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Case report

# Dysostosis in mucopolysaccharidosis type 2: A case of longitudinal follow up and literature review ☆

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ABSTRACT

Mucopolysaccharidosis type 2 is a congenital lysosomal disease characterized by iduronate-2-sulfatase deficiency, which leads to excessive accumulation of glycosaminoglycans in tissue. Dysostosis, which primarily involves decreased bone mineralization with morphological changes in the bone, is a major skeletal condition in mucopolysaccharidosis, but its pathophysiology is not well known. Here, we report a case of mucopolysaccharidosis type 2 diagnosed at the age of 2 years with longitudinal follow-up data for more than 15 years. Although the patient underwent bone marrow transplantation, the developmental quotient did not improve, and cranial hyperostosis progressed prominently with a faintly dilated perivascular space. Other dysostoses and contraction of the joints were observed but did not improve either.



## Introduction

Mucopolysaccharidosis (MPS) type 2 or Hunter syndrome is an X-linked recessive lysosomal disease characterized by deficiency of iduronate-2-sulfatase, which leads to excessive accumulation of glycosaminoglycans (GAGs) such as dermatan sulfate (DS) and heparan sulfate (HS) in tissue [1–4]. MPS can affect various organs, especially the central nervous system and skeletal system. In addition, it may cause hepatosplenomegaly, retinal degeneration, corneal opacity, obstructive pulmonary disorder, and vulvar disease [5]. On the basis of GAG overaccumulation, symptoms may be classified as follows: (1) symptoms caused by overaccumulation of GAGs itself, such as hepatosplenomegaly and corneal opacity, and (2) those caused by interference of the excessive GAGs with

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the metabolism of glycosylation as well as the collagen in the cytoplasm and extracellular matrix.

The major skeletal finding in MPS can be characterized as dysostosis, which primarily involves bone mineralization, thickened bone, and skeletal deformity [6,7]. However, the relationship between enzyme deficiency and dysostosis remains unknown. Here, we report a case of iduronate-2-sulfatase deficiency that presented with disproportionally worsened cranial hyperostosis after bone marrow transplantation and review the skeletal findings while focusing on the pathophysiology of the enzymatic deficiency.

## Case report

A 2-year-old boy with a history of overgrowth (+1.5 SD in height), mild macrocephaly, and recurrent inguinal hernia was brought to our hospital. His birth weight was 3.512 kg, height was 51.5 cm, head circumference was 34.2 cm, and chest circumference was 33.0 cm at 40 weeks of gestation. His development quotient score was 56. He showed facial deformity, saddle nose, and mild limitations in the range of motion in multiple joints, but no hepatosplenomegaly. His brother had been diagnosed with Hunter syndrome and had died as a result of complications of bone marrow transplantation.

His urinary test revealed elevated DS and HS levels. Iduronate-2-sulfatase activity was undetectable, which was diagnostic for MPS type 2. Subsequently, he underwent allogeneic bone marrow transplantation with mild normocytic normochromic anemia for 3 months; his hemoglobin level ranged from 10 to 13 g/dL. His iduronate-2-sulfatase activity subsequently improved within normal limits.

The patient developed mitral valvular regurgitation at 3 years of age, and was repeatedly hospitalized for the treatment of cardiovascular conditions and evaluation of development and skeletal rehabilitation. Brain MRI showed no apparent abnormality at 6 years of age (Fig. 1A). At the age of 12 years, his height was 134.4 cm (-2.5 SD), and progression of multiple joint contractures was noted. The development quotient was 36, which was equivalent to that at the age of 17 months. Follow-up brain MRI revealed progressive cranial hyperostosis and mild brain atrophy with mildly dilated perivascular spaces at the age of 12 years (Fig. 1B). Chest radiography showed bilateral hypertrophy in the ribs and clavicles at the age of 9 years (Fig. 2A), which had not changed in size for 8 years (Fig. 2B: at 17 years of age). A bilateral hand radiograph obtained at 12 years of age showed decreased bone density, delayed carpal ossification, short distal phalanges, and proximal pointing of the metacarpals (Fig. 3). At 16 years of age, an anterior–posterior pelvic radiograph revealed scoliosis, coxa valga, acetabular dysplasia, and widened iliac wings (Fig. 4A). Lateral lumbar radiography showed posterior scalloping, lower lumbar dislocation, and a fan-shaped deformity (Fig. 4B).

The patient was admitted to the hospital for evaluation of aortic regurgitation at the ages of 14 and 15. The examination revealed cardiac function was stable. However, he was followed up at an outpatient clinic with unchanged joint contracture, bone deformities, and mental status.

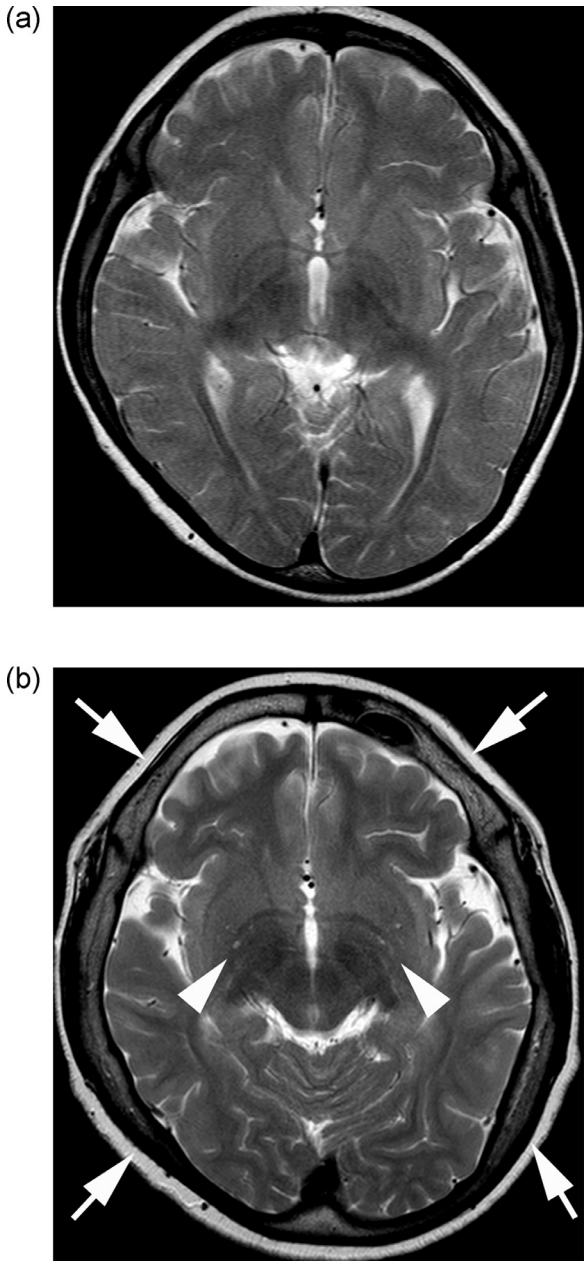


**Fig 1 – Axial T2-weighted imaging at (A) 6 years and (B) 12 years of age showing progressive cranial hyperostosis (arrows) and worsened cerebral atrophy with faintly dilated perivascular spaces (arrowheads).**

## Discussion

The patient in the present case presented with overgrowth in the early stage, but eventually showed short stature, disproportional progression of hyperostosis in the cranium in comparison with the axial skeleton, and severe mental retardation, which did not improve after bone marrow transplantation. The patient also developed dysostoses with degeneration of the spine and hip joints and valvular insufficiency. GAG metabolism plays an important role in the CNS, skeletal

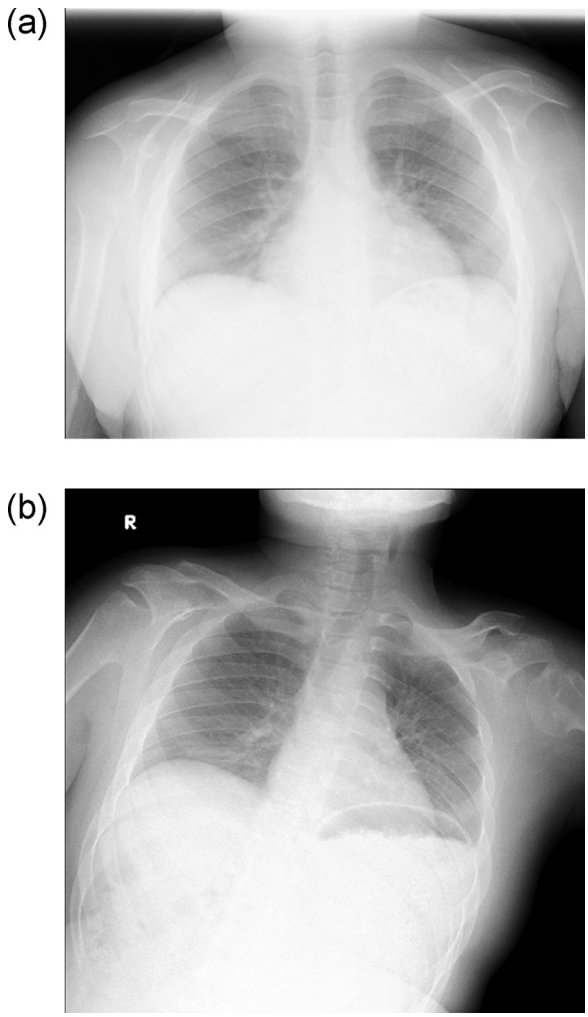


**Fig. 2 – (A) A chest radiograph showing bilateral hypertrophy in the ribs and clavicles at 9 years of age. (B) A follow-up chest radiograph at 17 years of age showing that the findings did not progress.**

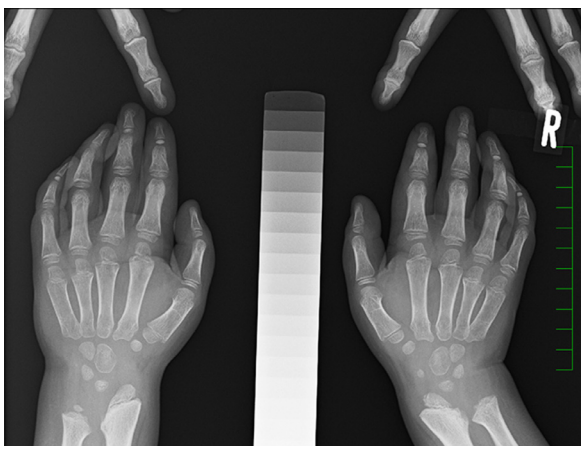


**Fig. 3 – A hand radiograph at 12 years of age showing decreased bone density, delayed carpal ossification, and proximal pointing of the metacarpals.**

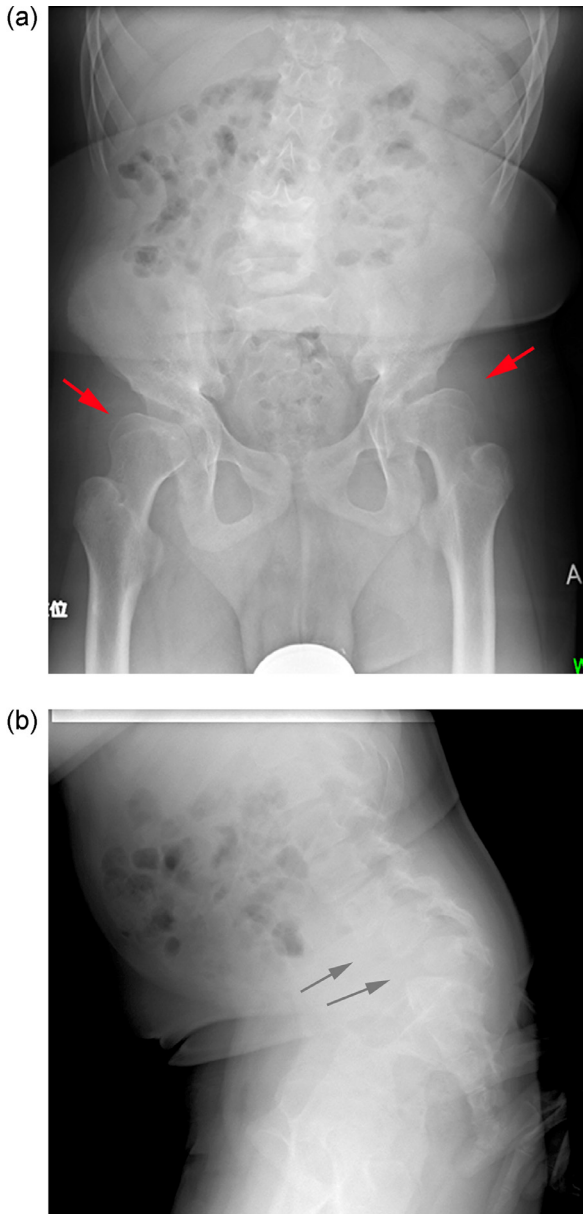


**Fig. 4 – (A) An anterior-posterior pelvic radiograph at 16 years of age showing scoliosis, coxa valga, acetabular dysplasia with deformity of femoral head (arrows), and widened iliac wings. (B) A lateral lumbar radiograph at 16 years of age showing dislocation of the lower lumbar and a fan-shaped deformity (arrows).**

system, and cardiovascular system. Even though bone marrow transplantation was performed as soon as possible after birth, the brain and skeletal damage have not improved [8,9].

MPS is usually known to cause a short stature [10,11]. Patel et al. demonstrated that patients with MPS type 2 presented with overgrowth for the first several years and finally showed a short stature because the growth rate had decreased from 1 year of age [11]. Overgrowth in the first several years can also be observed in other types of MPS [12,13]. The mechanism underlying this finding is still unknown, but it may involve the

interaction of DS with fibroblast growth factors or other types of growth factors [14]. Furthermore, overaccumulation of DS and HS could affect the quality of cartilage and bone as well as collagen [15–18]. As a result, the fragile ligamentous tissue and osteochondral tissue might not be able to tolerate weight gain with growth, eventually resulting in a short stature.

Iduronate-2-sulfatase deficiency leads to the accumulation of GAGs (DS and HS) in the lysosome. Excessive GAGs can gradually accumulate in joints, ligaments, and cartilage, leading to constriction of joints and deformities [5,19,20]. In oncology, decreased activity of iduronate-2-sulfatase has been identified as one of the mechanisms underlying breast cancer metastasis [21,22]. Increased levels of DS can affect not only type 1 collagen in the extracellular matrix but also the cellular structure [21,22]. GAGs, including glucuronic acid or sulfate, have a highly negative charge and might have the potential to interact with surrounding proteins, such as decorin or collagen [14]. Excessive GAGs can also interact with collagen components through lysyl oxidase, which catalyzes pyridinoline for collagen cross-linking [23,24]. Increased levels of lysyl oxidase or lysyl oxidase-like proteins can promote metastasis and tumor progression, deteriorating the quality of the extracellular matrix, especially collagen, which plays an important role as a barrier [25–28].

Excessive GAGs can also interfere cathepsins, a family of proteases with each type located in a specific tissue [29]. For the skeletal system, cathepsin K plays an important role in degrading collagen and cartilage in osteoclasts [17,18]. Decreased cathepsin K functioning can induce abnormal bone remodeling, leading to bone fragility and finally resulting in dysostosis [17,18]. In the cardiovascular areas, in addition to the GAG deposition in tissues, MPS showed an abnormality in the turnover of collagen and elastin [15,16] and induced overexpression of cathepsin B in the fibroblasts of the heart, vascular wall, and valves, which can lead to degradation of collagen and elastin even in the extracellular matrix [30]. Although cardiovascular events could be fatal in MPS, enzyme replacement treatment with optimal administration might improve the prognosis [31,32].

The dysostosis multiplex group for cranial bones and spine in MPS is based on an abnormal ossification process with secondary degeneration, especially in the spine [6]. In MPS, the skull may be enlarged or dolichocephalic, showing premature closure of the sutures, underdeveloped mastoid or sinuses, J-shaped sella turcica, thickened dura, and cranial hyperostosis [6,33]. Defective development of the anterosuperior portion of the vertebrae, scalloping of the vertebrae, instability of the spine, and scoliosis or kyphosis were observed in the spine [5,6]. With age, secondary degenerative changes might develop in the loaded joints, such as lumbar or hip joints, probably due to the fragility of the surrounding ligaments and tendons. The spinal instability might lead to secondary spinal stenosis or spinal compression [5].

Other features of this condition include osteopenia and an imbalance in bone thickening with joint contracture or dislocation. Patients may show thickened ribs and clavicles in the axial skeleton [6], and the findings for the hands include diffuse decreased bone density, cortical thinning, ballet-shaped phalanges, proximal pointing of the metacarpals, or delayed ossification in the carpal bones [6,7]. Coxa valga is congenitally observed in the femoral head, and it might result in constriction of the joints and varus deformities [6,7]. The presence of coxa valga after birth in MPS might imply incomplete collagenogenesis, which also generates fragile collagen.

In the central nervous system, excessive GAGs can accumulate in the perivascular space, resulting in a dilated perivascular space [5]. Disease progression causes delayed myelination, demyelination, gliosis, and eventual brain atrophy [5]. GAGs are a major component of the extracellular matrix in the central nervous system. The heterogeneity or variety of 3-dimensional structures as sites for attachment of molecules or receptors is well controlled by various enzymes of glycosylation [34]. Thus, unbalanced amounts of these enzymes could lead to morphological or functional changes in the brain. In patients with MPS, the therapeutic effects of enzyme replacement therapy or bone marrow transplant are limited by the restricted entry of the infused enzymes into the brain via the blood–brain barrier [20]. Although bone marrow transplantation has been shown to prevent the progression of skeletal features in mice [8], cranial hyperostosis progresses disproportionally after bone marrow transplantation without any progression of skeletal thickness in the ribs and clavicles. This finding suggests that the cranial hyperostosis in MPS might not be worsened cranial GAG metabolism but rather a secondary reaction to severe disturbances in CNS development. In this patient, the severe mental retardation did not improve despite bone marrow transplantation at 2 years of age. Cranial hyperostosis can develop due to the reduction of intracranial volume or a severe MPS phenotype [33,35].

We encountered a case of type 2 MPS showing disproportional progression of skeletal features after bone marrow transplantation. The deficiency of iduronate-2-sulfatase via excessive GAGs might have influenced the microenvironment in the cytoplasm and extracellular matrix, especially the collagen, cartilage, and GAG metabolism in the central nervous system and skeletal system. The brain and spinal symptoms and features of MPS might develop based on abnormal metabolism of both the central nervous system and skeletal system.

## Patient consent

We obtained the written informed consent from the patient's parents for publication.

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