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Research Article

A Case of Neonatal Diabetes and Multiple Congenital Anomalies: Variant of Mitchell-riley/Martinez-frias Syndrome

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Abstract

Neonatal diabetes along with congenital anomalies like duodenal atresia, tracheoesophageal fistula, intra uterine growth retardation, extrahepatic biliary obstruction and hypoplasia of pancreas is a very rare occurrence with evidence linking it to RFX6 gene mutation. The presence in newborn babies necessitates a detailed genetic evaluation and multidisciplinary management. Here, we present a preterm baby with persistent neonatal hyperglycemia and gastrointestinal anomalies similar to cases associated with Mitchel-riley/Martinez-frias syndrome.

Keywords: Neonatal diabetes; Congenital anomalies; RFX6 mutation; Mitchel riley/martinez frias syndrome.

Introduction

Neonatal diabetes is an uncommon presentation in newborn babies.

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Its association with other major congenital anomalies is seldom seen and there are very few such cases reported in the literature. Here, we present a preterm baby with neonatal diabetes along with duodenal atresia, tracheoesophageal fistula and neonatal cholestasis. The constellation of congenital defects in this case were considered to be similar to earlier reported cases of Mitchell-riley/Martinez-frias syndrome, which is an extremely rare condition. The genetic analysis confirmed the mutation of RFX6 gene further corroborating the association with this syndrome.

Case

A preterm baby girl was born at 36 weeks of gestation by cesarean section to a 30 year old primigravida mother. The baby girl's birth weight was 1.1 kg, suggestive of severe intrauterine growth retardation. The infant was the product of a consanguineous marriage. There is no family history of diabetes, and the mother's prenatal glucose profile was normal. The placenta had calcifications, there was polyhydramnios, and the prenatal scan revealed a dilated colon that may indicate duodenal atresia.

The baby required resuscitation at birth and was kept on ventilator support. The patient was also anemic at birth and received a unit of blood transfusion. X-ray abdomen showed a dilated stomach with absent distal bowel gas (Figure 1). An exploratory laparotomy confirmed the presence of an atretic segment in the first part of the duodenum along with multiple diverticula in the jejunum (Figure 2). The patient underwent a surgical repair during which distal patency of the bowel was ascertained and gastroduodenostomy performed. Another finding which was evident intra-operative was the ballooning of stomach with every ventilation, that led to a suspicion of trachea-esophageal fistula(TEF) without atresia.

The patient experienced continuous hyperglycemia on the second day of life, with a range of 29 to 33 mmol/L. And also, had very low insulin levels, <0.39 mU/L (laboratory reference: 2.6-37.6 mU/L) and <0.07 ng/mL (laboratory reference: 0.48-5.05 ng/mL). After the patient's condition was determined to be neonatal diabetes, a continuous intravenous insulin infusion was started, gradually increased to maintain ideal blood glucose levels. Investigations into the cause of neonatal diabetes were conducted in full. The patient started on total parenteral nutrition and gained weight.

Since there was persistent gastric distention which required almost continuous aspiration with minimal air in distal bowel (Figure 3), baby was taken for laryngoscopy and thoracotomy on post-operative day 10. Laryngoscopy was done with video laryngoscope to visualize any laryngotracheal cleft which was not found. A wide trachea-esophageal fistula was noted 1 cm above the carina, with pouch like dilatation of upper esophagus. The fistula was divided and repaired.

Post operatively there was no further gastric distention requiring persistent aspiration but there was prominent gastric shadow with no distal air. The baby was taken again for exploration laparotomy in view of missed distal atresia and was noted to have jejunal

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atresia 15 cm distal to the gastroduodenostomy repair. Jejunal atresia was repaired, and a feeding gastrostomy was done. Gastrostomy feeding was started, and the baby's insulin demand decreased but a week later the patient developed diarrhea and progressive cholestasis with acholic stools. There was failure to thrive with progressive weight loss and increasing obstructive jaundice. The results of the patient's liver function tests pointed to extrahepatic cholestasis. The abdominal ultrasound revealed a small sized cystic structure at the region of gallbladder bed with no contraction after feeding. The HIDA scan was planned for further evaluation, but the baby developed sepsis and the study was deferred. The diagnosis of Mitchell-riley/Martinez-frias syndrome was considered after taking the clinical course into account. Targeted next generation sequencing was used for genetic testing to identify a homozygous frameshift mutation on exon 9, c.854_855dup, p.(Glu286Lysfs*59), in the regulatory factor X6 (RFX6) gene. At 3 months, the patient died from severe Gram positive sepsis.

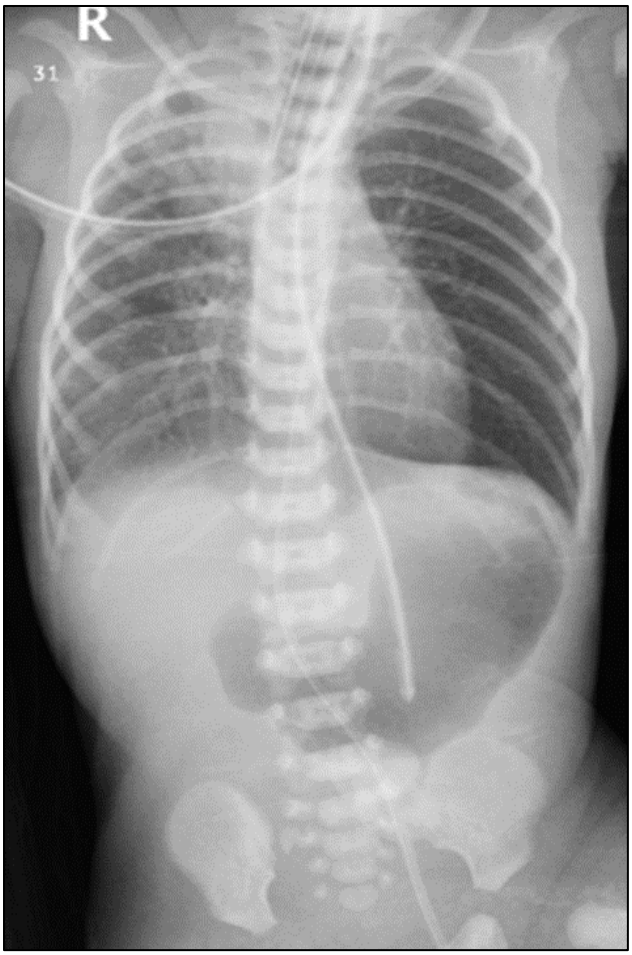

Figure 1: X-ray abdomen on day 1 of life.

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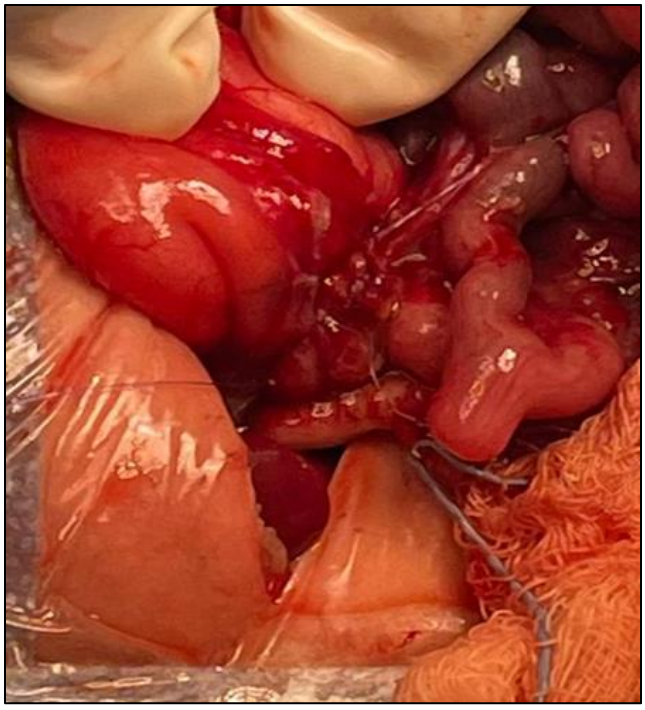

Figure 2: Intra-op-duodenal atresia with jejunal diverticulum (1st surgery day 2 of life).

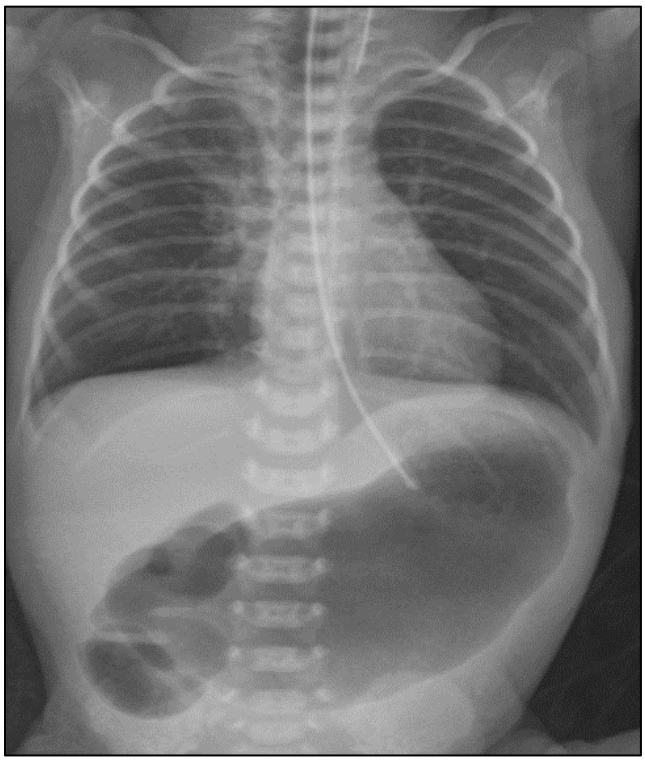

Figure 3: Day 15 of life. Post gastroduodenostomy and TEF repair-persistent gastric distention with paucity of distal gas.

Discussion

In this case the baby had multiple congenital anomalies along with neonatal diabetes which were managed by a multidisciplinary team. Neonatal diabetes management proved to be challenging with frequent blood glucose monitoring and continuous insulin infusion. Around half the cases of permanent neonatal diabetes mellitus show a gene mutation which usually affects pancreas beta cell development and function [1]. The most frequent gene with identified mutations is KCNJ11 and to a lesser extent GCK, ABCC8, and HNF1β [1]. Martinez Frias syndrome is a rare condition characterized by tracheoesophageal fistula, intra uterine growth retardation, duodenal atresia, extrahepatic biliary obstruction and hypoplasia of pancreas with neonatal diabetes [2,3]. It is inherited in an autosomal recessive manner and has evidence linking it to RFX6 gene mutation [4].

RFX6 gene is involved in the development of the gut and pancreatic tissue. There are studies showing the involvement of this gene in the differentiation of islet cells and regulation of transcription factors involved in beta cell function thereby affecting insulin production [4]. Mitchell-riley syndrome is considered to be an association of a particular phenotype of Martinez-frias syndrome, and it was suggested that both represent an RFX6 malformation complex [5,6]. The expression of RFX6 gene starts early in embryonic development throughout the anterior endoderm and later on is confined to the gut and pancreas endocrine cells [1,7]. This gene's mutations result in decreased secretion and manufacture of the glucose-dependent insulinotropic polypeptide (GIP) by intestinal cells, which lowers insulin responsiveness [7]. It is a transcriptional activator of the expression of the insulin gene (INS) and is necessary for the regular activation of calcium channels in human beta-cells, which triggers the release of insulin when depolarization occurs [8]. There are several mutations occurring in the RFX6 gene that are associated with neonatal diabetes and other congenital anomalies especially of the gastrointestinal system [8-13].

There is a case reported by Concepcion JP, et al., [9] where a baby with neonatal diabetes, gallbladder agenesis, duodenal atresia and intestinal malrotation was associated with RFX6 gene mutation [9]. Another recent case of neonatal diabetes, duodenal atresia and progressive neonatal cholestasis reported from the middle east showed a similar mutation [14]. A study by Mitchell, et al., [10] described the association between neonatal diabetes and intestinal atresia. No conclusive evidence of genetic mutations could be obtained in this study [10]. The underlying pancreatic anomalies in this syndrome could be isolated anatomical defects like hypoplastic or annular pancreas or combination of exocrine and endocrine deficiencies. In the majority of cases, there is an early presentation of neonatal diabetes in the first few days of life and there is both an anatomical defect as well as both pancreatic and endocrine pancreatic dysfunction as noted in this case [8,9,10,13]. There was a report which described two novel RFX6 variants in siblings with Mitchell-riley syndrome with late diabetes onset and heterotopic gastric mucosa [15]. In one of the reports describes two siblings with milder

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phenotypes and with later diabetes onset, at 3 and 6 years [16]. Duodenal atresia is the most common gastrointestinal anomaly seen in these patients [9,14]. This case had trachea oesophageal fistula in addition to duodenal atresia which were surgically corrected. In some patients like in this case, severe anemia was present in the early neonatal period [5,6,12]. According to Skopkova, et al., [15] anemia may be caused by gastric mucosa heterotopy, which can lead to bleeding and inflammation of the gut mucosa. The clinical management of these patients can often be difficult owing to the presence of neonatal diabetes and hepatic dysfunction in addition to the presence of gastrointestinal anomalies necessitating complex surgical intervention. To maintain appropriate glycemic control, and nutritional adjustments along with pancreatic enzyme supplementation for adequate growth, is a big challenge for clinicians.

Conclusion

The presence of neonatal diabetes along with intestinal atresia and progressive cholestasis should raise the suspicion of Mitchell-riley/Martinez-frias syndrome. Owing to the increased morbidity and mortality in these children, prompt genetic evaluation, especially the associated mutation in RFX6 gene and early detection is essential to establish a diagnosis and for appropriate counselling of the family.

There is a need for further studies exploring the linkage of gene mutations specifically that of RFX6 and its association with congenital anomalies involving the gastrointestinal system.

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