Introduction

Mucolipidosis (ML) II and ML III are rare autosomal-recessive inherited disorders of lysosomal metabolism with a combined frequency of 1:422,000. These are characterized by the defective processing of multiple lysosomal degradative enzymes caused by the deficiency or abnormal function of UDP-N-acetylglucosamine: lysosomal enzyme N-acetylglucosaminyl-1-phosphotransferase, UDP-GlcNAc 1-phosphotransferase (GlcNAc-PT). These defects result in deficient post-translation al modification of numerous lysosomal enzymes, which depend on mannose phosphorylation for uptake and localization by cells where substrate degradation occurs. This results in deficiencies of lysosomal degradative enzymes with concomitant intracellular accumulation of both partly degraded glycosaminoglycans and sphingolipids. ML II is characterized by coarse facial features, short stature, hyperplastic gums, organomegaly, and retarded psychomotor development. ML III is a milder disorder with attenuated characteristics and survival to adult life. Intermediate forms of ML II and III have been previously described.

ML is a kind of skeletal dysplasia. Characteristic X-ray findings of the bone may contribute to the early diagnosis and treatment of ML II/III. Skeletal radiographs show distinctive patterns at different ages: neonatal hyperparathyroidism, osteodystrophy (similar to chronic osteitis fibrosa cystica), and dysostosis multiplex. Patients with ML II/III show a mixture of osteodystrophic bone changes and atypical changes of dysostosis multiplex: proximal pointing of the metacarpals in the wrist, dysplastic changes in the lower third of the ilia, marked broadening of the ribs becoming oar-shaped, and beaking of the lower thoracic and lumbar vertebrae. In ML II, the osteodystrophy has clinical and radiographic features of neonatal hyperparathyroidism. In some neonatal subjects, chemical hyperparathyroidism is also demonstrated. After transient hyperparathyroidism in newborns, the progressive osteitis fibrosa cystica develops from 3–6 months of age. Patients with ML III show prominent skeletal involvement, particularly the destruction of vertebral bodies and the femoral heads. Intravenous pamidronate treatment is well tolerated, and it can produce clinical effects, with a reduction in bone pain and improvements in mobility in patients with ML III. In this review, the skeletal manifestations of ML II and III are investigated.

Radiographic Findings of Lysosomal Storage Disorders

Many lysosomal storage disorders, particularly the mucopolysaccharidoses, are characterized by “dysostosis multiplex.” The combination of radiographic features includes “J”-shaped sella turcica, oar-shaped ribs, anterior inferior beaking of the lower thoracic to upper lumbar vertebral bodies, flared iliac wings, constricted iliac bodies, dysplastic femoral heads, “bullet-shaped” proximal phalanges, and central pointing of the proximal metacarpals. Dysostosis multiplex develops with age, but it cannot be detected in newborns with ML. In addition to dysostosis multiplex, osteodystrophy is another characteristic of ML II and III.
Skeletal radiographs of ML show distinctive patterns at different ages: neonatal hyperparathyroidism, osteodystrophy (similar to chronic osteitis fibrosis cystica), and dysostosis multiplex.

**Skeletal Manifestations in Mucolipidosis II**

ML II is characterized by severe clinical and radiological features, including a coarse face, retarded psychomotor development, and restricted joint mobility\(^8\). Neonates with ML II often show small birth weight/length, inguinal hernia, gingival hypertrophy, and hip dislocation. ML II is usually more severe than Hurler disease, which has similar phenotypes and a poor prognosis. In ML II, the osteodystrophy has clinical and radiographic features of neonatal hyperparathyroidism. In some neonatal subjects, chemical hyperparathyroidism is also demonstrated. A characteristic finding on X-rays of the long bones is the transient increase of periosteal bone formation followed by severe osteopenia\(^9\); however, the causes of this transient change

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**Fig. 1.** Radiographs of 21-month-old Korean girl with ML II. (A) Radiograph of hands and wrists showing broad and under-modelled proximal phalanges (bullet-shaped) and proximal pointing of metacarpals. (B) Radiograph of pelvis and proximal femurs showing dysplasia/resorption of the lower third of the ilia femoral heads and femoral necks and "shepherd's crook deformity." (C) Radiograph of spine showing thoracolumbar kyphosis and beaking of the vertebrae. (D) Radiograph of skull showing J-shaped sella turcica.
remain unknown. At an early stage, subperiosteal resorption, rickets-like changes, and cloaking may look similar to neonatal hyperparathyroidism. Some cases of ML II are associated with neonatal hyperparathyroidism\(^\text{10}\). After transient hyperparathyroidism in newborns, the progressive osteitis fibrosa cystica develops from 3–6 months of age. Postnatally, the radiographic features could be consistent with an increased sensitivity of bone to normal circulating levels of parathyroid hormone. One possible hypothesis is that the progression of osteodystrophy is due to the hypersensitivity of bone to PTH, because it is similar to chronic osteitis fibrosa cystica without an increase in PTH levels. Another possibility is that mannose-6-phosphate targeting is important for other proteins involved in signal transduction of PTH effects on bone formation and remodeling. Decalcification of bone and degradation of the bone matrix are undertaken at the site of a resorption pit sealed by a sealing zone and encircled by a ruffled border of osteoclasts and bone matrix, because it contains acids and proteolytic enzymes, such as cathepsin K\(^\text{11}\). The membrane of the ruffle border has characteristics identical to those of lysosome in osteoclasts, and thus, it is called hemilysosome\(^\text{12}\).

Therefore, it is reasonable to hypothesize that the function of osteoclasts is impaired in ML II, while bone resorption is enhanced in ML II\(^\text{13}\). The increased bone resorption in ML may imply that the targeting of enzymes involved in bone resorption is not disturbed in this disorder. Another possible mechanism by which bone resorption is enhanced in ML II is that the excessive release of lysosomal enzymes by osteoclasts leads to increased bone resorption.

Radiographs of a 21-month-old Korean girl with ML II show features reminiscent of “osteitis fibrosa cystica” in Fig. 1. Erosive changes, especially in the hands and hips, are seen (Fig. 1A, 1B). The proximal phalanges are broad and under-modelled. The proximal metacarpals show a mixture of features of osteodystrophy and dysostosis multiplex, becoming eroded and narrowed to a point. The carpal bones are osteopenic and hypoplastic. There is also over-modelling of the long bones and bowing of the proximal end of the femur leading to coxa valga or “shepherd’s crook deformity” (Fig. 1B). The lower third of the ilia is hypoplastic and resorbed (Fig. 1B). In addition, there is osteopenia of the spine. The spine shows thoracolumbar kyphosis, beaking of
the vertebrae (Fig. 1C), and the skull shows J-shaped sella turcica (Fig. 1D), which are typical of lysosomal storage disorders with skeletal involvement.

**Skeletal Manifestations in Mucolipidosis III**

ML III occurs approximately between 3 and 5 years of age, with skeletal and facial abnormalities, short stature, normal intelligence or mild mental retardation, corneal opacity, and scoliosis, unlike other forms of ML that have visceral involvement and a gloomy vital prognosis in childhood\(^\text{14}\). In ML III, evolution is slow, and patients can reach up to the fifth decade of life. ML III is a rare lysosomal storage disease in which skeletal involvement is prominent, particularly the destruction of vertebral bodies and the femoral heads. Bone alterations in children may be confused with juvenile idiopathic arthritis or scleroderma, primarily due to the involvement of the hands\(^\text{15}\). Radiographs of a 19-year-old Korean female with ML II are shown in Fig. 2. The characteristic radiologic findings of the hands are small and irregular carpal bones and relatively wide proximal phalanges (Fig. 2A). In the lumbar spine, irregular delineation of the vertebral bodies is seen (Fig. 2B). In the pelvis, progressive hip dysplasia with a flattened acetabulum and femoral head destruction are seen (Fig. 2C). In some cases of ML, pamidronate has been used intravenously in order to reduce osteodystrophy. Intravenous pamidronate treatment is well tolerated, and it can produce clinical effects with a reduction in bone pain and improvements in mobility\(^\text{16}\).

**Conclusion**

Skeletal manifestations of ML II/III include short stature, joint contractures, hyperparathyroidism, progressive osteodystrophy, bone and joint pain, and locomotor disabilities. Two radiological patterns in ML are transient neonatal hyperparathyroidism and progressive osteodystrophy\(^\text{17}\). More neonatal cases of ML are necessary to reach a conclusion on the pathogenesis of the bone phenotype. ML II/III patients surviving the first year of life show a mixture of osteodystrophic bone changes and atypical changes of dysostosis multiplex. These include proximal pointing of the metacarpals in the wrist, dysplastic changes in the lower third of the ilia, marked broadening of the ribs becoming oar-shaped, and beaking of the lower thoracic and lumbar vertebrae. The osteodystrophy of the ML contributes significantly to the skeletal and joint symptoms, and these result in additional burdens of weakness, pain, and disability. A better understanding of the pathogenesis is important to improve the quality of life of those affected. Treatment with cyclic intravenous pamidronate is a promising adjunctive therapy that is presently being evaluated for those affected by ML III.

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