Case report describing a patient with diazoxide resistant congenital hyperinsulinism resulting from compound heterozygous mutations in the ABCC8 gene

**Running title:** diazoxide resistant congenital hyperinsulinism resulting from compound

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Abstract
Congenital hyperinsulinism (CHI) is an over-secretion of insulin by pancreatic β-cells, causing hypoglycemia which can inhibit brain development in infants. CHI is primarily associated with mutations in the ABCC8 or KCNJ11 genes, which encode the SUR1 and KIR 6.2 subunits of the ATP-sensitive potassium (K$_{ATP}$) channel. Here, we report a case of hyperinsulinemic hypoglycemia with ABCC8 gene mutation in a full term, female, Korean infant who developed early onset hypoglycemia but was not subject to either genetic or metabolic workup. This infant was later admitted to the ER because of a hypoglycemic seizure, but her metabolic work up revealed that both her fasting insulin and C-peptide levels were within the normal range. Despite this glucagon stimulation produced positive results and the genetic workup revealed c.[298G>T(;)4252C>T] mutations in the ABCC8 gene. This indicated diazoxide treatment, but following an unsuccessful course of treatment we switched to octreotide which helped stabilize her glucose. Over 5 years of follow-up, the patient treated with a low dose of octreotide has had no hypoglycemic event, and her growth and psychomotor development remained within normal ranges. However, she is severely obese (BMI over 97 %) despite using octreotide. Thus, we report a mild case of CHI with octreotide treatment, wherein the patient has normal insulin and C-peptide levels and normal development, but is severe obese.

Keywords: Congenital hyperinsulinism, octreotide, diazoxide, infant
Introduction

Congenital hyperinsulinism (CHI) is a rare disorder with an estimated incidence of only one in 27000 to 50000 depending on population [1-4] (1/27000 Irish, 1/35400 Japanese, 1/40000 Finnish, 1/50000 Dutch). Despite this it is the most common cause of persistent hypoglycemia in neonates and infants, caused by the dysregulated secretion of insulin from pancreatic β-cells [5]. In addition, because brain function is heavily reliant on glucose metabolism, CHI patients are forced to compromise this metabolism during hypoglycemia. Therefore, early diagnosis and treatment are important to prevent permanent brain damage [6]. There are 16 different genes including ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, KCNQ1, CACNA1D, FOXA2, EIF2S3, PGM1, and PMM2 associated with the regulation of insulin secretion from pancreatic β-cells, each of which has been shown to be mutated in some way in individual cases of CHI [5]. In addition, there are two treatment options for correcting this kind of dysregulation, medical and surgical. There are three types of drugs used in CHI including glucagon, diazoxide, and octreotide [5]. Diazoxide reacts with pancreatic β-cells, opening the K_{ATP} channel, which inhibits insulin secretion, whereas octreotide (second-line therapy for diazoxide-unresponsive patients) acts as a somatostatin analog and inhibits insulin secretion via its antagonistic effects on the associated receptors. Therefore, octreotide is recommended for obese patients to reduce insulin resistance [7]. Clinical symptoms may differ depending on the type and location of the mutated gene, and this may have a significant impact on the therapeutic response [5, 6, 8]. We report the long-term follow-up of a full-term Korean female infant with diazoxide-unresponsive CHI resulting from an ABCC8 gene mutation, who exhibits normal growth and development, but is severely obese despite using octreotide.
Case report

A 2-day-old female, full term baby began to present as desaturated and cyanotic and was thus transferred to the NICU (neonatal intensive care unit). This patient was delivered via c-section at a gestational age of 38 weeks 1 day and weighing 4780 g. She had a history of macrosomia and was large for her gestational age (LGA) without any sign of maternal gestational diabetes mellitus (GDM) and following her cyanosis and desaturation was transferred to our NICU where we determined her initial blood sugar level to be 20 mg/dL. Serum evaluations revealed a blood glucose of 13 mg/dL on initial chemistry (BST was 20 mg/dL), sodium level of 136 mmol/L, and a potassium level of 5.1 mmoL/L. Serum insulin level was 39.9 µIU/mL (reference range 1.1-11.6 uIU/mL), and C-peptide levels were 6.04 ng/mL (reference range 0.48-3.30 ng/mL). Given these results we recommended genetic and metabolic tests to determine the cause of the patient’s distress but her parents refused. Her blood sugar level was only controlled using frequent feeding and at 9-month-old, her BST often dropped to 30 mg/dL at dawn, forcing her primary physicians to recommended that she consume corn starch before bed.

When she was 1-year-1-month-old, she was admitted to the ER following a hypoglycemic seizure. She presented with upper respiratory symptoms and a fever and had consumed only half what she would usually eat. In addition, she had only 2/3 of her daily milk bottle before bed and experienced a general tonic-clonic seizure in the early hours of the morning. Her BST was 76 mg/dL (self-checked) at the time of the seizure, but she was admitted to the ER with an alert mental status, and her BST was 27 mg/dL. She was given a bolus of 10% dextrose solution and kept on continuous 10% dextrose solution with GIR (glucose infusion rate) at 4.5 mg/kg/min. Her initial serum insulin level was 6.2 µIU/mL, and C-peptide was 0.83 ng/mL (after 10% dextrose solution bolus). Her ammonia was 31 ug/dL, lactic acid was 1.55 mmoL/L (reference range 0.7-2.00 mmoL/L), and free fatty acid was 186 μEq/L (reference range 172-
586uEq/L). She experienced no more seizures after admission and entered a euglycemic state. Her insulin and C-peptide levels were within the normal range following glucose injection and while quite low still relatively normal without glucose injection (1.3 µIU/mL and 1.12 ng/mL, respectively). Given these outcomes we then went on to perform a glucagon stimulation test which produced a positive result [9]. In this evaluation, a 1 mg injection of glucagon induced and initial BST of 47 mg/dL, which then increased to 122 mg/dL after 30 min, and 120 mg/dL after 60 min (Table 1). Taken together this meant that this patient presented with no acidemia, normal free fatty acid levels, normal lactic acid levels, low blood sugar levels, and a positive glucagon stimulation test, strongly suggesting that she may have hyperinsulinemic hypoglycemia. Given this we revisited both the genetic and metabolic studies previously denied by the parents. Her metabolic findings were within normal limits but gene panel testing revealed a c.[298G>T;4252C>T] mutation (Table 2) in the ABCC8 gene. One of these mutations was previously described in a Korean CHI patient and the other in a French patient, making both known mutations associated with CHI [8, 10]. The patient’s parents refuse to undergo genetic analysis. Once the genetic mutation was confirmed we went on to evaluate diazoxide treatment at a minimal dose (3 mg/kg/dose), with administration at bedtime to prevent early morning hypoglycemia. There was no initial response and so we increased the dose to 5 mg/kg/dose, but no effect was observed. After 4 weeks with no change we switched to treatment with octreotide 1.67 µg/kg/dose (normal treatment dosage range is 5-35 µg/kg/day, divided to 3-4 doses or continuous subcutaneous infusion) [11] before bed. While she did respond to this treatment her blood sugar levels still dropped to 60–70 mg/dL at 5 am when she received an injection at 11pm. However, this was increased to 70-80 mg/dL (Figure 1) when we increased her octreotide to 3.67 µg/kg/dose. She is now 5 years and 1 month old and has 4 meals per day. She is 115.3 cm tall and weighs 28.8 kg (BMI 21.6 kg/m², over 97%) (Figure 2), presenting with a bone age of 6 years old, C-peptide levels of 5.62 ng/mL, insulin at 38.9
µIU/mL and her psychomotor development is within the normal range. She was fitted with a continuous glucose monitoring device (Freestyle® Libre) (Figure 3) and receives a single 90 µg (4µg/kg/day) octreotide injection every day before bedtime preventing hypoglycemia.

**Discussion**

Congenital hypoglycemia can cause serious brain damage and even death. There are several causes of congenital hypoglycemia, including congenital hyperinsulinism, glycogen storage disorders, hypoketotic hypoglycemia, growth hormone deficiency, cortisol deficiency, and other hypoglycemic disorders. Of these, those caused by genetic mutations usually result in the development of congenital hyperinsulinism, which is the most common cause of persistent hypoglycemia in infants [12]. *ABCC8* mutation is the most common mutation in CHI and is usually treated with diazoxide, although not all *ABCC8* mutations respond to this compound. These diazoxide-unresponsive *ABCC8* and diazoxide-responsive *ABCC8* mutations often present as heterozygous changes [8] with one study which evaluated 41 patients with heterozygous mutations reporting that as many as 25 of these patients were unresponsive to diazoxide [13]. In addition, 88.8% of these patients had *ABCC8* mutations, which was consistent with the recessive mode of inheritance identified in 28% of these patients. In addition, a further 18% of these patients presented as compound heterozygotes [8]. Evaluations of these cases revealed that disease severity varies based on mutation with five of these CHI patients being unresponsive to diazoxide forcing them to undergo near-total pancreatectomy [14]. A similar case report from the USA, described an 11-month-old patient diagnosed with severe hyperinsulinism despite presenting with normal insulin levels. This patient presented with a novel compound heterozygote mutation in the *ABCC8* gene making him unresponsive to medical treatment [15]. In another case report from London, a neonate presented with hyperinsulinism that was unresponsive to diazoxide, and genetic evaluation revealed a
compound heterozygous missense mutation in the ABCC8 gene. However, this patient’s hyperinsulinemic hypoglycemia spontaneously improved after 7 weeks of age [16]. In this case, the patient was unresponsive to diazoxide but responded to octreotide at 4 µg/kg once per day. Given this we went on to compare our patient with other Korean cases of CHI, identifying a total of 12 additional cases three of which were heterozygous mutations (Table 3). Cases 2, 3, and 8 presented with two mutations, and cases 3 and 8 demonstrated recessive inheritance.

Patients 2 and 3 underwent subtotal pancreatectomy and were confirmed to present with diffuse CHI. Case 3 was in remission and had no developmental delays and 7 cases were responsive to medical treatment (Case 1, 7-12). Cases 1, 8, 10, and 12 were unresponsive to diazoxide while cases 10 and 12 showed remission after octreotide treatment. Unfortunately, despite this case 12 did experience a developmental delay. Our patient presented with a genetic mutation that was partially identical to that of case 9, but case 9 was responsive to diazoxide. Case 8 was also heterozygous and responsive to octreotide treatment.

Octreotide is a somatostatin which binds to the somatostatin receptor-5 of the β-cell membrane and controls insulin release [17]. Therefore, it is recommended for use in hypothalamic obesity pediatric patients and in patients with insulin resistance obesity-related acanthosis nigricans [18, 19] to manage their weight. However, in this case the patient is severely obese with octreotide injection. The possible reason is the dosage of this patient (4 µg/kg once per day) is slightly lower than normal octreotide treatment (5 µg/kg/day) for obesity patients. Another possible reason is our patient eats more frequently to reduce hypoglycemic events, and it may cause obesity [18].

In conclusion, we report a compound heterozygous mutation in ABCC8 in a patient with congenital hyperinsulinemia. Abnormal insulin and c-peptide level may delay early diagnosis and treatment; however, it is critical to prevent permanent brain damage in newborn patients with CHI. Therefore, it is important to perform genetic analysis on suspected CHI patients as
early as possible. Many patients are unresponsive to diazoxide; under such conditions, octreotide can be used as second-line therapy. In this case, the patient received early treatment and low-dose octreotide which resulted in normal growth and development. However, despite using octreotide as a treatment for obesity, our patient is severely obese, which has not been reported till date. It is important to balance the dosage of octreotide and diet to treat hypoglycemia, so patient can be normal height, normal weight, and normal development.

To summarize, we report a case of CHI treated with minimal octreotide in the early stage, which resulted in normal growth and development, but the patient is severely obese.

**Conflict of interest**

The authors have no conflicts of interest to declare.
References


10. Park, S.E., et al., Characterization of ABCC8 and KCNJ11 gene mutations and


### Tables

Table 1. Glucagon stimulation test (glucose levels in mg/dL)

<table>
<thead>
<tr>
<th>Glucagon stimulation test (glucose levels in mg/dL)</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
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<tbody>
<tr>
<td>Glucagon 1mg IV</td>
<td>47</td>
<td>122</td>
<td>120</td>
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Table 2. *ABCC8* Gene analysis report

<table>
<thead>
<tr>
<th>Gene</th>
<th>Isoform</th>
<th>NT change</th>
<th>AA change</th>
<th>Zyg</th>
<th>IHR</th>
<th>Type</th>
</tr>
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<tr>
<td><em>ABCC8</em></td>
<td>NM_000352.3</td>
<td>c.298G&gt;T</td>
<td>p.(Glu100*)</td>
<td>Het</td>
<td>AD/AR</td>
<td>PV</td>
</tr>
<tr>
<td><em>ABCC8</em></td>
<td>NM_000352.3</td>
<td>c.4252C&gt;T</td>
<td>p.(Arg14118Cys)</td>
<td>Het</td>
<td>AD/AR</td>
<td>LPV</td>
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</table>

Table 3. Clinical characteristics and *ABCC8* gene mutations in 12 Korean CHI Patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case</th>
<th>Sex</th>
<th>Onset</th>
<th>Follow-up</th>
<th>Treatment</th>
<th>Operation</th>
<th>Mutation</th>
<th>ETC</th>
</tr>
</thead>
<tbody>
<tr>
<td>JS Park et al.[20]</td>
<td>1</td>
<td>F</td>
<td>2d</td>
<td>22days -&gt; transfer to China</td>
<td>Diazoxide, Octreotide-&gt;no treatment</td>
<td>-</td>
<td><em>ABCC8</em>(4608G&gt;A) exon38</td>
<td>Chinese/Korean Intermittent seizures</td>
</tr>
<tr>
<td>SE Park et al.[10]</td>
<td>2</td>
<td>M</td>
<td>1d</td>
<td>44.m Remission</td>
<td>OP-&gt; Octreotide</td>
<td>1.5m/diffuse</td>
<td><em>ABCC8</em>(2509C&gt;T) exon21, (2767C&gt;T) exon23</td>
<td>DD</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>M</td>
<td>6m</td>
<td>6.7m Remission</td>
<td>OP</td>
<td>6.7m/ diffuse</td>
<td><em>ABCC8</em>(1289G&gt;A) exon8, (3403C&gt;T) exon28</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>F</td>
<td>0d</td>
<td>54.7m Diabetes</td>
<td>OP</td>
<td>1.5m/diffuse</td>
<td><em>ABCC8</em>(4160C&gt;T) exon34</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>M</td>
<td>3d</td>
<td>Diazoxide</td>
<td>OP-&gt;Diazoxide</td>
<td>13.5m/ diffuse</td>
<td><em>ABCC8</em>(2437G&gt;A) exon20</td>
<td>DD</td>
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<tr>
<td></td>
<td>6</td>
<td>F</td>
<td>3d</td>
<td>22m Remission</td>
<td>OP</td>
<td>22m/ diffuse</td>
<td><em>ABCC8</em>(3402G&gt;T) exon27</td>
<td>DD</td>
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<tr>
<td></td>
<td>7</td>
<td>M</td>
<td>3d</td>
<td>12.2m Remission</td>
<td>Diazoxide</td>
<td>-</td>
<td><em>ABCC8</em>(3403C&gt;T) exon28</td>
<td>DD</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>M</td>
<td>0d</td>
<td>Octreotide</td>
<td>Octreotide</td>
<td>-</td>
<td><em>ABCC8</em>(1630+1G&gt;C) intron10, (E1087-A1094delins DKSDT) Exon26</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>F</td>
<td>1d</td>
<td>Diazoxide</td>
<td>Diazoxide</td>
<td>-</td>
<td><em>ABCC8</em>(298G&gt;T) exon3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>M</td>
<td>2d</td>
<td>28m Remission</td>
<td>Octreotide</td>
<td>-</td>
<td><em>ABCC8</em>(3627_3628insCGTA) exon29</td>
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<tr>
<td></td>
<td>11</td>
<td>M</td>
<td>4m</td>
<td>Diazoxide</td>
<td>Diazoxide</td>
<td>-</td>
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<tr>
<td></td>
<td>12</td>
<td>F</td>
<td>1d</td>
<td>70.7m Remission</td>
<td>Octreotide</td>
<td>-</td>
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<td>DD</td>
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<tr>
<td>Current patient</td>
<td>F</td>
<td>2d</td>
<td>octreotide</td>
<td>octreotide</td>
<td>-</td>
<td><em>ABCC8</em>(298G&gt;T(;4252C&gt;T)</td>
<td>Normal growth</td>
<td></td>
</tr>
</tbody>
</table>

DD. developmental delay; OP. operation.
Figure 1. Effectiveness of Diazoxide and Octreotide treatment
여자 0-35개월 백분위수

신장 (cm)

세중 (kg)
Figure 2. Growth chart
여자 2-18세 체질량지수 백분위수

Figure 2. Growth chart
Figure 3. Continuous glucose monitoring (Freestyle® Libre)

- 보호자 동의 후 업로드 예정

Figure 3. Continuous glucose monitoring (Freestyle® Libre)