MEDDOCS Open Access Publisher

ISSN 2641-6522

Annals of Obstetrics and Gynecology

Open Access | Case Report

The "Trisomy 18" in Isolated Fetal Bowel Obstruction

Sau-lan MOK[1]*; Tsz-kin LO[2]; Yuet-Yee Chee[3]; Rosanna Ming-sum Wong[4]; Yuk-him TAM[5]; Ivan Fai-man Lo[6]; Wai-fu Ng[7]

[1]Associate Consultant, Department of Obstetrics and Gynaecology, Princess Margaret Hospital, HKSAR, China.

[2]Consultant, Department of Obstetrics and Gynaecology, Princess Margaret Hospital, HKSAR, China.

[3]Consultant, Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, HKSAR, China.

[4]Chief of Service, Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, HKSAR, China.

[5]Professor, Department of Surgery, Hong Kong Children's Hospital, HKSAR, China.

[6]Consultant, Clinical Genetic Service, Department of Health, HKSAR, China.

[7]Consultant, Department of Pathology, Hong Kong Children's Hospital, HKSAR, China.

***Corresponding Author(s): Sau-lan MOK**

Associate Consultant, Department of Obstetrics and Gynaecology, Princess Margaret Hospital, HKSAR, China.

Tel: +852-61838236; Email: juliaslomok@yahoo.com.hk & msl233@ha.org.hk

Received: Sep 10, 2023

Accepted: Sep 29, 2023

Published Online: Oct 06, 2023

Journal: Annals of Obstetrics and Gynecology

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

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 testis. 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 alters the perspective and management for a fetus with seemingly isolated bowel obstruction.

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.

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

Cite this article: Sau-lan MOK, Tsz-kin LO, Chee Y-Y, Ming-sum Wong R, Yuk-him T, et al. The "Trisomy 18" in Isolated Fetal Bowel Obstruction. Ann Obstet Gynecol. 2023; 6(2): 1054.

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 facilate 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 inotropes 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) support 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).

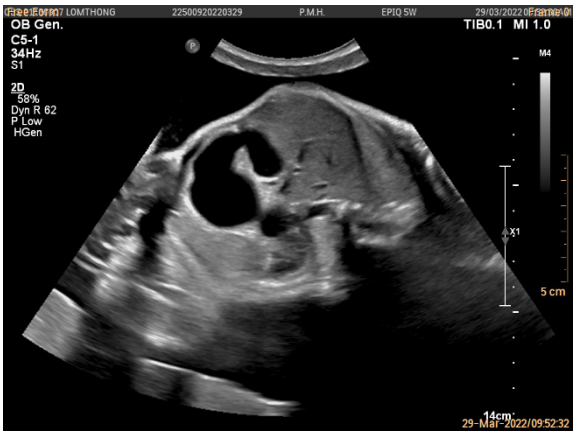

Figure 1: Antenatal USG showing prominent stomach bubble and the distended duodenum

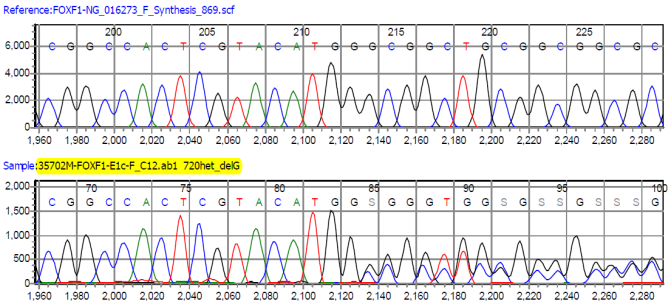

Figure 2: Sequence analysis of *FOXF1.* The baby was heterozygous for a single base pair deletion variant (c.677del; arrow) in *FOXF1*.

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 take 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 hypoplastic 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,

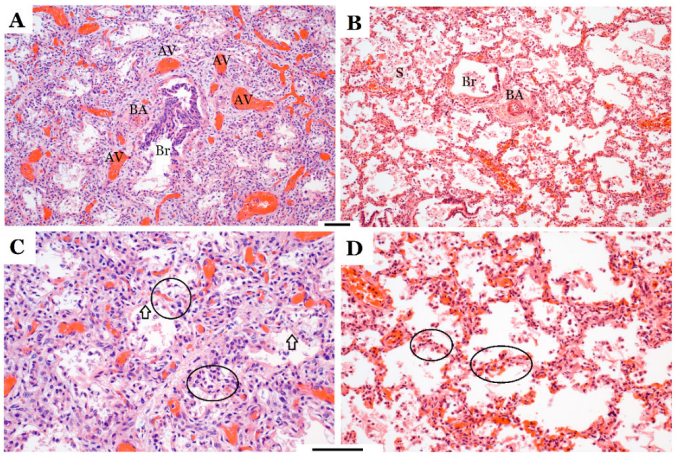

Figure 3: Histopathologic findings of the deceased baby with alveolar capillary dysplasia with misalignment of pulmonary veins Photomicrograph of the lung with control.

A. Case lung under low power showing normal bronchiolar-vascular bundle in the center with alveoli in background. Br indicates lumen of the bronchiole with accompanying bronchiolar artery (BA). There are several abnormal veins (AV) clustering around the bronchiolar-vascular bundle and these are absent in the control lung in B. These veins should normally be confined to the interlobular septa (not included in this photo). The alveoli are poorly formed and with thick alveolar septa.

B. Normal control lung under the same magnification as A. Note the absence of abnormal veins around the bronchiolar-vascular bundle and well-formed alveoli with thin congested alveolar septa. Some aspirated squames (S) in alveolar lumen are noted (neonatal death due to asphyxia, same gestational week as case).

C. Case lung under medium power showing the poorly formed alveoli with thick septa (two septa circled) that have scanty capillary vessels and some larger congested vessels in the center of the thick septa. Thin hyaline membrane (two arrow) in the alveoli is likely related to hyperbaric oxygen therapy.

D. Normal control lung under the same magnification as C showing well-formed alveoli with thin septa and abundant congested capillaries (two septa circled).

Hematoxylin and eosin stain. A and B - original magnification x100. C and D - original magnification x200. Black bar on the lower middle part of each set of photo indicates 100 micrometer length.

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 developed PPHN after birth and finally succumbed. Two cases had histological confirmation of ACDMPV, while the last case did not due to parental refusal so it was diagnosed clinically. Genetic testing was not mentioned but was likely not available then [10]. Although antenatal USG may not be able to diagnose the lung condition, the diagnosis should be considered if there is present with polyhydramnios and other features of fetal GI obstruction.

With the advent of CMA, came prenatal molecular diagnosis of ACDMPV. Two cases have been reported both were caused by micro-deletions. In one case, the fetus had thick nuchal translucency and univentricular congenital heart malformation. Chorionic villi sampling (CVS) was performed and CMA demonstrated a de novo 1.17 Mb deletion in 16q24.1 encompassing FOXF1 gene. The pregnancy was terminated and the diagnosis of ACDMPV with hypoplastic left heart syndrome were confirmed by postmortem examination of the abortus [8]. In another case, CVS was performed for fetal cystic hygroma at 11 weeks of gestation and CMA showed a chromosome 16q24.1 microdeletion, containing the *FOXF1* gene. Subsequently, USG showed the presence of AVSD, bilateral superior vena cavae, a low-normal-sized aortic valve, and suspected bowel atresia. The mother was counseled prenatally about the provisional diagnosis of ACDMPV and its poor prognosis, with a plan to avoid futile invasive therapies. After birth, the infant's respiratory status declined within 24 hours of life despite respiratory support. Comfort care was provided, surgery for small bowel atresia was not performed and the baby died on day two of life [9].

Prenatal diagnosis of ACDMPV, as in the two reported cases, drastically changes the prognosis, counseling, obstetric and neonatal management of a fetus otherwise thought to have salvageable conditions. Antenatal ultrasound cannot detect the abnormalities of microscopic pulmonary vasculature pathognomonic of ACDMPV. However, bowel involvement is telltale even prenatally. With the leaps and bounds in molecular technology, targeted sequencing on the *FOXF1* gene is becoming increasingly handy when routine CMA fails to reveal a diagnosis. Turnaround time for urgent test is around two weeks. (In our case, the turn-around-time was merely 9 days.) The real stumbling stone is awareness of the condition.

In conclusion, ACDMPV related to *FOXF1* mutation is a lethal condition featuring prominently with fetal bowel obstruction on prenatal ultrasound. Compounded by insensitivity of prenatal imaging on fetal lung vasculature, relative inaccessibility of molecular means in the past, and a lack of awareness among the obstetric community, it has very likely been under-reported. Nevertheless, a prenatal diagnosis drastically alters the perspective and management, both obstetric and neonatal, for a fetus with seemingly isolated bowel obstruction. This diagnosis is now made handily available by modern molecular technology. A "trisomy 18" in fetal bowel obstruction, it is time it came to light long before taking further tolls.

Postnatally, 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.

We do not receive any financial support or funding.

Acknowledgments: Nil

References

1. Choudhry MS, Rahman N, Boyd P, Lakhoo K. Duodenal atresia: associated anomalies, prenatal diagnosis and outcome. Pediatr Surg Int. 2009; 25: 727–730.

2. "FOXF1 gene: MedlinePlus Genetics" [Cited 2022 Jun] Available from: https://medlineplus.gov/genetics/gene/foxf1/

3. McKusick VA. Online Mendelian Inheritance in Man (OMIM). Baltimore. MD: The Johns Hopkins University. 2020.

4. Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. Am J Respir Crit Care Med. 2011; 184: 172-9.

5. FOXF1 gene expression. National Center for Biotechnology Information. Available from: https://www.ncbi.nlm.nih.gov/gene/2294/?report=expression

6. Stankiewicz P, Sen P, Bhatt SS, Storer M, Xia Z, Bejjani BA, et al. Genomic and genic deletions of the FOX gene cluster on 16q24.1 and inactivating mutations of FOXF1 cause alveolar capillary dysplasia and other malformations. Am J Hum Genet. 2009; 84: 780–791.

7. Childs Interstitial Lung Disease Foundation. https://child-foundation.org/?s=ACD

8. Puisney-Dakhli C, Gubana F, Petit F, Bouchghoul H, Gautier V, Martinovic J, et al. Early prenatal diagnosis of alveolar capillary dysplasia with misalignment of pulmonary veins due to a 16q24.1 deletion. Am J Med Genet Part A. 2021; 185A: 1494–1497.

9. Prothro SL, Plosa E, Markham M, Szafranski P, Stankiewicz P, Killen SA. Prenatal Diagnosis of Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins. J Pediatr. 2016; 170: 317-8.

10. Usui N, Kamiyama M, Kamata S, Yoneda A, Tazuke Y, Fukuzawa M. A Novel Association of Alveolar Capillary Dysplasia and Duodenal Atresia with Paradoxical Dilatation of the Duodenum. Journal of pediatric surgery. 2004; 39: 1808-11.