Clinical remission in a patient with congenital hyperinsulinism due to paternally inherited two novel mutations in KCJN11 gene

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Background

Congenital hyperinsulinism (CHI) is the most common cause of persistent and profound hypoglycemia in infants. There are two distinct histologic forms of CHI, diffuse and focal. The distinction between these forms is important in patients who fail medical therapy since surgical strategies may vary. Focal lesions occur due to paternally inherited recessive mutation in ABCC8 or KCJN11 genes with somatic loss of the maternal 11p15 region (paternal uniparental disomy). Patients with focal CHI can be cured with partial pancreactomy, but a few cases with focal lesion have been reported to have spontaneous resolution. We present a unique case with CHI due to paternally inherited two novel mutations in KCJN11 gene who demonstrated clinical remission spontaneously.

Case Report

Twenty-seven months old male patient has been diagnosed with diazoxide unresponsive CHI in neonatal period in another hospital. He has been using octreotide treatment since his discharge. He was born on term, his birth weight was 3750 gr, and had a history of birth asphyxia due to nuchal cord. His parents were consanguineous with no family history of diabetes. He had a four year-old healthy brother. The patient was fed enterally through a feeding tube until two years of age. For the last three months he has been fed orally and it was expressed that he was tolerating overnight fasting without having hypoglycemia. He was receiving octreotide 9.26 mcg/kg/day (0.1 mg/day).

On physical examination the patient had microcephaly, bilateral medial strabismus and neuromotor retardation. His height was 83.5 cm (-1.98 SDS), weight: 10.8 kg (-1.86 SDS). Other systemic examination revealed normal. The etiology of microcephaly was investigated but no pathologic results were found in metabolic screening and TORCH antibody analysis. The cranial magnetic resonance imaging revealed agenesis of corpus collosum. The laboratory findings are demonstrated in Table 1. The patient was subjected to genetic analysis for determining long-term therapeutic approach. Mutational analysis revealed paternally inherited two novel mutations of KCJN11 gene (p.L270M and p.E288K). A maternally inherited KCJN11 mutation has not been found and therefore a focal lesion is highly suspected.

Since 18-Floro-L-DOPA positron emission tomography (PET) is not available in our country, the focal lesion could not be identified. In the clinical course we observed that the patient tolerated overnight fasting under very low dose octreotide and consider clinical remission. He has been receiving no medications for the last sixteen months and is still euglycemic.

Table 1: Laboratory findings of the patient

	At diagnosis (46 days old)	On admission (27 months old)	10 months after discontinution of octreotide (39 months old, after fasting for 12 hours)
Glucose (mg/dl)	37	89	72
Insulin (mU/L)	25.7	5.5	5.46
C-peptide (ng/mL)	0.646	1.17	1.34
Growth hormone (ng/ml)	20.8	-	-
Cortisol (µg/ml)	3.71-23.34	16.51	9.31
Ammonia (mg/dl)	-	32	-
HbA1c (%)	-	-	5.0

Mutation analysis

Result:	**Heterozygous mutations identified**
Mutation details:	Gene : *KCNJ11* Location : Exon 1 DNA Description: c.[808C>A];[862G>A] Protein Description: p.[Leu270Met];[Glu288Lys] (p.[L270M];[E288K]) Consequence: Missense

Interpretation

Mert is heterozygous for the novel *KCNJ11* missense mutations p.L270M and p.E288K. The leucine residue at codon 270 and the glutamic acid residue at codon 288 are conserved across species and have been identified *in cis* in other patients with congenital hyperinsulinism. It is therefore likely, that at least one of these mutations is pathogenic (see accompanying information sheets). Mert has inherited the p.L270M and p.E288K mutations from his father, Murat (report dated 22/03/2013). A maternally inherited *KCNJ11* mutation has not been found and sequencing analysis of the *ABCC8* gene has failed to identify a change from the normal sequence. A focal lesion is therefore possible and ^{18}F-DOPA PET-CT scanning is recommended.

CONCLUSIONS

- The diagnosis of CHI can be made on the basis of clinical and laboratory findings, but long-term treatment and prognosis depend upon histologic type. Infants presenting with severe CHI may have the focal form of disease like our patient.
- 18F-DOPA PET is the most useful imaging modality in differentiating focal and diffuse forms, but currently is available in a limited number of centers. Genetic analysis is very useful to identify focal CHI in those patients who could be not subjected to 18F-DOPA PET.
- Although very rare, patients with paternally inherited KCJN11 mutations might response to medical treatment and subsequently clinical remission might be observed.

References

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