Clinical Characterisation of a novel RFX6 mutation - a rare cause of neonatal diabetes syndrome

Moira Cheung; Simon Chapman; Katie Hunt; Erin Makin; Ann Hickey; Jonathan Hind; Sian Ellard;
Charles Buchanan; Ritika Kapoor

King’s College Hospital NHS Foundation Trust

BACKGROUND

Mitchell Riley syndrome is a rare syndrome caused by mutations in the RFX6 gene, a winged helix transcription factor that is expressed in the developing pancreas and in the gut endoderm.

Clinical Features:
Neonatal diabetes
Intestinal atresia
Pancreatic abnormalities
Biliary hypoplasia

Previous eight case reports highlight poor outcomes with usually a fatal course in infancy.

CASE PRESENTATION

Twin 2 of a dichorionic diamniotic IVF pregnancy was antenatally diagnosed with duodenal atresia. On day 2 of life, at planned repair of this defect, she was noted to have an annular pancreas and absent gallbladder (figure 1). Preoperatively, pigmented stool and bile were noted, but postoperatively she became acholic with rising conjugated hyperbilirubinaemia. Subsequent investigation revealed a patent but hypoplastic biliary tree with absence of gallbladder (figure 2).

She was also diagnosed with neonatal diabetes and difficult to control initial blood glucose levels. Feed intolerance and poor weight gain were also problematic, complicated by stricture formation at the site of the duodenal atresia repair. Pancreatic exocrine insufficiency was excluded. Surgical intervention helped to improve feed tolerance but she remains PN-dependent due to presence of malabsorptive diarrhoea to achieve adequate nutrition.

Currently, aged 1 year, conjugated hyperbilirubinaemia has resolved (figure 3), weight gain is improving, and neurodevelopment is appropriate (figure 4). Diabetes is well controlled with insulin pump therapy (HbA1C of 6.3%).

REFERENCES

Taieb et al (2011) RFX6 is needed for the development and maintenance of the beta cell phenotype. Islets 2:291-293.

GENETICS

Genetic analysis identified a novel homozygous intronic mutation, c. 1556-40T>G in RFX6. This mutation is predicted to create a cryptic splice acceptor site in intron 14 and cause aberrant splicing.

CONCLUSIONS

Mutations in RFX6 are a rare cause of neonatal diabetes associated with poor prognosis. Death within 6 months of life has been reported in 5/8 cases reported so far, mostly due to end stage liver disease and multi-organ failure. This report describes the clinical characteristics of a new case due to a novel homozygous splice site mutation in RFX6. It also illustrates that careful management of the critical phase in early infancy may be followed by a relatively favourable outcome than previously reported.