

A boy with diazoxide-unresponsive congenital hyperinsulinism due to a homozygous ABCC8 missense mutation previously reported to be dominant

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Background

Congenital hyperinsulinism is a complex condition in which insulin secretion from pancreatic beta-cells is unregulated leading to hyperinsulinaemic hypoglycaemia. This condition possesses considerable clinical heterogeneity attributed partly to its diverse genetic causes.

Medical history



(+0.95 SDS);

- Second child in the family;
- Born preterm at 37 weeks of gestation;
- Nonconsanguineous parents;
- BW 3600 g (+1.49 SDS), BL 51 cm

- retarded cardiopulmonary adaptation and perinatal asphyxia;
- no signs or symptoms consistent with syndromic HH;
- recurrent hypoglycaemic episodes with generalized seizures appeared after birth
- the baby was commenced on i.v. glucose infusions with GIR > 8 mg/kg/min, but BG levels varied between 1.0-2.0 mmol/l

Follow-up

- normal physical and neurological development

Age	Weight (kg)	Height (cm)	Octreotide (mcg/kg/day)	BGLs (mmol/l)
5 mo	6.500	65.4	17.75	2.8-7.4
9 mo	7.850	70.3	17.32	3.3-6.2
1 y 5 mo	9.440	76.5	17.02	4.3-8.4
1 y 8 mo	11.15	81	15.4	3.8-7.7

Genetic testing

Homozygous missense mutation in ABCC8 gene, initially described as a dominant mutation

Location: Exon 2

DNA description: c.275G>A; protein description: p.Gly92Asp

Inherited from his unaffected heterozygous parents

Objective

We present a boy with diazoxide unresponsive hyperinsulinaemic hypoglycaemia (HH) due to a homozygous ABCC8 missense mutation, initially reported as dominant and being inherited by his unaffected heterozygous parents.

On 14-days of age

- Still had hypoglycaemic episodes and was referred to our Expert center of rare endocrine diseases
- "Critical sample" taken at capillary BG 1.3 mmol/l

Investigation	Result	RR
Lab glucose mmol/l	0.7	3.9-5.6
Insulin mIU/ml	31.4	<2.0
Cortisol nmol/l	320.32	118.0- 660.0
GH ng/ml	8.19	0.5-8.0
Ketone bodies nmol/l	0.4	> 2.5

- All other laboratory and imaging tests were normal

Treatment

- commenced on i.v. glucose with GIR > 8.5 mg/kg/min
- diazoxide (up to 15 mg/kg/day) and chlorothiazide (7 mg/kg/day) started on 15 days of age without response to the therapy
- i.v. glucagon was initiated in order to control the blood glucose above 3.5 mmol/l
- At the age of 34 days octreotide therapy (up to 18.5 mcg/kg/day) was started as 4 s.c. injections daily
- able to fast for 4 hours without detecting hypoglycaemia



2 years old now....

- no side effects
- normal thyroid function, growth and neurodevelopment
- started on Sandostatin LAR 30 mg
- single hypos during infections

Conclusion

Our patient has a recessive form of diazoxide-unresponsive hyperinsulinism due to a homozygous loss-of-function mutation in the SUR1 subunit of the K_{ATP} channel, previously reported as a dominant mutation.

Further genotype-phenotype association studies in congenital hyperinsulinism are needed due to the variability in its inheritance and clinical presentation.

The photos are published with the IC and assent of the family and the patient.

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