Achondroplasia and Biliary Atresia: A Rare Association and Review of Literature

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Abstract

Keywords

- biliary atresia
- achondroplasia
- skeletal dysplasia
- fibroblast growth factors
- fibroblast growth factor 21
- fibroblast growth factor 23
- fibroblast growth factor receptor 3
- glypican 1

Achondroplasia (ACH) occurs in most cases as de novo mutations of the gene-encoding fibroblast growth factor receptor 3 (FGFR3). Biliary atresia (BA) is a progressive neonatal inflammatory and fibro-obliterative cholangiopathy affecting the extra- and intrahepatic biliary tree to varying degrees, and it results in obstruction to bile flow and cholestatic jaundice in neonates. BA is thought to be a multifactorial disease, genome association studies have shown abnormalities in susceptibility genes, and levels of fibroblast growth factor 21 (FGF21) and fibroblast growth factor 23 (FGF23) have been noted to be increased. These two conditions occurring in the same patient has never been reported before.

Introduction

The most common form of skeletal dysplasia causing short stature is achondroplasia (ACH), affecting 1 per 10,000 to 30,000 live births.¹ Point mutations in the gene-encoding fibroblast growth factor receptor 3 (FGFR3) are responsible for 95% of patients with ACH, and more than 80% of these are de novo mutations.¹

Biliary atresia (BA) is a progressive neonatal inflammatory fibro-obliterative cholangiopathy primarily affecting the extrahepatic biliary duct, resulting in obstruction to bile flow and cholestatic jaundice in neonates.² The incidence of BA is highest among Asian populations, occurring in 1.46 per 10,000 live births in Taiwan, compared with 0.65 to 0.85 per 10,000 live births in the United States and northern Europe.² The etiology of BA was thought to be multifactorial and still unclear. There is some evidence pointing to viral, toxic, and multiple genetic factors. Some studies indicate an

association with factors such as laterality genes, epigenetic regulation, or microRNA function.^{2,3}

These two rare conditions occurring in the same patient have never been reported. We report a patient diagnosed with FGFR3 mutation and BA in the neonatal period with the challenges in diagnosis, management, and to look at potential links in pathogenesis.

Case Summary

A female infant was born at 37 weeks' gestational age to a 42-year-old, gravida 6, Hispanic woman whose prenatal screening blood tests were normal. The woman had five healthy children, and there was no relevant family history or history of consanguinity. Pregnancy was complicated by advanced maternal age, polyhydramnios, pregnancy-induced hypertension, prenatally detected bilateral renal pelviectasis, and fetal skeletal dysplasia. The baby's birth weight was 2,865 g

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Fig. 1 Plain radiograph demonstrating the proximal long bone shortening.

(35th percentile), length 44 cm (5th percentile), and head circumference was 36 cm (97th percentile). At birth facial dysmorphism with frontal bossing, depressed nasal bridge, and disproportionately large head with widely open anterior fontanel was noted. She had a small bell-shaped chest, short proximal limbs and trident-shaped hands, and shortened extremities with significant tapering from the base to the tip. The rest of the examination was normal apart from slightly brisk ankle and knee tendon reflexes. Radiographs revealed a bell-shaped thorax with flared rib ends, normal cardiac silhouette with relatively small lungs, and shortening of the femora and the humeri bilaterally (►Fig. 1).

The patient had mild respiratory distress and a persistent oxygen requirement. At 3 days the patient's total bilirubin was 216 $\mu\text{mol/L}$ (12.6 mg/dL) and direct bilirubin was 21 $\mu\text{mol/L}$ (1.2 mg/dL), and at 6 days of age, total bilirubin was 160 $\mu\text{mol/L}$ (9.4 mg/dL) and direct bilirubin rose to 46 $\mu\text{mol/L}$ (2.7 mg/dL). She had a normal abdominal ultrasound apart from lack of visualization of gallbladder. Cholescintigraphy on day 15 showed

Fig. 3 Cholangiogram shows absence of contrast in biliary tract or in the bowel.

retention of tracer in liver but none in the gallbladder, extrahepatic biliary ducts, or bowel (►Fig. 2). A liver biopsy and cholangiogram on day 21 confirmed the diagnosis of BA and bridging fibrosis of the liver (►Fig. 3). After portoenterostomy procedure on day 25 of life, she had good tolerance to enteral feeds decrease in total bilirubin to 5 $\mu\text{mol/L}$ (0.3 mg/dL) and direct bilirubin to 3 $\mu\text{mol/L}$ (0.2 mg/dL) and normal liver function. Associated anomalies detected included a secundum atrial septal defect (ASD) and a mild hydronephrosis on the left. Imaging of the head and neck revealed small foramen magnum and no evidence of hydrocephalus or cervical spine instability. Genetic testing using polymerase chain reaction (PCR) and fluorescent hybridization probes for c.1138G > A and c.1138G > C were done (ARUP, Salt Lake, Utah, United States). It was positive for one copy of the G1138A mutation—c.1138G > A (p.Gly380Arg) in the *FGFR3* gene, consistent with a diagnosis of ACH. After discharge home with nasal cannula oxygen at 0.2 L/min and G tube feeds, the patient's last follow-up at 3.5 years of age showed a relatively normal native liver function and normal development apart from short stature.

Fig. 2 Mebrofenin cholescintigraphy (BrIDA scan) with no radiotracer activity in gallbladder, extrahepatic biliary ducts, or in the bowel.

Discussion

Fibroblast growth factors (FGFs) are a family of more than 20 polypeptides. These proteins act as pluripotent growth factors, having roles in mitogenesis, angiogenesis, wound healing, embryonic development, endocrine signaling pathways, neural induction, and development.^{4,5} The FGFs can activate four receptor subtypes: FGFR1, FGFR2, FGFR3, and FGFR4, which can then trigger a cascade of actions within the cell. The *FGFR3* gene regulates FGFR3.^{4,5}

The genetic cause of ACH, discovered in 1994, and two mutations in the *FGFR3* gene cause most of the cases—c.1138G > A (p.Gly380Arg) in 98% and c.1138G > C (p.Gly380Arg) in 1%.^{1,6} These activating mutations exaggerate signaling of the receptor tyrosine kinase FGFR3.^{1,6} In the growth plate, FGFR3 is a negative regulator of chondrocyte proliferation and differentiation. As FGFR3-related skeletal dysplasias are caused by growth attenuation of the cartilage, chondrocytes appear to be unique in their response to FGFR3 activation. Many clinical conditions are caused by similar mutations in FGFR3, including skeletal syndromes (hypochondroplasia and thanatophoric dysplasia), skin disorders (epidermal nevi, seborrheic keratosis, and acanthosis nigricans), and malignancy (multiple myeloma, prostate and bladder carcinoma, seminoma).^{6,7} However, the reasons why FGFR3 inhibits chondrocyte growth while causing excessive cellular proliferation in cancer are not clear.^{6,7} There are reports of unusual association of Down's syndrome with ACH.⁸

The etiology of BA is thought to be multifactorial but is still unclear, and there appears to be two subgroups: an embryonic type with congenital complete absence of a patent biliary system and a perinatal form that is much more common.⁹ In about 5% of patients, BA is associated with laterality features, suggesting a genetic cause to the disease. The association of structural anomalies in BA is reported between 12 and 20%.^{10–12} Serious cardiac malformations including hypoplastic left heart syndrome, malrotation, and heterotaxy syndromes have been reported.^{10–13} Maegawa et al reported a unique association of BA with duodenal atresia (DA), microtia facial, and thyroid anomalies.¹⁴ Another constellation of features with splenic malformation called BA with structural malformation (BASM) has been well documented.^{3,15,16} Martinez-Frias syndrome (MFS) is a rare, and likely autosomally recessive, disorder with DA, esophageal atresia, BA, hypoplastic pancreas, and intrauterine growth retardation.^{17–19} In a cytogenetic study of BA, only 2 of 35 patients were found to be abnormal, one of whom had 2q37.3 deletion and the other had 47 XXY.3 There are reports of Kabuki's syndrome, in which short stature is prominent feature, associated with BA.^{20–22} A familial case of an autosomal dominant disorder, with hypoparathyroidism, sensorineural deafness, and renal dysplasia—HDR syndrome complicated by BA due to a heterozygous *GATA3* gene mutation (c.736delGinsAT)—was recently reported.²³ There has been an explosion of DNA and gene sequencing studies that seem to point to a genetic susceptibility in BA. Genome association studies show that there are abnormalities in different susceptibility genes, which have roles in organogenesis, like glypican 1 (GPC1),

adenosine diphosphate ribosylation factor 6 (ARF6), and adducin 3 (ADD3).^{24–28} BA has been associated with abnormal notch signaling, missense mutations, or nodal cofactor cryptic (CFC1) mutations.^{2,15,24,27,28} A recent report of two cases of BA showed an association of elevated serum levels FGF23 and hypophosphatemia, which returned to normal levels after liver transplant.²⁹ Levels of FGF21 and FGF21 messenger RNA (mRNA) have been shown to be elevated in infants with BA.³⁰ MFS has been linked to mutation of *RFX6* gene.³¹ Early expression of connective tissue growth factor (CTGF) and transforming growth factor- β_1 (TGF- β_1) in biliary cells and hypomethylation of DNA have been implicated in the pathogenesis of BA.^{32,33} We report the only case with this unique association of BA, ACH, and ostium secundum ASD. A complete review of literature failed to identify a similar constellation of findings, and we could not find any possible common etiologic explanations. In our patient the possibility of maternal exposure to teratogens was considered and ruled out as there was no maternal history. She also had no history of diabetes mellitus (DM) and gestational DM was ruled out. The interesting associated findings of increased FGF21 and FGF23 in BA and the FGFR3 mutation in ACH and the rarity of the coexistence of these two conditions pose some interesting questions. Further studies with whole exome analysis or whole genome sequencing techniques may reveal causative and modifying genes relevant to these patients with multiple anomalies and may help with better predictive and therapeutic tools.

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