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

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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.

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 follow-up, 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.

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.

### Table 1 anthropometric, clinical and laboratory characteristic of the patients

<table>
<thead>
<tr>
<th>CASE</th>
<th>Birth weight SDS</th>
<th>Birth height SDS</th>
<th>Weight SDS at 1.5 years</th>
<th>Length SDS at 1.5 years</th>
<th>Insulin levels at diagnosis (µIU/ml)</th>
<th>Verbal IQ score</th>
<th>Performance IQ score</th>
<th>Total IQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.92</td>
<td>0.00</td>
<td>-0.53</td>
<td>0.00</td>
<td>39.6</td>
<td>96.0</td>
<td>98.0</td>
<td>91.0</td>
</tr>
<tr>
<td>2</td>
<td>-1.30</td>
<td>0.00</td>
<td>-1.10</td>
<td>0.00</td>
<td>39.6</td>
<td>96.0</td>
<td>98.0</td>
<td>91.0</td>
</tr>
</tbody>
</table>

**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.