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

Dinesh Giri1, Sarah E. Flanagan2, Julie Park1, Sian Ellard2, Mo Didi1, Senthil Senniappan1

1Department of Paediatric Endocrinology, Alder Hey Children’s Hospital, Liverpool, UK 2Department of Molecular Genetics, Royal Devon and Exeter Hospital, Exeter, UK

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
- 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.