Bristol Royal Hospital For Children

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Congenital Hyperinsulinism due to Compound Heterozygous mutations in *ABCC8* fully responsive to Diazoxide therapy

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Background

- Congenital Hyperinsulinism (CHI), a condition characterised by dysregulation of insulin secretion from the pancreatic beta cells. If untreated, this can result in severe hypoglycaemia causing permanent neurological damage.
- CHI is the most common cause of persistent and recurrent hypoglycaemia in neonates, affecting approximately 1 in 50,000 live births[1].
- Mutations in *ABCC8* and *KCNJ11* constitute the majority of genetic forms of CHI. Biallelic inactivating mutations (homozygous or compound heterozygous) in *ABCC8* and *KCNJ11* are known to result in severe, diffuse, diazoxide unresponsive hypoglycaemia.
- We report a neonate with CHI due to compound heterozygous mutations in *ABCC8* and fully responsive to diazoxide.

Clinical Case Presentation

- Term male infant, born macrosomic 4.81kg (+3 SDS).
- Pregnancy complicated by polyhydramnios. Nil gestational diabetes mellitus .
- Persistent hypoglycaemia within first few hours of birth.
- Hypoglycaemia screen showed plasma blood glucose level 0.5mmol/L, plasma insulin 50.4mIU/L, suppressed free fatty acids and beta-hydroxy butyrate, confirming the diagnosis of CHI.
- Normoglycaemia sustained with higher dose diazoxide 15mg/kg/day and full enteral nasogastric formula feeding 150ml/kg/day.
- Discharged following an age appropriate 6 hour fast.

Take home messages

Established facts:

- Mutations in ABCC8 and KCNJ11 are the most common causes of genetic Congenital Hyperinsulinism. Recessive mutations in ABCC8 and KCNJ11 are considered to be diazoxide unresponsive.

Novel insights:

- Recessive mutations in ABCC8 and KCNJ11 can rarely cause diazoxide responsive CHI.
- An adequate trial of diazoxide is necessary before considering non-reversible therapies, such pancreatectomy.

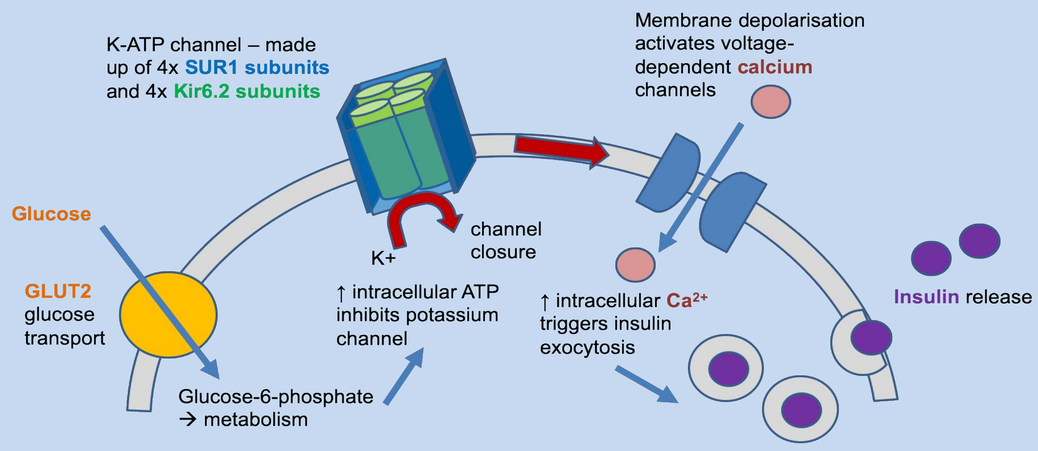

Figure 1. Pancreatic beta cell and the role of the ATP-Sensitive Potassium (K-ATP) channel in insulin secretion.

Genetic Diagnosis

- Molecular genetic analysis of the child and both the parents confirmed autosomal recessive CHI due to **biallelic *ABCC8* mutations**: missense c.4079C>T p.(Pro1360Leu) and splicing c.4122+1G>A variants inherited from the unaffected father and mother respectively.

Progress

- The patient is now 7 months old and is showing a sustained response to the diazoxide, current dose 2mg/kg/day. His blood glucose levels range between 3.7 to 5.7mmol/L.
- He is gaining weight appropriately. Continuing to receive nasogastric feeds as a formal speech and language team assessment showed an unsafe swallow. A plan for a future gastrostomy insertion is in place.
- Although Diazoxide dose requirement has significantly reduced from 15 to 2 mg/kg/day, occasional hypoglycaemia persists when the diazoxide dose is missed or not tolerated because of vomiting.
- Although a complete cessation of diazoxide treatment is a future possibility in our patient, we plan to try this by a controlled fast when the patient is older.

Discussion

- Recessive *ABCC8* and *KCNJ11* mutations result in defective SUR1 and Kir6.2 subunit co-assembly in the endoplasmic reticulum, as well as reduced K_{ATP} channel biogenesis, trafficking, and regulation[1,2]. The defective octameric K_{ATP} channel has been postulated for why recessive mutations are diazoxide-unresponsive.
- Our patient shows a striking response to diazoxide treatment despite harbouring a compound heterozygous mutation in ABCC8. The same paternal mutation has been previously described in a compound heterozygote patient but was diazoxide-unresponsive (c.4079C<T and c.1562G>C)[3].
- Complete diazoxide-responsiveness in recessive compound heterozygous and homozygous *ABCC8* mutations are very rarely described in the literature
- The exact molecular interaction causing this diazoxide responsive phenotype in recessive ABCC8 mutations is unclear.
- Compound heterozygote *ABCC8* mutations may result in complex interactions, and it is possible that this interaction may modify the potential disease pathogenesis.

References

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