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Case Peport | Praca Kazuistyczna
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Musculoskeletal/Radiological Manifestations of Mucolipidosis II (I-Cell disease) in late Adolescence/Early Adulthood

Mieśniowoszkieletowa/radiologiczna manifestacja mukolipidozy II (choroba komórkowa typu I) w późnym okresie młodzieńczym/wczesnym dorosłym

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Abstract
Mucolipidosis type II (I-Cell disease) is a rare autosomal recessive lysosomal disorder, resulting from functional deficiency of lysosomal enzymes due to an impaired targeting of the enzymes to lysosomes, which leads to an abnormal cell architecture and the overflow of lysosomal enzymes into the body fluids. The life expectancy of the patients is poor, with multisystem deterioration leading to death in early childhood. According to the available reports, patients with I-cell disease do not survive beyond the first decade of life. Here, we describe and illustrate various radiological-musculoskeletal manifestations of a rare case of mucolipidosis II who has been a survivor up to now, 20 years old. The course of her disease has been complicated by early severe visual compromise due to optic nerve swelling, hearing loss and mitral valve regurgitation/stenosis, bilateral carpal tunnel, and severe growth impairment. Our case demonstrates several skeletal features of dysostosis multiplex. At the age of 20, she is wheelchair bound and her medical course is complicated by recurrent pneumonia, treated with multiple hospitalizations, antibiotics, and BiPAP. She is on outpatient palliative care, Do Not Resuscitate/Do Not Intubate (DNR/DNI) status.
Key words
Mucolipidosis II, I-Cell disease, Bone, X Ray, Musculoskeletal

Streszczenie
Mukolipidoza typu II (I komórkowa choroba) jest rzadkim zaburzeniem lizosomalnym dziedziczonym autosomalnie recesywnie, wynikającym z niedobórów funkcjonalnych enzymów lizosomalnych spowodowanych zaburzeniami. Prognoza przeżywalności pacjentów jest zła. Liczne zaburzenia prowadzą do śmierci we wczesnym dzieciństwie. W aktualnej literaturze nie znaleziono opisu pacjenta żyjącego dłużej niż 10 lat. Przedstawiamy opis pacjentki, która przeżyła 20 lat z radiologiczno-mięśniowoszkieletową postacią rzadkiego schorzenia mukolipidozy II. Przebieg schorzenia jest skomplikowany wczesnymi zaburzeniami wynikającymi z obrzęku nerwu wzrokowego, ubytku słuchu stenozą mitralną, dwustronnym kanałem nadgarstka oraz ciężkimi zaburzeniami wzrastania. Pacjentka prezentuje ciężkie zaburzenia szkieletowe dyzostozy rozsianej. W wieku 20 lat pacjentka nie chodzi (porusza się na wózku). Medyczny przebieg choroby jest wikłany nawracającymi zapalenia płuc, wymagającymi wielokrotnie hospitalizacji, leczona antybiotykami i BiPAP. Znajduje się w opiece paliatywnej w statusie DNR/DNI (nie reanimować, nie intubować).
Słowa kluczowe
mukolipidoza II, choroba komorkowa I, kości, rtg, zaburzenia mięsniowo-szkieletowe

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Introduction

The mucolipidoses are a heterogeneous group of inherited metabolic disorders caused by enzyme deficiencies that lead to progressively debilitating disorders affecting many body organs. Mucolipidosis II, also known as Inclusion Cell or I-Cell disease, is an autosomal recessive lysosomal disorder, resulting from the deficiency of the heterohexameric lysosomal hydrolase N-acetylglucosamine-1-phosphotransferase enzyme caused by mutations in the GNPTAB gene. An impaired phosphotransferase activity inhibits the synthesis of the critical lysosomal trafficking marker mannose 6-phosphate on to lysosomal hydrolases and other glycoproteins [1, 2], which results in a functional deficiency of lysosomal enzymes and a progressive development of abnormal cell architecture, vacuolated lymphocytes and unusual intracytoplasmic inclusion bodies in cells of mesenchymal origin, especially fibroblasts (I-cells). On the other hand, targeting of lysosomal enzymes to lysosomes is impaired, leading to the overflow of lysosomal enzymes into the serum, spinal fluid, and urine [3].

The life expectancy of the patients is poor, with multisystem deterioration leading to death in early childhood. According to the available reports, patients with I-cell disease do not survive beyond the first decade of life [4]. Here we report radiographic musculoskeletal findings of a rare case of I-cell disease, who has been a survivor up to now, 20 years old.

Case report

Our patient was born as a full term pregnancy complicated by pre-eclampsia. According to her parents she was first noted to have an abnormal grasp of her bottle and a trigger finger. Genetic and metabolic testing led to the diagnosis of the I cell disease. She walked at one year of age and cognitive and language development was normal. She subsequently developed severe visual compromise due to optic nerve swelling, hearing loss and mitral valve regurgitation/stenosis. At five years of age, she had bilateral carpal tunnel surgery.

At the age of 9 years, the patient presented to our hospital with bilateral hip pain. On physical examination, her height was below the 5th percentile at 82cm. She had coarse facial features typical for mucolipidosis and a protuberant abdomen due to marked hepatomegaly. She walked somewhat hunched over with a wide-based waddling gait on supinated feet. Proximal muscle weakness and restricted range of motion of the joints of all extremities were also noted. Radiographs showed dystrophic changes of the hips (Fig. 1).

At the age of 12, she presented with new onset headaches. Her mobility was limited and she complained of weakness and back and hip pain. Growth was arrested at a height of 85.8 cm. Cognitive and neurologic examination remained normal. Increase in hip flexion contractures to 40 degrees and compensatory increase in lumbar lordosis resulted in her being able to walk only a few steps in a pitched forward position. Elbow and knee contractures as well as short and broad fingers were also

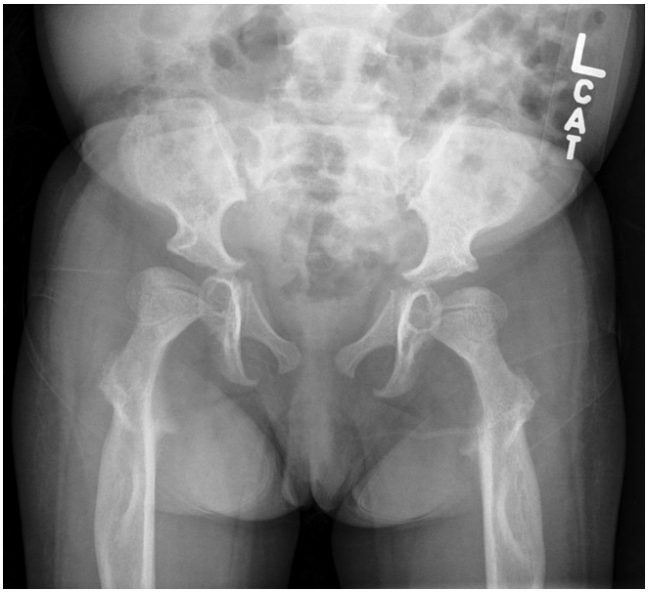

Fig. 1. Dysostosis multiplex in adolescence. A) Frontal radiograph of the pelvis (at age of 9 years). Both acetabula are shallow with lateral subluxation and uncovering of bilateral femoral heads, right greater than left, and proximal femoral epiphysis are flattened and dysplastic, consistent with bilateral hip dysplasias. Widened femoral diaphyses and coxa valga deformity are identified. Abnormal configuration of pelvis with rounded or flared iliac wings and poor development of anterior superior iliac spine are noted. The diastasis of pubic symphysis and aplasia of bilateral pubic rami is also noted

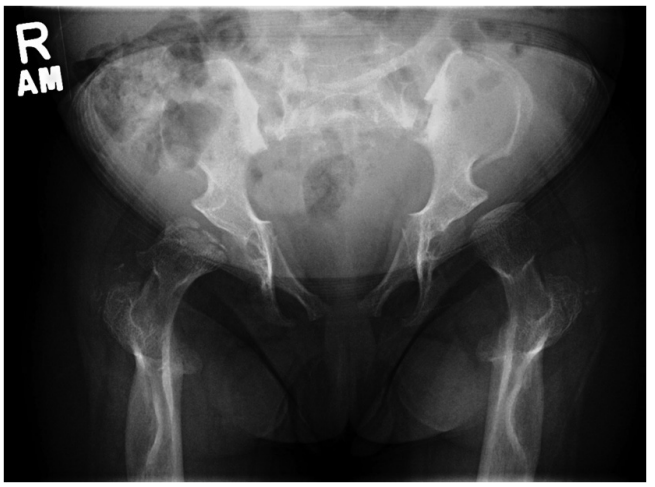

Fig. 1. B) Follow-up frontal pelvis radiograph at the age of 15 years shows bilateral femoral epiphyses remained unfused with no evidence of significant skeletal maturation. Progressive lateral uncovering of the left hip, now with more than 50% uncovered as well as interval increased fragmentation and loss of height of both proximal femoral epiphyses, indicating worsening of hip dysplasia and superimposition of avascular necrosis

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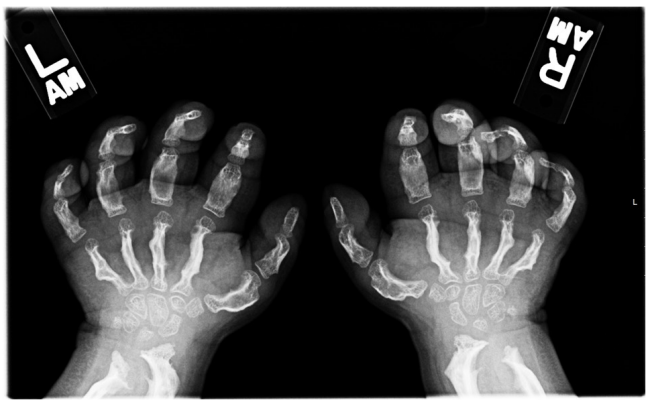

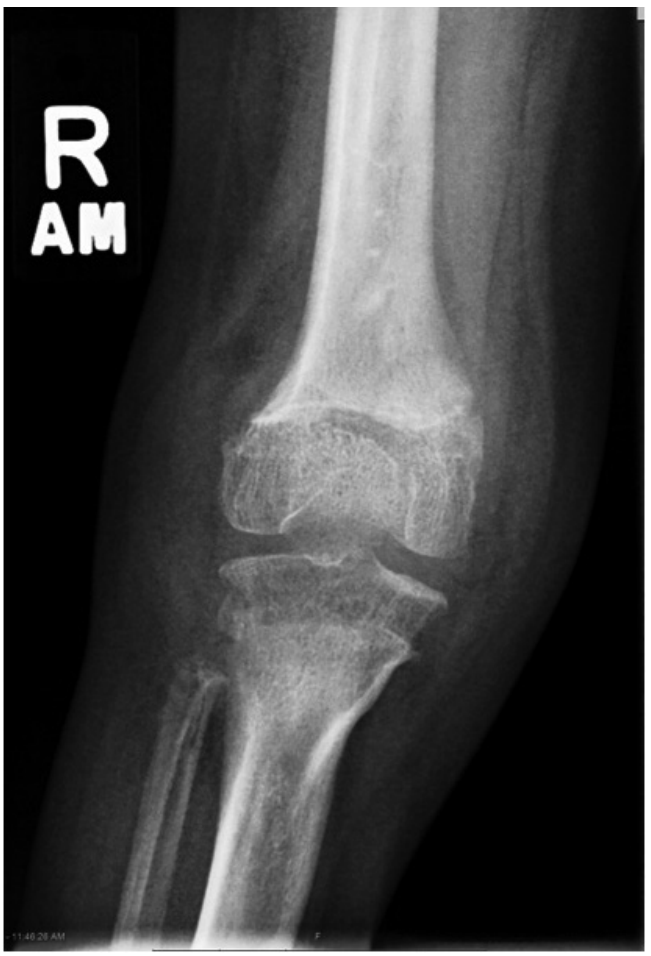

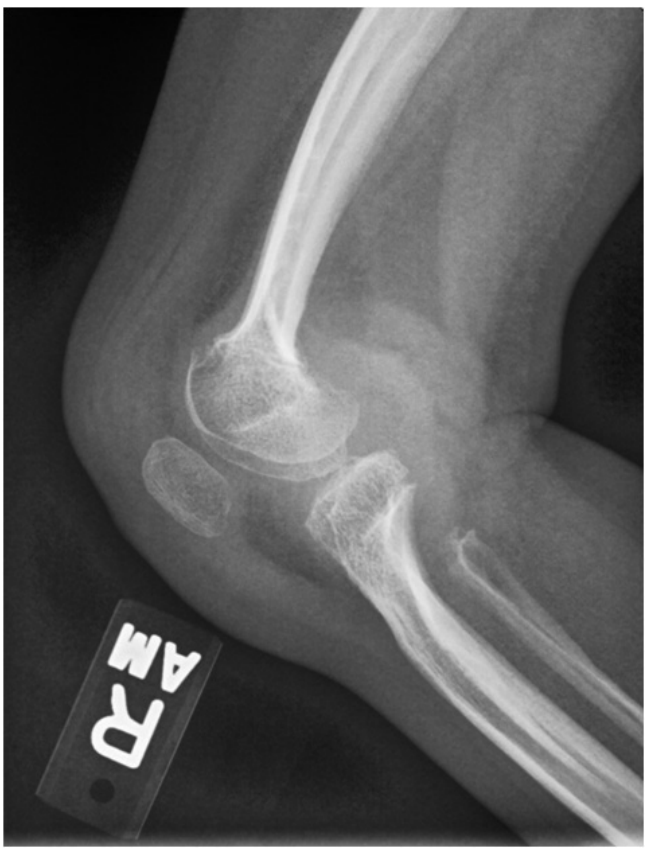

Fig. 2. Dysostosis multiplex in adolescence. A) Frontal radiograph of the hands demonstrates diaphyseal thickening of metacarpals, more pronounced in first and fifth metacarpals. Bullet shape deformity of phalanges is also noted. Madelung deformity with markedly dysplastic meta-epiphysis of distal radius and ulna is also partially visualized. Of note, limited evaluation of wrist shows the development of the carpal osseous structure is normal. Frontal (B) and lateral (C) radiographs of the knees at the age of 15 demonstrate Erylenmyer flask deformities (flared metaphyseal regions), mainly involving the proximal tibia and fibula. Epiphyseal dysplasia and submetaphyseal overconstriction are seen involving proximal tibia and fibula as well as the distal femur. Tiny ill-defined areas of sclerosis secondary to bone infarcts are noted within the distal femoral metaphysis. The partially visualized diaphyses are undermodeled

noted. Radiographs confirmed the musculoskeletal changes (Fig. 2) Head CT was normal and headaches were attributed to migraine. MRI of the spine showed mild anterolisthesis of C1 on C2, mild posterior effacement of the thecal sac and minimal effacement of the cord posteriorly (not shown). The thoracolumbar spine showed findings consistent with her storage disease without cord compression (Fig. 3).

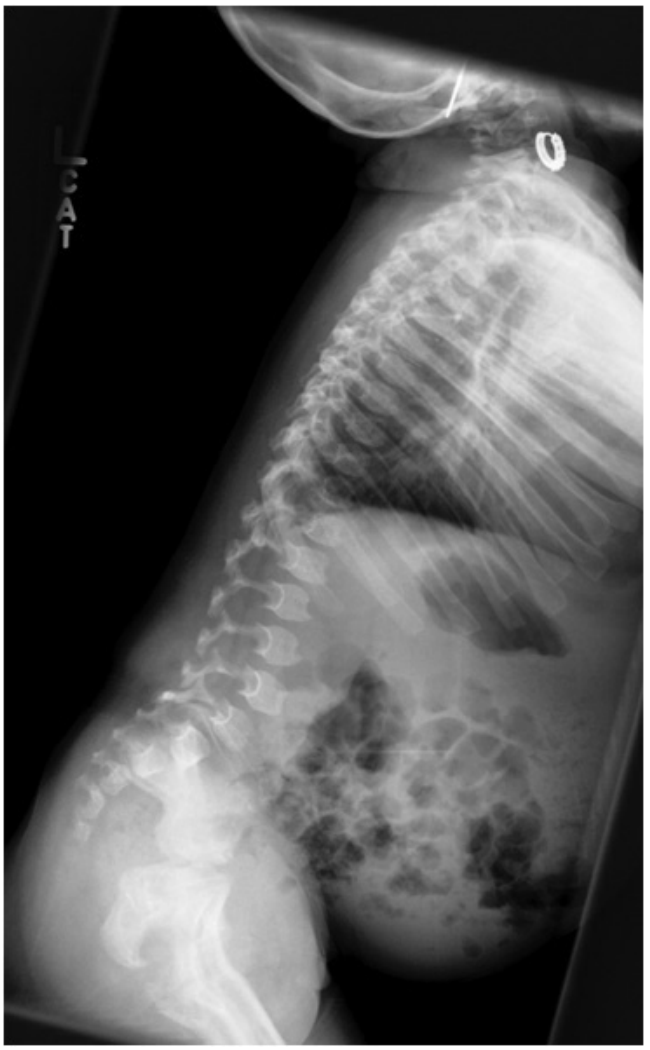

Fig. 3. Hook – shaped deformity of thoracolumbar vertebral bodies with inferior beaking of L1-L3. Widening of the lumbar spinal canal and elongation of the lumbar pedicles are noted. Mild anterolisthesis of L4 on L5 is identified. Posterior scalloping of T12-L5 is another feature of the spine in this patient

Between the ages of 15 and 16, her pain continued to worsen and she ceased to ambulate. Her height decreased to 78.8cm. She developed flexion contractures at the waist and knees, decreased range of motion of elbows and fingers and clawing of the hands. Her weakness on physical exam became more profound, her lower extremities became hyper-reflexic and her feet pronated. Kyphosis of the thoracolumbar spine worsened.

At the age of 20 she is wheelchair-bound and her medical course is complicated by recurrent pneumonia, treated with multiple hospitalizations, antibiotics, and BiPAP. Her recent abdominal ultrasound shows focal fatty infiltration of the liver as well as cholelithiasis with no evidence of cholecystitis. She is on outpatient palliative care, Do Not Resuscitate/Do Not Intubate (DNR/DNI) status.

Discussion

Storage diseases encompass a large group of more than 100 rare inherited metabolic disorders, including mucolipidoses, mucopolysaccharidoses and sphingolipidoses, which show certain similarities, but also significant differences in their phenotypic and clinical picture. This partly depends on the specific tissue or organs most affected and the type of abnormal substrate that accumulates [4–10]. For example, the visceral storage of patients with mucolipidoses may consist of both mucopolysaccharides and glycolipids, while it consists of mucopolysaccharides in patients with mucopolysaccharidoses and glycolipids in those with sphingolipidoses. However, unlike mucopolysaccharidoses, mucopolysaccharidoses is not seen in patients with mucolipidoses. Phenotypically, although dysostosis multiplex is not a feature of sphingolipidoses, it is common in both mucolipidoses and mucopolysaccharidoses [11]. As the biochemical and clinical features of these storage diseases are overlapping, one can expect overlapping radiological features as well [12,13]. More specifically, the radiographic findings of mucolipidoses have significant overlap and similarity to those observed in mucopolysaccharidoses, a condition with which I-cell disease may be easily confused [11].

Mucolipidoses are a spectrum of diseases with significant overlap between underlying pathogenesis and molecular mechanisms as well as clinical manifestations. There are eight distinct mucolipidoses, including Gangliosidosis I, Gangliosidosis II, Fucosidosis, Mannosidosis, Juvenile Sulfatidosis (Austin type), Mucolipidosis I (Lipomucopolysaccharidosis), Mucolipidosis II (I Cell disease), and Mucolipidosis III (Pseudopolydystrophy) [11]. Unfortunately, due to the severity of the progression of the I cell disease, the affected patients typically do not survive past the first decade and pass away within the first 5-6 years of life [4]. To the best of our knowledge, this is the first report in the literature of the I-Cell disease of the case-who has been a survivor up to the late second decade of life. Our report has the potential to improve our understanding of a natural course of the skeletal abnormalities associated with mucolipidoses and can help investigators and clinicians to develop musculoskeletal-specific therapies.

As confirmed by our case, the developmental delay and progressive psychomotor deterioration are common presentations of metabolic storage diseases [3, 11]. Growth is severely impaired [11], as our case suffered from the arrest of height

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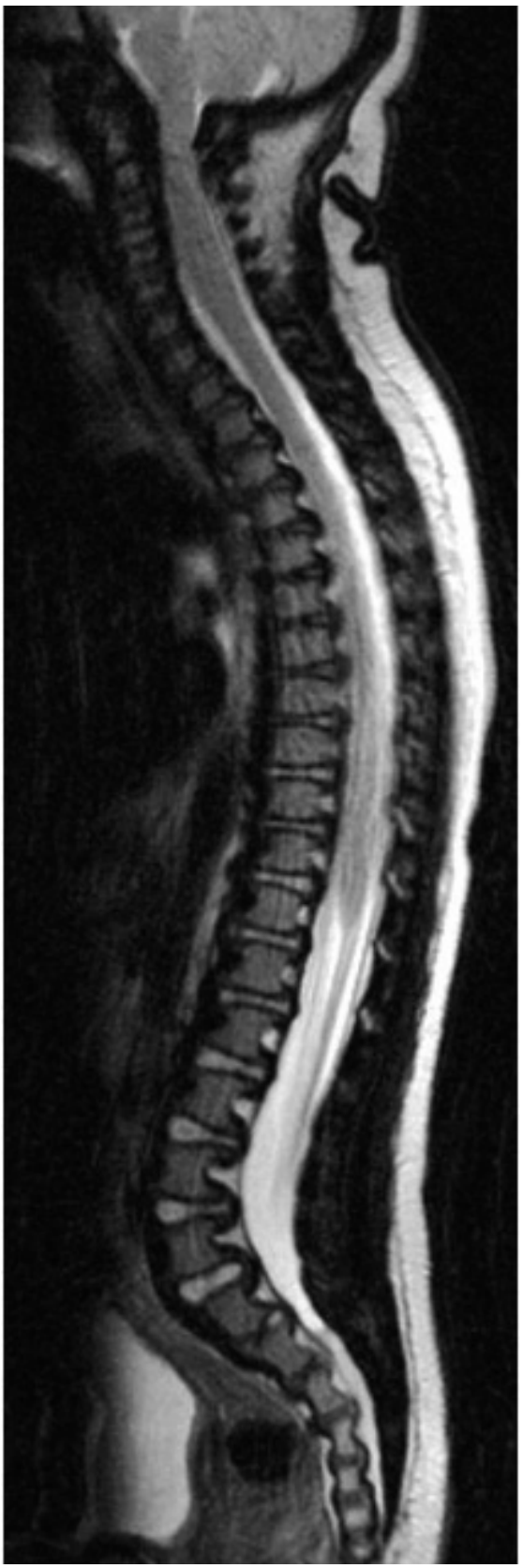
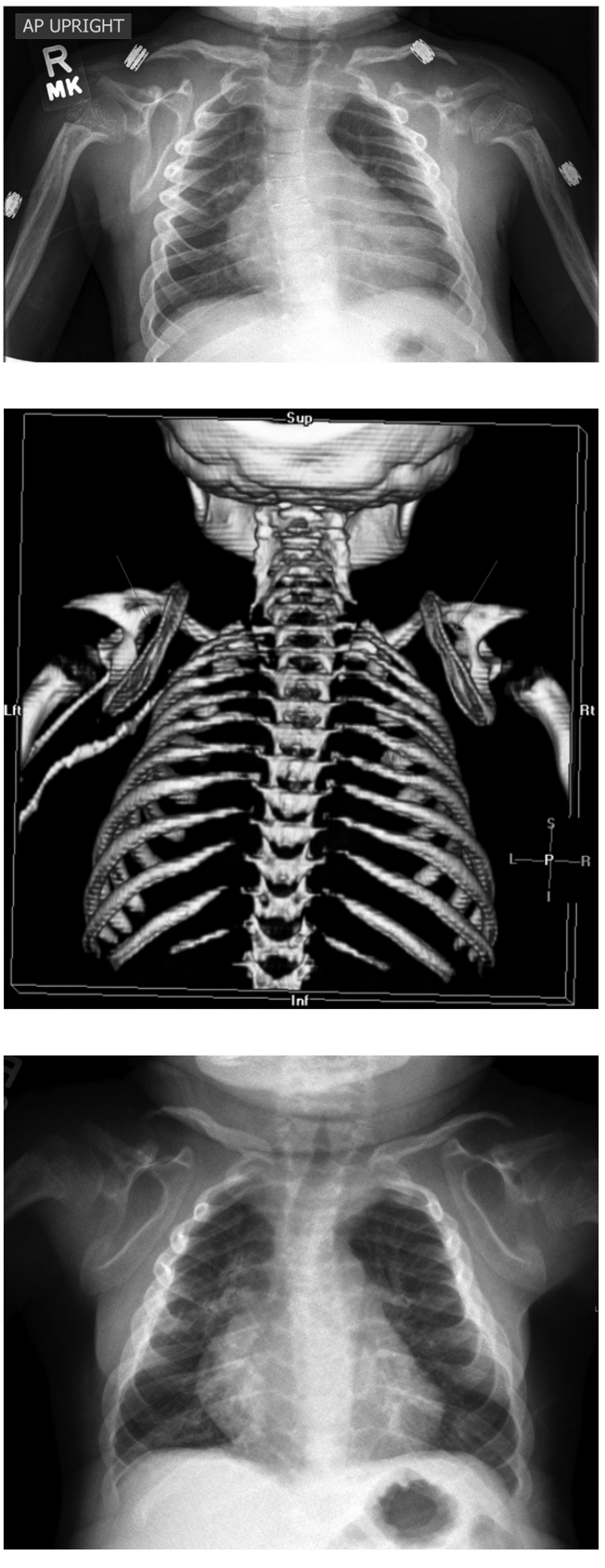


and weight gain since her first decade of life. A Progressive ambulation decline is also an important clinical feature. The I Cell disease most severely affects the skeletal system, in which trabeculation of osseous and cartilaginous structures are abnormal. Craniofacial and orthopedic manifestations can be evident at birth, but become more obvious within the first year [1], and mainly include dysostossis multiplex, but also facial dysmorphism, kyphosis, clubfeet, deformed long bones, and/or the dislocation of the hips [4]. Herman and McAlister also reported radiographic skeletal features of I-Cell disease in neonates [7]. They described it as a transient osteopathy resembling rickets and hyperparathyroidism with butterfly vertebral body and dysharmonic epiphyseal ossification. The diagnosis is sometimes missed or delayed, especially in those with more attenuated forms of disease, as it may present with rickets-like picture [5]. In fact, the major challenge for radiologists is the overlap of radiological and musculoskeletal features of storage diseases. For example, almost all types of mucopolysaccharidoses show dysostosis multiplex. However, the severity of the musculoskeletal involvement can be milder in type III (Sanfilippo syndrome), but often more severe in type IV (Morquio syndrome) [9].

Our case shows that dysostosis multiplex is the main imaging feature of the disease. Dysostosis multiplex, previously known as Gargoylism [12], is the name proposed to describe a syndrome of progressive skeletal dysplasia and constellation of radiographic changes characteristically seen in different metabolic disorders, including storage diseases. The syndrome is caused by the lack of skeletal remodeling, resulting in ossification abnormalities, as well as cartilaginous, ligamentous, and tendinous abnormalities due to deposition of abnormally metabolized substances. As shown by our case, dysostosis multiplex can be considered the main musculoskeletal feature of the I-Cell disease [9, 13, 14]. Radiographic features of dysostosis multiplex include clavicular abnormalities (Fig. 4), oar-shaped ribs (Ribs that widen at or adjacent to the costochondral junctions and are narrower than typical in the dorsal juxtavertebral arches, Fig. 4) [15], gibbus deformity of thoracolumbar spine [9], which is caused by vertebral body wedge deformity or hypoplasia, flaring of the iliac wings (Fig. 1), hip dysplasia and coxa valga (Fig. 1), abnormal development of phalanges and metacarpals (Fig. 3), thickening of the diaphyseal regions of long bones (Fig. 3), and metaphyseal cupping and fraying, resembling rickets [9]. Previously described malformation and deformity of tubular bones (including disproportion of width and length of the tubular bones due to periosteal new-bone formation leading to cloaking of the long bone, diaphyseal widening and expansion with shortened and undermodeled diaphyses, and epiphyseal dysplasia and submetaphyseal overconstriction of the tubular bones), coarse bony trabeculation, hypoplastic/dysplastic capital femoral epiphyses, delayed

Fig. 4. Posterior scalloping of T12-L5 on non-contrast T2 weighted sagittal MR image (age: 12 years). No dural ectasia is identified



epiphyseal ossification, vertebral body deformity with concave anterior, superior, or inferior borders and kyphosis, pelvic dysplasia with narrow basilar portions of the ilia and relatively long pubic and ischial bones, slanting acetabular roofs, coxa valga, and clubfoot deformity have been reported as characteristic musculoskeletal features of the disease [15–17], are consistent with radiological findings of our case. Restricted range of motion in all peripheral joints, contractures, and generalized hypotonia are also another main musculoskeletal presentation of the I-cell disease.

As shown by our case, the respiratory insufficiency and recurrent pulmonary infections are one of the major morbidities of these patients and have been reported as the main cause of their mortality [15]. This can be partly explained by obstructive oropharyngeal and upper airway disease (e.g. caused by macroglossia) and partly due to severe kyphosis and gradual stiffening of the thoracic cage. Our case had evidences of pulmonary infiltrates and fibrosis, which can be indicative of sequela of recurrent infections.

The basis for the musculoskeletal abnormalities characteristic of the mucolipidoses is not fully understood. However, as many of patients with storage diseases need orthopedic attention for perceived musculoskeletal discomfort, musculoskeletal and pediatric radiologists should be aware of their radiographic manifestations. Our case shows that some of these musculoskeletal abnormalities become more conspicuous with time (Fig. 1) and cause significant morbidity. Radiological studies reveal the arrest of osseous maturation from the end of first decade to late adolescence/early adulthood.

Acknowledgement

Dr Mark Robbin, the senior author of this publication and professor of radiology, passed away peacefully in Cleveland, Ohio, on January 21, 2017 (few months after the initial submission of this manuscript), after a long battle with renal cancer. He was program director of diagnostic radiology residency and musculoskeletal imaging fellowship and served as the vice chairman of education at the Department of Radiology, University Hospitals of Cleveland, Case Western Reserve University. He was a physician, radiologist, teacher, scholar, author, researcher, and athlete. God bless him.

Fig. 5. Clavicular and rib dysplasias are commonly seen in dysostosis multiplex. A) Frontal radiograph of chest at the age of 14 years demonstrates clavicular dysplasia with sharpening and hook shaped appearance of the distal clavicle as well as thickening of the medial aspects of bilateral clavicles. Widening of the anterior ribs (Oar shaped or paddle ribs) is also noted. B) 3D reconstruction of CT demonstrates a large central ossification defect (scapular hole) within bilateral scapulae. C) No significant interval change is seen in osseous dysplasias of the chest at the age of 18 years

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