Improved diagnostic procedures in attenuated mucopolysaccharidosis

General physicians and rheumatologists play a key role in suspecting a diagnosis of mucopolysaccharidosis for a range of multi-organ presenting symptoms in adults. Prompt diagnosis and treatment maximizes outcomes for these rare and extremely debilitating diseases. Earlier diagnosis may help to prevent irreversible disease.

It is often assumed that mucopolysaccharidosis is a disorder purely of childhood; an assumption supported by the fact that the median age for patients in the global registry for the most common form of this disease is just 9 years old (Pastores et al, 2007). However, the upper quartile of the mucopolysaccharidosis I registry includes patients who are well into their 60s. While life expectancy for those with the severe Hurler-type forms of mucopolysaccharidosis is less than 10 years, it is common for patients with the milder attenuated forms to live well into adolescence and adulthood. These patients may remain undiagnosed for many years, subject to ineffectual therapies and gradual progression of a disease that will become increasingly debilitating and life-threatening.

Inadequate diagnosis of attenuated mucopolysaccharidosis is a significant problem. The condition is relatively rare, although perhaps not as rare as many physicians suppose. Between 1981 and 2003 the birth prevalence of mucopolysaccharidosis I was 1.07 cases per 100 000 births in England and Wales (Moore et al, 2008). Mucopolysaccharidosis II is estimated to affect one person in 132 000 in the UK. The Society for Mucopolysaccharide Diseases has maintained a research database of cases since 1980. According to this database, the overall minimum incidence of mucopolysaccharidosis and related diseases is 1:26 000 (Society for Mucopolysaccharide Diseases, 2010). Other forms of the disease are less common still. The Society for Mucopolysaccharide Diseases data shows that over a 10-year period five babies with mucopolysaccharidosis VI disease were born in Britain (Society for Mucopolysaccharide Diseases, 2010).

Most general physicians will come across cases only infrequently and thus their index of suspicion is low, but the consequences of delayed diagnosis can be significant. In recent years, the use of enzyme replacement therapy has demonstrated significant benefits in patients with mucopolysaccharidosis including improved exercise tolerance, apnoea/hypopnoea index, shoulder flexion and health assessment scores indicating a clinically meaningful improvement in activities of daily living (Pastores, 2008; Clarke et al, 2009).

Prompt diagnosis and early treatment is essential to maximize these treatment outcomes (Clarke et al, 2009). By having an index of suspicion, general physicians and specialists such as rheumatologists could help adult patients with mucopolysaccharidosis receive earlier treatment.

Presenting symptoms

Mucopolysaccharidosis presents as a diverse array of symptoms (*Table 1*) leading to a long list of potential misdiagnoses (*Table 2*).

Undiagnosed patients with attenuated mucopolysaccharidosis usually present with musculoskeletal symptoms including joint pain, contractures and bony deformities. The most likely specialist referral is to a rheumatologist. However, rheumatologists fare little better than general physicians in their ability to identify attenuated mucopolysaccharidosis. In one international survey, only 13% of paediatric rheumatologists and 19% of rheumatologists considered the condition when presented with a description of an 8-year-old girl or a 23-year-old woman exhibiting musculoskeletal

Table 1. Presenting symptoms of mucopolysaccharidosis in all age groups

Joint involvement with or without inflammation
Recurrent ear, nose and throat infections
Growth deficits
Facial dysmorphism
Corneal clouding, glaucoma or retinopathy
History of umbilical and/or inguinal hernia
Recurrent hernias even after corrective surgery
Hepatomegaly
Carpal tunnel syndrome
Heart valve disease
Obstructive airway disease
Hearing loss
Skeletal deformities

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signs of mucopolysaccharidosis I (Manger, 2008). Only 20% of the paediatric rheumatologists and none of the rheumatologists could identify the appropriate diagnostic tests.

The mucopolysaccharidosis disorders

The term mucopolysaccharidosis describes a family of genetic metabolic disorders that result from deficiencies in the lysosomal enzymes needed to degrade glycosaminoglycan (Yano et al, 2009). Glycosaminoglycan is an important constituent of the extracellular matrix, joint fluid and connective tissue. If allowed to accumulate it can compromise the function of a variety of organs. The most common forms of mucopolysaccharidosis are described below:

Mucopolysaccharidosis I

This is an autosomal recessive disorder caused by deficiency of the alpha-L-iduronidase enzyme. The most common form of mucopolysaccharidosis, mucopolysaccharidosis I is divided into three categories according to severity: Hurler syndrome, Hurler–Scheie syndrome and Scheie syndrome.

Children with Hurler syndrome have a normal appearance at birth but, over their first year, develop characteristic coarsened facial features and gibbus deformity of the spine. Their symptoms, including cognitive impairment, are progressive, debilitating and usually lead to death within 10 years.

In contrast, patients with milder attenuated forms of mucopolysaccharidosis I often have no obvious physical or mental abnormalities and their facial appearance is quite normal. Early symptoms include joint pain and stiffness, corneal clouding, umbilical and/or inguinal hernia, carpal tunnel syndrome, hearing loss, frequent ear, nose and throat infections, and 'noisy' breathing. Musculoskeletal abnormalities include progressive arthropathy, hip dysplasia, dysostosis multiplex, spine deformities, and spinal cord compression. Cardiac valve disease is also very common (*Table 3*).

Enzyme replacement therapy is with laronidase (Aldurazyme, Genzyme, Cambridge, USA). Spinal cord compression is not affected by current enzyme replacement therapy and a trial of intrathecal enzyme replacement therapy has recently started.

Table 2. Common misdiagnoses of mucopolysaccharidosis

Autoimmune disease
Muscular dystrophy
Connective tissue disease
Osteogenesis imperfecta
Polymyositis
Dermatomyositis
Polyneuropathy
Fibromyalgia
Rheumatoid arthritis
Growing pains
Scleroderma
Juvenile idiopathic arthritis
Spondyloarthritis
Legg–Perthes disease
Other systemic rheumatic disorder

Mucopolysaccharidosis II

This is an X-linked recessive disorder caused by deficiency of the iduronate sulfatase enzyme. Most patients are male.

Also known as Hunter syndrome, mucopolysaccharidosis II causes similar symptoms to those seen in mucopolysaccharidosis I with the exception of corneal clouding. Progression of the disease also tends to be slower than in mucopolysaccharidosis I but hearing loss is encountered earlier and is more significant. Patients who live into middle and old age are at high risk of cardiac valve disease and carpal tunnel syndrome.

Enzyme replacement therapy is with idursulfase (Elaprase, Shire HGT, Cambridge, USA). An intrathecal enzyme replacement therapy trial has recently started using a special idursulfase formulation as the current enzyme does not cross the blood–brain barrier.

Mucopolysaccharidosis III

This represents a group of four enzyme deficiencies and tends to have more aggressive neurological involvement but adults have been described presenting with mental retardation or psychiatric symptoms (Gabrielli et al, 2005; Moog et al, 2007). Unexpected anaesthetic diffi-

Table 3. Presenting symptoms of mucopolysaccharidosis in the older population

Joint involvement with no inflammation
Joint laxity
Joint destruction or early degenerative changes
Facial dysmorphism
Corneal clouding or raised intraocular pressure
Easy recurrence of repaired hernias
Hepatomegaly
Carpal tunnel syndrome or other peripheral entrapment syndromes
Heart valve disease
Obstructive airway disease or restrictive airways disease
Hearing loss
Skeletal deformities

culties may be the first sign in both adults and children (Ingrosso et al, 2003).

Intrathecal enzyme replacement therapy trial has recently started for this condition.

Mucopolysaccharidosis IV

This is an autosomal recessive disorder caused by deficiency of the galactose 6-sulfatase or beta-galactosidase enzymes.

Also known as Morquio syndrome, mucopolysaccharidosis IV is characterized by distinctive and severe skeletal dysplasia, short stature, dysplastic odontoid process, and joint hyper-extendibility. This condition also has overlap with the other mucopolysaccharidosis disorders with involvement of eyes, cardiac valve changes, and respiratory system with death in early adulthood as a result of respiratory failure.

Enzyme replacement therapy is currently in development and a phase 1/2 clinical trial is in progress showing some promising preliminary data.

Mucopolysaccharidosis VI

This is an autosomal recessive disorder caused by deficiency of the arylsulfatase B enzyme.

Mucopolysaccharidosis VI is also known as Maroteaux–Lamy syndrome. Patients usually have a period of normal growth which then stops, resulting in dwarfism. Clinical symptoms include frequent respiratory infections or otitis media, inguinal or umbilical hernias, hepatosplenomegaly, coarse facial features, joint or spine abnormalities, and corneal clouding. Diagnosis can be difficult as seen from the case history (*right*).

Enzyme replacement therapy is with galsulfase (Naglazyme, Biomarin, Novato, USA).

Mucopolysaccharidosis VII

An autosomal recessive disorder caused by deficiency of the beta-glucuronidase enzyme. Also known as Sly syndrome, mucopolysaccharidosis VII is extremely rare and varies widely in its severity.

Clinical features include dysmorphic features, corneal clouding, hepatosplenomegaly, gastrointestinal symptoms, growth abnormalities, dislocated hip, joint contractures, inguinal and umbilical hernias, heart valve disease, hearing loss, hirsutism, chronic inflammatory lung disease and recurrent respiratory infections.

Enzyme replacement therapy is currently in development.

Diagnosis of mucopolysaccharidosis

A number of paediatric and rheumatology specialists attended a 1-day meeting to discuss the difficulty in diagnosing mucopolysaccharidosis (Cimaz et al, 2009). The result was a diagnostic algorithm (*Figure 1*) that offers all physicians a step-by-step guide to diagnosis, taking as its starting point a patient presenting with joint contractures (the most common early symptoms among mucopolysaccharidosis patients with attenuated disease). The authors concluded that suspicion of mucopolysaccharidosis should be raised in any patient presenting with evolving joint pain and joint contractures in the absence of inflammation. This algorithm will not identify patients affected by mucopolysaccharidosis III as their presentation can be distinctly different because the

Case History

Jane was a 61-year-old woman with mucopolysaccharidosis VI. She probably had problems from a very early age although they did not become very significant until about the age of 30 years when she noticed some unsteadiness. Suggestions of earlier involvement were that she was not keen on sport as she could not keep up with her peers. She was also excluded from some physical education sessions as she could not manage some of the movements. She had a very active social life and enjoyed dancing in her twenties but she seemed clumsier than others for most of her life. She had dentures in her twenties.

Jane's vision started to deteriorate in her 30s and she was diagnosed with glaucoma but did not respond to regular medication and over time lost her vision in the right eye. When she was about 40 years old she developed difficulty in walking and getting up from a sitting position. At that time she was diagnosed as having hip dysplasia and was not given any specific treatment. Her mobility problems got progressively worse over the next decade but she was still able to walk with some difficulty for up to 2 miles in an hour in the 1980s. In the early 1990s she could not walk for more than ½ hour at a time. Her mobility worsened in this decade and by the late 1990s she could not walk more than 5 minutes at a time without great discomfort; she was able to get up and down stairs at this point with some difficulty. She had frequent falls at this stage and she also described difficulty in putting on her clothes and difficulty in raising her arms above the shoulders by the late 1990s.

In 1999 she had a sudden increase in weakness of her limbs and was admitted to hospital where she was diagnosed with compression of the cervical spine with weakness in all four limbs. She underwent surgery for this and she was in hospital for 11 weeks. Following surgery there was improved power in all four limbs but not back to previous levels. She could walk with a Zimmer frame and could do some activities with her hands such as eating and cooking. In 2001 she fell down in the kitchen and fractured her left hip joint. Since then she has been wheelchair bound.

At this point she was diagnosed with Maroteaux–Lamy syndrome after a urine glycosaminoglycan screen was performed. In the last 3 years she has increased arthritic pains in her knees and hips, ankles and arms. She cannot move her left knee very much. She also describes having muscle spasms, more on the left than the right side, over the last 5 years; these are apparently controlled on medication. Currently she has weakness in all four limbs but she can stretch and move her limbs against gravity. She can manage to drink with a beaker and just about manage with a spoon, but she is completely wheelchair bound. Her current medications include tizanidine, aspirin, clonazapam, Cosopt eye drops, Viscotear eye gel and Lacri-lube eye ointment.

Jane's is a very unusual case of Maroteaux–Lamy syndrome, which usually presents in childhood with joint stiffness, mobility problems, upper airway obstruction and possibly dysmorphism. Jane has an attenuated form of this condition and she is one of the oldest individuals with this condition. Early diagnosis and treatment with enzyme replacement therapy may have prevented some of her current difficulties but sadly this was not considered until by pure chance the physician heard about this condition and sent the appropriate samples to the reference laboratory.

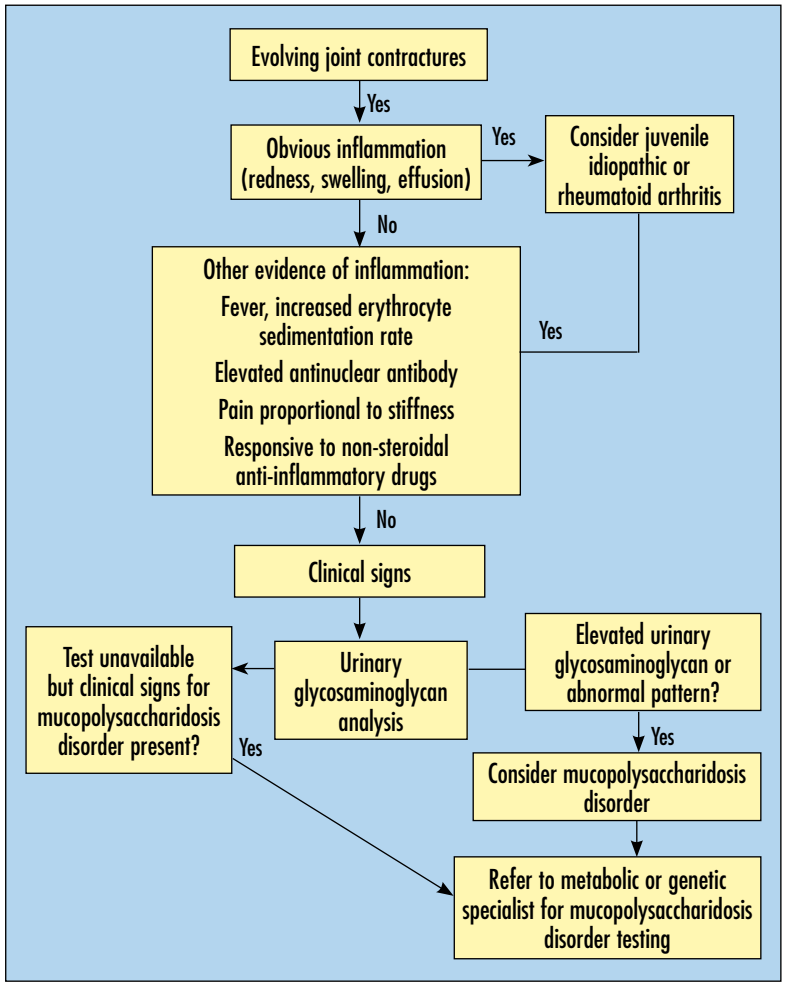

Figure 1. Mucopolysaccharidosis diagnostic algorithm. Adapted from Cimaz et al (2009).

skeletal system is not that severely affected. The commonest presentation in this group will be the result of developmental delay, regression or behavioural problems. These patients should undergo urinary glycosaminoglycan analysis without delay and the assay should be performed in an experienced specialist laboratory. Early morning samples are the most reliable; mucopolysaccharidosis IV in particular can be missed if not tested in an experienced laboratory. Where there is a strong suspicion of mucopolysaccharidosis IV on clinical grounds it is important to pursue enzyme diagnosis as even in experienced laboratories this condition can be missed in a urine sample.

Cimaz et al (2009) recommend that spot screens should be avoided as 'they are inaccurate and false negatives can occur'.

Patients with an elevated urinary glycosaminoglycan level are highly likely to have a mucopolysaccharidosis disorder and should undergo specific enzyme testing to determine which lysosomal enzyme is deficient. Falsely elevated urinary glycosaminoglycan levels can be seen in some patients and where the glycosaminoglycan:creatinine ratio is elevated glycosaminoglycan electrophoresis should be performed before enzyme analysis. Mucopolysaccharidosis may also exist in patients with normal urinary glycosaminoglycan levels but an abnormal urinary glycosaminoglycan profile. These patients should also undergo specific enzyme testing.

Where urinary glycosaminoglycan analysis is unavailable, patients exhibiting common signs or symptoms of an mucopolysaccharidosis disorder, such as corneal clouding, history of hernia surgery, frequent respiratory and/or ear, nose and throat infections, carpal tunnel syndrome or heart murmur should proceed directly to enzymatic testing.

Once mucopolysaccharidosis has been confirmed the patient should be referred to a geneticist or metabolic specialist for further evaluation and treatment. A full family history is also important to identify other family members who may be affected.

Referral and treatment

Mucopolysaccharidosis is a multisystemic disorder that should be managed by a multidisciplinary team. Consultation may be required with specialists in neurology, cardiology, orthopaedics, respiratory, ophthalmology and audiology.

Initial referral, however, should be to a geneticist or metabolic specialist. The patient should be offered supportive care including patient education, genetic counselling, psychosocial support and occupational therapy.

Some patients may require corneal transplants and/or corrective surgery for joint contractures or foot and hand deformities (Arn et al, 2009). Before surgery, however, appropriate precautions should be taken to counter any problems with the airways or cervical spine issues that may increase the risk of anaesthetic complications.

There are now effective enzyme replacement therapies available for mucopolysaccharidosis types I, II and VI.

Laronidase (Aldurazyme, Genzyme, Cambridge, USA) is indicated for patients with attenuated mucopolysaccharidosis I. Dosage is 0.58 mg/kg per week administered intravenously over 4 hours. Clinical trials of patients with attenuated mucopolysaccharidosis I have demonstrated that treatment with laronidase results in improved exercise tolerance, apnoea/hypopnoea index, shoulder flexion and health assessment scores indicating a clinically meaningful improvement in activities of daily living (Clarke et al, 2009).

In children under the age of 2 years with mucopolysaccharidosis I, haematopoietic stem cell transplantation can prolong life and preserve cognition. However, owing to the high mortality rate (10–15%) this therapy is not considered acceptable in older patients with attenuated mucopolysaccharidosis (Muenzer et al, 2009).

Idursulfase (Elaprase, Shire HGT, Cambridge, USA) improves walking capacity in patients with Hunter syndrome (Muenzer et al, 2006). Dosage is 0.5 mg/kg body weight every week by intravenous infusion over a 3-hour period, which may be gradually reduced if no infusion-associated reactions are observed.

Galsulfase (Naglazyme, Biomarin, Novato, USA) improves walking and stair-climbing ability in people with Maroteaux–Lamy syndrome (Harmatz et al, 2005, 2006, 2008). Recommended dosing is 1 mg/kg once weekly via a 4-hour infusion, with pretreatment 30–60 minutes beforehand with antihistamines (with or without antipyretics) to reduce potential infusion reactions in high-risk cases.

Conclusions

The availability of effective enzyme replacement therapies, together with the continued need for patients to receive supportive and palliative care, emphasizes the importance of early diagnosis in mucopolysaccharidosis. While the diagnosis of severe disease in young children is relatively straightforward, there is convincing evidence that diagnostic procedures for older patients with attenuated disease are currently inadequate. In particular, the index of suspicion among both general physicians and their specialist colleagues is too low.

The availability of a simple, easy-to-use diagnostic algorithm may improve this situation. It is clear that any patient who presents with evolving joint pain and joint contractures in the absence of inflammation should be investigated for mucopolysaccharidosis. Simple and definitive diagnostic tests are available. Greater use of these protocols may result in earlier diagnosis, more effective treatments and spare many patients years of inadequate care. **BJHM**

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KEY POINTS

- Mucopolysaccharidosis affects adults as well as children.
- Attenuated mucopolysaccharidosis may go undiagnosed for many years.
- A diagnostic algorithm for mucopolysaccharidosis is now available.
- Effective enzyme replacement therapy is available for mucopolysaccharidosis.
- Improved diagnosis of attenuated mucopolysaccharidosis may allow earlier treatment.
- Earlier diagnosis of mucopolysaccharidosis may enable appropriate treatment before the development of irreversible disease.