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Abstract

Traditional approaches to prenatal genetic diagnosis for common presentations such as short femurs or intrauterine growth restriction are imperfect, and whole-exome sequencing is an emerging option. Mucolipidosis type II (I-cell disease) is an ultra-rare autosomal recessive lysosomal storage disorder with the potential for prenatal-onset skeletal and placental manifestations. We describe the prenatal signs in two recent unrelated patients with confirmed diagnoses soon after birth. In both cases, parents were consanguineous but there was no known family history of mucolipidosis type II. False reassurance was provided after negative testing for another disease with overlapping prenatal manifestations already present in one of the families, emphasizing that offspring of consanguineous parents can be at risk for more than one recessive condition. Our experience illustrates the potential advantages in expanding prenatal applications of WES for the identification of rare single gene disorders in offspring of consanguineous unions.

Keywords
- lysosomal storage disease
- mucolipidosis
- prenatal diagnosis
- genetic testing
- skeletal dysplasia

Introduction

The application of whole-exome sequencing (WES) in the prenatal setting offers myriad advantages for the detection of rare single gene disorders.[1] Parental consanguinity provides further impetus to consider atypical causes of common prenatal presentations. For example, mucolipidosis type II (ML-II; OMIM #252500), also known as I-cell ("inclusion cell") disease, is a rare autosomal recessive lysosomal storage disorder.[2] ML-II is a panethnic condition but is more likely to occur in populations with a high rate of consanguinity and/or a known founder mutation (e.g., French Canadians[3]). Biallelic loss-of-function of

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the gene *GNPTAB* leads to a profound deficiency of the enzyme GlcNAc-1 phosphotransferase.[4] The resulting defect in targeting acid hydrolases on the surface of lysosomes impedes their entry into these organelles. Undigested substrates accumulate in the lysosome, leading to the characteristic I-cells and multitissue dysfunction. Affected individuals typically present between 6 and 12 months of age, with manifestations resembling Hurler syndrome and a radiological picture of dysostosis multiplex.[5] In severe cases, ML-II manifests in the newborn period with radiological changes of hyperparathyroidism or rickets.[6] Identifying the condition even late in pregnancy can benefit families, in light of the significant associated morbidity and mortality. There are few reports of prenatal manifestations of ML-II,[5–10] and prenatal diagnosis in the absence of a known family history is difficult. We recently diagnosed two unrelated newborns with ML-II after following their mothers in pregnancy because of abnormal fetal ultrasounds. Although clues were appreciable prenatally, these were highly nonspecific and in neither case was this rare condition considered until after birth.

Case Reports

Patient 1

A 24-year-old G3A1P1L1 woman presented with an ultrasound at 21 weeks' gestation showing echogenic kidneys and mildly thickened femoral diaphyses. At 23^{+2} weeks, there had been appropriate interval growth and fetal biometry was consistent with dates, but at 32^{+1} weeks all long bones measured well below the third centile. The couple was healthy, consanguineous (first cousins), and of Pakistani descent. A fetal echocardiogram was normal. Care was transferred to our high-risk perinatal center, and ultrasounds done after 33 weeks continued to show short long bones (►**Fig. 1**).[11] Skull shape, chest size, and ribs were normal, and there were no apparent fractures. The kidneys appeared normal in size and echogenicity. Counseling focused on the fact that these findings were not consistent with a lethal skeletal dysplasia, and that genetic diagnosis would be more feasible after birth (in the absence of any opportunity for prenatal genome-wide sequencing).[12]

A male baby was born at 39^{+2} weeks by an elective, repeat cesarean section with a complete breech presentation. No neonatal resuscitation was required. Birth weight was 2,970 g (10th–50th centile), length 47 cm (~10th centile), and head circumference 35 cm (~50th centile). On examination, he had coarse features with full lips and prominent gingiva, joint contractures, and club feet. Skeletal X-rays were abnormal (►**Supplementary Fig. S1**, available in the online version only).[5] Laboratory investigations later revealed mildly elevated ionized calcium (1.38 mmol/L), normal phosphate (1.72 mmol/L), elevated alkaline phosphatase (873 U/L), and normal parathyroid hormone (72 ng/L). The placenta showed abundant vacuolization in the cytoplasm of the syncytiotrophoblast cells.[8] Urine was positive for oligosaccharides. A diagnosis of ML-II was confirmed, based on markedly elevated total serum hexosaminidase enzyme activity (33,080 nmol/h/mL [normal 439–1,300 nmol/h/mL]) and identification of a homozygous pathogenic[4] variant (NM_024312.4: c.3335 + 1G > A) in the *GNPTAB* gene. The child was ultimately transferred back to his Canadian home province for follow-up care.

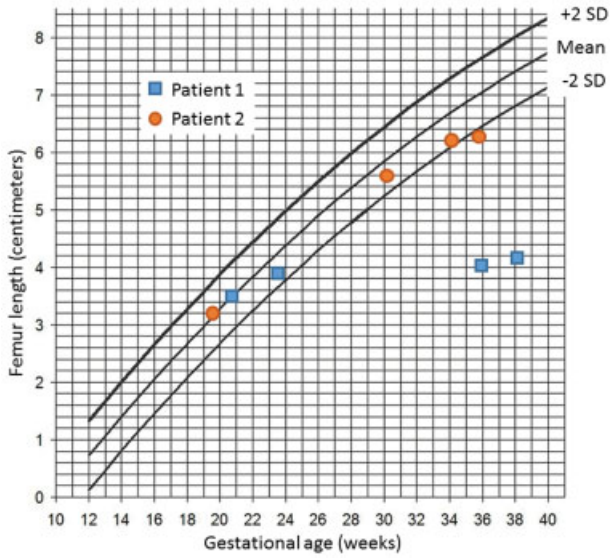

Fig. 1 Selected fetal femur lengths for two fetuses diagnosed postnatally with ML-II. For Patient 1 (box), femur lengths at 20^{+5}, 23^{+3}, 35^{+6}, and 38^{+2} weeks' gestation were 35 mm (52nd centile), 39 mm (14th centile), 40.7 mm (<< 1st centile), and 41.5 mm (<< 1st centile), respectively. For Patient 2 (circle), femur lengths at 19^{+4}, 30^{+1}, 34^{+1}, and 35^{+5} weeks' gestation were 32 mm (58th centile), 55.8 mm (17th centile), 62 mm (4th centile), and 62.5 mm (0.6th centile), respectively. Mean and SD data are from Hadlock et al.[11]

Patient 2

A 34-year-old G6A4P1L1 woman presented for prenatal diagnosis of 3M syndrome, an autosomal recessive primordial growth disorder (MIM #612921). The parents were healthy, consanguineous first cousins of Pakistani descent. Their first pregnancy resulted in a child with a molecularly confirmed diagnosis of 3M syndrome (homozygous *OBSL1* variant), following which they had four pregnancy terminations for prenatally diagnosed 3M syndrome. Chorionic villus sampling (CVS) at 12 weeks' gestation revealed that this fetus was unaffected with 3M syndrome and had a normal female chromosomal microarray result, albeit with multiple regions of loss of heterozygosity consistent with the known consanguinity. Detailed fetal ultrasound at 20 weeks showed no abnormalities and normal growth. Gestational diabetes mellitus was diagnosed on routine screening and treated with insulin. Ultrasounds after 30 weeks demonstrated borderline intrauterine growth restriction (IUGR) with progressive fall off in growth (►**Fig. 1**). The caregivers were reassured by the CVS result that the fetus did not have 3M syndrome or chromosome abnormalities, and ascribed the ultrasound findings to placental dysfunction.

A female baby was born at 35^{+6} weeks by cesarean section following preterm, premature rupture of membranes. No neonatal resuscitation was required. Birth weight was 1.730 g (~3rd centile), length 43 cm (~10th centile), and head circumference

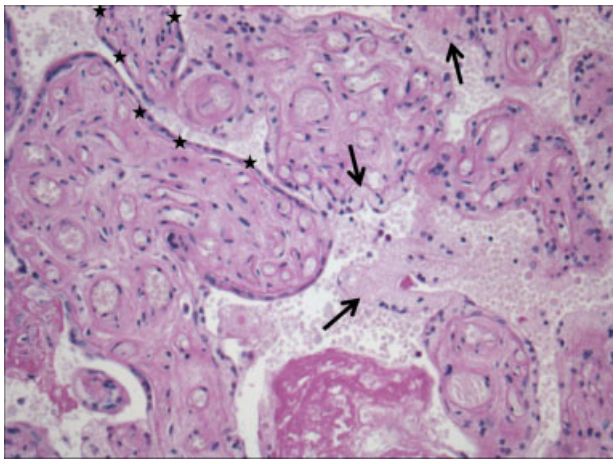

Fig. 2 Placental villi in Patient 2 (200× magnification, Periodic acid–Schiff stain). Multiple villi are seen lined by syncytiotrophoblast cells that show a markedly expanded cytoplasm with prominent vacuolization (black arrows) due to lysosomal accumulation of undigested molecules. This is particularly evident in contrast to more normal appearing areas of syncytiotrophoblast lining (black stars). The villi also show villous maturation that is delayed for 35 weeks' gestation.

28 cm (< 3rd centile). On examination, she had coarse features with puffy eyelids, prominent gingiva, and full lips, club feet, and the skin had a thick texture. Laboratory investigations revealed elevated alkaline phosphatase (1,296 U/L) and parathyroid hormone (31.2 pmol/L), consistent with secondary neonatal hyperparathyroidism, as seen previously in prenatal-onset ML-II.[6] Skeletal X-rays were abnormal (►**Supplementary Fig. S2**, available in the online version only). Placental pathology was consistent with a lysosomal storage disorder (►**Fig. 2**).[8] Urine was positive for oligosaccharides. A diagnosis of ML-II was confirmed, based on markedly elevated total serum hexosaminidase enzyme activity (31,000 nmol/h/mL) and identification of a homozygous pathogenic[3,4] variant (NM_024312.4: c.3503_3504delTC) in *GNPTAB*. At last follow-up at > 1 year of age, she was clinically stable with feeding/growth issues and global developmental delay.

Discussion

Anticipatory care and treatment of complications are the mainstays of postnatal management in ML-II.[2] Vitamin D therapy is indicated in those with hyperparathyroidism. However, there are no proven treatments that can alter the progressive course of the disease, with most children dying within the first decade of life. The current literature does not decisively support hematopoietic stem-cell transplantation or any other disease-modifying treatment. Our experiences illustrate challenges inherent in the prenatal diagnosis of ML-II. In contrast, diagnosis after birth is typically more straightforward. The risk of recurrence in a family is 25%. The potential for preimplantation and prenatal genetic diagnosis in subsequent pregnancies is an important counseling consideration, particularly as ultrasound anomalies are typically absent or observed only later in pregnancy.

Prenatal manifestations of ML-II are variable, and can include late-onset short long bones suggestive of a skeletal dysplasia and IUGR. For Patient 2, CVS was done for 3M syndrome, because of the known family history. Inclusion bodies in the syncytiotrophoblast can be seen as early as 12 weeks' gestation in ML-II.[13] If CVS is done for any reason on fetuses of consanguineous couples, we now consider doing histopathological investigation to identify lysosomal storage disorders[13] if a sufficient sample is obtained. In this case, when short long bones were detected later in pregnancy, the normal CVS result for 3M syndrome shifted the clinical suspicion from a skeletal dysplasia toward a diagnosis of placental dysfunction. This highlights that consanguineous couples can share multiple pathogenic variants in different genes, and are at risk for having offspring affected with more than one inherited condition. Reproductive genetic carrier screening is recommended, but many conditions affecting offspring of consanguineous couples are rare and thus are not included in commercial pan-ethnic carrier screening panels. Despite advances in fetal imaging, prenatal diagnosis of skeletal dysplasias is challenging[12] and the skeletal dysplasia "gene panel" usually does not include lysosomal storage disorders. In both of our patients, the causal variants were loss-of-function, predicted (Patient 1) or proven (Patient 2) to result in no significant residual GlcNAc-phosphotransferase enzyme activity,[4] and previously classified as pathogenic for ML II, and thus would have been readily identifiable with WES. Our experience emphasizes potential advantages in expanding prenatal applications of WES for the identification of rare single gene disorders such as ML-II.[1]

Conflict of Interest

None.

Ethics Statement

Both families provided informed consent for inclusion in this report. Approval from a Research Ethics Board is not required at our institution for publication of a case series.

Acknowledgments

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