CONGENITAL HYPERINSULINISM DUE TO SUR1(ABCC8) MUTATION IN NEWBORN TWINS: IMPROVEMENT OF CLINICAL OUTCOME AFTER EIGHT YEARS FOLLOW-UP

Betül ERSOY1, Nermin TANSUĞ2, Abdülkadir GENÇ3, Deniz KIZILAY1, Seniha KİREMİTÇİ1, Semin AYHAN4, Pascale DE LONLAY5

1Division of Pediatric Endocrinology and Metabolism, 2Division of Neonatology, 3Department of Pediatric Surgery,4 Department of Pathology, Celal Bayar University, School of Medicine, Manisa, TURKEY,5University Paris Descartes, Hospital Necker Enfants Malades, APHP, Paris, France

Congenital hyperinsulinism (CHI) is one of the main causes of hypoglycaemia and is characterised by inappropriate insulin secretion. The severity of hyperinsulinism varies and may be transient or persistent. The pancreatic β-cell ATP-sensitive potassium channel (KATP channel) regulates glucose-mediated insulin release and is composed of two subunits: Kir6.2 encoded by *KCNJ11* and SUR1 encoded by *ABCC8* gene. There are two main forms of CHI (focal and diffuse) that are clinically identical. Diffuse CHI is genetically heterogeneous and most commonly due to mutations in *ABCC8* or *KCNJ11* genes.

The main goal of the therapy is to maintain normoglycemia in these patients. Inappropriate management of hypoglycaemia can lead to brain damage and associated complications such as mental retardation, epilepsy and cerebral palsy. When the blood glucose concentration is stabilized, pharmacological agents need to be introduced to decrease insulin secretion. If a patient is unresponsive to medical treatment, pancreatectomy may be required.

In here, we present different clinical and therapeutic aspects of twins with CHI due to identical SUR1 (ABCC8) mutation and the improvements of clinical outcome after 8 years follow-up.

Cases:Term male infants were born to consanguineous parents by caesarean section. Maternal antenatal screen was unremarkable. There was no history of gestational diabetes mellitus in the mother. They had healthy sister and brother. The first clinical signs were crying, irritability, cyanosis and poor feeding, observed on the second day of life. Severe persistent hypoglycaemia and hyperinsulinemia during hypoglycaemia (20 mg/dl) were detected in both patients. Their physical examinations were normal. Table 1 shows anthropometric, clinical and laboratory characteristic of the patients. In both patients, plasma growth hormone and cortisol levels during hypoglycaemia were high and lactate, ammonia and other biochemical parameters were in normal range. Urine was negative for ketone bodies and reducing agent. They required infusion of high concentration glucose (glucose infusion rate 20 mg/kg/minute) to maintain normal blood glucose level. At the age of 1 month, octreotide treatment (15 µcg/kg/d) was started. After two weeks, diazoxide (8-15 mg/kg/d) was added. Case 1 (AS) responded to medical treatment.

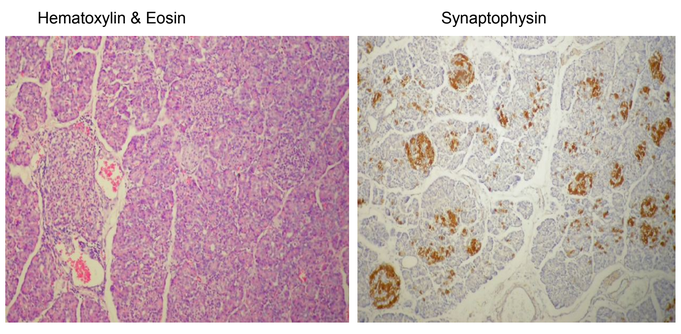
Case 2 (VS) showed severe hypoglycemia after using medical treatment, which indicated that the patient was unresponsive to medical treatment. This patient underwent subtotal pancreatectomy at the age of 60 days. Although the distal 95% of the pancreatic tissue was removed, he still needed medical treatment. The pancreatic histopathology showed diffuse type congenital hyperinsulinism, with significant increase of endocrine cells, different nuclear sizes of islet cells and some larger cells in the Hematoxylin & Eosin stain. An increase of islet cells was seen with the Synaptophysin immunostain (Picture 1). In abdominal CT (MRI) examination, pancreatic size was estimated 9.2 grams at one year of age. After 7 years, size of the pancreas rose 27.2 grams (Picture 2)

After written informed consent was obtained from the parents, blood samples of the patients and their parents were sent to Paris, for genetic analysis. In genetic analysis of both patients, homozygous nonsense mutation p. E791X (c. 2371G>T) in the ABCC8 gene in exon 19 (mutations occurring on each allele) was identified by Pascal de Lonlay. Both parents were found to be heterozygous carriers of this mutation.

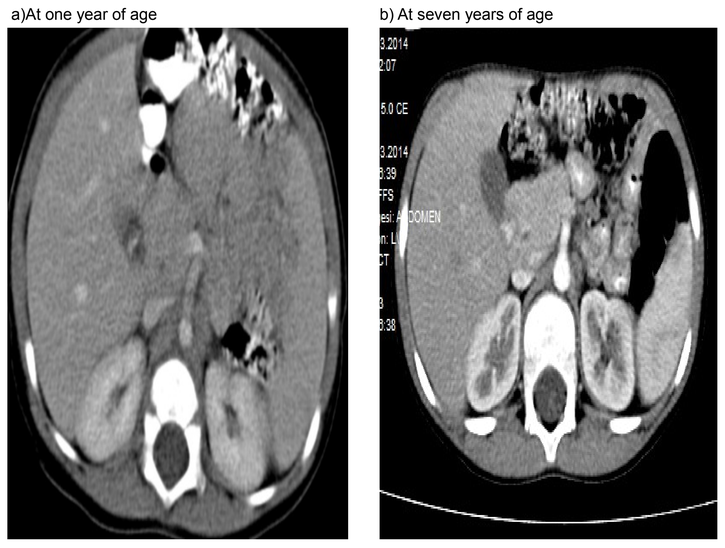
At the clinical follow up of patients, drug dosages were gradually reduced in the first 2 years. Medical therapy was stopped by their parents after about 3 years. At 4 years old, physical and neurologic examination of the patients were normal. No hypoglyceamia was found in blood glucose monitoring. At 8 years of age, patients were completely normal. Intelligence quotient (IQ) scores of the patients were normal for their age in the Wechsler Intelligence Scale for Children (WISC) (Table 1).

CASE	1	2
Birth height SDS	-0,75	0
Birth weight SDS	-0,92	-0,06
Insulin levels at diagnosis (µIU/ml)	50,9	51,9
Height SDS at the age of 1,5 years	-1,10	-0,77
Weight SDS at the age of 1,5 years	-0,53	-0,60
Height SDS at the age of 4 years	-1,30	-1,16
Weight SDS at the age of 4 years	-0,82	-0,58
Height SDS at the age of 8 years	-0,21	-0,08
Weight SDS at the age of 8 years	-0,27	0,35
WISC-R testing	verbal IQ score: 83 performance IQ score: 100 total IQ score: 91	verbal IQ score: 83 performance IQ score:100 total IQ score: 91

Table 1 anthropometric, clinical and laboratory characteristic of the patients



Picture 1. Histopathologic finding of pancreas



Picture 2. Pancreas in abdominal CT

Conclusion

These cases have some points for consideration. **First,** it is unclear how the identical mutation causes such marked clinical heterogeneity. The mechanism(s) underlying this clinical variability is unknown. Patients carrying the same mutant allele may show considerable phenotypic variability owing to modifying genes (genetic polymorphisms for example) and epigenetic and environmental factors. **Second** is spontaneous recovery of the manifestations. Despite of severe clinical picture of the patients at the neonatal period, they had no need of therapy after 3 years. **Third** is regeneration of residual pancreatic tissue. In mice and rats, there is clear evidence of pancreatic regeneration after some types of injury. **Finally,** neurological and intellectual abilities of the patients can be sustained by aggressive hypoglycemia management. These patients may provide an understanding of the prognosis and treatment for patients who carries homozygous mutation 2371G>T, E791X, in the *ABCC8* gene.