Diazoxide Responsive Congenital Hyperinsulinism in a Patient with Dual Genetic Aetiology (*HNF4A* and *ABCC8* mutation)

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Background

Congenital Hyperinsulinism (CHI) results from unregulated insulin secretion from pancreatic β-cells, which leads to persistent hypoglycaemia. Mutations in 9 different genes are reported and phenotypic variability exists both within and between the genetic subgroups. Variable penetrance has been described in some families with the same mutation; for example *HNF4A* mutations cause neonatal hypoglycaemia and/or maturity onset diabetes of the young (MODY).

Case

- Male infant, born at 35 weeks gestation with a birth weight of 4.3kg (+3.6SDS)
- No h/o gestational diabetes in Mum
- Recurrent hypoglycaemic episodes from day one of life.

Investigations

- Glucose<0.5mmol/L
- Plasma insulin 1357pmol/L
- C-peptide 3280pmol/L
- Plasma free fatty acids and β-hydroxybutyrate<100µmol/l

Treatment

- Diazoxide (5mg/kg/day), with a progressive increase to 20mg/kg/day to maintain euglycaemia.

Family History

- Father was slim, Type 2 diabetes mellitus from his thirties, on Metformin.
- Paternal grandmother-Type 2 Diabetes.
- No family history of hypoglycaemia.

Genetics

- Heterozygous *HNF4A* mutation (p.R245P) and two heterozygous *ABCC8* mutations (p.G92S; p.A1185V) in the proband.
- p.A1185V *ABCC8* mutation-inherited from the baby's unaffected mother
- p.R245P *HNF4A* and p.G92S *ABCC8* mutations-inherited from the father.
- All three mutations are novel, affect conserved residues
- Predicted to be pathogenic by in silico analysis.

It is therefore likely that the CHI in the proband is resulting from a dual aetiology. Identification of a HNF4A mutation in the father is consistent with a diagnosis of MODY. He has subsequently been switched treatment to Gliclazide resulting in improved glycaemic control.

Conclusion

HNF4A CHI is often transient and responsive to diazoxide. In contrast recessively inherited *ABCC8* mutations usually cause diazoxide-resistant CHI. Interestingly, our patient is responsive to diazoxide despite the dual genetic aetiology. The mechanism(s) underlying the molecular interaction between *HNF4A* and *ABCC8* mutations are unclear.