 years)[24]. The authors emphasized the importance of range of motion (ROM) exercises to preserve joint function. They should be started early on in the treatment process. The indications for physical therapy and its benefits in MPS should be further studied[6,8,25].

Shoulder Joint

Restrictions in shoulder joints are the earliest symptoms observed in MPS II patients[26]. The shoulder joint has the largest range of movement in the human body. Functionally, the shoulder provides sufficient mobility in synergy with the elbow and wrist to allow many different positions and orientations of the hand. Shoulder motion is limited by overlying soft tissue, and shoulder abduction is the first movement that becomes restricted in patients with MPS II[24]. Restrictions of shoulder abduction are more pronounced than those of shoulder flexion, and therefore,

they could be a more sensitive marker for measuring the efficacy of ERT[26]. Restrictions in shoulder flexion and abduction in MPS II patients have been observed before their second year of life[26]. In all patients, ROM limitations intensify and become more severe with age. A medium correlation between patient age and passive shoulder flexion was observed (R=0.563, *P*=0.001)[26]. In attenuated patients, the restriction of passive shoulder movement progresses more slowly. In the case of attenuated patients, younger boys (11–12 years) already have joint ROM limitations in the upper limbs; however, they only require minimal help with daily activities. Older attenuated patients are more dependent on external help, especially when getting dressed and bathing[26].

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in adults, but it is rarely seen in children[27]. However, CTS is commonly seen in young patients with MPS II (affecting 27.4% of patients with a median onset at 7.0 years)[24]. When it occurs in childhood, most cases are secondary to MPS[27]. CTS may result in contracture of distal interphalangeal joints, dysesthesia, loss of feeling in the first three fingers, and paresis of the thenar muscles[28]. Patients do not have typical symptoms until severe compression happens. CTS appears to be a common complication of mucopolysaccharidoses and is probably due to a combination of excessive lysosomal storage in the connective tissue of the flexor retinaculum and a deformed anatomy because of the underlying bone dysplasia[29]. This syndrome can cause loss of thumb function and significant handicap in combination with skeletal dysplasia, leading to decreased hand movements. Since 1969, several studies on childhood CTS have been carried out, and in many cases, the etiology was lysosomal storage disease, mainly MPS[29-31]. One study described two affected children below 5 years of age, and another study reported three children with mild forms of MPS II who underwent standard decompression of the median nerve[28,32].

Decompression surgery is recommended in patients in whom either loss of hand function or a large decrease in nerve conduction is present. Furthermore, decompression surgery is reported to result in rapid and sustained improvement in function[33]. The treatment is usually surgical, and the outcome has been satisfactory in terms of restoring motor hand activity in some patients and partial improvement in others[6].

Hip and Knee Joint

Hip deformity in terms of acetabulum dysplasia was found to be apparent in more than half of all patients for whom hip images were available. Acetabulum dysplasia is probably the result of disturbances in the architecture of the growth plate and the decreased ability of bone cells to synthesize new bone on calcified cartilage[17]. Hip dysplasia is predictive of osteoarthritis and poor mobility[34]. Flexion contractures in hip and knee joints lead to smaller values of patients' height[26]. In general, shorter patients tend to have greater ROM restrictions, while taller patients have less ROM restrictions, especially in the lower limbs (knee joints)[35,36]. A hip abnormality was found in 26 of 30 patients (86.7%) for whom hip images were included in the HOS (all X-rays). The most common abnormality was acetabulum dysplasia (affecting 53.3% of patients), followed by femoral head dysplasia (affecting 26.7% of patients)[24].

Conflict of Interest

We have no potential conflicts of interest relevant to this review article to report.

References

1. Dorfman A, Matalon R. The mucopolysaccharidoses (a review). Proc Natl Acad Sci U S A 1976;73:630-7.
2. Froissart R, Moreira da Silva I, Guffon N, Bozon D, Maire I. Mucopolysaccharidosis type II--genotype/phenotype aspects. Acta Paediatr Suppl 2002;91:82-7.
3. Muenzer J. The mucopolysaccharidoses: a heterogeneous group of disorders with variable pediatric presentations. J Pediatr 2004;144:S27-34.
4. Mossman J, Blunt S, Stephens R, Jones EE, Pembrey M. Hunter's disease in a girl: association with X:5 chromosomal translocation disrupting the Hunter gene. Arch Dis Child 1983;58:911-5.
5. Tuschl K, Gal A, Paschke E, Kircher S, Bodamer OA. Mucopolysaccharidosis type II in females: case report and review of literature. Pediatr Neurol 2005;32:270-2.
6. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York: McGraw Hill, 1995:2465-94.
7. Schmitt HP. Changes in the voluntary muscles and the peripheral nerves in an autopsy case of MPS type II (Hunter).

Neuropediatrics 1981;12:83-91.
8. Young ID, Harper PS. The natural history of the severe form of Hunter's syndrome: a study based on 52 cases. Dev Med Child Neurol 1983;25:481-9.
9. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw Hill, 2001.
10. Martin R, Beck M, Eng C, Giugliani R, Harmatz P, Munoz V, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatrics 2008;121:e377-86.
11. Jones SA, Almassy Z, Beck M, Burt K, Clarke JT, Giugliani R, et al. Mortality and cause of death in mucopolysaccharidosis type II-a historical review based on data from the Hunter Outcome Survey (HOS). J Inherit Metab Dis 2009;32:534-43.
12. Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 2006;8:465-73.
13. Crawley AC, Niedzielski KH, Isaac EL, Davey RC, Byers S, Hopwood JJ. Enzyme replacement therapy from birth in a feline model of mucopolysaccharidosis type VI. J Clin Invest 1997;99:651-62.
14. Norrdin RW, Simske SJ, Gaarde S, Schwardt JD, Thrall MA. Bone changes in mucopolysaccharidosis VI in cats and the effects of bone marrow transplantation: mechanical testing of long bones. Bone 1995;17:485-9.
15. Hinek A, Wilson SE. Impaired elastogenesis in Hurler disease: dermatan sulfate accumulation linked to deficiency in elastin-binding protein and elastic fiber assembly. Am J Pathol 2000;156:925-38.
16. Pastores GM, Meere PA. Musculoskeletal complications associated with lysosomal storage disorders: Gaucher disease and Hurler-Scheie syndrome (mucopolysaccharidosis type I). Curr Opin Rheumatol 2005;17:70-8.
17. Simonaro CM, D'Angelo M, He X, Eliyahu E, Shtraizent N, Haskins ME, et al. Mechanism of glycosaminoglycan-mediated bone and joint disease: implications for the mucopolysaccharidoses and other connective tissue diseases. Am J Pathol 2008;172:112-22.
18. Simonaro CM, D'Angelo M, Haskins ME, Schuchman EH. Joint and bone disease in mucopolysaccharidoses VI and VII: identification of new therapeutic targets and biomarkers using animal models. Pediatr Res 2005;57:701-7.
19. Simonaro CM, Ge Y, Eliyahu E, He X, Jepsen KJ, Schuchman EH. Involvement of the Toll-like receptor 4 pathway and use of TNF-alpha antagonists for treatment of the mucopolysaccharidoses. Proc Natl Acad Sci U S A 2010;107:222-7.
20. Simonaro CM, Haskins ME, Schuchman EH. Articular chondrocytes from animals with a dermatan sulfate storage disease undergo a high rate of apoptosis and release nitric oxide and inflammatory cytokines: a possible mechanism underlying degenerative joint disease in the mucopolysaccharidoses. Lab Invest 2001;81:1319-28.
21. MPS II-SGM-HCPA, Servic¸o de Gene´tica Me´dica – Hospital de Cli´nicas de Porto Alegre RS, Brasil. Mucopolissacaridose II 2004:6.
22. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.
23. Morini SR, Steiner CE, Gerson LB. Mucopolysaccharidosis type II: skeletal-muscle system involvement. J Pediatr Orthop B 2010;19:313-7.
24. Link B, de Camargo Pinto LL, Giugliani R, Wraith JE, Guffon N, Eich E, et al. Orthopedic manifestations in patients with mucopolysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey. Orthop Rev (Pavia) 2010;2:e16.
25. Wraith JE, Scarpa M, Beck M, Bodamer OA, De Meirleir L, Guffon N, et al. Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr 2008;167:267-77.
26. Marucha J, Jurecka A, Syczewska M, Rozdzynska-Swiatkowska A, Tylki-Szymanska A. Restricted joint range of motion in patients with MPS II: correlation with height, age and functional status. Acta Paediatr 2012;101:e183-8.
27. Van Meir N, De Smet L. Carpal tunnel syndrome in children. Acta Orthop Belg 2003;69:387-95.
28. Norman-Taylor F, Fixsen JA, Sharrard WJ. Hunter's syndrome as a cause of childhood carpal tunnel syndrome: a report of three cases. J Pediatr Orthop B 1995;4:106-9.
29. Wraith JE, Alani SM. Carpal tunnel syndrome in the mucopolysaccharidoses and related disorders. Arch Dis Child 1990;65:962-3.
30. McArthur RG, Hayles AB, Gomez MR, Bianco AJ, Jr. Carpal tunnel syndrome and trigger finger in childhood. Am J Dis Child 1969;117:463-9.
31. Miner ME, Schimke RN. Carpal tunnel syndrome in pediatric mucopolysaccharidoses. Report of four cases. J Neurosurg 1975;43:102-3.
32. Bona I, Vial C, Brunet P, Couturier JC, Girard-Madoux M,

Bady B, et al. Carpal tunnel syndrome in Mucopolysaccharidoses. A report of four cases in child. Electromyogr Clin Neurophysiol 1994;34:471-5.
33. Muenzer J, Beck M, Eng CM, Escolar ML, Giugliani R, Guffon NH, et al. Multidisciplinary management of Hunter syndrome. Pediatrics 2009;124:e1228-39.
34. Oniankitan O, Kakpovi K, Fianyo E, Tagbor KC, Houzou P, Koffi-Tessio V, et al. [Risk factors of hip osteoarthritis in Lome, Togo]. Med Trop (Mars) 2009;69:59-60.
35. Sifuentes M, Doroshow R, Hoft R, Mason G, Walot I, Diament M, et al. A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. Mol Genet Metab 2007;90:171-80.
36. Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344:182-8.