A Case Report on Congenital Hyperinsulinism Associated with ABCC8 Nonsense Mutation: Good Response to Octreotide

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Abstract

A 2.4 kg baby boy born via Caesarian section at 35 weeks had the first onset of hypoglycemia at 2 hours of life. The infant required a glucose load of 30 mg/kg/min. Insulin level was 19.6 pmol/L (normal value 17.8-173.0) in the absence of ketosis. He was resistant to oral diazoxide but responded to octreotide infusion. The boy was found to be heterozygous for an ABCC8 nonsense mutation, p.R934*. We present our experience on the use of subcutaneous octreotide for 2 years for the treatment of diazoxide resistant congenital hyperinsulinism (CHI).

Key words: congenital hyperinsulinism, PHHI, ABCC8 mutation, diazoxide, octreotide, KATP channel

INTRODUCTION

Congenital hyperinsulinism, also known as persistent hyperinsulinenic hypoglycemia of infancy (PHHII), is a group of genetic diseases characterized by inappropriate insulin release during hypoglycemia due to a mutation in the β cells of the pancreas.1 Involving at least 8 genes with more than 100 mutations, it is genetically and clinically heterogenous. The most common mutation affects the adenosine triphosphate-sensitive potassium channel (KATP). The molecular diagnosis in CHI could only be found in about 45% of all cases.2 There are many other genes that have yet to be discovered. Mutations of the β cells of the pancreas are basically divided into channelopathies, affecting the KATP channel, or metabolopathies, affecting other metabolites and transcription factors.3

CASE

The proband is the only child in the family. There was no history of parental consanguinity. He was born at 35 weeks via emergency low segment Caesarian section due to bleeding placenta previa. He had an Apgar score of 9 at 1 minute and 10 at 5 minutes. His anthropometric measurements were below the 3rd percentile (birth weight 2.4 kg, length 44 cm, head circumference 32 cm). Midline defects, such as cleft lip and cleft palate, were absent. There were no neurocutaneous stigmata. He had normal male external genitalia, with a normal-sized penis and descended testes. He had no phenotypic features to suggest Beckwith-Wiedemann syndrome. Other systemic examinations were unremarkable.

The first onset of hypoglycemia was seen at 2 hours of life. Despite regular breastfeeding, he continued to have multiple episodes of hypoglycemia manifesting as jitteriness. His capillary blood sugar ranged from low reading to 2.5 mmol/L. At the Neonatal Intensive Care Unit, he received boluses of intravenous dextrose 10% in water (D10W), followed by maintenance dextrose solution of increasing strength. Additionally, intravenous glucagon and hydrocortisone were started for persistent hypoglycemia. His blood sugar could only be maintained more than 3.0 mmol/L after a glucose load of 30 mg/kg/min and a glucagon infusion of 50 μg/kg/hr. Oral diazoxide was started at 5.0 mg/kg/day in divided doses, combined with chlorothiazide at 7.0 mg/kg/day. As he had poor response to oral diazoxide, it was titrated up to 20 mg/kg/day. Oral nifedipine 2.5 mg/kg/day was also added to the combination therapy. Octreotide was initially started as a continuous infusion after diazoxide dose was maximized. Within an hour after starting octreotide infusion, his blood sugar began to improve. Subsequently, subcutaneous octreotide was administered every 4 to 6 hours. We then decided to put him on a portable subcutaneous pump for the purpose of convenience, reducing the number of injections per day and making glucose regulation more physiologic.

The parents were educated on the identification and treatment of hypoglycemia. They were advised to perform home monitoring and recording of capillary blood sugar 3 to 4 times a day. During episodes of hypoglycemia, the boy was observed to be pale and inactive. His mother would then treat him with milk. In the first 1 year of life, he had hypoglycemia about 3 to 4 times a week.

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eISSN 2308-118x
Printed in the Philippines
Copyright © 2016 by the JAFES
Received: May 23, 2016. Accepted: August 2, 2016.
https://doi.org/10.15605/jafes.031.02.16

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particularly if he took very little milk or refused to eat. The episodes of hypoglycemia occurred less as he grew older, with a frequency of 2 to 3 episodes in a month.

Currently 1 year and 9 months old, the boy has fairly normal neuro-developmental milestones. He was diagnosed very early and received the appropriate treatment within the neonatal period. He started to walk at the age of 1 year. At almost 2 years, he is able to talk in two-word sentences, help in dressing and scribble spontaneously. A formal IQ test is being planned before school entry. He is seen regularly every 3 months.

DISCUSSION

There are many causes of recurrent and persistent hypoglycemia in the neonatal period. Hyperinsulinism is the most common cause of recurrent and persistent hypoglycemia.4 Hyperinsulinism could be primary, due to a defect in the pancreatic β cells, or secondary.5 Mutation of the genes that regulate insulin secretion is a rare condition. It is estimated to occur in 1 in 50,000 live births worldwide. The prevalence is higher, about 1 in 2000, in isolated populations with high rates of consanguinity, such as in Saudi Arabia and central Finland.6 The most common genetic mutation is in the ABCC8 gene that encodes for the subunit of sulfonylurea receptor 1 (SUR1). Eighty percent of diazoxide-resistant cases of CHI is due to KATP channel mutation. Other mutations that cause dysregulated insulin secretion by the β cells include KCNJ11, GLUD1, GCK, HADH, HNF1A, HNF4A, SLC16A1 and UCP2 genes.7 Secondary hyperinsulinism is a more common condition observed in large for gestational age, macromosaic and syndromic babies; and perinatal asphyxia. The triggers of excessive insulin release in these babies are unknown.8

Clues for hyperinsulinism in our patient include persistent hypoglycemia; the need for a very high glucose load, more than 2 to 3 times the usual requirement; the presence of inappropriate levels of insulin during hypoglycemia (19.6 pmol/L, normal value 17.8-173.0) and the absence of ketones during hypoglycemia (Table 1). The significant response to glucagon demonstrated that persistent hypoglycemia was less likely caused by metabolic causes, such as glycojen storage disease and gluconeogenic enzyme deficiencies.9 Persistent hypoglycemia associated with the absence of ketones may be caused by congenital hyperinsulinism and defects in β-oxidation of fatty acids. As insulin was present during hypoglycemia, congenital hyperinsulinism was the more likely cause. The clinical parameters that may suggest KATP channel mutation in the boy are the very early onset of hypoglycemia at the second hour of life and severe hypoglycemia and diazoxide resistance.10

Comparing the findings of a large cohort of diazoxide resistant CHI treated with octreotide (n=28), our patient had lower birth weight (2.4 kg, as against 4.0±0.8 kg with a range of 2.5-6.0) at 35 week period of gestation (versus 37.5±2.4 weeks with a range of 33-40). The boy had unrecordable or low blood sugar on presentation, compared to 1.9±0.8 mmol/L with a range of 0.1-3.0 mmol/L. Our patient’s measured insulin during hypoglycemia was 2.82 μU/L, while the levels documented in the cohort ranged from 31.4±39.1 μU/L.11 However, there is no single physical finding or biochemical parameter that is able to predict diazoxide resistance or sensitivity in CHI, as the condition is clinically and genetically heterogenous.

There is a limited choice of drugs to treat persistent hypoglycemia from hyperinsulinism. First line therapy is oral diazoxide at 5 to 20 mg/kg/day in divided doses, which acts by opening KATP channels to inhibit insulin production. It works synergistically with chlorothiazide to reduce fluid retention. Nifedipine works by blocking voltage-gated calcium channels, as calcium is required for insulin exocytosis, but the experience for this indication is limited. Octreotide, a somatostatin analog, suppresses insulin release by acting on a KATP channels and binding to somatostatin receptors.12 The boy was treated with a combination of glucagon, diazoxide, nifedipine and hydrocortisone to treat persistent and refractory hypoglycemia, following the protocol suggested by the European Network for Research Into Hyperinsulinism of Infancy.13 The mean dose of octreotide infusion from the largest cohort of patient with CHI was 17.8±7.5 μg/kg/day (range 7.5-30).11 Our patient’s dose of 10 μg/kg/day was comparatively lower but still within the range of that

Table 1. Laboratory results on initial investigation and on follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5 days</th>
<th>1 month</th>
<th>2 months</th>
<th>5 months</th>
<th>13 months</th>
<th>19 months</th>
<th>22 months</th>
<th>26 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, pmol/L</td>
<td>19.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cortisol, mmol/L</td>
<td>185.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FTA, pmol/L</td>
<td>27.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TSH, mIU/L</td>
<td>3.3</td>
<td>-</td>
<td>-</td>
<td>3.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IGF-1, μg/L</td>
<td>36.6</td>
<td>-</td>
<td>-</td>
<td>17.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17-OHP, nmol/L</td>
<td>11.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRA, ng/ml</td>
<td>20.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ammonia, μmol/L</td>
<td>93.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.8</td>
<td>5.9</td>
<td>5.3</td>
<td>-</td>
<td>5.2</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-</td>
<td>35</td>
<td>48</td>
<td>43</td>
<td>56</td>
<td>45</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>-</td>
<td>320</td>
<td>422</td>
<td>339</td>
<td>394</td>
<td>345</td>
<td>342</td>
<td>317</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>-</td>
<td>45</td>
<td>38</td>
<td>20</td>
<td>26</td>
<td>15</td>
<td>14</td>
<td>17</td>
</tr>
</tbody>
</table>
study. The primary aim of starting octreotide is to turn off excessive insulin production, which has detrimental effects on brain development. Glycated hemoglobin increased from 4.8 to 5.2%, and 80% of his seven-day continuous glucose monitoring system readouts fell within the targeted blood sugar range (Figure 1). These indicated that insulin production was suppressed to some extent, with fewer incidences of hypoglycemia.

Octreotide is known to cause gastrointestinal tract dysmotility, elevation of liver enzymes, gallbladder stones and growth and thyroid axis suppression. Use of octreotide for a mean follow up of 53.6±32.9 months on octreotide. The age at initiation of treatment (n=13). Octreotide dose did not seem to be correlated with elevation of liver enzymes. In contrast, median age was found to be significantly lower in those with high liver enzymes (0.25 versus 1.5 months).11 Due to very early onset hypoglycemia, regular octreotide has been maintained for about 2 years, starting as early as 2 weeks of life, with acceptable levels of transaminases (Table 1).

**(Sensor Data (mmol/L))**

<table>
<thead>
<tr>
<th>Sensor Data (mmol/L)</th>
<th>Tue 12/04</th>
<th>Wed 13/04</th>
<th>Thu 14/04</th>
<th>Fri 15/04</th>
<th>Sat 16/04</th>
<th>Sun 17/04</th>
<th>Mon 18/04</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>7.0</td>
<td>7.6</td>
<td>9.0</td>
<td>5.7</td>
<td>3.8</td>
<td>7.3</td>
<td>N/A</td>
<td>9.0</td>
</tr>
<tr>
<td>Lowest</td>
<td>3.4</td>
<td>3.6</td>
<td>3.8</td>
<td>3.1</td>
<td>2.2</td>
<td>4.1</td>
<td>N/A</td>
<td>2.2</td>
</tr>
<tr>
<td>Average</td>
<td>5.1</td>
<td>5.3</td>
<td>5.0</td>
<td>4.2</td>
<td>3.1</td>
<td>5.8</td>
<td>N/A</td>
<td>5.1</td>
</tr>
<tr>
<td>Standard Dev.</td>
<td>0.9</td>
<td>1.0</td>
<td>1.1</td>
<td>0.5</td>
<td>0.5</td>
<td>0.9</td>
<td>N/A</td>
<td>1.2</td>
</tr>
<tr>
<td>MAD %</td>
<td>23.4</td>
<td>24.0</td>
<td>20.4</td>
<td>13.2</td>
<td>0.5</td>
<td>5.5</td>
<td>N/A</td>
<td>18.7</td>
</tr>
<tr>
<td>Correlation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Average</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Excursion Summary (mmol/L/day)**

<table>
<thead>
<tr>
<th>Excursion Summary (mmol/L/day)</th>
<th>Tue 12/04</th>
<th>Wed 13/04</th>
<th>Thu 14/04</th>
<th>Fri 15/04</th>
<th>Sat 16/04</th>
<th>Sun 17/04</th>
<th>Mon 18/04</th>
<th>Average / Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Excursions</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># High Excursions</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># Low Excursions</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AUC Above Limit</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>N/A</td>
<td>0.01</td>
</tr>
<tr>
<td>AUC Below Limit</td>
<td>0.02</td>
<td>0.01</td>
<td>0.00</td>
<td>0.05</td>
<td>0.77</td>
<td>0.00</td>
<td>N/A</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Duration Distribution (hh:mm)**

Figure 1. Results of seven days on continuous glucose monitoring system.

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**www.asean-endocrinejournal.org Vol. 31 No. 2 November 2016**
Gallbladder pathology was detected in 32.1%: 6 presented with gallstones and another 3 with bile sludge. There was no difference in the dose of octreotide between those with and without gallbladder pathology. The mean duration of treatment before the development of gallbladder pathology was 4.3±4.6 months in 9 patients. The 19 patients remained free of the complication after a follow up of 53.6±32.9 months on octreotide. The age at initiation of octreotide and development of gallbladder pathology was not found to be significant. As there is a small risk of gallbladder pathology from literature, we plan to do regular hepato-biliary ultrasonography for the boy.

The birth weights of patients with the primary form of CHI or those with genetic mutations varied from low to large for gestational age. In contrast, secondary hyperinsulinism may be seen in some newborns large for gestation, macrosomic, infant of diabetic mothers and asphyxia. What really triggers hyperinsulinism in the transient/secondary form of CHI is unknown. Secondary hyperinsulinism is a more common condition observed in large for gestational age, macrosomic and syndromic babies; and perinatal asphyxia.

Three out of 28 patients (10.7%) had height measurements less than -2 standard deviations (SD) for height-for-age. However, as their projected height was still within the target height, it was concluded that the patients had familiar short stature. From the cohort, there was no significant difference in the levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) before and after octreotide treatment. Our patient had a height less than -2 SDs or 3rd percentile. With his mother’s height at 146.0 cm and father’s height at 160.0 cm, the target/mid-parental height is 159.5 cm. The boy’s projected height is not more than 10 cm from the target height, indicating that he has familiar short stature.

Looking at the boy’s growth curve, his weight was also less than the 3rd percentile for weight-for-age, and the magnitude of his serial weight decrement was more abnormal than his height deficit. There are a number of reasons for failure to thrive. Nutritional intake is the predominant factor that affects the size of the child during the first 2 years of life, while growth hormone mainly exerts its influence later. Being a very picky eater with very little solid intake contributed to the boy’s poor nutrition. Other factors were low birth weight, small for gestational age and small-built biological parents. The boy had no history of recurrent vomiting and diarrhea.

Congenital hyperinsulinism is most often sporadic. While uncommon, familial disease connotes different genetic changes. Homozygous mutation is usually associated with severe disease, diazoxide resistance and KATP channel mutation. In contrast, autosomal dominant disease is milder, diazoxide-responsive and involves a non-KATP mutation. Genetic or molecular studies can guide treatment, especially in the case of diazoxide resistance as it is highly suggestive of KATP channel mutation. Interestingly, CHI is also characterized by a unique genetic feature. There is loss of normal maternal chromosome during embryonic development, indicating a loss of heterozygosity via a non-Mendelian mechanism. The patient would then have only a copy of mutant SUR1 genes from the unaffected father. The presence of growth-stimulating genes together with the absence of growth suppressing genes, the affected area would grow into a discrete focal lesion.

Histologically, congenital hyperinsulinism is classified into focal (40% of cases) or diffuse forms. Eighty percent of diazoxide resistance cases is due to the focal form, which is cured by surgical treatment. As such, diazoxide resistance warrants further workup to determine if surgery may be indicated.

For the proband, analysis of coding and flanking intronic regions of the KCNJ11 gene, all coding regions and exon/intron boundaries of the ABCC8 gene (U63421 and L78208), P2 promoter and all coding regions and exon/intron boundaries of the HNF4A gene were performed by Sanger sequencing. The boy had heterozygous nonsense mutation, p.Arg934Ter (p.R934*) involving the amino acids c.2800C>T. This mutation resides in exon 23 of ABCC8 gene. He inherited this from his unaffected father who had the same mutation. No mutation was detected upon screening his mother. It is highly likely that he had loss of heterozygosity, and that his CHI is focal in nature. The only way to confirm this is by extracting DNA from the focal site during surgery. 18F-fluorodihydroxyphenylalanine (18F-DOPA) positron emission tomography scan is required to localize the focal lesion before surgery. Arrangements are being made to fund and eventually refer this boy to the CHI Centre in Europe for 18F-DOPA scan and definitive surgery of the focal lesion.

This is the first case of diazoxide resistant CHI in our hospital since the Paediatric Endocrine Services opened to serve the East Coast of Malaysia 5 years ago. The uniqueness of this case is due to the boy’s response to treatment with octreotide and the high possibility of a having focal form of CHI based on the genetic analysis. If he did not respond to the specified medical treatment, pancreatic surgery may have been the only option. However, this entails long term morbidities such as diabetes, pancreatic exocrine dysfunction and neurobehavioural deficits.

As there is a likelihood of focal CHI based on the genetic study, this short review and follow-up of a confirmed case of diazoxide resistant congenital hyperinsulinism was able to demonstrate the efficacy of octreotide in turning off excessive insulin production, and the safety of long term use while awaiting definitive treatment.
CONCLUSION

Diazoxide resistant congenital hyperinsulinism may respond to octreotide. The latter proved to be safe and effective for this patient.

Ethical Consideration

Patient consent form has been procured prior to the case report study.

Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

The authors declare that the abstract has been published in the International Journal of Paediatric Endocrinology entitled, "Diazoxide-unresponsive congenital hyperinsulinism associated with ABC8 nonsense mutation with the following link: Int J Pediatr Endocrinol. 2015(Suppl1):86 and online on 28 April 2015 [doi: 10.1186/1687-9856-2015-51-P86].

Funding Source

None.

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