Mucolipidosis Type III: A Rare Disease in Differential Diagnosis of Joint Stiffness in Pediatric Rheumatology

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ABSTRACT
Mucolipidoses are metabolic disorders with autosomal recessive inheritance caused by deficiency of N-acetylglucosamine-1-phosphotransferase leading to accumulation of glycosaminoglycans and sphingolipids intracellularly. The differential diagnosis of mucolipidosis II or III is based on the age of onset, clinical findings and degree of severity. In this article, we present four pediatric patients with mucolipidosis III or pseudo-Hurler polydystrophy who admitted to our hospital with joint stiffness. They were from consanguineous families with characteristic radiographic findings. The joints were painless and the rheumatologic evaluation and inflammation markers were negative. Mucolipidosis is a rare disease in pediatric patients to remember in differential diagnosis of joint stiffness.

Keywords: Differential diagnosis; joint stiffness; mucolipidosis; pediatric rheumatology.

Mucolipidosis (ML) is a rare autosomal recessive inherited metabolic disorder of lysosomal metabolism characterized by defective processing of multiple lysosomal degradative enzymes due to the absent or deficient activity of N-acetylglucosamine-1-phosphotransferase. Deficient activity of N-acetylglucosamine-1-phosphotransferase leads to defective post-translational modification of lysosomal enzymes, promoting the intracellular accumulation of both partly degraded glycosaminoglycans and sphingolipids.¹⁻³ The trafficking process that transports the lysosomal enzymes to the interior of lysosomes is impaired. Thus the degradative enzymes accumulate at high concentrations in plasma serving as a diagnostic evidence for mucolipidosis II/III. The differential diagnosis of ML II or III is based on the age of onset, clinical findings and degree of severity.⁴⁻⁵ In this article, we present four pediatric patients with joint stiffness and diagnosed as ML III or pseudo-Hurler polydystrophy with characteristic radiographic findings to attract attention to this rare entity in pediatric rheumatology.

CASE REPORT

Case 1, 2- A five-and-a-half-year-old girl patient from Syrian origin referred to the Department of Pediatric Metabolism and Nutrition due to the presence of claw-hand deformity and joint stiffness (Figure 1). This girl was the second child of a consanguineous couple. Lateral cervical spine and posteroanterior chest radiographs of the patient diagnosed with ML III showed
abnormal vertebral bodies with anterior vertebral beaking on the lateral cervical radiogram and chest X-ray demonstrated short and thick clavicles (Figure 2). In physical examination; her body weight was 15 kg (3%-10% percentile) and height was 106 cm (3%-10% percentile). Her neurological development was normal for her age. However, she had claw-hand deformity, limited in maximum flexion and extension of the fingers, elbows and shoulders. Ophthalmological and rheumatologic laboratory evaluations were normal, but cardiac examination revealed aortic insufficiency.

Her elder brother was eight years old and had more severe similar clinical findings. Around four years of age, skeletal alterations were manifested by short stature, difficulty to run, go upstairs and downstairs, joint stiffness and difficulty in leaning forward (Figure 3). His body weight was 22 kg (3%-10% percentile) and height was 120 cm (3%-10% percentile). He had mitral insufficiency. None of the patients had history of fever, extremity pain or swelling. Urine dermatan sulphate concentrations were elevated in both of them and the gross elevations of plasma beta-hexosaminidase, arylsulphatase A and alpha-mannosidase were consistent with a diagnosis of ML II/III. A written informed consent was obtained from the parents of patients.

**Case 3, 4-** A five-and-a-half-year-old girl patient from Turkish origin was admitted to the Department of Pediatric Metabolism and Nutrition due to the presence of claw-hand deformity (Figure 4). This girl was the sixth child of a consanguineous couple. Around three years of age, skeletal alterations were manifested by short stature, difficulty to run, go upstairs and downstairs and joint stiffness. In physical examination; her body weight was 19 kg (25%-50% percentile) and height was 111 cm (25%-50% percentile). Her neurological development was normal for her age. However, she had claw-hand deformity, limited in maximum flexion and extension of the fingers, elbows and shoulders. There was no history of fever, extremity pain, tenderness or swelling. Hand

![Figure 1](image1.png)

**Figure 1.** Physical appearance of case 1; Five-and-a-half-year-old Syrian girl, showing short stature, claw-hand deformity, limited in maximum flexion and extension of the fingers, elbows and shoulders.

![Figure 2](image2.png)

**Figure 2.** Lateral cervical spine and posteroanterior chest radiographs of case 1 diagnosed with mucolipidosis III. (a) On lateral cervical radiogram, note abnormal vertebral bodies with anterior vertebral beaking (white arrows). (b) Chest X-ray demonstrates short and thick clavicles (white arrows). Note slightly small humeral heads (black arrows).
radiograph showed short and wide metacarpal tubular bones. Pelvis radiograph demonstrated the flaring of the iliac wings, shallow acetabular fossae and lateral subluxation of the femoral heads (Figure 5). Ophthalmological and rheumatologic laboratory evaluations were normal, but cardiac exam revealed aortic insufficiency and mitral valve prolapse. A written informed consent was obtained from the parents of the patient.

Her elder brother was 18 years old and had more severe similar clinical findings (Figure 6). His body weight was 41 kg (<3% percentile) and height was 147 cm (<3% percentile). He has scoliosis, dysostosis multiplex, mild mental retardation, waddling gait, height stunting and coarse face. Echocardiographic evaluation revealed aortic insufficiency. Urine dermatan sulphate concentrations were elevated in both of them and the gross elevations of plasma beta-hexosaminidase, arylsulphatase A and alpha-mannosidase were consistent with a diagnosis of ML II/III. A written informed consent was obtained from the parents of the patient.

Figure 3. Physical appearance of case 2; Eight-year-old Syrian boy showing short stature, joint stiffness of elbows and shoulders.

Figure 4. Claw-hand deformity (impossible flexion and maximum extension) in case 3 diagnosed with mucolipidosis III.

Figure 5. Hand and pelvis radiographs of case 3 diagnosed with mucolipidosis III. (a) Hand radiograph shows short and wide metacarpal tubular bones (white arrows). Also, note claw-hand deformity. (b) Pelvis radiograph demonstrates flaring of iliac wings (white asterisk), shallow acetabular fossae and lateral subluxation of femoral heads (white arrows).
The demographic and clinical data, radiologic findings and laboratory evaluations of the patients are given in Table 1.

**DISCUSSION**

We reported four pediatric patients with complaints of immobility and painless joint stiffness and diagnosed as ML. ML is a rare autosomal recessive lysosomal storage disease, which can be classified into four types. ML II/III are caused by deficiency of the enzyme N-acetylglucosamine-1 phosphotransferase. ML III is a milder disorder with attenuated characteristics and survival to adulthood. Patients usually present between two and four years of age with symptoms referable to the joints. The typical clinical symptoms include short stature, cardiac valve involvement, normal intelligence or mild mental retardation, normal corneal appearance or steaminess of the cornea, and scoliosis and skeletal and orthopedic complications including hand and shoulder stiffness, claw-hand deformities, short iliac wings, erosion of the femoral heads, dysostosis multiplex of the vertebral bodies, long bones, skull, phalanges and clavicles with no to mild organomegaly. Cardiopulmonary complications are the usual reasons of mortality in patients with ML III. Aortic and mitral valve insufficiencies are the most common forms of cardiac involvement. All of our patients with ML III had cardiac valve insufficiency. A carpal tunnel syndrome may develop in these patients. Flexion contracture of knees, hips, and elbows may lead to shortness of stature. Progressive destructive changes in the hip may lead to a waddling gait. Late effects are destruction of the femoral heads and vertebral bodies leading to a compromised mobility. The laboratory findings of patients with ML III involve the abundance of some lysosomal enzymes in plasma including arylsulfatase. Genetic transmission is autosomal recessive and consanguinity was observed in all of our patients with ML III.

The differential diagnoses of ML should include juvenile idiopathic rheumatoid arthritis, mucopolysaccharidoses, oligosaccharides and progressive pseudorheumatoid arthritis of childhood.

The therapeutic methods for ML III are essentially symptomatic treatment and genetic counselling. Intravenous pamidronate has been used in order to reduce bone pain and improve mobility. Supportive orthopedic management and physiotherapy may be useful in such patients. In ML III, evolution is slow and patients can usually reach up to the fifth decade of life. Prenatal diagnosis is possible by assay of the enzyme in

![Figure 6. Physical appearance of Case 4; 18 years old Turkish male, (a) showing coarse face, short stature and scoliosis in physical examination, (b) hands of the patients showing contractures.](image)
### Table 1. Demographic data, clinical and laboratory findings of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years-old)</th>
<th>Race</th>
<th>Clinical findings</th>
<th>Radiologic findings</th>
<th>Urinary mucopolysaccharides</th>
<th>Arylsulfatase A</th>
<th>Alpha mannosidase</th>
<th>Hexominidase A&amp;B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>Five-and-a-half</td>
<td>Syrian</td>
<td>Claw-hand deformity, Limitation in maximum flexion and extension of the fingers, elbows and shoulders. Aortic insufficiency.</td>
<td>Abnormal vertebral bodies with anterior vertebral beaking on the lateral cervical radiogram short and thick clavicles</td>
<td>Trace of dermatan sulphate seen</td>
<td>5500</td>
<td>4134</td>
<td>17655</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>8</td>
<td>Syrian</td>
<td>Claw hand deformity Short stature Joint stiffness in elbows, fingers, shoulders and spine. Mitral insufficiency.</td>
<td>Dysostosis multiplex</td>
<td>Trace of dermatan sulphate seen</td>
<td>5231</td>
<td>4130</td>
<td>15722</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Five-and-a-half</td>
<td>Turkish</td>
<td>Short stature, Joint stiffness. Aortic insufficiency. Mitral valve prolapse</td>
<td>Short and wide metacarpal tubular bones. Flaring of the iliac wings, shallow acetabular fossae and lateral subluxation of the femoral heads</td>
<td>Trace of dermatan sulphate seen</td>
<td>4181</td>
<td>3550</td>
<td>14451</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>18</td>
<td>Turkish</td>
<td>Coarse facies. Mild mental retardation. Waddling gait. Height stunting. Aortic insufficiency</td>
<td>Scoliosis Dysostosis multiplex</td>
<td>Trace of dermatan sulphate seen</td>
<td>4800</td>
<td>3860</td>
<td>17702</td>
</tr>
</tbody>
</table>
cultured amniocytes or chorionic villus cells or by molecular genetic analysis.\textsuperscript{5-8}

Due to the manifestations in the skeletal system and involvement of joints in ML, the first application should be to the clinics of pediatric rheumatology. Family history, consanguinity, lack of pain and inflammation are key points to consider for the diagnosis of this rare disease.

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\textbf{REFERENCES}