Attenuated type I mucopolysaccharidosis in the differential diagnosis of juvenile idiopathic arthritis: a series of 13 patients with Scheie syndrome

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Abstract

Objective

Mucopolysaccharidosis type I (MPS I) is a genetic lysosomal storage disorder caused by deficient activity of the enzyme α-L-iduronidase. Incomplete breakdown of glycosaminoglycans leads to progressive accumulation of these substances in many tissues throughout the body. Patients with the less severe form of MPS I (Scheie syndrome) usually present in the first decade of life with frequent articular involvement, and may survive into adulthood. Especially in these attenuated phenotypes, a definitive diagnosis may be delayed for years because clusters of early symptoms are difficult to recognize for physicians not familiar with the disease, and since the disease progresses slowly over decades. We would like to increase the awareness of this type of MPS I disease among rheumatologists and unravel diagnostic pitfalls.

Methods

We have reviewed medical histories of 13 patients (6 males and 7 females) with Scheie syndrome seen in 5 European centers.

Results

All patients had prominent musculoskeletal involvement at the onset of their disease in childhood. Diagnosis was delayed in almost all cases (range 4-54 years).

Conclusion

We suggest that patients who present with progressive non-inflammatory joint involvement in the first decade of life, particularly with stiffness of the fingers and difficulty using the hands, should be screened for metabolic diseases, including MPS I. MPS I should be considered if patients with arthropathy lack the typical characteristics of inflammatory arthropathy.

Key words

Arthritis, lysosomal storage disorder, metabolic, rheumatologic, mucopolysaccharidosis, Scheie syndrome.

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Introduction

Arthritis in childhood can be due to many different causes, the most common chronic arthropathy occurring in children being juvenile idiopathic arthritis (JIA). The differential diagnosis of JIA encompasses a wide variety of diseases, including metabolic storage disorders. For example, in infancy, a polyarthritic onset can be caused by Farber's disease, which is caused by a deficiency in acid ceramidase and is accompanied by subcutaneous nodules and hoarseness, or by Mucolipidosis type III that often presents in older children with multiple joint stiffness and tightness of the skin over the hands.

Mucopolysaccharidoses (MPS) are a group of inherited disorders characterised by the accumulation of glycosaminoglycans (GAG) in the lysosomes in all cells in the body except red blood cells, and increased GAG excretion in the urine. As with many lysosomal storage disorders, the MPS disorders affect multiple organ systems and are generally characterized by a diverse spectrum of severity and disease progression (1). This report focuses on the less severe form of type I mucopolysaccharidosis MPS (also called Scheie syndrome, MPS I S), a disorder that can go unrecognized for years and that often presents with rheumatological signs or symptoms. In particular, children who present with stiffness of the joints and flexion contractures (particularly of the hands an shoulders) without evidence of swelling and inflammation, may be suffering from MPS type I. MPS I has a variable phenotype. At the severe end of the disease spectrum (Hurler syndrome), coarse face and mental retardation with developmental delay are apparent, and the disease is often fatal within the first decade of life. On the other hand, in the milder form (MPS I S) the patient can have a normal life expectancy and no gross phenotypic abnormalities.

To our knowledge, there have been no published series on patients with MPS I S who presented with articular signs or symptoms, but only rare and isolated case reports. We present 13 patients with onset of disease during childhood, in every case with musculoskeletal involvement. All the patients were subsequently diagnosed with MPS I S (Scheie syndrome).

Materials and methods

Specialists at three European centers specializing in lysosomal storage disorders (Lyon, France; Jena, Germany; Manchester, UK) were asked if patients with the less severe form of MPS I (Scheie syndrome) were attending their clinic. More specifically, patients with noticeable musculoskeletal symptoms at disease onset (prior to diagnosis) were to be included in the review. Additionally, three Italian cases known to the authors were included in this series. Available medical data and/or clinical records were reviewed by one of the authors (RC), and relevant data were recorded. The medical history of one of these patients (n. 1 in Table I) had been previously published as a case report (2), and part of the histories of patients n. 4, 5, and 6 are included in a series that has been recently published, but in a review describing all clinical features of attenuated MPS I, without focus on rheumatologic features (3). Patients' consents and institutional ethical approval were obtained, as appropriate.

Results

We were able to collect a series of 13 cases patients seen in 5 different centers (Lyon, 4; Manchester, 3; Jena, 3; Ancona, 2; Milano, 1). All centers were within pediatric departments. All of the patients are Caucasians and no sex predominance was seen (6 males and 7 females). Family history was positive only for the three patients from Jena, who are brothers, and for another French case (n.13 in Table I). No consanguinity between parents was recorded. The main demographic and clinical characteristics of all patients in our series are shown in Table I. As illustrative examples underlining the typical musculoskeletal pathology, the course of disease is described below in more detail for three of these patients. *Case 1* (n. 11 in Table I). This female newborn of non-consanguineous parents was first seen by an orthopedist at 7 days of age because of bilateral hip snapping,

with marked eccentricity of both hips on X-rays. This hip subluxation was treated with an orthopedic harness for a few months. No significant family history was present. At the age of 18 months she was not yet able to walk, nor could she sit down or get up by herself. Hypotonia and an umbilical hernia were noted at physical examination. At the age of 8 years, a hip flexion deformity and hyperlordosis were noted and X-rays of the spine, perfomed at age 9, were abnormal, demonstrating posterior vertebral scalloping as a prominent abnormality. Soon after, she started to complain of lower back pain upon exertion; and physical exercise at school was difficult due to joint pains and limitation of movements. At the age of 12 years, another orthopedist suggested a diagnosis of arthrogryposis, on the basis of a worsening hip flexion deformity combined with a moderate knee flexion deformity and stiffness of the thumbs. Despite orthopedic surgery, mechanical joint pains in the shoulders, ankles and lower back, and limitations in the range of motion of elbows, shoulders, and hips were present. Growth slowed down (-1 SD at the age of 3 and -1.5 SD at the age of 4 years), and her final adult height is 146.5 cm. For many years, the patient had been complaining about digestive troubles, including repeated episodes of diarrhea. An echocardiography showed a thickening of the mitral and aortic valves with insufficiency and with aortic stenosis as well; a hereditary metabolic disease was then suspected based on the combination of these symptoms, and a definitive diagnosis of MPS I S was made at age 21. The patient was started on enzyme replacement therapy.

Case 2. (n. 3 in Table I) A healthy girl, with no significant family or past medical history, presented to medical attention at 3 years of age with stiffness of one finger. The physician referred the child to a rheumatologist, who made a diagnosis of "arthritis" and treated her with a short course of steroids. At 24 years of age further symptoms appeared, with equino varus foot deformity bilaterally and the identification of corneal opacities. At 31 years of age she was referred to an orthopedist because of a limp; x-rays of the hips showed dysplasia of the femoral head and of the acetabulum. A clinical diagnosis of rheumatoid arthritis was further confirmed by several different rheumatologists despite the lack of inflammatory symptoms, a negative rheumatoid factor, and hand joint deformities based on dislocation rather than on erosion. Therapy with gold salts and non-steroidal anti-inflammatory drugs was started, but without any significant benefit. At 35 years of age, progressive cardiac dysfunction due to valvular disease appeared, and after seven years the patient underwent cardiac surgery. Immediately after surgery her visual problems worsened, with clouding and thickening of the cornea, and retinal degeneration. She underwent laser-based surgeries and corneal transplants with no significant improvement, and eventually became blind. Meanwhile, hearing impairment also appeared, and progressed to partial deafness. At age 52, because of vertigo, she went to a neurologist, who was interested in lysosomal disorders. The neurologist suspected MPS I S as the correct diagnosis. Enzyme replacement therapy was started one year after diagnosis.

Case 3. (n. 13 in Table I) This female patient was diagnosed at age 41, more than 30 years after the onset of her symptoms. Her first complaints, when she was about 8 years old, were joint stiffness and restricted mobility in her shoulders. Stature was short, puberty and menarche occurred at a normal age. At the age of 22, she experienced back pain with recurrent bilateral sciatic painful crises during which times she was unable to work. Over time she developed a cardiac dysfunction, secondary to mitral and aortic valve stenosis. At the age of 34, hepatomegaly was noted, and severe, progressive diarrhea appeared. At the age of 36 years she was breathless on exertion. At this time, she also developed her first neurologic symptoms, comprising dysesthesia in the hands, followed by muscle weakness and exertional pain in her legs. At the age of 40, her neurological abnormalities became more pronounced and imaging showed thickening of the dura and the vertebral ligaments, resulting in cervical medullar compression from C2 to C7. The patient underwent a laminectomy, with improvement in her neurological symptoms within a short period of time after neurosurgery. At the time of surgery, hepatomegaly, obstructive airway disease, limitation of shoulder movements and signs and symptoms of carpal tunnel syndrome were still present. The final diagnosis of MPS I was made, and this patient has been on enzyme replacement therapy since then. Of note, the patient's sister died from endocarditis at the age of 39 years. This relative had been diagnosed with rheumatic fever, but she might also have been affected by MPS I since her medical history included cardiac valvular disease, umbilical hernia and hip dysplasia.

Discussion

MPS I is a complex, multisystemic, progressive, heterogeneous and potentially fatal disease (4). The estimated worldwide incidence is 1:100.000 newborns. and the genetic defect is transmitted as an autosomal recessive pattern. The gene mutation leads to a deficiency of the lysosomal enzyme α-L-iduronidase. Approximately 100 mutations have been described (5, 6). The enzyme deficiency causes disturbances in glycosaminoglycan (GAG) metabolism and excretion. Traditionally, MPS I patients have been classified as Hurler, Hurler-Scheie, or Scheie syndrome (severe, intermediate, and mild form); however, there are no clear-cut clinical or biochemical criteria to define this classification. In the more severe form, diagnosis is usually established at an early age, mental retardation is present, and patients die within the first decade of life as a result of rapidly progressive disease. Patients with the Hurler-Scheie (intermediate) form can have normal intelligence, but a decreased life expectancy due to cardiac or respiratory disease. Signs and symptoms common to both forms are obstructive airway disease, cardiovascular involvement, decreased visual acuity, and joint contractures and skele-

Table I. Characteristics of the cohort.

Case num. (country)	Sex	Family history	Age at onset of symptoms (years)	Symptoms at onset	Misdiagnosis	Other joints involved during the disease course (arthropathy)	Other musculoskeletal findings	Carpal tunnel syndrome	Extraskeletal MPS involvement	Age at diagnosis (years)
1 (Italy)	M		6	Stiffness hands (metacarpophalangeal, proximal interphalangeal)		Hands (flexion contractures); knees; hips; ankles		+		7
2 (Italy)	M		8	Stiffness and pain in the hands	Scleroderma	Shoulders; elbows; wrists; knees; ankles			Cardiac (aortic valve); hearing loss; visual loss	54
3 (Italy)	F		3	Stiffness finger	Juvenile idiopathic arthritis		Equinovarus foot; dysostosis multiplex		Corneal opacities; hearing loss; cardiac (aortic, tricuspid, mitral)	53
4 (UK)	F		7	Flexion contractures hands	Juvenile idiopathic arthritis	Widespread	Feet (?); scoliosis	+	Corneal clouding	13
5 (UK)	F		3	Flexion deformity fingers			Dysostosis multiplex	+	Cardiac (aortic, tricuspid, mitral), umbilical hernia; corneal clouding; hepatomegaly; sleep apnea	10
6 (UK)	F		1	Limp; stiff hands; stiff neck	Scleroderma			+	Cardiac (aortic); frequent otitis, corneal clouding; umbilical hernia	4
7 (Germany)	M	+	5	Flexion contracture hands			Scoliosis	+	Corneal clouding, cardiac (mitral insufficiency)	9
8 (Germany)	M	+	5	Flexion contracture hands				+	Corneal clouding	5
9 (Germany)	M	+	6	Contracture finger				+	Corneal clouding	6
10 (France)	M		1	Flexion contracture hands; inguinal hernia; frequent otitis	Arthrogriposis	Shoulders; elbows; hips, knees; ankles	Trigger finger; sciatica; kyphosis; lordosis	+	Umbilical hernia; diarrhea; corneal clouding; hepatosplenomegaly; cardiac (mitral, aortic)	33
11 (France)	F		7 days	Hip dysplasia	Arthrogriposis	Cervical spine; shoulders; elbows; hands; knees; ankles	Sciatica; lordosis	+	Umbilical hernia; diarrhea; short stature; cardiac (mitral, aortic)	21
12 (France)	F		1	Flexion contracture hands	Connective tissue disorder	Shoulders; elbows; knees	Trigger finger; dysostosis multiplex	+	Cardiac (aortic and mitral); chronic otitis; umbilical hernia; corneal clouding; hepatosplenomegaly	4
13 (France)	F	+	8	Shoulder movement restriction		Cervical spine; elbows; hands; hips	Sciatica; kyphosis, lordosis, scoliosis		Short stature; hepatomegaly; diarrhea; cardiac (mitral, aortic), cervical cord compression	41

tal abnormalities (dysostosis multiplex), which can cause significant morbidity. Patients with the less severe form, such as those described in this report, can have an almost normal appearance (i.e. no coarse facial features), and a near-normal life expectancy, and therefore diagnosis is sometimes difficult because of a low index of clinical suspicion. For patients with the attenuated phenotype, MPS I may in fact not be considered because of the absence of facial dysmorphism - a manifestation prominent at the most severe end of the spectrum but less typical for attenuated disease. Notably, in none of our patients were clear dysmorphic signs present.

Biochemical diagnosis is usually initially suspected by analysis of urinary excretion of GAG (dermatan sulphate and heparin sulphate); however this method is not 100 % sensitive, since in the more attenuated phenotype, lower urinary GAG excretion may be found. Indeed in two of our cases (n. 7 and 9) this test was negative. In MPS I, the biochemical diagnosis is confirmed by demonstration of a deficient α-L-iduronidase activity in the leukocytes or fibroblasts. Therefore, in doubtful cases where the clinical suspicion is very strong but the urinary GAG not contributive, enzymatic activity should also be determined. The two most frequent mutations among European MPS I patients are W402X and Q70X representing 72% of the mutations (7). There is, however, a considerable ethnic and geographical genotypic variability. Patients with an attenuated phenotype do often present with one of the severe nonsense mutations (W402X or Q70X) but their genotype has limited predictive value regarding the rate of progression of the diseases.

Skeletal manifestations are common at the onset of disease and result from secondary disruptive changes induced by GAG accumulation in the synovium, bones, and periarticular soft tissues. Usually, other clinical features have to appear before the diagnosis of MPS I is suspected. Rheumatological involvement is mainly represented by stiffness and contractures of the joints, in particular of the hands and of the shoulders (8), and was present in most of the patients included in this report. Indeed all of them, even those diagnosed at a rather advanced age, had a rheumatological presentation in the first decade of life. In all but two patients, this consisted of stiffness and/or flexion contracture of the fingers, that eventually appeared in 100% of the cases. Figure 1 shows the hands of one of our patients, with joint subluxation and flexion contractures. Loss of function is progressive and debilitating, but clinical and laboratory inflammatory findings are usually absent. Carpal tunnel syndrome is common (9-13), and can even lead to rupture of the flexor pollicis longus tendon (14); of note, ten out of the thirteen patients in our series had clinical signs of carpal tunnel syndrome. In MPS I, carpal tunnel syndrome is often asymptomatic but all patients diagnosed with this disease should be tested by means of median nerve conduction testing.

Myopathy, manifesting as exercise intolerance, has also been described in MPS I S (15). Growth failure is not a prominent finding in Scheie sindrome, unlike the other more severe forms of MPS, and indeed in only two of our patients was final height significantly impaired. Besides carpal tunnel syndrome, other relevant musculoskeletal findings include kyphosis of the spine, genu valgum, trigger fingers (16), and bone abnormalities (dysostosis multiplex) that can include hip dysplasia and cranial, vertebral (17) and metacarpal deformities. Extra-skeletal manifestations such as cardiac valvular disease (in our cases mainly mitral and aortic stenosis with regurgitation), diarrhea, corneal clouding, and upper airway obstruction are common. A history of recurrent otitis media is a common finding at presentation, and can later lead to hearing loss. Radiological alterations can involve almost all bones, and include bone cysts as well (18-20). Late in the disease course, neurological signs or symptoms can appear, with cervical cord compression due to thickened dura as a potential severe complication (21, 22). As described in Table I, these features were present in many of our patients.

The existence of milder phenotypes of MPS I is probably possibly due to a residual enzymatic activity, that reduces the rate of GAG accumulation in tissues. Diagnosis of these forms is more difficult compared to the severe phenotype which is more uniform in its clinical presentation. Indeed, in our cases diagnoses were made at a mean age of 20 years, even though onset of symptoms was always in the first 8 years of life. For some patients there was a long period of unrecognized disease (even 50 years from the onset of symptoms), and only the appearance of more "typical" MPS I signs or symptoms such as those related to cardiac or neurological involvement ultimately led to the diagnosis.

We believe that there are some cases of Scheie syndrome that are currently misdiagnosed as having other forms of rheumatic disorders; in fact, several of our cases as well as others in the literature initially received diagnoses such as scleroderma, muscular dystrophy, juvenile idiopathic (rheumatoid) arthritis, Legg-Perthes disease, osteogenesis imperfecta, growing pains, rheumatoid arthritis, arthrogryiposis, dermato/polymyositis, and rheumatic fever. In particular, we would like to point out that although both MPS I and juvenile idiopathic arthritis can have joint stiffness and contractures within their clinical features, signs of local inflammation and morning stiffness are absent in the former and present in the latter. A synovial biopsy is almost never necessary to establish the correct diagnosis.

Based on the findings reported here, we want to underline the importance of an early recognition of these mild MPS I phenotypes characterized by a normal appearance and normal intelligence. Even if there is a possibility of mass screening (23), current newborn programs do not include MPS I. and therefore, current incidence and prevalence data may underestimate the real disease frequency.

In addition, musculoskeletal involvement is common at the disease onset and not only during the course of the disease, and in some patients these features (in particular, isolated joint contractures) have been the only pre-

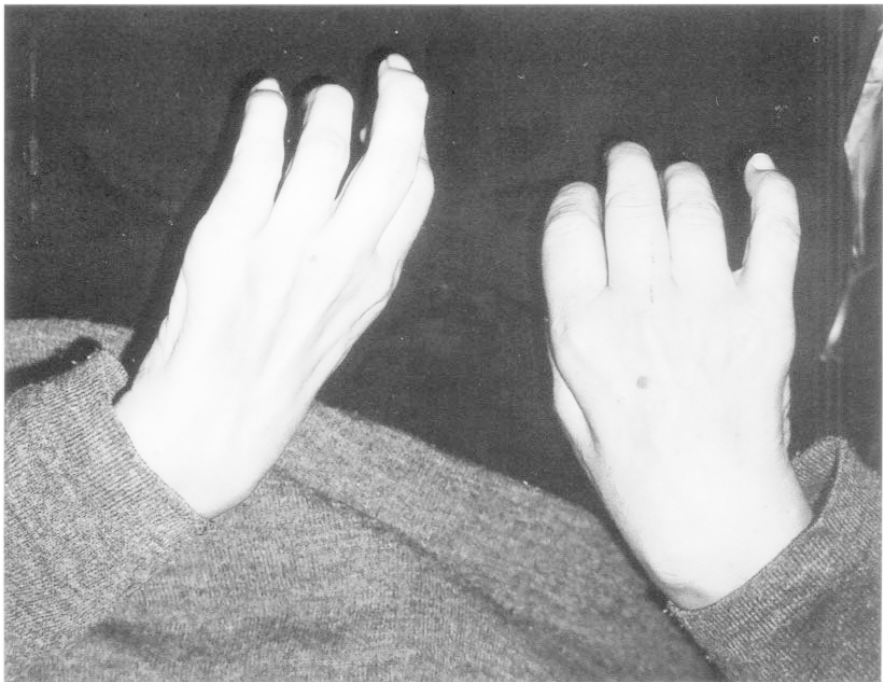

Fig. 1. Appearance of the hands of a representative patient, showing flexion contracture of all digits.

senting sign. Indeed, a recent questionnaire-based study on MPS I families (24) showed that stiff joints and limited mobility were the most frequent findings at the time of diagnosis and those that most frequently prompted the family to bring the child for a physician visit (in almost 75% of cases). Moreover, in the same study it was reported that symptoms relating to joint stiffness, pain, and mobility had by far the greatest impact on individuals with MPS I, even more than symptoms relating to visual and auditory impairment. In another study (3), 100% of a series of Scheie patients reported joint stiffness during their disease course.

Until recently, treatment of this disorder was mainly symptomatic and treatment of musculoskeletal symptoms consisted of supportive measures such as analgesia, physical therapy and orthopedic surgery. However, a correct and timely diagnosis is now very important because of the progressive nature of the disease and of the possibility of potentially curative treatment. Enzyme replacement therapy for MPS I disease has been available in Europe since June 2003 and has been shown to be safe and effective in its use (25-29). Given the unfavourable benefit/risk ratio of bone marrow transplantation in non-Hurler patients, this treatment option is not offered to patients with milder forms of MPS I but only to selected young Hurler patients under 2 years of age.

Other mucopolysaccharidoses (i.e. type II, III, IV, VI and VII) also have skeletal manifestations (30). The analysis of urinary GAG, the most common screening test for MPS, will detect any of these disorders and this will become of even greater importance since enzyme replacement therapies for MPS II (Hunter) and MPS VI (Maroteaux-Lamy) are currently at an advanced stage of clinical development.

In summary, we have described a cohort of patients with Scheie syndrome who had significant musculoskeletal impairment at the onset of their disease and who were diagnosed years, or even decades, later. We believe that this disorder is under-recognized, and would like to raise awareness among rheumatologists so that they can play an important role, not only in the management but also in the diagnosis of these patients. We suggest a urinary GAG analysis in any young patient presenting with symmetrical flexion contractures of the hands and diminished hand function, without inflammatory features, even in the absence of other disease characteristics. In cases with a high index of suspicion, such as those with a positive family history or those with other characteristic features of MPS I, enzymatic activity should be determined even if urinary GAG excretion is low.

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