INFORMATION for Rheumatologists

This leaflet outlines:

- **the rheumatologic symptoms and complications of MPS II**
- **current opinion from the literature on how rheumatologic disease is managed in MPS II patients**

This leaflet is a summary of the published information as of February 2018, is not exhaustive and does not constitute any recommendations. It is the responsibility of the rheumatologist to determine the optimal management plan for the individual patient.

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INFORMATION for Rheumatologists

MPS II

A combination of common childhood complaints in your patient could indicate Hunter syndrome (MPS II), a rare genetic disorder that predominantly affects males. MPS II is caused by a mutation that stops the lysosomal enzyme iduronate-2-sulfatase (I2S) from being produced. I2S normally breaks down molecules called glycosaminoglycans (GAGs); without I2S, GAGs accumulate, causing progressive, multi-systemic disease, leading to early mortality.[1]

Early symptoms that should raise suspicion of MPS II include otitis media, abdominal hernia, nasal obstructions, and enlarged tonsils/adenoids and tongue.[2] These symptoms overlap with common childhood complaints. MPS II patients also almost always have musculoskeletal involvement, consisting of discomfort or deformity in the joints, which can be mistaken for inflammatory arthritis if the MPS II diagnosis has not yet been made.[3]

The key difference in MPS II patients from healthy children is that these symptoms occur early in combination, and may be refractory to treatment.[4] It is important to be able to diagnose MPS II in patients early, so that appropriate management may be initiated.[5]

ACT EARLY

If joint contractures or joint pain are evolving without evidence of inflammation, consider **Hunter syndrome (mucopolysaccharidosis type II; MPS II): a rare, multisystemic, life-threatening disease.**

If you suspect Hunter syndrome: REFER TO A SPECIALIST TODAY

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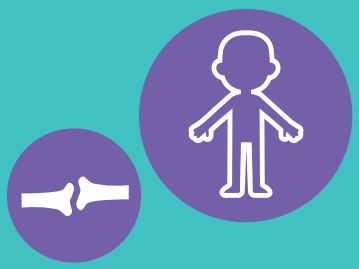

Presentation

The precise course and presentation of disease is unique in each MPS II patient, although there are common features. Patients typically appear normal at birth before developing a large head circumference, a broad nose and flared nostrils, a prominent brow, large jowl, thick lips, and an enlarged, protruding tongue.[2] Otitis media, abdominal hernia and enlarged tonsils/adenoids are common symptoms, and patients may receive multiple surgeries for these issues before a diagnosis of MPS II is made.[2]

Musculoskeletal manifestations are also nearly universal in MPS II patients, due to GAG accumulation in the soft tissues and chondrocytes.[3,5] These manifestations include a short stature, claw-like hands, joint contractures, joint stiffness, arthropathy, spine and rib deformities (kyphosis, scoliosis), gait problems, fine motor impairment, atlantoaxial instability, and diffuse, symmetrical skeletal deformities.[2,3]

The musculoskeletal pathologies in MPS II are collectively known as dysostosis multiplex, and abnormalities may 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.[3] As with the other features of MPS II, musculoskeletal manifestations and pathologies may be attributed to other causes.

Musculoskeletal changes can profoundly limit the mobility and quality of life of MPS II patients. For example, if stiffness and contractures involve the ankles and Achilles tendons, patients begin toe-walking. A combination of joint contractures, foot abnormalities, hip joint abnormalities and, frequently, severe genu valgum, can have a serious impact on gait, and the patient's ability to walk independently.[3] Therefore it is important to recognise the symptoms of MPS II early, to differentiate these features from the inflammatory arthritides, and to achieve a diagnosis that puts the patient into appropriate management.[3]

Differential diagnosis

Musculoskeletal manifestations in MPS II overlap with the symptoms of several other conditions, so achieving a differential diagnosis of MPS II is crucial.[3] For example, axial growth is affected in MPS II, ultimately resulting in a short stature. In contrast, patients with the inflammatory arthritides are more likely to develop localised growth disturbances (e.g. micrognathia or leg length discrepancies) or proportional short stature. Further, such disturbances only occur in those patients who have inflammatory arthritides before reaching skeletal maturity.[3]

Joint stiffness and contractures in MPS II may mimic conditions such as rheumatoid arthritis and juvenile idiopathic arthritis, but unlike the stiffness seen in those inflammatory arthritides, stiffness in MPS II is not typically worse in the morning, and is not exacerbated by rest, or relieved by activity. Further, there are no local signs of inflammation such as swelling, warmth or tenderness in MPS II, nor are there the systemic signs of inflammation such as fever and/or elevated laboratory markers of inflammation (ESR and CRP). MPS II joints may have a swollen appearance, but this is due to underlying bony enlargement, in contrast with the presence of synovial effusions in inflammatory arthritides. Furthermore, the articular abnormalities in MPS II **do not** respond to corticosteroids or other anti-inflammatory treatments.[3]

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MPS II patients may suffer from odontoid hypoplasia, consequently leading to atlantoaxial instability, spinal cord compression, and further neurological complications. Cervical instability is also found in juvenile idiopathic arthritis and enthesitis-related arthritis, but without any neurological involvement.[3]

In contrast to patients with MPS II, patients with inflammatory arthritides may have radiographic anomalies such as erosive bone lesions, periarticular osteopenia, joint space narrowing, and joint effusions, changing the shape or length of bones at the sites of inflammation. However, the diffuse, symmetrical skeletal changes seen in MPS II are not present.[3]

Look beyond a diagnosis of juvenile idiopathic arthritis. If joint contractures or joint pain are evolving without evidence of inflammation, consider Hunter syndrome (mucopolysaccharidosis type II; MPS II): a rare, multisystemic, life-threatening disease.

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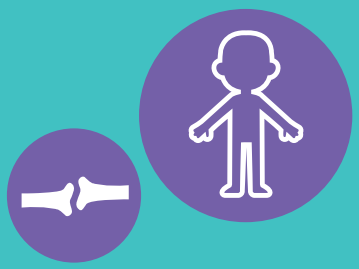

The following summary describes the current opinion in the literature (as of February 2018), however, it is the responsibility of the rheumatologist and the multidisciplinary team to determine the optimal management plan for the individual patient.

Management

Initial clinical examination of musculoskeletal features in MPS II patients by a rheumatologist can be followed by more in-depth evaluations:[2]

- Joint stiffness and contractures, arthropathy and spine deformities can be evaluated using the 6-minute walk test, to interrogate posture and walking ability, and by measuring joint range-of-motion as the disease progresses.[2]
- X-ray radiography can characterise anomalies such as abnormal bone thickness and shape, irregular epiphyseal ossification of the joints in the hands, shoulders and elbows, notching on the lateral surfaces of vertebrae, destructive hip arthropathies, and spinal cord deformities.[2,5,6]

After ruling out neurologic influences (e.g. spinal cord compression causing spastic gait or weakness) action may be taken to preserve and improve physical function, for example with a physiotherapy programme including mobilisation, strength and endurance training, enhancement of fine motor skills for the hands, and gait training for the lower limbs. Regular, short training sessions may be more successful than weekly sessions, and progress can be documented with baseline and periodic evaluations.[5] Orthopaedic devices such as orthotic footwear, braces, corsets and walking aids, may also assist the patient with daily activities.[2]

Surgery has a role in the management of more severe musculoskeletal manifestations of MPS II, in order to preserve long-term mobility.[5] Surgical procedures can include decompression of the spinal cord or median nerve, instrumented fusion (to stabilise and strengthen the spine), arthroscopy, hip or knee replacement, correction of the lower limb axis, and trigger finger release (secondary to carpal tunnel syndrome).[2]

Summary

Musculoskeletal manifestations are nearly universal in MPS II patients, due to GAG accumulation in the soft tissues and chondrocytes; the constellation of musculoskeletal pathologies found in MPS II is known as dysostosis multiplex.[3,5] Musculoskeletal changes can profoundly limit the mobility and quality of life of MPS II patients, for example leading to toe-walking or an inability to walk independently.[3]

As with the other features of MPS II, musculoskeletal manifestations and pathologies may be attributed to other causes, so rheumatologists must be able to differentiate these features from the inflammatory arthritides.[3] Once MPS II is diagnosed, rheumatologists can help to assess and record musculoskeletal symptom progression with simple clinical examinations, the 6-minute walk test, joint range-of-motion assessments, and X-ray radiography to help guide a physiotherapy programme, suggest orthopaedic devices, or recommend surgery.[2,5]

References:

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