A case of neonatal diabetes and pancreatic hypoplasia (Wolcott-Rallison syndrome)

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Introduction and objectives

Neonatal diabetes mellitus (NDM) is a rare form of insulin-dependent monogenic diabetes mellitus (1/400,000 live births) diagnosed in the first six months of life. It can be either transient (TNDM) or permanent (PNDM). A cause of PNDM is Wolcott-Rallison syndrome (WRS). It is a rare autosomal recessive disorder characterized by the association of permanent neonatal or early-infancy insulin-dependent diabetes, multiple epiphyseal dysplasia, growth retardation, and other variable multisystem clinical manifestations. Typically, diabetes occurs before six months of age, and skeletal dysplasia is diagnosed within the first year or two of life. Hepatic dysfunction has been reported in 60% of patients. WRS is caused by recessive loss of function mutations in the EIF2AK3 gene.

We describe a male infant, 2.5 months old with WRS, presented with PNDM and pancreatic hypoplasia.

Methods

The infant was admitted via the Paediatric Emergency Department with a two-week history of reduced feeding, irritability, failure to thrive and loose stools 6-10 times/day. He was the first child of healthy, unrelated parents, born at 40+3/40 by emergency caesarean section, IUGR, birth weight 2300gr. Clinically, he was alert, pale, with mild dehydration, vital signs normal. Biochemistry showed hyperglycaemia without ketoacidosis, blood glucose 919 mg/dl (51mmol/l), Na+ 121 mmol/L (NR 135-145 mmol/L), K+ 5.6 mmol/l NR 3.5-5.1 mmol/L, pH 7.418, HCO3 25.3 mmol/l, BE 1.3 mmol/l, HbA1c 13.6% (125.1mmol/mol) (NR 4-6, 20.2-42.1), C-peptide 0.449 ng/ml/NR 1.1-4.4), serum amylase 15 U/L (NR 28-100) and serum lipase 4 U/l (NR 13-60). He was treated with intravenous fluids and insulin, then with subcutaneous insulin. Diarrhoea improved gradually, and he started gaining weight and had normal stool on day 8. Subsequently, he started on CSII with synchronous continuous glucose monitoring (CGM). His development is normal for age, growth <3rd percentile, latest HbA1c is 8.1% (65mmol/mol) (Fig 1 & 2).

Results and Conclusions

Antibodies to glutamic acid decarboxylase (anti-GAD) 0.1 (<10U/ml) and insulin (IA2) 8.7 (<10U/ml) were negative, pancreatic islet cell antibodies (ICA) marginally positive 1.6 U/ml (>1.05 U/ml positive). Faecal elastase was detected at very low levels (<15 grams/gr of faeces, NR >200) on two occasions. Series of abdominal ultrasounds showed a hypoplastic pancreas for age, confirmed by abdominal MRI. Genetic testing revealed that the patient is compound heterozygous for an EIF2AK3 partial gene deletion and a novel missense variant, p.(Cys215Arg), result is consistent with a genetic diagnosis of WRS syndrome. Both parents are carriers of WRS, mother is heterozygous for the EIF2AK3 partial gene deletion variant, c.(2820+1_2821-1166)del and father is heterozygous for the EIF2AK3 missense variant, p.(Cys215Arg). Both variants are predicted to be likely pathogenic. The EIF2AK3 gene encodes a protein called pancreatic PKR-like endoplasmic reticulum kinase (PERK), which plays a key role in detecting and initiating the cellular response to endoplasmic reticulum stress. Failure of appropriate PERK response results in accumulation of misfolded proteins, which leads to cell damage and apoptosis (fig 3).

Genetic counselling and antenatal diagnosis is recommended for parents of a WRS patient with confirmed EIF2AK3 mutation. Close therapeutic monitoring of diabetes and treatment with an insulin pump are recommended because of the risk of acute episodes of hypoglycaemia and ketoacidosis. Interventions under general anaesthesia increase the risk of acute aggravation, because of the toxicity of anaesthetics, and should be avoided. Prognosis is poor and most patients die at a young age. Intervention strategies targeting ER dysfunction provide hope for future therapy and prevention.

References/Bibliography

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