A NOVEL MUTATION IN THE ABCC8 GENE CAUSING A VARIABLE PHENOTYPE OF IMPAIRED GLUCOSE METABOLISM IN THE SAME FAMILY

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Background:
Dominantly acting loss-of-function mutations in the ABCC8 gene, encoding the sulfonylurea receptor 1 (SUR1) subunit of the β-cell potassium channel (KATP), are usually responsible for mild diazoxide-responsive congenital hyperinsulinism (CHI). In rare cases dominant ABCC8 mutations can cause diffuse diazoxide-unresponsive CHI. Recent reports suggest that medically responsive CHI due to a dominant ABCC8 mutation may confer an increased risk of diabetes mellitus (DM) in adulthood. The mechanism is not clear at present; possible explanations include a progressive failure in β-cell function due to “exhaustion”, increased β-cell apoptosis as a result of raised intracellular calcium concentration and the influence of other genetic or environment factors.

Case Presentation:
The index patient (patient n.1) was born at 35 weeks to non consanguineous parents with a birth weight of 3900 g (> 97th percentile). Pregnancy was complicated by gestational diabetes. Biochemical diagnosis of CHI was performed during the first week of life. The patient started diazoxide (5 mg/Kg/day) when he was 3 months old because the drug was not available in his country (Albania). He was diazoxide-responder.
F-DOPA PET/CT scanning was not conclusive.
Molecular genetic analysis revealed a novel heterozygous ABCC8 missense mutation (p.A478T). His mother (patient n. 2) had gestational diabetes and after delivery she fulfilled the criteria for DM. She did not present hypoglycemia during childhood. The patient’s grandfather (patient n. 3) was diagnosed with DM at the age of 45 years. He also had no past history of hypoglycaemia.
Patient’s mother and grandfather were heterozygous for the p.A478T ABCC8 mutation.

Figure: family tree (the arrow indicates the proband).

Conclusions:
Our experience confirms that dominantly acting ABCC8 mutations can cause CHI during childhood and/or gestational diabetes and DM later in life (1,2).
The novel mutation identified in our patient was not previously reported in diazoxide-responsive forms of CHI; nevertheless a different mutation at the same residue has been reported in a family with CHI (3). The p.A478T ABCC8 mutation confers an increased risk of diabetes in adulthood but, as observed in our family, seems to be associated to an incomplete penetrance of hypoglycaemia in infancy.

References: