CASE REPORT

Mucopolysaccharidosis type IVA (Morquio A): a close differential diagnosis of spondylo-epiphyseal dysplasia

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SUMMARY

Patients with mucopolysaccharidoses (MPS) have a plethora of multisystemic manifestations depending on the particular type, and atypical presentations are not uncommon. MPS type IVA (Morquio A syndrome) has predominant musculoskeletal system involvement and corneal clouding with normal intelligence and can be misdiagnosed as primary skeletal disorders in clinical practice. The absence of corneal clouding with normal urinary glycosaminoglycans (GAGs) level in a proportion of patients with MPS IVA makes the correct diagnosis even more challenging for physicians. Healthcare providers across specialties should have a high degree of suspicion for MPS IVA in all patients with suspected spondylo-epiphyseal dysplasia as early diagnosis and early treatment significantly improve the clinical outcome and activity of daily living.

BACKGROUND

Mucopolysaccharidoses (MPS) are a group of disorders caused by partial/complete deficiency of any of the enzymes responsible for stepwise degradation of the glycosaminoglycans (GAGs).[1] Most of them are inherited as autosomal recessive disorders, except MPS II which is transmitted as an X-linked recessive trait. Partially degraded GAGs such as chondroitin sulfate, keratan sulfate, dermatan sulfate or heparan sulfate accumulate in various organs of the body including the brain, liver, spleen, eyes, bones and ligaments leading to progressive organ dysfunction. The different GAG remnants can be detected in urine, blood or cerebrospinal fluid and are used as a screening tool for the diagnosis of MPS. Skeletal involvement remains one of the most prominent clinical features of this group of disorders. MPS IV (both A and B) in particular is known for its predominant skeletal involvement with minimal or no involvement of other organ systems.[2] The point prevalence of MPS IVA has been estimated at 1 per 926 000 in Australia, 1 per 599 000 in the UK and 1 per 1 872 000 in Malaysia. Birth prevalence of MPS IVA ranges from 1 per 71 000 to 1 per 500 000 according to reports from several countries including Australia, Brazil, Canada, Germany, Japan, Netherlands, Saudi Arabia, Taiwan, United Arab Emirates and UK.[3] A German study estimated the incidence of MPS IVA at 1 per 270 000[4] whereas, in Italy, the incidence has been estimated at 1 per 300 000 live births.[5]

CASE PRESENTATION

A 19-year-old boy presented to the surgery outpatient department for management of a grade 3 pressure sore over his back which developed following prolonged immobility. He had been diagnosed with spondylo-epiphyseal dysplasia during his childhood and advised rehabilitation therapy.

Born of a non-consanguineous union, he had normal developmental milestones (motor, social and language) and normal physical activities until 11 years of age when he developed progressive bowing of both legs. Gradual but progressive deformities of the limbs and spine and loss of movement thereafter rendered him completely bedbound for 3 years before presentation. He had satisfactory scholastic performances and completed higher secondary school education.

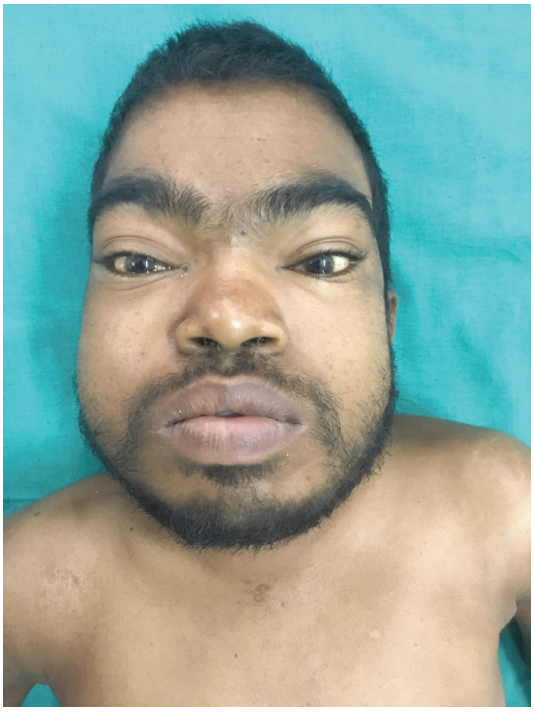

Figure 1 Coarse facies with thick bushy eyebrows, thick lips and broad nose.

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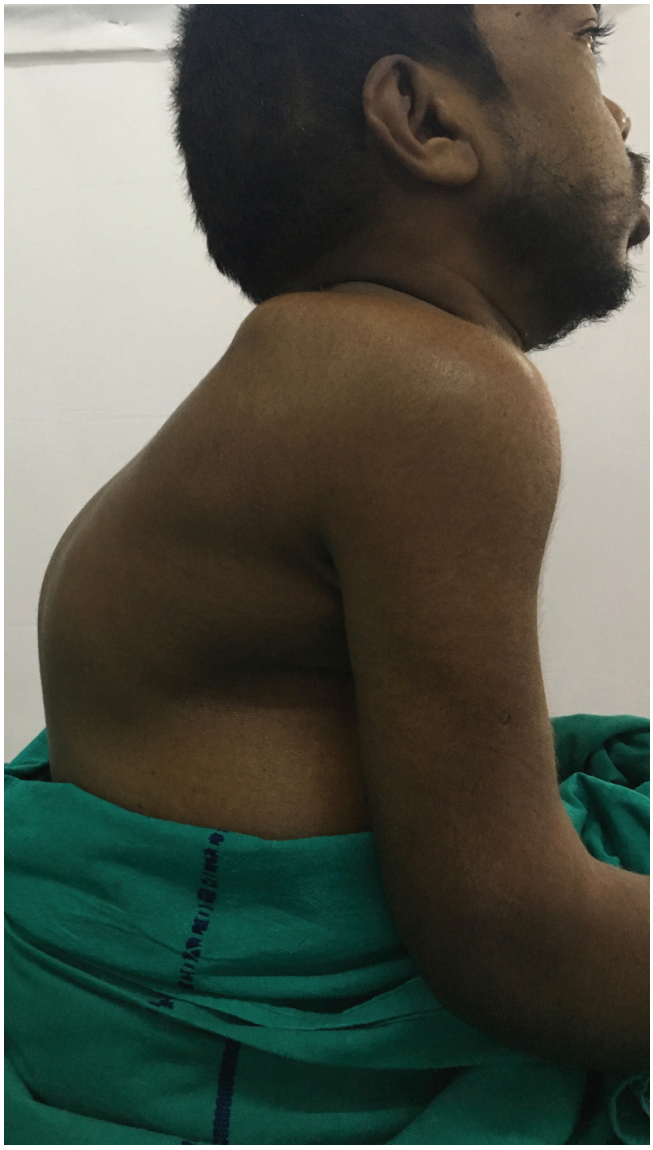

Figure 2 Clinical photograph showing kyphoscoliosis and short stature.

Clinical examination revealed severe short stature (supine length 138 cm; height SD score −6.4) with coarse facies, thick bushy eyebrows and dental malocclusion (figure 1). He also had kyphoscoliosis (figure 2), pectus excavatum, mildly widened wrists (figure 3) and genu valgum (figure 4). The peripheral joints were hypermobile. The rest of the systemic examination including evaluation of intelligent quotient (IQ) was unremarkable with absence of corneal clouding (figure 5) and hepatosplenomegaly. His body weight was 46 kg and he had no clinical signs suggestive of spinal cord compression or tracheal obstruction.

INVESTIGATIONS

Leishman stain of the peripheral blood smear revealed typical Alder–Reilly anomalies (partially degraded protein-carbohydrate complexes within the lysosomes which are seen as inclusion bodies within mature white blood cells; figure 6).

Complete blood count, baseline biochemistry, echocardiography, abdominal ultrasonography and pure-tone audiometry were otherwise normal. The whole body skeletal survey was

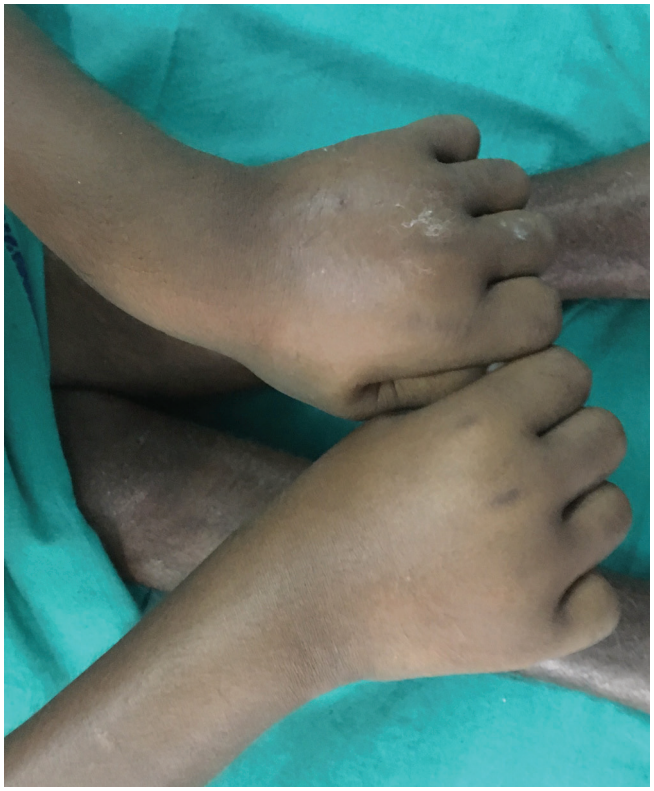

Figure 3 Widening of left wrist.

suggestive of dysostosis multiplex consisting of odontoid hypoplasia, thoracolumbar kyphoscoliosis, thickened short clavicles, oar-shaped ribs (figure 7), flattened acetabula and dysplastic femoral heads. Definite platyspondyly or anterior beaking of the vertebral bodies were absent (figure 8).

MRI of cervical spine confirmed odontoid hypoplasia and atlanto-axial subluxation with compression of the spinal cord at the C1 vertebral level (figure 9). A urine sample for MPS screening by the toluidine-blue test was positive. Subsequently, urine electrophoresis (qualitative) revealed abnormal bands in the regions of chondroitin sulfate and keratan sulfate. Enzyme assays of whole blood leucocytes by fluorometry using artificial substrate for type I (serum alpha-L-iduronidase enzyme activity 19.50 nmol/hour/mg compared with control value of 17 nmol/hour/mg (reference 9–26)), type VI (serum arylsulphatase B enzyme activity 285.50 nmol/hour/mg compared with control value of 266 nmol/hour/mg (reference >100)) and type IVB MPS (serum β-galactosidase enzyme activity 113.2 nmol/hour/mg compared with control value of 128 nmol/hour/mg (reference 58–623)) did not reveal any deficiency. However, the value of N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme was very low (1.1 nmol/17 hour/mg test value compared with control value of 118 (reference 45–443)), suggesting deficiency of GALNS and thus confirming MPS IVA.

DIFFERENTIAL DIAGNOSIS

1. Spondylo-epiphyseal dysplasia (progressive pseudorheumatoid dysplasia)
2. Spondylometaphyseal dysplasia
3. Brachyolmia (types 1, 2 and 3)
4. Legg–Calvé–Perthes disease
5. Juvenile idiopathic arthritis
6. Rickets
7. Mucopolysaccharidoses (type IV/Morquio's disease)

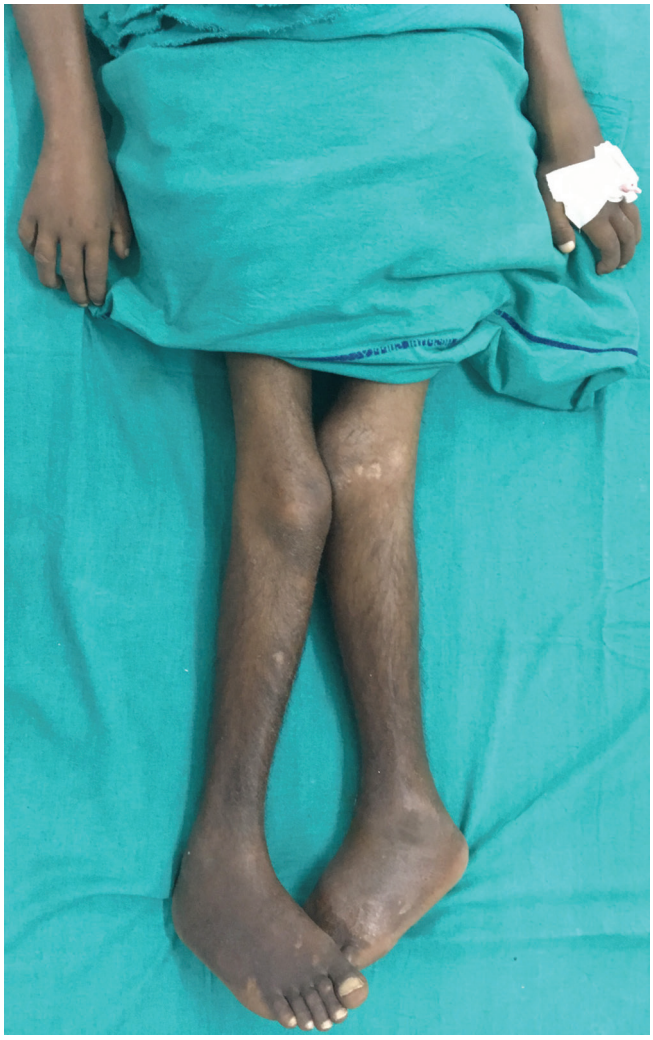

Figure 4 Genu valgum and widening of ankle joints.

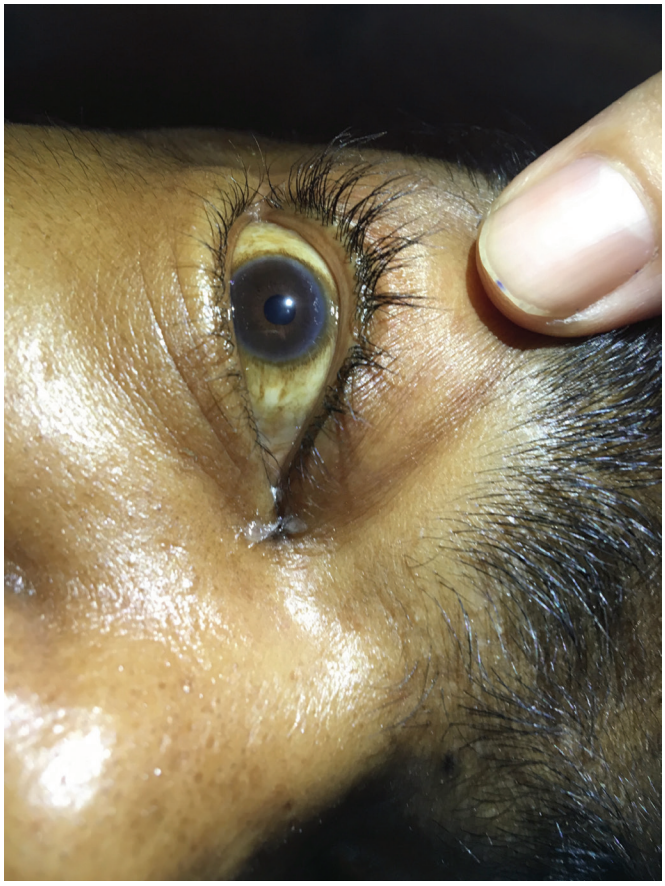

Figure 5 Absence of corneal clouding.

OUTCOME AND FOLLOW-UP

The pressure sore was treated with appropriate antibiotics, regular dressing and plastic surgery. He was advised appropriate medical rehabilitation therapy. Possible future requirements of interventions such as spinal cord decompression and fusion surgery, knee and hip surgery were also discussed. Enzyme replacement therapy was declined due to cost constraints.

DISCUSSION

MPS is classified into the following types depending on the deficient enzyme: I (having three subtypes: Hurler syndrome, Hurler–Scheie syndrome and Scheie syndrome), II (Hunter syndrome), III (Sanfilippo syndrome), IV (Morquio syndrome), VI (Maroteaux–Lamy syndrome), VII (Sly syndrome) and IX. Although MPS is a multisystem disorder, it is possible to differentiate the different types clinically by age of presentation and dominant clinical features. Depending on presentation, MPS may be broadly classified into the following groups:

- Primarily skeletal disorders (type IV)
- Soft tissue and skeletal involvement (type VI)
- Soft tissue storage and skeletal disease with or without brain disease (type I, II, VII)
- Primarily CNS involvement (type III)

MPS is a spectrum disorder and the phenotype of each group varies from mild to severe multisystemic decapacitating disease depending on the amount and activity of residual enzyme, which again depends on the genotype of the affected individual and other unknown genetic or environmental factors.[6]

Detection of urinary GAGs either qualitatively or quantitatively and fractionation of GAGs by electrophoresis or chromatography or tandem mass spectrometry in morning urine specimens can identify the types of MPS while a definite diagnosis requires assay of particular enzymatic activity, usually in the peripheral blood leucocytes, although fibroblasts or other cells can be tested. Molecular analysis, also known as mutation analysis, can also be used to confirm enzyme activity results and facilitate genetic counselling. Alder–Reilly granules and typical skeletal radiographs are potential clues and are particularly useful in resource restricted settings. In the case of MPS IV (both A and B), evaluating both total urinary GAGs (quantitative analysis) and specific types (qualitative analysis) of GAGs (keratan sulfate, chondroitin sulfate) simultaneously is critical to avoid false negative results as keratan sulfate can be present without elevating the total amount of urinary GAGs. The definitive diagnosis of MPS IVA requires the demonstration of deficiency in GALNS activity, the enzyme that degrades chondroitin-6-sulphate and keratan sulfate.

Enzyme replacement therapy (ERT) with recombinant human GALNS (elosulfase alfa) is approved by the US Food and Drug Administration for the treatment of MPS IVA, although the long-term outcome on the skeletal and non-skeletal features is not yet known. ERT does not penetrate the bone and thus does not improve the skeletal outcomes, even if introduced early in the course of the disease. Bone pathology remains unchanged and skeletal deformities worsen even after 30 months of ERT.[7] Haematopoietic stem

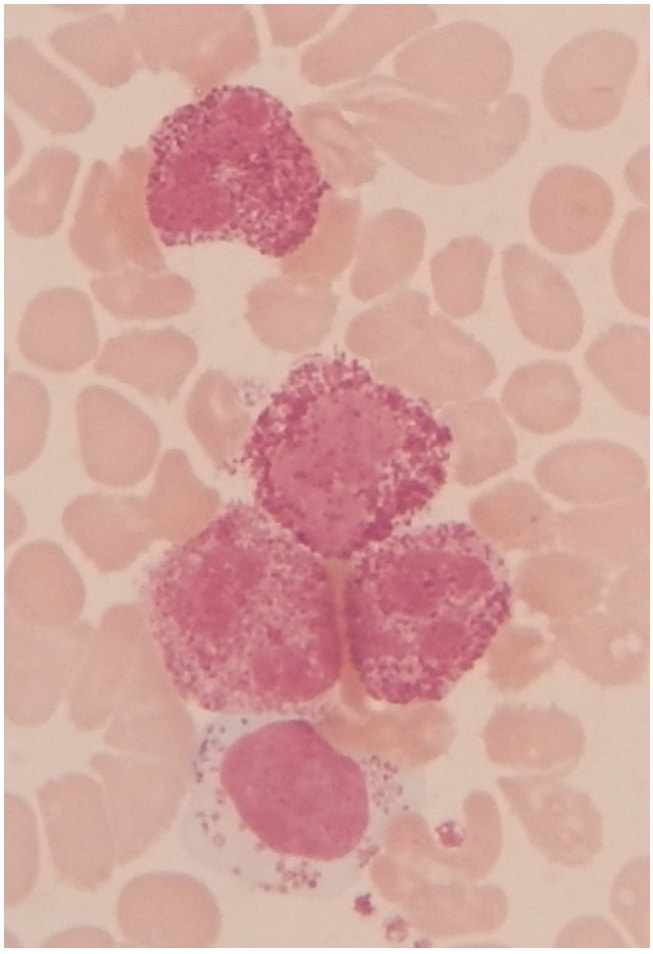

Figure 6 Leishman stain of the peripheral blood smear showing Alder–Reilly anomalies (inclusion bodies within mature white blood cells).

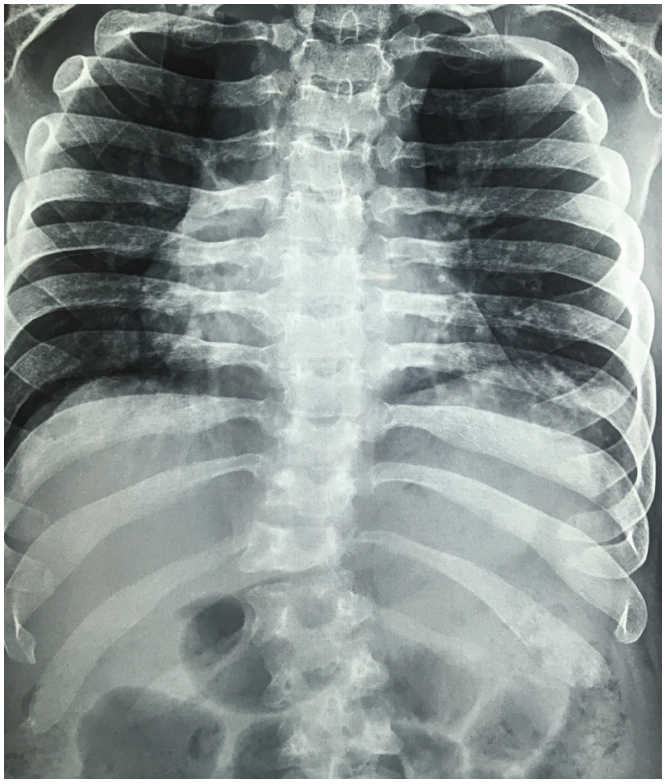

Figure 7 Scoliosis and characteristic oar-shaped ribs (narrowing at the takeoff from the vertebral column and broadening of the anterior distal end).

cell therapy (HSCT) is another treatment option in patients with MPS IVA and has been shown to favourably affect respiratory functions, radiograph findings, activity of daily living (ADL) and biochemical findings.[8 9] Although both therapies produce a partial improvement in symptoms and ADL, they have a limited effect on established bone and cartilage lesions. HSCT perhaps scores a bit better than ERT in preventing and retarding the progression of skeletal defects.[10] Certain features such as upper airway obstruction, organomegaly and corneal clouding improve significantly; hearing and motor functions improve to a certain extent; valvular heart disease improves in some patients but progresses in others; and short stature and speech skills show little improvement after HSCT in patients with different types of MPS including type IVA.[11] Patients with MPS IV (both A and B) demonstrate a plethora of non-skeletal manifestations which have a significant impact on overall quality of life. Initial evaluation, appropriate management and regular assessment of such individuals are therefore best undertaken by multiple specialists including otorhinolaryngologists, pulmonologists, ophthalmologists, cardiologists, orthopaedics and physiotherapists to facilitate timely intervention and maximise the quality of life potential.

After the initial clinical examination of our patient, the possible diagnoses were MPS II and IV. Type III was effectively ruled out because of the complete absence of neurological manifestations. The patient presented with skeletal involvement only with hypermobile joints but without visceromegaly and corneal opacity. Patients with MPS IVA usually have corneal clouding, but corneal opacity may be subtle or even absent.[12] In contrast to the joint stiffness that is observed in other MPS subtypes, the joints in MPS IVA are typically hypermobile secondary to ligamentous laxity.[13] Although patients with MPS IVA have a normal birth length, growth velocity usually decreases between 1 and 3 years of age, with an average height of 123 cm at 18 years of age compared with 177 cm in unaffected males.[14] In our patient, a height of 138 cm is definitely higher than the average height attained by MPS IVA male patients, but it is lower than that of unaffected males, signifying growth retardation.

Patients with progressive pseudorheumatoid dysplasia, a variety of spondylo-epiphyseal dysplasia, present in late childhood with non-inflammatory peripheral joint involvement, genu valgum and short stature. The radiographs of the hip and spine X-rays show degenerative joint changes, widening of the femoral heads and flattened thoracic and lumbar vertebrae simulating MPS IV (both A and B).[15] As a result, many patients with MPS IV (both A and B) may be misdiagnosed as spondylo-epiphyseal dysplasia or Legg–Calvé–Perthes disease, particularly in the absence of corneal clouding and hepatosplenomegaly.[16 17] The other close differential diagnoses are juvenile idiopathic arthritis and rickets due to joint pain and deformities and widening of joints; however, unlike MPS, spine involvement does not occur in these disorders.[18 19]

Although radiological abnormalities suggestive of dysostosis multiplex are quite unique to MPS IV (both A and B), flattened vertebral bodies (platyspondyly) with anterior beaking was not conspicuous in this patient. Another interesting aspect of this particular patient is the absence of corneal clouding and

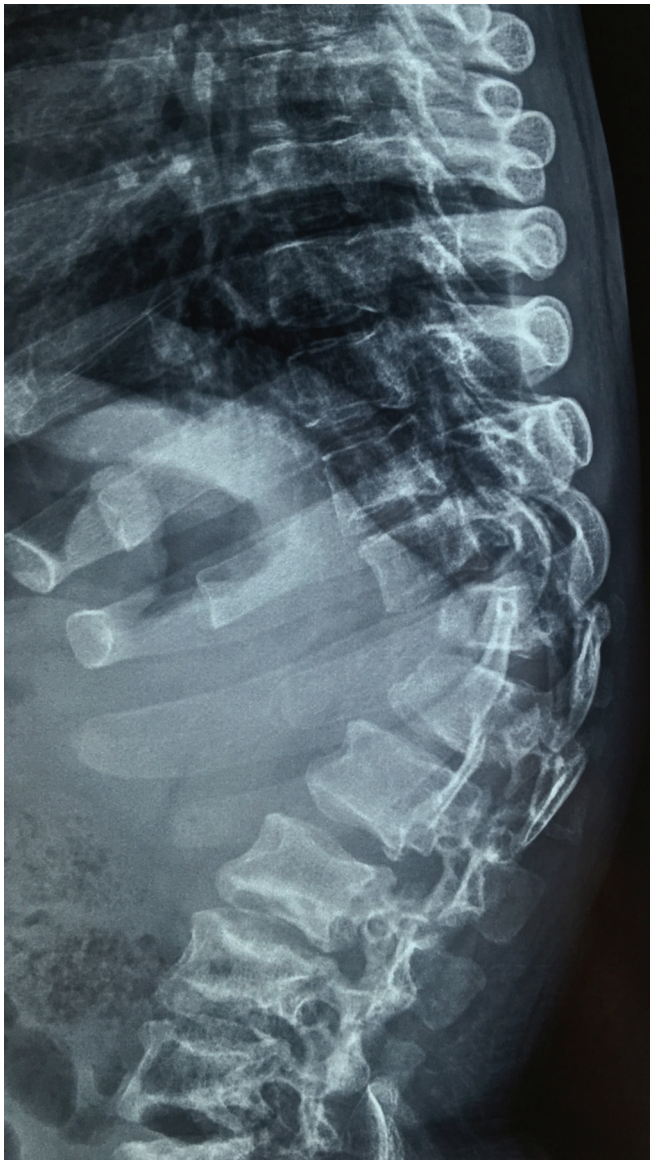

Figure 8 Gibbus formation without definite platyspondyly.

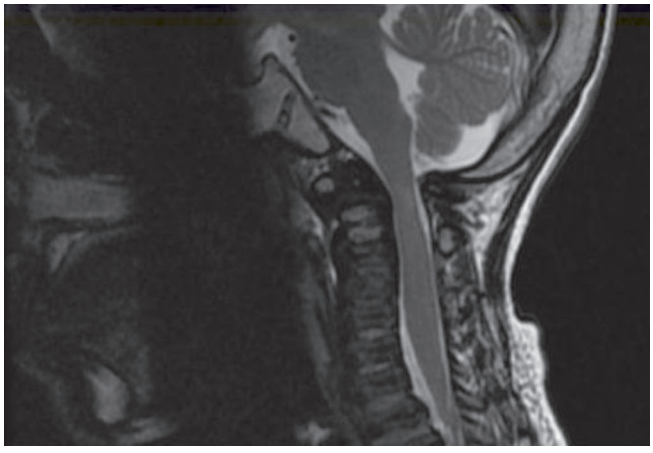

Figure 9 MRI of cervical spine (T2-weighted image) documenting obscure tip of dens with soft tissue/pannus around it. Atlas is dislocated anteriorly with consequent compression of the spinal cord at the C1 vertebral level and cord oedema.

hepatosplenomegaly, which is quite uncommon in MPS IVA. However, adolescents with MPS IVB may not manifest corneal clouding and hepatosplenomegaly.[20] Thick bushy eyebrows, Alder–Reilly anomalies in the peripheral blood smear and oar-shaped ribs were the clues to underlying MPS in this patient.

Learning points

- Although mucopolysaccharidoses (MPS) is a multisystem disorder, MPS IV or Morquio's disease can present with predominant or isolated muskuloskeletal involvement.
- The diagnosis is particularly challenging in the presence of subtle or atypical presenting signs or symptoms such as the absence of visceromegaly and corneal clouding. Thick bushy eyebrows are an important clinical clue in such patients.
- Morquio's disease is often misdiagnosed as spondylo-epiphyseal dysplasia or other primary musculoskeletal disorders. A high degree of clinical suspicion is required to consider Morquio's syndrome as a differential diagnosis, especially for patients who may have a non-classical phenotype of the syndrome.
- Clinicians across different specialties, in particular orthopaedic surgeons, rehabilitation specialists and rheumatologists, should be aware of Morquio's disease as early diagnosis and treatment has a favourable outcome.

Contributors SNB: diagnosis and patient management. SP and PPC: diagnosis, literature search and preparing the manuscript. HB: patient management.

Competing interests None declared.

Patient consent Obtained.

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