Mucolipidosis type II (MLII; MIM#252500) and type III alpha/beta (MLIIIA; MIM#252600) are very rare lysosomal storage diseases caused by deficient activity of UDP-N-acetylglucosamine:lysosomal hydrolase N-acetyl-1-phosphotransferase (GlcNac-phosphotransferase). The few estimates of the prevalence of ML II confirm that it is rare (approximately 1:123,500–1:625,000)\(^1\)\(^-\)\(^3\)). Estimates of the prevalence of ML IIIA based on objective data are not available. In this context, we will be discussing overview about the history, pathophysiology and treatment of ML II and ML IIIA. In the following reviews of this journal will be covered in more detail for clinical manifestation, molecular genetics, diagnostic approach for ML II and ML IIIA and new treatment strategies.

**Keywords:** Mucolipidosis, I-cell disease, GNPTAB

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### Introduction

Mucolipidosis type II (MLII; MIM#252500) and type III alpha/beta (MLIIIA; MIM#252600) are very rare lysosomal storage diseases caused by deficient activity of UDP-N-acetylglucosamine:lysosomal hydrolase N-acetyl-1-phosphotransferase (GlcNac-phosphotransferase). The few estimates of the prevalence of ML II confirm that it is rare (approximately 1:123,500–1:625,000)\(^1\)\(^-\)\(^3\)). Estimates of the prevalence of ML IIIA based on objective data are not available. In this context, we will be discussing overview about the history, pathophysiology and treatment of ML II and ML IIIA. In the following reviews of this journal will be covered in more detail for clinical manifestation, molecular genetics, diagnostic approach for ML II and ML IIIA and new treatment strategies.

### History

In 1967, Leroy and Demars\(^4\) reported the presence of unusual cytoplasmic granular inclusions in cultured fibroblasts from two patients with a Hurler-like syndrome. These characteristic fibroblasts were named inclusion-cells or ‘I-cells’ and the syndrome, I-cell disease. Maroteaux, Hors-Cayla, and Pont proposed the name of mucolipidosis type II (ML II)\(^5\). I-cells are fibroblasts, which contain numerous dense inclusions, most evident on phase contrast microscopy. The content of these inclusions is variable, mostly depending on the time elapsed since the last subculture. At first relatively homogeneous and osmiophilic, the granules become progressively loaded with pleomorphic material strongly suggestive of defective digestion of autophagic residues\(^6\). The first enzymatic studies of I-cells, by Leroy and Demars\(^4\) indicated that β-glucuronidase activity was low but not totally absent. In addition, the activity of acid β-galactosidase, 3-hexosaminidase, and α-fucosidase was found deficient in fibroblasts from the patient reported, in 1968, by Matalon et al.\(^7\), who most probably suffered from mucolipidosis type II.

Mucolipidosis type III alpha/beta (ML IIIA) was first outlined by Maroteaux and Lamy\(^8\) in 1966. Clinically it resembles the
Hurler syndrome. Cultured fibroblasts display somewhat enlarged lysosomes, which contain mostly lamellar and vesicular structures. The cytoplasmic changes in these cells are much less important than in I-cell disease. ML IIIA is milder than other forms of mucolipidoses, and its clinical features most significantly involve abnormalities in cartilage and bone with a mild coarsening of facial features. Valvular heart disease and mild intellectual disability may also be seen. Features of this disease are evident in early childhood and slowly progress throughout life, generally becoming fatal in early adulthood.

N-acetylglucosaminyl-1-phosphotransferase and Mannos-6-phosphate pathway

ML II and ML IIIA are characterized by disordered processing of multiple lysosomal degradative enzymes caused by the deficiency or abnormal function of GlcNAc-1-phosphotransferase. ML II is caused by a total or near total loss of GlcNAc-1-phosphotransferase activity whether enzymatic activity in patient with ML IIIA is reduced.

GlcNAc-phosphotransferase is essential for the lysosomal trafficking of most lysosomal hydrolases. Most lysosomal hydrolases are targeted to the lysosome via a mannose 6-phosphate (M6P)–dependent pathway. In this pathway, lysosomal enzymes are modified by the phosphorylation of mannose in a two-step reaction. In the first step, GlcNAc-phosphotransferase catalyzes the transfer of GlcNAc-1-phosphate from UDP-GlcNAc to certain terminal or penultimate mannoses on high-mannose–type glycans. The lysosomal enzymes, now modified with M6P, bind to M6P receptors in the trans-Golgi network and are translocated to the endosome and subsequently to the lysosome. The recognition of lysosomal hydrolases by GlcNAc-phosphotransferase is the determining step in lysosomal hydrolase trafficking. Lysosomal hydrolases that are substrates for GlcNAc-phosphotransferase exhibit low Km values, whereas nonlysosomal glycoproteins bearing similar glycans have high Km values. This difference in Km appears to explain the substrate-specific modification in lysosomal targeting. GlcNAc-phosphotransferase has an α2β2γ2-subunit structure with a molecular mass of 540 kDa. In 2000, the cDNA and genomic DNA encoding the a/b-subunits precursor gene (GNPTAB) in 2005. Interestingly, before the subunits and gene structures were determined, substantial evidence for heterogeneity in the mucolipidoses had been described. Varki et al. identified a variant form of MLIII on the basis of substrate recognition, which was later designated MLIIIC. To date, more than 100 different GNPTAB mutations have been reported, causing either ML II or ML III (Human Gene Mutation Database website, http://hgmd.org).

Treatment

1. Management of clinical manifestations

Supportive and symptomatic treatment is indicated in patients with ML II and ML IIIA. In aspect of skeletal manifestation, low-impact physical therapy to avoid joint and tendon strain, including aqua therapy is generally well tolerated for osteodystrophy of ML II and ML IIIA. The classic physiotherapeutic early intervention programs that are often beneficial in children with developmental delay, neuromotor delay, or cerebral palsy cannot be recommended unequivocally in ML IIIA because they can be ineffective and painful. Furthermore the unknowing therapist may inflict damage to the surrounding joint capsule and adjacent tendons and cause subsequent soft tissue calcification. Carpal tunnel signs may require open carpal tunnel release operation. Encouraging results have been obtained in several individuals with ML IIIA with monthly IV administration of pamidronate, a bisphosphonate. Bone pain in the two individuals about whom information has been published was reduced within a few months of initiating therapy. In some wheelchair-bound individuals, ambulation has been transiently restored for more than one year. Bone densitometry is improved. However, the long-term effects are unknown. In older adolescents and adults with milder phenotypic variants of ML IIIA, bilateral hip replacement has been successful. Recurrent otitis media occurs more often in ML IIIA than in a control population. The prevalence decreases with age. Myringotomy tube placement may be considered necessary as a preventive measure of conductive hearing loss. Myringotomy tube placement may be considered necessary as a preventive measure of conductive hearing loss.
2. Prevention of secondary complications

Because of concerns about airway management, surgical intervention should be avoided as much as possible and undertaken only in tertiary care settings with pediatric anesthesiologists and intensivists. Individuals with and ML II and ML IIIA are small and have a narrow airway, reduced tracheal suppleness from stiff connective tissue, and progressive narrowing of the airway from mucosal thickening\(^{29}\). The use of a much smaller endotracheal tube than for age- and size-matched controls is necessary. Fiberoptic intubation must be available. Poor compliance of the thoracic cage and the progressively sclerotic lung parenchyma further complicate airway management, especially in older individuals. Functional decline of lung parenchyma is likely due at least in part to slowly progressive degeneration of soft connective tissue in the extracellular matrix, a phenomenon insufficiently studied but concomitant to the osteopenia in bone\(^{30}\). As subclinical cardiac failure may become overt during anesthesia, any surgical intervention should be preceded by a thorough cardiologic evaluation. Exubation may also be a challenge.

3. Hematopoietic stem cell transplantation

Allogenic hematopoietic stem cell transplantation (HSCT) has been attempted for ML; however, Lund et al.\(^{31}\) reported that the clinical course of ML such as survival and psychomotor development may be unchanged by HSCT. Umbilical cord blood transplantation (UBCT) also has been tried for 26-month-old girl with ML II. After UBCT, plasma lysosomal enzyme activities showed improvement, but effects on the clinical manifestations were limited\(^{32}\).

**Conclusion**

ML II and ML IIIA are very rare lysosomal storage disease cause by reduced enzyme activity of GlcNAc-1-phosphotransferase. ML II is caused by a total or near total loss of GlcNAc-1-phosphotransferase activity whether enzymatic activity in patient with ML IIIA is reduced. Therefore, ML II and ML III share similar clinical features, including skeletal abnormalities, ML II is the more severe in terms of phenotype. GlcNAc-1-phosphotransferase is encoded by two genes, GNPTAB and GNPTG, mutations in GNPTAB give rise to ML II or ML IIIA. There is no specific treatment available for patients with ML II and ML IIIA yet, only supportive and symptomatic treatment is indicated.

**References**


