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 births2.
- 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 ABCB8 and KCNJ11 can rarely cause diazoxide responsive CHI.
- An adequate trial of diazoxide is necessary before considering non-reversible therapies, such as pancreatectomy.

Genetic Diagnosis

- Molecular genetic analysis of the child and both the parents confirmed autosomal recessive CHI due to biallelic ABCB8 mutations: missense c.4079C>T (p.(Pro1360Leu)) and splicing c.4122+1G>A variants inherited from the unaffected father and mother respectively.

Discussion

- Recessive ABCB8 and KCNJ11 mutations result in defective SUR1 and Kir6.2 subunit co-assembly in the endoplasmic reticulum, as well as reduced KATP channel biogenesis, trafficking, and regulation1-3. The defective octameric KATP 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 ABCB8. 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 ABCB8 mutations are very rarely described in the literature.
- The exact molecular interaction causing this diazoxide responsive phenotype in recessive ABCB8 mutations is unclear.
- Compound heterozygote ABCB8 mutations may result in complex interactions, and it is possible that this interaction may modify the potential disease pathogenesis.

References

6. Tashunka Taylor-Miller1, Ruma Deshpande1, Christine P Burren1, Paul Munyard2, Dinesh Giri1

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