

CASE REPORT

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

Çiğdem Seher KASAPKARA,¹ Meltem AKÇABOY,² Fehime KARA EROĞLU,³ Betül Emine DERİNKUYU⁴

¹Department of Pediatric Metabolism and Nutrition, Dr. Sami Ulus Maternity and Children's Health and Diseases Research and Education Hospital, Ankara, Turkey

²Department of Pediatrics, Dr. Sami Ulus Maternity and Children's Health and Diseases Research and Education Hospital, Ankara, Turkey

³Department of Pediatric Nephrology, Dr. Sami Ulus Maternity and Children's Health and Diseases Research and Education Hospital, Ankara, Turkey

⁴Department of Pediatric Radiology, Dr. Sami Ulus Maternity and Children's Health and Diseases Research and Education Hospital, Ankara, Turkey

ABSTRACT

Mucopolipidoses 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 mucopolipidosis 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 mucopolipidosis 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. Mucopolipidosis is a rare disease in pediatric patients to remember in differential diagnosis of joint stiffness.

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

Mucopolipidosis (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 mucopolipidosis 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

Received: November 01, 2016 **Accepted:** March 23, 2016 **Published online:** May 25, 2017

Correspondence: Meltem Akçaboy, MD. Sağlık Bilimleri Üniversitesi Ankara Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, 06080 Altındağ, Ankara, Turkey. Tel: +90 532 - 647 69 97 e-mail: meltemileri@yahoo.com

©2018 Turkish League Against Rheumatism. All rights reserved.



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.

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

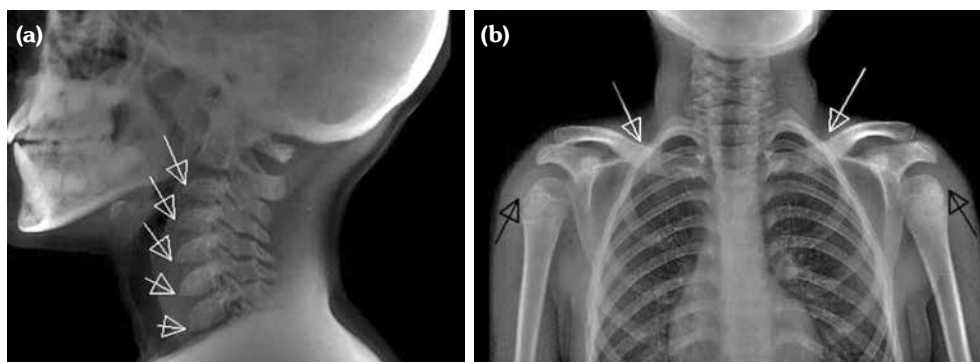


Figure 2. Lateral cervical spine and posteroanterior chest radiographs of case 1 diagnosed with mucopolipidosis III. **(a)** On lateral cervical radiogram, note abnormal vertebral bodies with anterior vertebral beaking (white arrows). **(b)** Chest X-ray demonstrates short and thick clavicles (white arrows). Note slightly small humeral heads (black arrows).



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 mucopolipidosis III.

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.

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

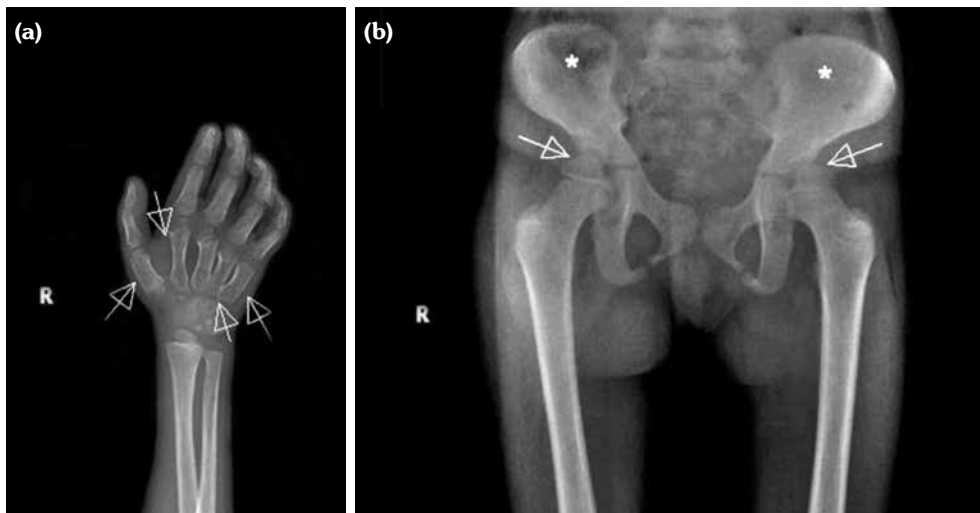


Figure 5. Hand and pelvis radiographs of case 3 diagnosed with mucopolipidosis III. **(a)** Hand radiograph shows short and wide metacarpal tubular bones (white arrows). Also, note claw-hand deformity. **(b)** Pelvis radiograph demonstrates flaring of iliac wings (white asterisk), shallow acetabular fossae and lateral subluxation of femoral heads (white arrows).

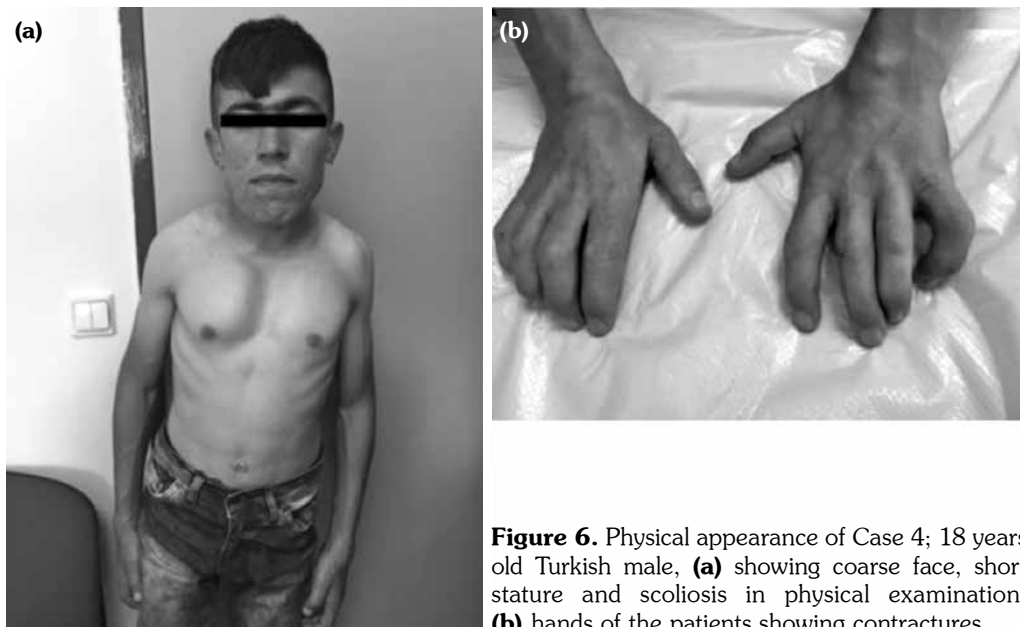


Figure 6. Physical appearance of Case 4; 18 years old Turkish male, **(a)** showing coarse face, short stature and scoliosis in physical examination, **(b)** hands of the patients showing contractures.

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.⁴⁻⁶ The typical clinical symptoms include short stature, cardiac valve involvement, normal intelligence or mild mental retardation, normal corneal appearance or steamininess 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.³⁻⁷ 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.¹ 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.⁸

The differential diagnoses of ML should include juvenile idiopathic rheumatoid arthritis, mucopolysaccharidoses, oligosaccharides and progressive pseudorheumatoid arthritis of childhood.^{6,7}

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

Table 1. Demographic data, clinical and laboratory findings of patients

Patient	Sex	Age (years-old)	Race	Clinical findings	Radiologic findings	Urinary mucopolysaccharides	Arylsulfatase A Nv: 140-250 nmol/mL/h	Alpha mannosidase Nv: 20-100 nmol/mL/h	Hexosaminidase A&B Nv: 600-3500 nmol/mL/h
1	Female	Five-and-a-half	Syrian	Claw-hand deformity, Limitation in maximum flexion and extension of the fingers, elbows and shoulders. Aortic insufficiency.	Abnormal vertebral bodies with anterior vertebral beaking on the lateral cervical radiogram short and thick clavicles	Trace of dermatan sulphate seen	5500	4134	17655
2	Male	8	Syrian	Claw hand deformity Short stature Joint stiffness in elbows, fingers, shoulders and spine. Mitral insufficiency	Dysostosis multiplex	Trace of dermatan sulphate seen	5231	4130	15722
3	Female	Five-and-a-half	Turkish	Short stature, Joint stiffness. Aortic insufficiency Mitral valve prolapse	Short and wide metacarpal tubular bones. Flaring of the iliac wings, shallow acetabular fossae and lateral subluxation of the femoral heads	Trace of dermatan sulphate seen	4181	3550	14451
4	Male	18	Turkish	Coarse facies. Mild mental retardation. Waddling gait. Height stunting. Aortic insufficiency	Scoliosis Dysostosis multiplex	Trace of dermatan sulphate seen	4800	3860	17702

cultured amniocytes or chorionic villus cells or by molecular genetic analysis.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.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Abualsuod A, Hacıoglu Y, Vallurupalli S, Deshmukh A, Paydak H. Cardiac MRI findings in mucopolipidosis III. *Acta Cardiol* 2014;69:564-5.
2. Liu S, Zhang W, Shi H, Meng Y, Qiu Z. Three novel homozygous mutations in the GNPTG gene that cause mucopolipidosis type III gamma. *Gene* 2014;535:294-8.
3. Pantoja Zarza L, Diez Morrondo C. Skeletal deformities in mucopolipidosis III. *Reumatol Clin* 2014;10:340-1.
4. Hara M, Inokuchi T, Taniwaki T, Otomo T, Sakai N, Matsuishi T, et al. An adult patient with mucopolipidosis III alpha/beta presenting with parkinsonism. *Brain Dev* 2013;35:462-5.
5. Khalifa H, Grubisa HS, Lee L, Lam EW. Enlarged follicles and temporomandibular joint abnormalities in mucopolipidosis Type III. *Dentomaxillofac Radiol* 2013;42:22822014.
6. Simsek-Kiper PO, Topaloglu R, Sahin Y, Utine GE, Boduroglu K. Mucopolipidosis type III in an adolescent presenting with atypical facial features and skeletal deformities. *Genet Couns* 2013;24:7-12.
7. Sharma R, Ramachandran S, Bhat D, Bindu PS, Devi BI. Bilateral carpal tunnel syndrome in two children: common manifestation of an uncommon disease. *Pediatr Neurosurg* 2013;49:300-2.
8. Cavalcante WC, Santos LC, Dos Santos JN, de Vasconcellos SJ, de Azevedo RA, Dos Santos JN. Oral findings in patients with mucopolipidosis type III. *Braz Dent J* 2012;23:461-6.