Introduction

Fetal proximal bowel obstructions may present with bowel dilatation and polyhydramnios on prenatal ultrasound. Conventionally, if the bowel obstruction appears sonographically isolated with normal fetal chromosomal micro-array analysis (CMA), the prognosis is thought to be positive. [1] We recently encountered one case that challenged this time-tested wisdom.

Abstract

**Background:** Duodenal atresia is one of the intestinal obstructions that can be diagnosed by prenatal ultrasound. It is commonly associated with Down’s syndrome and other congenital anomalies.

**Case Presentation:** We report a case of antenatal diagnosis of duodenal atresia with polyhydramnios in late third trimester. Chromosome microarray (CMA) test of amniotic fluid was normal. Postnatal surgery revealed duodenal atresia, annular pancreas, non-rotation of mid-gut, Ladd’s bands, volvulus, small contracted gallbladder and bilateral intra-abdominal tests. Duodenoduodenostomy and Ladd’s procedure were performed on day one of life. However, the baby developed persistent pulmonary hypertension of newborn (PPHN) after operation, refractory to medical treatment and ventilatory support. Finally, the baby succumbed. Genetic testing showed pathogenic mutation of FOXF1 gene. Postmortem examination of the baby confirmed the diagnosis of alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV).

**Conclusion:** The rare diagnosis of ACDMPV should be considered in neonates with refractory PPHN and bowel pathology. Prenatal diagnosis by targeted sequencing on the FOXF1 gene can be considered in cases with USG findings of bowel distension, when routine CMA fails to reveal a diagnosis. Prenatal and early neonatal diagnosis of ACDMPV would drastically alter the perspective and management for a fetus with seemingly isolated bowel obstruction.

Case Report

Our case was a 26 years old Thai lady who enjoyed good past health. She had normal first-trimester Down syndrome screening and mid-trimester fetal morphology scan. She was referred to us for large-for-date uterine size at 35 week gestation. Ultrasound by our team showed a small-for-date fetus, with prominent stomach bubble and distended duodenum as shown in...
Figure 1. The amniotic fluid index (AFI) was 39cm. Obstruction at duodeno-jejunal junction was suspected. Oral glucose tolerance test (OGTT) was normal. Amnioreduction was performed twice to relieve pressure symptoms and facilitate induction of labour. CMA test showed no copy number gain or loss.

At 37 week, a male baby weighed 1.885kg (<3rd centile) was delivered by emergency lower segment caesarean section (LSCS) for intrapartum fetal distress. Apgar score was 5 at one minute, 8 at five minutes and 10 at ten minutes of life. He was transferred to the neonatal intensive care unit (NICU) for antenatal suspicion of small bowel obstruction.

Physical examination of the baby in NICU found the chest was clear with good air entry. Baby had bilateral undescended testes. Chest X-ray showed no consolidation of lungs. Abdominal X-ray (AXR) showed the Ryle’s tube was in stomach and absence of bowel gas distal to stomach bubble. His oxygen saturation was maintained with 1 liter of oxygen supplement. Oral feeding was not commenced.

The baby underwent laparotomy at 12 hours of life. Intra-operatively found type 1 duodenal atresia located just 1cm distal to pylorus with annular pancreas. There was also complete non-rotation of mid-gut, very narrow root of mesentery associated with Ladd’s bands between the caecum and proximal jejunum, volvulus with twisting of 90 degrees. The spleen was located at a relatively low position on left side of abdomen. Bilateral testes were intra-abdominal near the deep rings. Duodenoduodenostomy and Ladd’s procedure were performed. The operation was uneventful. Baby was transferred back to NICU with mechanical ventilatory support.

However, the baby developed pulmonary hypertension on the same night with increased FiO2 requirement. His condition drastically deteriorated on day 4 of life, with refractory pulmonary hypertension and right heart failure despite high ventilator settings, multiple inropes and nitric oxide therapy. Chest x-ray showed non-specific mild perihilar haziness only and no other lesions. Echocardiogram showed persistent pulmonary hypertension of newborn (PPHN) with no cardiac structural abnormality. Extra-corporeal membrane oxygenation (ECMO) was considered not suitable in view of the low birth weight. Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) was suspected and urgent FOXF1 gene testing was arranged. However, baby developed right tension pneumothorax on day 7 of life and finally succumbed due to respiratory failure.

Genetic test result was available 7 days after the baby succumbed. Direct Sanger sequencing of the two coding exons of FOXF1 gene (Reference sequence: NM_001451.3) showed a heterozygous single base pair deletion variant c.677del. This changed the 226th codon from Glycine to Alanine with subsequent frameshift and premature STOP at the 378th codon [p.(Gly226Alafs*153)] as shown in Figure 2. This confirmed the molecular diagnosis of ACDMPV. Parental testing of this FOXF1 gene pathogenic variant was negative, indicating the mutation found in the affected baby was a de novo event. Postmortem examination of the baby also confirmed the histological diagnosis of ACDMPV. (Please refer to Figure 3 and legend for a more detailed description).

Discussion/Conclusion

FOXF1 gene is located on chromosome 16q24.1, it provides instructions for making the forkhead box F1 (FOXF1) protein, a transcription factor that binds to specific regions of DNA and helps to control the activity of many other genes. It is important in the development of pulmonary mesenchyme, the embryonic tissue from which blood vessels of the lung arise. It is also involved in the development of the gastrointestinal tract [2]. Heterozygous mutation in the FOXF1 gene is known to cause congenital alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) (OMIM #265380), a disorder that primarily takes a toll on the lung and gastrointestinal tract [3]. Extrapulmonary findings are present in 50 to 80% of cases. [4] Organs with a relatively high level of FOXF1 gene expression, for example the gallbladder and urinary tract, explain the associated anomalies of them in some cases of ACDMPV [5]. While point mutations in FOXF1 is associated with bowel malrotation; microdeletions of FOXF1 is associated with hypoplasic left heart syndrome and gastrointestinal atresias, probably due to haploinsufficiency for the neighboring FOXC2 and FOXL1 genes [6].

Majority of the affected infants present with cyanosis and respiratory failure resulting from pulmonary hypertension within 48 hours of birth. ACDMPV and its fatality is well recognized in neonatology. Survival with “patchy ACD” long enough to receive lung transplants is exceptional [7]. Up till now, there are approximately 200 cases of ACDMPV reported. Most cases of ACDMPV were diagnosed by histological examination of lung tissue in autopsy, while some by ante mortem lung biopsy. If histological diagnosis is not feasible or available but the diagnosis of ACDMPV is suspected clinically, clinician can arrange genetic test to detect mutations or deletions in the FOXF1 gene,
which can be found in around 40% of infants with ACDMPV. [4]

Identifying the mutant gene is a strong predictor of poor prognosis. It will help the clinicians to discuss with the parents on the disease course and the decision on withdrawal of invasive procedures (e.g. ECMO, cardiopulmonary resuscitation) as they are deemed futile.

The obstetric community at large is, unfortunately, still in the dark about the entity of ACDMPV. Nevertheless, a report of three cases almost two decades ago had rang the bell for its potential association with fetal bowel obstruction. All three fetuses in this series had USG showing dilated stomach and polyhydramnios in the third trimester of pregnancy. The neonates showed a high index of suspicion of ACDMPV in patient presenting with refractory PPHN and bowel obstruction is important. Timely workup and diagnosis of ACDMPV is crucial to facilitate redirection of care and avoid prolong suffering in patients with this lethal condition.

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References


