Clinical characteristics and long-term outcome of Taiwanese children with congenital hyperinsulinism

Cheng-Ting Lee, Shih-Yao Liu, Yi-Ching Tung, Pao-Chin Chiu, Mu-Zon Wu, Wen-Yu Tsai

Department of Pediatrics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan
Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
Department of Pathology, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan

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Background: Congenital hyperinsulinism (CHI) is a rare condition causing severe hypoglycemia in neonates and infants due to dysregulation of insulin secretion. This study aimed to review 20 years’ experience in the management of Taiwanese children with CHI.

Methods: Between 1990 and 2010, children diagnosed with CHI and followed up at the Pediatric Endocrine Clinic of the National Taiwan University Hospital were enrolled. Their medical records were thoroughly reviewed.

Results: In total, 13 patients (8 boys and 5 girls) were enrolled, including six patients with onset of hypoglycemia within 1 month of age and seven patients at 4.0/2.1 months of age. The birth weight standard deviation scores of these two age groups were 4.6/1.8 and 1.4/1.3 standard deviation score, respectively (p < 0.01). Initial intravenous glucose infusion at rates of 22.9/5.3 mg/kg/min and 13.4/5.6 mg/kg/min, respectively, were mandatory to maintain euglycemia in these two groups (p < 0.05). All received pancreatectomy after failure of initial medical treatment. Twelve patients were followed up for a period of 2.5–19.8 years. Eight of them remained euglycemic without any medication and three patients developed diabetes mellitus. Seven of the nine patients who underwent intelligence evaluation had normal mental outcomes. Mental retardation of two patients was too severe to be evaluated. All four patients with mental retardation had a delay in the maintenance of euglycemia, and three of them also had seizure disorder.

Conclusion: The age at onset of hypoglycemia reflects the severity of CHI. Early diagnosis and appropriate treatment are important for favorable mental outcomes.

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Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Department of Pediatrics, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan. E-mail address: wenyutsai@ntu.edu.tw (W.-Y. Tsai).

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Introduction

Congenital hyperinsulinism (CHI), previously known as persistent hyperinsulinemic hypoglycemia of infancy or nesidioblastosis, refers to the condition of severe hypoglycemia in neonates and infants caused by dysregulated insulin secretion. The incidence of CHI is estimated to range from one case/40,000–50,000 live births in northern Europe2,3 to one case/3000 live births in Saudi Arabia,4 an area with a high rate of consanguinity. Both dominant and recessive inheritances have been reported. The molecular genetic basis of CHI has been elucidated, and mutations in genes of ABCC8, KCNJ11, GLUD1, GCK, HADH, HNF4A, SLC16A1, and UCP2 have been reported in patients with CHI. Nonetheless, these mutations account for only about half of the CHI cases.5

Pathologies of CHI can be divided into diffuse and focal forms. The most common genetic causes of diffuse-type CHI are recessive mutations in the genes ABCC8 and KCNJ11 that encode the SUR1 and Kir6.2 subunits of adenosine triphosphate (ATP)-sensitive K⁺ channels (KATP channel) of the pancreatic β-cell.5–7 Focal CHI results from a paternally inherited KATP channel mutation together with somatic loss of the maternal chromosome 11p15 region.8

Hyperinsulinism can suppress the production of ketone bodies, which are alternative fuel for the brain, and there may be severe neurologic damage if treatment is delayed. Pharmacologic therapies with diazoxide,9 octreotide,10,11 calcium channel blockers,12 or glucagon13,14 have been tried, however, results vary due to the heterogeneity of underlying diseases. Those who do not respond to the conservative therapy need pancreatectomy to prevent irreversible brain damage due to persistent hypoglycemia.

Owing to a paucity of information on CHI in Taiwanese children, this study was conducted to elucidate experiences in the management of CHI in 13 Taiwanese children.

Patients and methods

Medical records of 13 children diagnosed with CHI at the National Taiwan University Hospital between 1990 and 2010 were reviewed. The diagnostic criteria were modified from those of the European Network for Research into Hyperinsulinism:9 (1) laboratory blood glucose level of <50 mg/dL; (2) glucose requirement >6–8 mg/kg/min to maintain a blood glucose level of >50 mg/dL; (3) detectable insulin at the point of hypoglycemia, with raised C-peptide; (4) inappropriate low ketone body concentrations at the time of hypoglycemia; and (5) glycemic response after glucagon administration during hypoglycemia. Patients with Beckwith–Wiedemann syndrome, congenital disorders of glycosylation, or insulinoma were excluded.

Among the patients, 11 were referred from other hospitals because of poorly controlled hypoglycemia. Twelve patients were followed up at the Pediatric Endocrine Clinic of National Taiwan University Hospital and Kaohsiung Veterans General Hospital for a median period of 11.6 years (range, 2.5–19.8 years). Only one patient was lost to follow up after discharge at the age of 1.6 months. During follow up, their blood glucose status was evaluated by regular checking of fasting blood glucose and HbA1c levels. Clinical neurological function was evaluated and electroencephalography examination was performed. Psychometric intelligence was assessed using the Chinese version of the Wechsler Intelligence Scale for Children, third edition, or the Wechsler Pre-school and Primary Scale of Intelligence-Revised in nine patients. An intelligence quotient (IQ) of 50–69 was classified as mild mental retardation.

Statistical analysis

Numerical variables were expressed as mean ± standard deviation. Differences in the continuous variables were evaluated using nonparametric Mann–Whitney U test, and categorical variables were analyzed using chi-square test or Fisher’s exact test. Statistical significance was set at p < 0.05. All statistical analyses were performed using the Statistical Program for Social Science 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

None of the total 13 patients (8 boys and 5 girls) had any family history of CHI or consanguinity. Except for one patient who was born at 36 weeks of gestation, all the others were born at full term. Ten patients (77%) had macrosomia and nine patients (69%) had seizures as their initial presentation. Other initial presentations included hypotonia (8%), irritability (46%), poor sucking/poor feeding (23%), cyanosis (15%), sweating (15%), apnea (8%), tremor (8%), and myoclonus (8%). By contrast, two asymptomatic patients were detected by routine glucose screening for macrosomia.

In terms of age at onset of symptoms, six of 13 patients (46%) had onset of hypoglycemia in the neonatal period (Table 1). Among them, four patients had onset within 24 hours after birth. Their age at diagnosis ranged from 1 day to 12 days. The other seven patients (54%) had onset of hypoglycemia in infancy, at a mean age of 4 months (range, 2–8 months), and were diagnosed at a mean age of 7 months (range, 2 months–1.6 years).

The birth weight standard deviation scores (SDS) of patients in the neonatal-onset group (age at onset <1 month) and those in the infantile-onset group (age at onset >1 month) were 4.6 ± 1.8 and 1.4 ± 1.3, respectively (p < 0.01). All six patients in the neonatal-onset group had birth weight SDS >2, while only two of seven patients in the infantile-onset group (29%) had birth weight SDS >2 (p < 0.01).

Upon diagnosis, the median level of their lowest documented glucose level was 20 mg/dL (range, 5–35 mg/dL) and the median level of their highest documented insulin level was 37.4 μU/mL (range, 6.1–>400 μU/mL). The median level of their maximal documented insulin to glucose (I/G) ratio was 1.07 (range, 0.21–21.14) (Table 1). Patients of the neonatal-onset group and those of the infantile-onset group had no significant difference in the lowest documented glucose level, highest documented insulin level, and maximal I/G ratio. The patient with the lowest I/G...
G ratio (Patient 9) had the focal form of CHI. In none of the patients was hyperammonemia detected during episodes of hypoglycemia.

Management

Intravenous glucose infusion at a rate of 17.8 ± 7.2 mg/kg/min was required to maintain blood glucose levels of >50 mg/dL. The glucose infusion rate was significantly higher in the neonatal-onset group than in the infantile-onset group (22.9 ± 5.3 mg/kg/min vs. 13.4 ± 5.6 mg/kg/min, p < 0.05) (Table 1).

Diazoxide (10–20 mg/kg/d) was given in seven patients, and nifedipine was tried in one patient after diagnosis, but without relief. Pancreatectomy was performed in all 13 patients at a median age of 6 months (range, 13 days–1.9 years) (Table 1). All six patients with neonatal-onset CHI and four of the seven patients with infantile-onset CHI had near-total pancreatectomy (>95% of the pancreas removed). Two patients had subtotal pancreatectomy (80–94% of the pancreas removed).

Twelve patients were confirmed to have diffuse lesions by pathological examination. The remaining patient (Patient 9) had only the lesion at the body of the pancreas removed, which was proved to be focal adenomatous hyperplasia. One patient (Patient 3) had ectopic pancreas at the gastric pylorus, aside from the pancreatic lesion. The heterotopic lesion also had islet cell hyperplasia, similar to the pancreatic lesion.

Five patients, including the patient with the focal form of CHI, became euglycemic after pancreatectomy. One patient (Patient 2) developed diabetes mellitus (DM) immediately after surgery. Seven patients still had hypoglycemic episodes after surgery and were treated with diazoxide. Among them, four were in the neonatal-onset group and three in the infantile-onset group. Their difference was not statistically significant (67% vs. 43%, p = 0.592).

Two of these seven patients had poor response to diazoxide, and they were shifted to octreotide. Of the other five patients, three achieved long-term stable glycemic control by diazoxide alone and two were treated with octreotide in addition to diazoxide for a period after pancreatectomy. One of them (Patient 7) still had recurrent episodes of hypoglycemia until the age of 1 year (10 months after pancreatectomy).

Long-term outcome

Among the seven patients with continued medical treatment after surgery, six stopped the medical treatment between 2.2 years and 10.6 years of age, and had no episodes of hypoglycemia. Only one patient (Patient 13) continued diazoxide therapy until the end of the study. Two patients developed hypertrichosis after diazoxide treatment and other two patients developed gallbladder sludge following octreotide treatment. No other serious adverse drug effect was elicited in other patients. In terms of postoperative complications, none had steatorrhea although one patient had mild fat intolerance. One patient (Patient 5) had recurrent adhesion ileus.

Of the 12 patients with long-term follow up, eight remained euglycemic until the end of the study even without any medication. One patient continued diazoxide therapy, while three patients had DM at the end of the study. One patient (Patient 2) developed DM immediately after surgery at the age of 1.1 months, while two patients (Patients 5 and 6) had DM at the age of 10.6 years and 12.3 years, respectively.

Two of 12 patients with long-term follow up had mental retardation (Patients 10 and 12) that was too severe for an IQ test, while one (Patient 3) was too young to undergo an

Table 1

Clinical characteristics of patients with congenital hyperinsulinism.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Birth weight (gram)</th>
<th>Age at presentation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Age at diagnosis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Lowest glucose level&lt;sup&gt;b&lt;/sup&gt; (mg/dL)</th>
<th>Highest insulin level&lt;sup&gt;b&lt;/sup&gt; (µU/mL)</th>
<th>Maximum I/G ratio</th>
<th>Initial max SIR&lt;sup&gt;b&lt;/sup&gt; (mg/kg/min)</th>
<th>Operation</th>
<th>Pathology</th>
<th>Outcome&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>4550</td>
<td>&lt;1 d</td>
<td>1 d</td>
<td>27</td>
<td>&gt;400</td>
<td>10.81</td>
<td>30.0</td>
<td>13 d</td>
<td>NP</td>
<td>diffuse (-)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>5664</td>
<td>&lt;1 d</td>
<td>1 d</td>
<td>22</td>
<td>37.3</td>
<td>1.07</td>
<td>25.3</td>
<td>1 m</td>
<td>NP</td>
<td>diffuse DM</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>3960</td>
<td>&lt;1 d</td>
<td>7 d</td>
<td>31</td>
<td>20</td>
<td>0.46</td>
<td>21.0</td>
<td>22 d</td>
<td>NP</td>
<td>diffuse (-)</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>4310</td>
<td>&lt;1 d</td>
<td>9 d</td>
<td>5</td>
<td>155.8</td>
<td>21.14</td>
<td>23.0</td>
<td>18 d</td>
<td>NP</td>
<td>diffuse (-)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>4100</td>
<td>1 d</td>
<td>12 d</td>
<td>18</td>
<td>62.7</td>
<td>2.41</td>
<td>24.0</td>
<td>8 m</td>
<td>NP</td>
<td>diffuse DM, MR</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>5840</td>
<td>2 d</td>
<td>2 d</td>
<td>34</td>
<td>37.4</td>
<td>1.01</td>
<td>14.0</td>
<td>1 m</td>
<td>NP</td>
<td>diffuse DM</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>4120</td>
<td>2 m</td>
<td>2 m</td>
<td>35</td>
<td>20.1</td>
<td>0.56</td>
<td>11.3</td>
<td>2 m</td>
<td>NP</td>
<td>diffuse MR</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>3900</td>
<td>2 m</td>
<td>2 m</td>
<td>24</td>
<td>119</td>
<td>2.9</td>
<td>11.6</td>
<td>9 m</td>
<td>SP</td>
<td>diffuse (-)</td>
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<tr>
<td>9</td>
<td>M</td>
<td>3920</td>
<td>3 m</td>
<td>5 m</td>
<td>15</td>
<td>6.1</td>
<td>0.21</td>
<td>15.0</td>
<td>6 m</td>
<td>EN</td>
<td>focal (-)</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>3670</td>
<td>4 m</td>
<td>6 m</td>
<td>20</td>
<td>21.2</td>
<td>0.63</td>
<td>13.0</td>
<td>6 m</td>
<td>NP</td>
<td>diffuse MR</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>4300</td>
<td>4 m</td>
<td>11 m</td>
<td>12</td>
<td>48.5</td>
<td>1.31</td>
<td>25.0</td>
<td>1 y</td>
<td>NP</td>
<td>diffuse (-)</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>3000</td>
<td>5 m</td>
<td>1.6 y</td>
<td>12</td>
<td>46.8</td>
<td>3.11</td>
<td>10.0</td>
<td>1.9 y</td>
<td>SP</td>
<td>diffuse MR</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>3400</td>
<td>8 m</td>
<td>10 m</td>
<td>18</td>
<td>31.4</td>
<td>0.73</td>
<td>8.0</td>
<td>1.3 y</td>
<td>NP</td>
<td>diffuse (-)</td>
</tr>
</tbody>
</table>

<sup>a</sup> d: day; m: month; y: year.
<sup>b</sup> Max SIR: maximum glucose infusion rate.
<sup>c</sup> NP: near total pancreatectomy; SP: subtotal pancreatectomy; EN: enucleation.
<sup>d</sup> (-): neither DM nor MR detected; DM: diabetes mellitus; MR: mental retardation.
IQ test but had normal neurological development during the 2.5 years of follow up. The other nine patients had IQ evaluated at a median age of 6.7 years (range, 3.3–12.2 years). Seven of nine patients had normal IQ, and the other two (Patients 5 and 7) had mild mental retardation. Among four patients with mental retardation, one (Patient 5) had neonatal-onset CHI and the other three had infantile-onset CHI.

In the four patients with mental retardation, maintenance of euglycemia was delayed for a period ranging from 2 months to 18 months after onset of symptoms. Delays in gross motor development were detected in three patients. Four (33%) of 12 patients with long-term follow up had seizure disorder, which was controlled using anticonvulsants. Three of them also had mental retardation.

Discussion
Clinical characteristics and long-term outcome of Taiwanese children with CHI were reviewed in this study. There were significant differences in birth weight and initial glucose requirement between the neonatal-onset and the infantile-onset groups. Because all six patients in the neonatal-onset group had symptoms within 2 days after delivery and a high demand of glucose was noted after birth, their macrosomia was thought to be due to severe prenatal hyperinsulinism. Similarly, Meissner et al.16 reported a trend of higher birth weight SDS in patients with neonatal onset than in those with manifestation in infancy or childhood. The age at onset and initial glucose requirement in patients with CHI thus reflected the severity of hyperinsulinism. Meissner et al.16 also reported that 27% of patients with neonatal-onset CHI had birth weight SDS >2. In this study, all six patients in the neonatal-onset group had birth weight SDS >2, implying that patients with neonatal-onset CHI were at the severe end of the spectrum of CHI.

An I/G ratio of >0.3–0.5 during hypoglycemia is considered a diagnostic criterion for CHI.7,17,18 However, one of the 13 patients had a maximal I/G ratio of <0.3. Some cases may be missed if diagnosis is based only on an I/G ratio of >0.3 as the gold standard for diagnosing CHI. Such an idea has also been raised by another study.19 Thus, for the diagnosis of CHI, it is prudent to consider other clinical parameters such as high glucose demand, low blood ketone body level, and positive glycemic response to glucagon during episodes of hypoglycemia.

One patient with pancreatic focal adenomatous hyperplasia had remission of hypoglycemia after resection of the focal lesion, while others with the diffuse form of CHI needed extensive pancreatectomy to control hypoglycemia. Thus, differentiating between focal and diffuse forms is important before surgery.20 Pancreatic venous blood sampling using transhepatic catheterization with or without pancreatic arterial calcium stimulation has been reported to locate pancreatic lesions.20,21 However, such a procedure is invasive and technically demanding, therefore, it is not widely used. Noninvasive fluorine-18 L-3,4-dihydroxyphenylalanine ([18F]-DOPA) positron emission tomography (PET) has been applied to localize pancreatic lesions based on the neuroendocrine nature of pancreatic islet cells.22 However, the accuracy of [18F]-DOPA PET varies between studies.23,24 Because the patients in this study were worked up before [18F]-DOPA PET was made available in our hospital, they were not studied using [18F]-DOPA PET.

Despite aggressive treatment, four of the 11 patients with CHI (36%) still developed mental retardation. Three also had seizure disorder. These findings are similar to other reports.16,25 Menni et al.25 reported that neonatal-onset CHI was the main risk factor for mental retardation. However, our study shows a higher percentage of mental retardation in patients with infantile-onset CHI, which is similar to that reported by Meissner et al.16 Because maintenance of euglycemia is important in preventing mental retardation in these patients, brain damage by undetected hypoglycemia in infantile-onset CHI may explain such a phenomenon. Difference in study populations may also account for such a discrepancy.

DM is a long-term complication of CHI.16,20,24,26 In non-pancreatectomized patients, glucose intolerance or DM may occur after their teenage years.26 By contrast, DM also occurs in patients treated with near-total pancreatectomy. It may occur immediately after surgery or before the 2nd decade of life.16,20,22 In this series, three of 12 patients (25%) had DM. One patient developed DM immediately postoperatively, and two patients had DM at the age of 10.6 years and 12.3 years. All of them had neonatal-onset CHI and were treated with near-total pancreatectomy. All other nine patients, aged 2.5–20 years, had no evidence of DM by the end of follow up. However, monitoring of their glucose levels was indicated for early detection of DM.

In summary, this study demonstrates clinical characteristics and long-term outcome of Taiwanese children with CHI. Our results showed that macrosomia and irritability of the nervous system were important clinical clues to the diagnosis of CHI. Our data also showed that the I/G ratio, used as a diagnostic criterion of CHI, was not so reliable as previously reported. Therefore, it is prudent to work up on patients with detectable serum insulin levels during the episode of hypoglycemia in order to prevent delayed diagnosis of CHI. Early diagnosis and appropriate treatment to maintain euglycemia remain the mainstay of management to prevent mental retardation of patients with CHI. We hope that the experience cited here can help physicians identify patients with CHI and institute appropriate management to improve outcome.

References

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Congenital hyperinsulinism


