Spontaneous Resolution of Congenital Hyperinsulinism With Octreotide Therapy

Hyperinsulinemic hypoglycemia is caused by dysregulated insulin secretion from the pancreatic β-cells. Congenital hyperinsulinism (CHI) is caused by genetic mutations in twelve known genes. Histologically, lesions can be focal or diffuse. Focal forms are often associated with paternal heterozygosity in *KCNJ11/ ABCC8* genes, whereas diffuse forms are seen in patients with maternal heterozygous, homozygous or compound heterozygous mutations. 18F-DOPA PET/CT imaging can precisely localize the lesion in focal forms, thereby facilitating cure by focal lesionectomy unlike diffuse form is mostly resistant to medical treatment and needs subtotal pancreatectomy [1].

We report the case of a term non-dysmorphic male baby (weight 2400 g) born to a non-consanguineous couple in Myanmar. He was born through meconium stained liquor with low Apgar scores, required resuscitation and was ventilated for ten days. Hypoglycemia (1.6 mmol/L) was noted at six hours of age, which required mini bolus followed by glucose infusion rate of 5.6 mg/kg/min. On day six, he developed seizures with hypoglycemia and GIR was gradually escalated to 19.5 mg/kg/min. Diagnosis of hyperinsulinemic hypoglycemia was made in the presence of detectable insulin (10.7 mU/L) with hypoglycemia (0.3 mmol/L) and hypoketonemia (0.3 mmol/L). Medical treatment was initiated with nifedipine while awaiting supply of diazoxide. Diazoxide was initiated at a dose of 5 mg/kg/day and was gradually increased to 15 mg/kg/day over a week with discontinuation of nifedipine. Subcutaneous octreotide (dose of 7.5 mcg/kg/day) was added as GIR continued to rise on diazoxide. With adequate response to octreotide, diazoxide was later discontinued.

DNA samples of the proband and parents were sent to UK for genetic study. A novel heterozygous *KCNJ11* missense variant, c.866G>C p. (Gly289Ala) was identified in the proband. Sequencing of the *ABCC8* gene was normal. Sanger sequencing of *KCNJ11* gene for the familial variant indicated heterozygous mutation in father whereas the mother was negative. The clinical significance of the *P*. (Gly289Ala) variant is uncertain. A focal lesion was suspected with the paternal mutation and 18F-DOPA PET/ CT scan was recommended.

DOPA PET/CT scan was unavailable in Myanmar and there was no funding source for overseas transfer. Treatment with octreotide was continued and GIR was successfully weaned off with feeding increments to achieve full feeds by six months of age. At nine months of age, octreotide dose was auto-tapered to 3 mcg/kg/day while maintaining normoglycemia and discontinued at 9.5 months of age. His glucose profile remained stable on follow-up but neurodevelopmental assessment at 22 months of age showed moderate mental and motor retardation. Vision and hearing tested normal. He is currently enrolled in an early intervention programme.

CHI is a heterogeneous disease caused by mutations in at least twelve known genes [1]. Loss-of-function mutations in K_{ATP} channel regulating genes constitute nearly 90% of cases of diazoxide-unresponsive CHI, of which *KCNJ11* is associated in 10% [2].

The index case had diazoxide-unresponsive CHI that detected a novel paternally inherited *KCNJ11* missense variant of uncertain significance at p. (Gly289Ala). A different missense variant at the same residue was previously reported by Mohnike, *et al*. [2] in a patient with diazoxide-responsive CHI, which was shown to have arisen *de novo* in the proband.

Similar spontaneous resolution has been reported at 1.6 and 1.9 year in patients with CHI [3,4]. DOPA tracer uptake may not correlate with the capacity of the pancreatic lesion to secrete insulin and the clinical remission of CHI could be a functional process without apoptosis of mutated β-cells [5]. This finding prompts long-term follow-up of our case to ensure optimal glucose regulation.

Most patients with K_{ATP} channel gene mutations do not respond to diazoxide treatment as it exerts its effects by keeping the channel open, preventing β-cell membrane depolarization and release of insulin. Octreotide reduces insulin secretion by inhibiting intracellular entry of calcium and by decreasing the insulin gene promoter activity [6]. These differences in the site action possibly explain the treatment response in the index case.

In summary, normoglycemia should be maintained to prevent brain injury with high GIR and/or high caloric enteral feeds in infants with CHI. Octreotide can be tried in diazoxide unresponsive patients and spontaneous resolution can be seen in CHI. Genetic studies help indicate the type of mutation. DOPA-PET scan confirms nature of lesion prior to surgery, which however remain poorly accessible in resource-limited settings.

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