

A case of neonatal association of cystic fibrosis with cholestatic jaundice and intestinal hypoganglionosis

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Introduction

Cystic fibrosis (CF) is a multisystem autosomal recessive disorder presenting as intestinal obstruction, pancreatic insufficiency, and recurrent sinopulmonary infections¹. In neonates, the presentation is mostly as delayed passage of meconium or meconium ileus while the rest remain undiagnosed till later infancy². Cholestatic jaundice and abnormal intestinal ganglionosis are very rare associations of CF presenting in the neonatal age group. Colonic hypoganglionosis, a variant of Hirschsprung disease, has not been reported yet as an association with CF. We report an unusual case of a neonate with meconium ileus diagnosed as CF along with neonatal cholestasis and colonic hypoganglionosis.

Case report

A 17-day-old full-term male baby weighing 2.8 kg, was born to a 30-year-old (G2P1L1) mother via caesarean section because of leaking per vagina for 12 hours. The baby was born of a non-consanguineous marriage by spontaneous conception. The anomaly scan was normal, but there was oligohydramnios with oedematous fetal bowel with high echogenicity, seen on the 3rd-trimester ultrasound. Baby cried immediately after birth with Apgar scores of 7 and 9 at 1 and 5 minutes respectively. Anthropometric parameters of the baby were between the 50th-90th centile and no dysmorphisms were noted. The orogastric tube,

passed through the rectum up to 5 cm, showed no meconium staining of the tube. The baby developed abdominal distension with bilious vomiting on the 1st day of life along with non-passage of meconium.

On examination, the abdomen was tense, distended, and resonant on percussion with feeble bowel sounds. No hepatosplenomegaly was noted. X-ray erect abdomen (Figure 1) was suggestive of multiple gas-filled bowel loops and a massively dilated transverse bowel loop.



Figure 1: Multiple air-filled bowel loops with massively dilated transverse colon

Ultrasound scan of the abdomen was suggestive of dilated bowel loops with small bowel obstruction. The baby had unconjugated hyperbilirubinaemia on day one requiring double surface phototherapy. The septic screen was negative and liver function tests were normal. On laparotomy, dilated bowel loops till 50 cm proximal to the ileo-caecal junction, filled with thick and tenacious meconium, were seen with microcolon, suggestive of meconium ileus (Figures 2 and 3).

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Figure 2: Meconium filled dilated small bowel with microcolon



Figure 3: Thick, tenacious meconium evacuated out of bowel which had led to ileus

Meconium was irrigated out of the bowel and a double barrel ileostomy was done. An intraoperative biopsy was taken to rule out Hirschsprung disease. There were bilious aspirates from the nasogastric tube for 48 hours after which they gradually decreased. Ileostomy started functioning by the 3rd postoperative day, following which oral feeds were initiated. The intestinal biopsy taken at the transition zone and ileum was suggestive of colonic hypoganglionosis while the rectal biopsy showed normal ganglion cells.

The baby was noted to be icteric for which liver function tests were done which were suggestive of transaminitis, raised alkaline phosphatase with conjugated hyperbilirubinemia without hypoalbuminemia or coagulopathy. The liver ultrasound examination showed normal echotexture of liver with visible gall bladder and no signs of extrahepatic biliary obstruction. Baby achieved full enteral feed by the 5th day of life with ileostomy output of 10-15ml/kg/day. Postoperative antibiotics were omitted with the advent of sterile blood cultures. The transaminitis kept on increasing although bilirubin started showing a declining trend (Table 1).

Table 1: Serial values of transaminases and bilirubin level

Days of life	AST (U/L)	ALT (U/L)	ALP (U/L)	Total SB (mg/dL)	Conjugated SB (mg/dL)
Day 2	11	39	11	17.2	3.1
Day 5	43	80	43	15.1	11.5
Day 6	53	87	53	18	13.3
Day 8	62	92	185	17.5	13.3
Day 11	74	110	240	9.9	3.7

Urine examination showed positive bile salts and bile pigments with absent reducing sugars. The thyroid screen was within normal limits. There was intermittent bile obstruction as suggested by occasional clay-coloured stools. The suspected intrahepatic cholestasis was managed conservatively after a gastroenterologist consultation. CF screening with immunoreactive trypsinogen was positive. The sweat chloride testing done at 6 weeks and 8 weeks postnatal age was 72 mmol/L and 84 mmol/L respectively which is confirmatory for CF. Genetic study could not be done due to financial constraints. The baby was discharged successfully on day 20 on breastfeeding with a functioning ileostomy.

Discussion

CF occurs due to mutation at chromosome 7q31.2 in the gene, which codes for a cell membrane protein termed cystic fibrosis transmembrane conductance regulator (CFTR)². In neonates, gastrointestinal involvement with pancreatic insufficiency is seen

whereas pulmonary involvement occurs after six months of age³. Meconium ileus is seen in 90% of neonates with CF and was the presenting feature in this case⁴.

Antenatal diagnosis can be suspected with the presence of ultrasonographic findings of dilated bowel, echogenic foci in intestines, and non-visualization of gall bladder but these signs have poor specificity and sensitivity for diagnosis. In our case, echogenic bowel and oedematous bowel loops were present antenatally.

A high degree of clinical suspicion is necessary for early postnatal diagnosis. For confirmed diagnosis of CF according to Consensus Guidelines from the Cystic Fibrosis Foundation, one component from each column should be present as represented in Table 2⁶.

Table 2: Diagnostic criteria for cystic fibrosis (CF)

Column 1	Column 2
Clinical features of CF	Elevated sweat chloride concentration
Positive newborn screening	Two CFTR gene mutations known to cause CF on separate alleles
History of CF in sibling	Abnormalities in nasal potential difference testing that are typical for CF

The advent of newborn screening (NBS) has reduced the median age of diagnosis from 6 months to <1 month⁶. Chloride levels in sweat >60 mmol/L are regarded as confirmatory, 30 to 59 mmol/L as intermediate and 29 mmol/L or less as negative in a neonate.

CF, being a multisystem disorder, can have a wide array of clinical symptoms like persistent airway infections, pancreatic insufficiency and failure to thrive. As an uncommon association, neonates may have prolonged direct hyperbilirubinaemia due to obstruction of the extra or intrahepatic biliary duct⁶. In our case, a similar observation of direct hyperbilirubinaemia was found which was intrahepatic in origin possibly due to the plugging of intrahepatic bile ducts by inspissated bile.

The case reported by Li L, *et al*⁸ also had the association of cholestasis with CF and further literature review identified 25 cholestatic cases related to (CF) out of which delayed meconium passage was found in 5 and meconium ileus in 6 cases. Similarly, Heidendaal JF, *et al*⁹ reported a case of a preterm neonate with only conjugated hyperbilirubinemia and transaminitis as presenting symptoms which were later found to be CF as a result of inspissated bile syndrome.

Association of Hirschsprung disease with CF is extremely rare and only a few cases have been reported in the literature to date. Hen J, *et al*¹⁰ first described the case of meconium plug syndrome associated with CF and Hirschsprung disease in 1980. The other was reported by Esposito C, *et al*¹¹ showing an association of CF with Hirschsprung disease which proved to be fatal for the baby.

Intestinal hypoganglionosis, a variant of Hirschsprung disease, is an enteric neuropathy with a decrease in ganglion cells with the presence of ganglion cells in rectal suction biopsies. Its diagnosis requires biopsies from different parts of the intestine showing a paucity of ganglionic cells in some segments and normal innervation in others. Our case had similar findings of hypoganglionosis in the transition area with normal rectal innervation. It can have long-term complications like chronic constipation or pseudo-obstruction in the intestine and diagnosis can be easily missed if only rectal biopsies are taken. Hence this case was reported to create awareness about this entity so that proper biopsy samples can be taken in suspected cases.

Conclusion

CF is a progressive, multiorgan disease with a varied clinical spectrum. Delayed passage of meconium, meconium ileus, and conjugated hyperbilirubinemia should raise suspicion of CF in the neonatal period. Rare associations like intestinal dysganglionosis, as seen in this case, should be kept in mind. Because of the complexity of CF, a multidisciplinary team management approach is key to reduce mortality and morbidity in neonates.

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