Placental pathology in an unsuspected case of mucolipidosis type II with secondary hyperparathyroidism in a premature infant

Parith Wongkittichote
Garland Michael Upchurch
Louis P Dehner
Timothy Wood
Jorge L Granadillo

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Mucolipidosis type II (MLII, MIM 252500) is a lysosomal storage disorders caused by defects in GNPTAB gene which encodes alpha and beta subunits of N-acetylglucosamine (GlcNAc)-1-phosphotransferase. Neonatal presentation includes coarse facial features, restricted postnatal growth, generalized hypotonia, gingival hypertrophy and multiple skeletal anomalies. Here we present a case of a 26-week gestational age preterm infant with MLII who did not exhibit the typical facial features at birth; however, the diagnosis was suggested from abnormal placental pathology showing trophoblastic lipidosis and initial skeletal abnormalities from chest radiograph revealing generalized diffuse severe bone demineralizing disease and multiple fractures. Biochemical testing revealed elevation of plasma lysosomal enzymes. Homozygous pathogenic variant, designated c.3505_3504del, was discovered from GNPTAB sequencing. Her course was complicated by respiratory distress, secondary hyperparathyroidism, abdominal distention and feeding difficulties. Urine mucopolysaccharides analysis revealed elevation of plasma lysosomal enzymes. Homozygous pathogenic variant, designated c.3505_3504del, was discovered from GNPTAB sequencing. Her course was complicated by respiratory distress, secondary hyperparathyroidism, abdominal distention and feeding difficulties. Urine mucopolysaccharides analysis

Keywords:
Mucolipidosis type II
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Trophoblastic lipidosis

1. Introduction

Mucolipidosis type II (MLII, also known as I-cell disease), along with mucolipidosis type III alpha/beta (MLIIIα/β) and mucolipidosis type III gamma (MLIIIγ), are lysosomal storage disorders caused by defects in N-acetylglucosamine (GlcNAc)-1-phosphotransferase [1,2]. GlcNAc-1-phosphotransferase is a hexameric enzyme composed of 2 alpha, 2 beta and 2 gamma subunits [2,3]. GNPTAB encodes the alpha and beta subunits, while GNPTG encodes the gamma subunit [4,5]. This enzyme catalyzes the phosphorylation of mannose residues on glycan chains to form mannose-6-phosphate, which is required for targeting lysosomal enzymes to lysosomes [6]. The defect of GlcNAc-1-phosphotransferase causes hypersecretion of lysosomal enzymes leading to the elevation of multiple acid hydrolase activities in the serum and their deficiency in the lysosomes. [7]. The subsequent accumulation of intracellular materials results in cellular dysfunction and eventually tissue and organ damage [8].

GNPTAB is located at chromosome 12q23.2 and contains 21 exons. Pathogenic variants in GNPTAB cause MLII (MIM 252500) and MLIIIα/β (MIM 252600) [2,9]. MLII is characterized by neonatal onset of coarse facial features, restricted postnatal growth, generalized hypotonia, gingival hypertrophy and multiple skeletal abnormalities including thoracic deformity, clubfeet, long bone deformity, hip dislocation, and cardiac valvular abnormalities [1,10–14]. MLIIIα/β is a later-onset form which is typically diagnosed around three years of age and has slower progression [1,10–14]. Those with MLIIIα/β typically live into early adulthood, while most patients with MLII die in early childhood, usually with respiratory compromise [15]. Genotype-phenotype correlation has been established in MLII and MLIIIα/β. Variants that severely affect enzyme function have been shown to be associated with more severe phenotypes [1,16].

Previous studies have reported abnormal placental lipid...
accumulation in newborns with mucolipidoses and other lysosomal storage diseases [17–19]. We present the case of a premature newborn with MLII who at birth did not exhibit any of the typical dysmorphic features including those of the facies. It was on the basis of the placental examination and radiographic findings of the chest that the diagnosis of I-cell disease was suspected and subsequently corroborated through biochemical and genetic testing.

2. Materials and methods

2.1. Case report

The patient was a 3-day-old female who was admitted to the neonatal intensive care unit due to prematurity at 26 weeks of gestation to a 26-year-old G1 P0 mother whose pregnancy was complicated by prolonged premature rupture of membranes, preterm labor, recurrent urinary tract infections and renal calculi. Family history was otherwise unremarkable. Prenatal ultrasound at 25 weeks of gestation was reported as normal. Her birth weight was 1000 g (90th percentile); birth length was 36.5 cm (94th percentile) and head circumference was 23 cm (44th percentile). APGAR scores were 6 and 9 at 1 and 5 minutes of life, respectively. She was started on continuous positive airway pressure (CPAP) due to prematurity and was later transitioned to non-invasive positive pressure ventilation (NIPPV) due to desaturations. She began on a course of ampicillin and gentamicin due to prolonged rupture of membranes. Her physical examination was unremarkable without coarse facial features; however, a chest radiograph revealed generalized diffuse severe bone demineralization and multiple fractures, which raised concern for hyperparathyroidism. Further evaluation revealed mildly elevated ionized calcium (5.26 mg/dL, normal range 3.90–5.20 mg/dL), an elevated parathyroid hormone (PTH) level (471 pg/mL, normal range 14–72 pg/mL), mildly low 25-hydroxyvitamin D (17 ng/mL, normal range 20–100 ng/mL), elevated magnesium (3.2 mg/dL, normal range 1.4–2.5 mg/dL), normal phosphorus (4.5 mg/dL, normal range 4.0–9.0 mg/dL) and elevated alkaline phosphatase (832 units/L, normal range 110–320 mg/dL). Maternal calcium, magnesium, phosphorus, PTH and 25-hydroxyvitamin D were within the normal range. PTH in subsequent studies of the proband showed improvement to suggest secondary hyperparathyroidism. Vitamin D was initiated with subsequent decrease in PTH level and normalization occurred at 8 weeks of age; however, alkaline phosphatase has remained elevated. She developed significant abdominal distention which improved with decrease feeding volume. Oral feeds were initiated at 14 weeks of life; however she struggled to achieve caloric goal. Gastrostomy tube was placed prior to discharge. In terms of respiratory support, she was later transitioned from NIPPV to nasal cannula; however, she developed desaturation on room air. She was then discharged at 16 weeks of life with low-flow nasal cannula. She failed auditory brainstem response (ABR) test. Repeat audiologic study revealed mild-to-moderate bilateral conductive hearing loss.

2.2. Molecular and biochemical analysis

Genetic testing for GNPTAB was performed on the index patient and her parents by Prevention Genetics (Marshfield, WI). Genomic DNA was extracted from buccal swabs of the proband as well as the parents. DNA corresponding to these regions was captured using an optimized set of DNA hybridization probes. Captured DNA was sequenced using Illumina’s Reversible Dye Terminator (RDT) platform (Illumina, San Diego, CA, USA). Regions with insufficient coverage by next-generation sequencing (NGS) were covered by Sanger sequencing. Copy number variants (CNVs) were detected from NGS data utilizing a CNV calling algorithm that compares mean read depth and distribution for each target in the test sample against multiple matched controls. The depth of coverage was more than 20 × for all coding exons of GNPTAB, GNPTC and NAPGA, plus approximately 10 bases flanking of noncoding DNA.

Lysosomal enzyme testing was performed by Lysosomal Diseases Testing Laboratory, Thomas Jefferson University (Philadelphia, PA) [20]. Urine mucopolysaccharidoses analysis and urinary oligosaccharide analysis were performed by Greenwood Genetic Center (Greenwood, SC) using mass spectrometry based methods [21–23]. Total glycosaminoglycans were measured using dye binding methods.

2.3. Gross and microscopic examination of the placenta

Gross examination with prospection of the placenta was performed by standard surgical pathology techniques. The weight of the placental disc with trimmed fetal membranes was measured and compared to a standard reference range of placental weights for reported fetal gestational age at birth. Placental sections submitted for microscopic examination were formalin fixed/paraffin embedded and cut slides were hematoxylin and eosin stained using standard histology techniques and were examined by light microscopy. An additional section of placenta was fixed in glutaraldehyde for electron microscopy by standard techniques, performed using standard techniques at the Washington University School of Medicine Department of Pathology and Immunology electron microscopy facility.

3. Results

3.1. Placental pathology

Gross examination showed a 12.5 × 12.0 × 2.7 cm singleton placenta with an attached segment of unremarkable trivascular umbilical cord inserting paracentrally 4.2 cm from the placental disc margin. Attached membranes were opaque with eccentric rupture 2.5 cm from the nearest placental disc margin. The fetal surface was pink in color with gross sub-amniotic hemorrhage. The maternal surface was disrupted. Trimmed weight of the placenta was 183.6 g which was small for pre-term female neonates born at 26 weeks gestational age and corresponding to less than the 10th percentile for gestational age. Sections of the placental disc showed no additional gross findings.

Microscopic examination showed a trivascular umbilical cord and fetal membranes showed no histopathologic abnormality. The chorionic villi with appropriate maturation for gestational age revealed fine vacuolization of syncytiotrophoblasts and stromal expansion by multi-vacuolated Hofbauer cells (fetal macrophages) (Fig. 1). Extensive cytoplasmic vacuolization of Hofbauer cells with some electron dense material within the vacuoles was identified ultrastructurally (Fig. 2). These vacuoles were most consistent with lysosomes containing lipid suggestive of mucolipidoses, namely MLII [17] or mucolipidosis type IV [18].

3.2. Biochemical and molecular analysis

Lysosomal enzyme testing in leukocytes was normal; however, plasma lysosomal enzymes including β-galactosidase, β-mannosidase, α-L-fucosidase, α-mannosidase and α-glucosaminidase activities were substantially elevated; this finding is consistent with MLII or MLIII/β. Targeted sequencing revealed that the patient was homozygous for a pathogenic variant in GNPTAB, denoted NM_024312.5: c.3505_3504del (p.Leu1168Glnfs*5). This variant has been previously reported to be causative for MLII. Both parents were found to be heterozygotes.

Urine mucopolysaccharides analysis revealed a non-specific pattern (Table 1). At 2 days of life, all individual GAGs, including chondroitin sulfate (CS), heparan sulfate (HS), dermatan sulfate (DS) and keratan sulfates (KS) were elevated, with normal total GAGs. Repeat study at 2 months of age consistently showed elevation of CS, HS and KS. The total GAGs were also elevated, while DS normalized. A similar pattern was noted in two additional samples taken at 2 months of age.

Urinary oligosaccharide analysis demonstrated significant elevations (3.6–11.3 times) of a siaiylated oligosaccharide marker.
(Neu5Ac1Hex3HexNAc2) in all four urine samples. Other markers (Hex1HexNAc1, Hex3HexNAc1, Hex3HexNAc2) were elevated in most samples but to a lesser degree (1–3.3 times).

4. Discussion

The placental examination provides the opportunity to identify both maternal and fetal findings which correlate a variety of pregnancy associated complications from maternal vascular malperfusion with intrauterine growth restriction to fetal infections of various types in the presence of fetal hydrops. Our case illustrates that clinically pertinent findings (and subsequent diagnoses made) are by no means restricted to these narrow diagnostic categories and can include a number of biochemical disorders – namely inborn errors of lipid metabolism. It has been appreciated for some time that electron microscopy is especially useful in a variety of inherited lipid storage disorders with the lysosomal accumulation of metabolic material in Hofbauer cells as it does elsewhere in fetal macrophages in the liver, spleen and lymph nodes [24]. Here we present a case where the findings of placental lipidosis raised concern for an inborn error of lipid metabolism, which was further confirmed by electron microscopic studies showing lysosomal lipid inclusions as well as biochemical and genetic evidence of MLII. While MLII is a rare genetic disease, even rarer are reports in the literature of diagnoses being made based on placental findings [17,18,25].

A diagnosis of MLII is usually suspected based on clinical characteristics include early signs of dysmorphic features and abnormal skeletal findings which may be present at birth to early infancy [10]. However, our case demonstrated that coarse facial features can be mild or even absent in preterm newborns with MLII, but may develop later. Skeletal findings, in combination with abnormal placental pathology, can lead to the early recognition of MLII.

Spontaneous abortion and stillbirth have been reported among cases with MLII [26,27]. In a cohort of individuals diagnosed with MLII, Cathey SS et al. reported that two out of 14 had preterm deliveries [10]. Aborted fetuses were found to have abnormal placental pathology with extensive cytoplasmic vacuolization of chorionic villi [27]. MLII might increase the risk of stillbirth and preterm labor, partially due to

Fig. 1. Hematoxylin and Eosin section showing trophoblastic lipidosis. Foamy vacuolization surrounding the periphery of the villus was noted, corresponding to lysosomal lipid inclusions.

Fig. 2. Electron micrograph of placental villus. Trophoblastic lipidosis was shown, consistent with lysosomal lipid inclusions.

Fig. 3. Electron micrograph of placental villus. Trophoblastic lipidosis was shown, consistent with lysosomal lipid inclusions.
placental injury from accumulation of storage material.

Our patient also had transient secondary hyperparathyroidism, which has been previously reported in association with MLII [28–31]. The initially elevated PTH later normalized; however, alkaline phosphatase has remained elevated, similar to previously reported examples [29,30]. The cause of this endocrine abnormality is currently unclear. Sathasivam, et al, proposed that abnormal placental structure and function may lead to impaired placental calcium transport and subsequent secondary hyperparathyroidism and ricket-like bone changes [31]. Alternatively, David-Vizcarra, et al, hypothesized that GlcNAc-1-phosphotransferase deficiency causes defective targeting of one of the components of PTH signal transduction, leading to tissue PTH hypersensitivity and PTH hypersecretion from disrupted biofeedback [30].

Abnormal elevation of GAGs has been reported in the settings of MLII and MLIIα/β patients [31]. One patient was reported to have elevation of DS, HS and KS, while another patient was found to have only DS elevation. Our patient showed elevated total and individual GAGs. This pattern differs from previous studies with the elevation of CS, HS, and KS. Additionally, normal urinary oligosaccharides have been reported [30,31]. Our patient showed persistent elevations of a sialylated oligosaccharide and to a lesser degree other non-sialylated oligosaccharides. The abnormal levels of GAGs and oligosaccharides in mucolipidoses are less significant than those in mucopolysaccharidoses and glycoproteinoses; respectively; however, in conjunction with other clinical features, mild nonspecific elevation of both tests can support a diagnosis of MLII. Additionally our data show these mild elevations persist over multiple samples and are present in the first week of life.

We have described a premature infant who was diagnosed with MLII on the basis of placental lipidosis, skeletal findings and subsequent genetic confirmation. To our knowledge, this patient is the most premature patient with MLII to date that has been reported. Given the absence of classical craniofacial features at the time of diagnosis, this report has highlighted the importance of placental pathological examination in cases of unsuspected disorders especially of an inherited metabolic nature.

Author contributions
Parith Wongkittichote and Jorge L. Granadillo were involved in obtaining consent and in paper concept and design. Parith Wongkittichote and Garland Michael Upchurch were involved in drafting and revising manuscript. Louis P. Dehner, Timothy Wood, and Jorge L. Granadillo were involved in reviewing and editing manuscript.

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Ethics approval was not required for this study.

A patient consent statement
Consent was obtained from the patient’s family for publication of this report.

Availability of data and materials
Not applicable.

Declaration of Competing Interest
The authors declare no conflict of interest.

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Table 1
Urine mucopolysaccharides and oligosaccharides profiles in the proband. Red text indicates abnormal levels.

| Normal range | Unit | D2 | D55 | D61 | D68 |
|--------------|------|----|-----|-----|-----|
| Chondroitin Sulfate | 0-36.81 | g/mol creatinine | 79.89 | 61.35 | 64.52 | 57.16 |
| Dermatan Sulfate | 0-18.47 | g/mol creatinine | 21.55 | 12.83 | 14.32 | 12.66 |
| Heparan Sulfate | 0-5.28 | g/mol creatinine | 19.10 | 8.14 | 6.66 | 11.52 |
| Keratan Sulfate | 0-18.8 | mg/mmol creatinine | 23.64 | 27.49 | 30.87 | 39.14 |
| Total GAGs | 0-53 | mg/mmol creatinine | 33.33 | 68.35 | 90.15 | 66.39 |
| Neu5AcHex3HexNAc2 | 0.06-0.72 | Relative response | 7.4 | 8.1 | 2.6 | 3.8 |
| HexHexNAc1 | 12.0-60.3 | Relative response | 106.4 | 104.4 | 60.0 | 68.5 |
| Hex3HexNAc1 | 7.4-33.6 | Relative response | 54.2 | 39.2 | 26.6 | 35.3 |
| Hex3HexNAc2 | 1.6-4.2 | Relative response | 13.7 | 8.4 | 5.5 | 6.6 |
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