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ORIGINAL ARTICLE

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

Cheng-Ting Lee [a], Shih-Yao Liu [a], Yi-Ching Tung [a], Pao-Chin Chiu [b], Mu-Zon Wu [c], Wen-Yu Tsai [a,*]

[a] *Department of Pediatrics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[c] *Department of Pathology, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*

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nesidioblastosis;
persistent hyperinsulinemic hypoglycemia of infancy

Background/purpose: 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.

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.[1] The incidence of CHI is estimated to range from one case/40,000–50,000 live births in northern Europe[2,3] 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 (K_{ATP} channel) of the pancreatic β-cell.[5–7] Focal CHI results from a paternally inherited K_{ATP} 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 glucagon[13,14] 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[15]: (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) inappropriately 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 (62%), hypoactivity (54%), consciousness disturbance (46%), 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 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