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Congenital Hyperinsulinism in a child with Alagille Syndrome

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Introduction

- Alagille syndrome (ALGS) is an autosomal dominant genetic disorder, with a highly variable phenotype affecting multiple organs, mostly the liver, heart, and other parts of the body.
- One of the major features of Alagille syndrome is liver damage caused by abnormalities in the bile ducts.
- Commonly presented in infancy or early childhood as cholestasis.
- ALGS is a rare condition and affects between 1:30,000 to 1:70,000 individuals.
- Mutations in the notch signaling pathway ligand (*JAG1*) in 94% of the patients or its receptor (*NOTCH2*) in 1-2% lead to ALGS (Figure 1).
- Notch signaling pathway is important for the pancreatic development.
- No cases of ALGS with Congenital Hyperinsulinism (CHI) have been reported to date.

Aim

- To report an atypical case of Alagille Syndrome presenting with Congenital Hyperinsulinism (CHI).

Case report

- A Full-term female infant, with birth weight of 2.78 kg (-1.91 SDS), presented 3rd day of life with two episodes of hypoglycaemic seizures and cholestatic jaundice.
- A hypoglycaemia screen showed hyperinsulinaemic non-ketotic hypoglycaemia confirming diagnosis of hyperinsulinism (table 1).
- On examination, the infant was noticed to have mild facial dysmorphism with bossed forehead, prominent nasal bridge and small chin.
- Microarray analysis showed monosomy of 20p11.21–p12.2 due to interstitial deletion of the short arm of chromosome 20, consistent with ALGS.

Figure 1. Notch-mediated juxtacrine signal between adjacent cells.

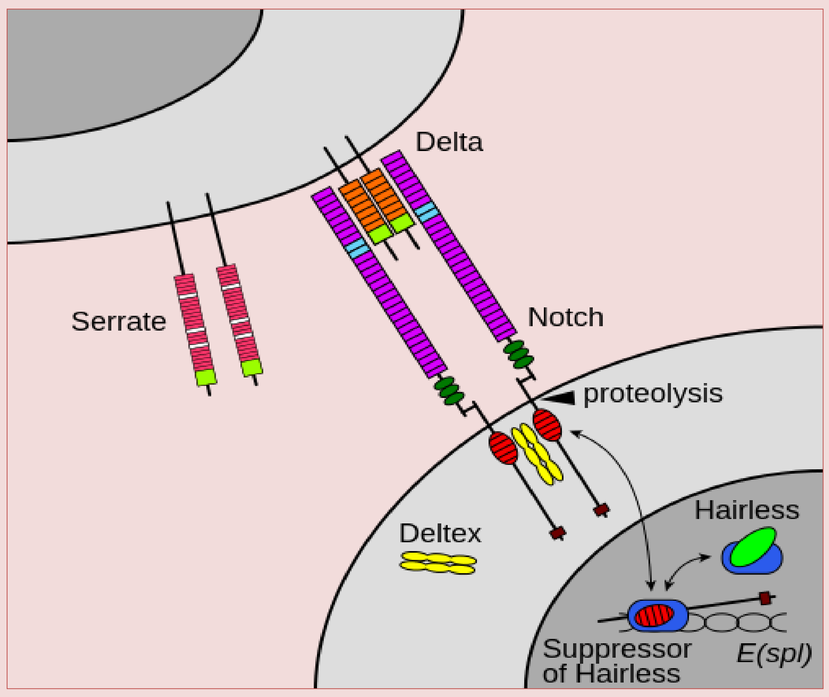

Table 1. Day 2 hyposcreen: Inappropriately elevated insulin concentration in the context of hypoglycaemia

Glucose	1.0 mmol/l
Insulin	9.3 mU/l
NEFA (Non esterified fatty acid)	0.15 nmol/l
BOHB (Beta hydroxy butyrate)	0.05 nmol/l

Intervention

- Treated with Diazoxide (5mg/kg/day) and Chlorothiazide (7mg/kg/day).
- The infant was discharged at 4 weeks of life on Diazoxide and 4 hourly bottle feeds.
- She had also a murmur due to a patent ductus, which subsequently closed by the age to 12 months.
- At 6 months, of age, she was noticed to have hepatomegaly (2cm) with mildly raised bilirubin, however, this resolved on its own without any further management.

Outcome

- The child remained stable on Diazoxide and Chlorothiazide treatment.
- Diazoxide was discontinued at the age of 1 year after self-weaning of the medications.
- She has been on regular follow-up visits up to the age of ten years without further episodes of hypoglycaemia or hyperglycaemia.

Discussion

- This is a case report of an atypical case of Alagille syndrome with CHI that responded to Diazoxide.
- She presented with no other typical symptoms of ALGS other than the initial complaint of cholestatic jaundice and mild facial dysmorphism.
- She had escaped many problems commonly seen in ALGS despite the fact that she has a large deletion on chromosome 20.

Conclusion

- ✓ ALGS is a rare inherited disease with variable phenotypic expressions.
- ✓ To the best of our knowledge, this is the first case of ALGS diagnosed with CHI that was Diazoxide-responsive and resolved at 12 months of age.
- ✓ Further work is needed to understand the mechanism of CHI in ALGS and children should be screened for CHI if any concerns regarding hypoglycaemia.

References

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