Editorial

Attenuated mucopolysaccharidosis: are you missing this debilitating condition?

Challenges in diagnosis

When rheumatologists think of mucopolysaccharidosis (MPS), if they think of it at all, it is likely they will think of a rare, inherited, chronic and progressive condition that affects young children. This is true for severe or fast-progressing MPS, which is usually diagnosed by paediatric rheumatologists. There are, however, attenuated or slow-progressing forms that are less well known and patients with these conditions may present to the adult rheumatology clinic. The attenuated or slow-progressing form develops slowly and insidiously and is often not diagnosed until the patient is an adolescent or an adult. Crude incidence rates from Baehner et al. [1] suggest between 3.4 and 4.5 per 100 000 live births are affected by various types of MPS, meaning this condition is only occasionally seen in clinical practice. Indeed, data from Cimaz et al. [2] show that only 9% of rheumatologists and paediatric rheumatologists have ever seen a patient with MPS I, but an additional 13% thought that they might have a patient with MPS I in their care. These percentages are likely to be similar for the other types of MPS. Patients with the attenuated or slow-progressing form of MPS will often fail to initially receive a correct diagnosis of their condition and may present to a rheumatologist with bone and joint symptoms. As ~20% of rheumatologists will consider MPS in the differential diagnosis, this condition may remain untreated [2], even though enzyme replacement therapy is available for some types of MPS. This delay in treatment can reduce the patient’s quality of life, may mean they receive unnecessary medical therapy and ultimately shorten their life expectancy.

MPS are a family of inborn metabolic conditions that are caused by the deficiency of one of the enzymes responsible for the degradation of glycosaminoglycans (GAGs). There are 11 known enzyme deficiencies that cause seven distinct types of MPS: namely I, II, III, IV, VI, VII and IX [1–4]. These enzyme deficiencies inhibit the catabolism of tGAGs, such as chondroitin, dermatan, heparan or keratan sulphate. Although it is accepted that MPS is a progressive disorder and the various types share many clinical features, the presenting symptoms vary depending on the enzyme affected and severity of the disease. The extent of symptoms and rate of progression will also vary between individuals affected by a specific type.

Patients with severe or fast-progressing MPS are often diagnosed by paediatric rheumatologists. In contrast, diagnosing patients with attenuated or slow-progressing form poses more of a challenge due to the perception that this is a disease of childhood. There is often a lack of mental impairment in some types of MPS disease, which may be viewed by some as a key feature of the disease. In addition, a diagnosis of the attenuated or slow-progressing form can be more problematic, as this condition is often mistaken for other diseases. Table 1 shows that the first symptoms include recurrent upper airway infection, cardiological involvement and skeletal deformities. Later in the course of attenuated or slow-progressing MPS (and while undiagnosed), patients will often be seen by rheumatologists because of pain and stiffness in the joints, contractures and hip and back pain. While eliciting the patient’s medical history, previous surgery for hip dysplasia is commonly reported. The similarity of attenuated or slow-progressing MPS to the more commonly seen rheumatological conditions means that patients are often misdiagnosed or that there is a delay before the patient’s symptoms are attributed to MPS. Joint disease in the absence of inflammation is a cardinal feature of attenuated or slow-progressing MPS, which should raise suspicion of this condition as a possible diagnosis.

If you as a rheumatologist suspect that one of your patients might have MPS, you should refer the patient to a specialist who is familiar with this condition. Often urinary GAG measurement is the first diagnostic step for paediatric patients, but this assay may fail to diagnose MPS in adults, who tend to have an age-related decline in GAG. Therefore, blood test is the preferred option and is performed either via a dry blood spot test for MPS I, II and VI or via an enzyme assay on heparinized blood for these and the other types of MPS.

Once diagnosed, enzyme replacement therapy is available for MPS I, II and VI and is under investigation in a Phase III trial for MPS IVA (Morquio A). At present, specific treatment is not available for MPS III, VII and IX and these patients receive supportive care. If untreated, MPS affects the skeletal system, heart, eyes, ears and lungs. Cranioocervical junction abnormalities with compression of the spinal cord are common and life-threatening features. Treatment can partly prevent these organs from being irreversibly damaged as well as slow disease progression and help the patient to maintain their quality of life. If treatment is not available, or if the attenuated or slow-progressing form remains undiagnosed, then the disease will progress and the patient may die at a younger age.
In conclusion, the attenuated, slow-progressing form of MPS is a rare condition that is often misdiagnosed due to the perception that this condition is a disease of childhood. These patients are often seen by rheumatologists due to their presenting symptoms of pain, stiffness and contractures of the joints. MPS should be included in the differential diagnosis for all patients and cardinal symptoms indicative of this condition are joint disease in the absence of inflammation. Once suspected, MPS should be confirmed by a blood test and a conventional enzyme assay. Although MPS I, II and VI can be treated with enzyme replacement therapy, and Phase III trials are ongoing in MPS IV, there is only supportive therapy available for MPS III, VII and IX at the present time. Treatment, if appropriate, is often able to slow the disease progression, maintain the patient’s quality of life and ultimately improve their life expectancy.

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