CASE REPORT

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Revealing Two New Features of a Rare Variant of Mucolipidosis Type II

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ABSTRACT A 12-hour-old female infant was referred to our hospital with significant indirect hyperbilirubinemia. She was delivered via cesarean section to a healthy 28-year-old mother at 36 weeks and 6 days gestational age, with a birth weight of 2,245 grams. The physical examination revealed features typical of mucolipidosis Type II. Laboratory tests showed indirect hyperbilirubinemia, thrombocytopenia, and elevated alkaline phosphatase levels. Osteopenia and dysostosis multiplex were observed on the radiographs. Enzyme and gene analysis confirmed the diagnosis: the activity of the N-acetylglucosamine-1-phosphotransferase (GlcNAc-PTase) enzyme was absent, and the baby's GNPTAB gene was homozygous for the c.3503_3504del variant. Fewer than 50 instances of this variant have been documented. We present this rare case and reveal 2 new characteristics of the condition: peripheral heterochromia of the iris and vacuoles in the nucleus of the polymorphonuclear leukocytes.

Keywords: Mucolipidosis Type II; I-cell disease; nucleus vacuoles; peripheral heterochromia

In 1971, Leroy et al. identified I-cell disease, also known as mucolipidosis Type II (MLII), in 8 patients who exhibited a distinctive "Hurler"-like body shape, severe skeletal dysplasia, and psychomotor delays. Electron microscopy revealed cytoplasmic inclusions in fibroblasts that were rich in lipids and mucopolysaccharides.[1] MLII is a rare genetic disorder with an incidence ranging from 0.22 to 2.70 per 100,000 live births. It is caused by mutations in the *GNPTAB* gene, located on chromosome 12q23.3, which disrupts the N-acetylglucosamine phosphotransferase complex, an essential enzyme involved in transporting lysosomal enzymes.[2]

Patients with MLII typically exhibit symptoms such as hypotonia, stiff skin, distinctive facial features, and various skeletal deformities.[1,2] Radiographic findings often include craniosynostosis and osteopenia, among other abnormalities.[3] A recent review has documented 516 cases of MLII, with 47 patients having the c.3503_3504del variant.[2]

Currently, there is no definitive treatment available for MLII, although life-extending surgeries raise ethical concerns. The median survival for affected individuals is approximately 5 years, often influenced by pulmonary and cardiac complications. However, the potential of gene therapy as a future treatment for MLII is a beacon of hope.[2] This report presents 2 unique characteristics of MLII in a patient with the c.3503_3504del variant, contributing to the existing literature.

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A female infant was born to a 28-year-old multigravida at a gestational age of 36 weeks and 6 days. The infant weighed 2,245 grams, measured 48 cm in length, and had a head circumference of 33 cm. The

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parents, who are 2nd-degree cousins, experienced one spontaneous abortion in the first trimester and had one healthy male offspring. Although the infant did not require resuscitation at birth, she was subsequently transferred to our facility within 12 hours of delivery due to indirect hyperbilirubinemia.

The physical examination revealed multiple dysmorphic features, including generalized hypotonia, stiff and doughy skin, thin/light hair, a flat face, shallow orbits with protruding eyes, deep infraorbital creases, a flat nasal bridge, anteverted nares, a long philtrum, prominent mouth, gingival hypertrophy, claw hands, short limbs, club feet, a hypoplastic chest, congenital hip dislocation, joint stiffness, and an umbilical hernia (Figure 1 and Figure 2). An ocular examination showed peripheral iris heterochromia without corneal haziness (Figure 3). Parental consent was obtained to share the baby's photographs and findings.

Radiographs indicated the presence of new bone formation in the limbs (Figure 4). Cranial ultrasonography identified a choroid plexus cyst, while abdominal ultrasonography yielded normal results. The echocardiogram revealed a 5 mm atrial septal defect and moderate tricuspid valve insufficiency, with an ejection fraction of 60%. The isthmus measured 4 mm.

FIGURE 1: The patient's general appearance from the front view

FIGURE 2: The patient's general appearance viewed from the back

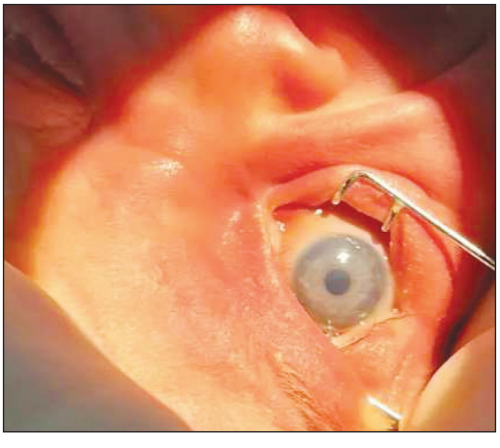

FIGURE 3: Ocular findings: peripheral iris heterochromia with no signs of corneal haziness

Periferic blood smear showed vacuoles in the nucleus of polymorphonuclear leucocytes (Figure 5).

She did not pass the otoacoustic emission test for a hearing screening.

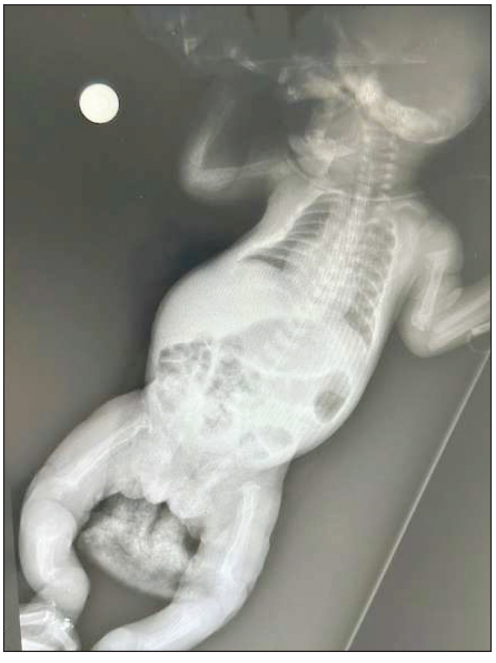

FIGURE 4: Babygram: indicates the presence of new bone formation in the limbs

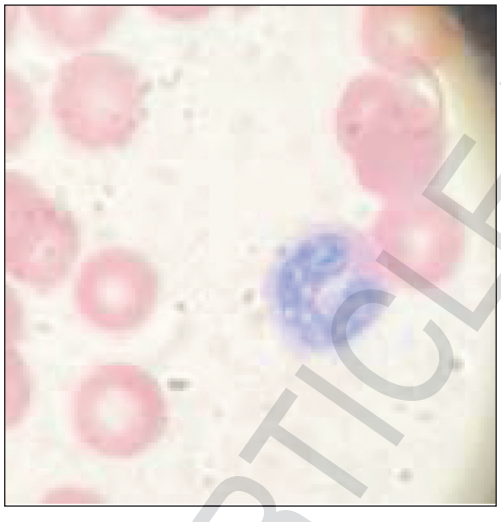

FIGURE 5: Peripheral blood smear: Vacuoles observed in the nuclei of polymorphonuclear leukocytes

After 12 hours of phototherapy, the patient's bilirubin levels decreased. Initial laboratory results indicated indirect hyperbilirubinemia and thrombocytopenia. She was hospitalized for 22 days due to feeding difficulties caused by a very narrow mouth and an inability to suck. On the 12th day, she experienced a septic episode and received antibiotics for 7 days. The plasma enzyme assay revealed elevated hexosaminidase A, total hexosaminidase, beta-mannosidase, and alpha-N-acetylgalactosaminidase enzyme activity in plasma. Deoxyribonucleic acid sequencing of the *GNPTAB* gene mutation revealed that she was homozygot for c.3503_3504del variant. The family declined a gastrostomy after the definite diagnosis and was trained to use a nasogastric tube for feeding. She was discharged after this training.

DISCUSSION

Mucolipidosis II is a rare lysosomal disorder characterized by its unique morphological features, which enable genetic experts to make a relatively quick diagnosis.[1-3] Established diagnostic methods include assessing clinical signs, conducting enzyme analyses, and performing genetic testing.[2] However, we would like to highlight 2 clinical aspects that have not been reported before: Iris heterochromia and the presence of vacuoles in the nuclei of polymorphonuclear leukocytes.

Hayasaka provided a thorough description of lysosomal enzyme activity in ocular tissues, emphasizing the role of lysosomes in various eye diseases, including storage disorders. Eye involvement is also anticipated in MCII.[4] Positive findings through light and electron microscopic examinations of ocular tissues have been noted as early as the 6th day postnatally.[5] However, ophthalmoscopic abnormalities such as corneal haziness, corneal edema, and megalocornea or glaucoma tend to appear later as clinical symptoms.[1,6] Notably, an ophthalmoscopic finding observed as early as the 1st day of diagnosis has never been reported. In this case, the patient displayed bluish eyes with central heterochromia, where the pupillary zone of the iris was a lighter blue than the ciliary zone. Usually, collagen trabeculae surrounding the borders of the crypts are visible in blue irises.[7] However, this patient showed a slight reduction in corneal transparency (Figure 5). We did not perform a biopsy to confirm an accumulation of fibro granular material, not to put the baby in further pain. Libert et al. reported that the iris muscles and posterior pigment epithelium were unaffected in their 6-day-old MCII patient on electron microscopy. Determining the genetic variant was not possible then, this finding of our baby may be specific to the c.3503_3504del variant. Iris color is determined primarily by the concentration and distribution of

melanin.[5,8] Melanin is produced in melanosomes, which originate from lysosomes ontogenically.[9] These babies' blue eyes and light hair may be related to incomplete melanin synthesis. Reduction in corneal transparency might be an early sign of the late symptoms like corneal haziness. Further genotype-phenotype correlation are needed.

Vacuoles in the cytoplasm of neutrophils can develop in response to cytotoxic stimuli, such as infections, or may be associated with cell degeneration and apoptosis.[10] When vacuoles are present in the cytoplasm of mature lymphocytes, they often indicate lysosomal storage diseases.[11] Nuclear vacuolization in neutrophils has not been previously reported in lysosomal storage disorders, particularly in the case of MLII. This type of vacuolization is associated with cell degeneration and apoptosis, and suggests an irreversible state of cell death.[12] Two hypotheses have been proposed regarding its pathophysiology: the formation of true holes in the nucleus and nuclear invagination by the cytoplasm. In the case of ML II, non-mannose enzymes that the lysosome cannot capture accumulate in the cytoplasm, leading to their possible invagination into the nucleus.[13,14] Vacuoles found in the nucleus of an ML II patient may also signify irreversible apoptosis, suggesting that these vacuoles could indeed be true holes. Lysosomal storage disorders are associated with impaired fusion between lysosomes and autophagosomes, obstructing the autophagic process. This blockage leads to the accumulation of toxic proteins, resulting in cellular damage that ultimately causes apoptosis and cell death.[15]

Understanding the pathophysiological context is essential when considering the timing of potential future gene treatments. If signs of irreversible apoptosis appear in a neonate with MLII as early as the first few days, then for optimal effectiveness, such treatments should ideally begin *in utero*. More research is necessary to understand the effects of lysosomal diseases on the nucleus.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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