Hyperinsulinemic Hypoglycemia in Beckwith-Wiedemann, Sotos, and Kabuki Syndromes: A Nationwide Survey in Japan

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Hyperinsulinemic hypoglycemia in Beckwith-Wiedemann, Sotos and Kabuki syndromes: A nationwide survey in Japan

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome that is occasionally associated with hyperinsulinemic hypoglycemia (HH) in the neonatal period. Sotos syndrome (SS) and Kabuki syndrome (KS) are other malformation syndromes that may be complicated with HH, however, the detailed clinical characteristics of HH accompanied with these syndromes remain unclear. We herein conducted a nationwide questionnaire survey in Japan. We sent a primary questionnaire concerning the clinical experience for these syndromes to 347 perinatal care institutions. As a result, 222 departments or hospitals returned the questionnaires and the total numbers of BWS, SS and KS patients were 113, 88 and 51, respectively. We sent a secondary questionnaire to 31 institutions where patients with these syndromes presented with HH during infancy. The secondary questionnaires were returned from the institutions and the numbers of patients were 16 for BWS, 9 for SS, and 3 for KS, respectively. Then, we compared the clinical characteristics of infants suffering from transient HH with and without these dysmorphic syndromes. As a result, BWS, SS and KS patients showed significantly larger body size, lower Apgar scores, higher insulin levels at HH and shorter durations of HH than non-dysmorphic infants with transient HH. We propose that a careful observation for the signs of HH, even if not specific to

the syndromes, is important for the diagnosis of patients with BWS, SS and KS in the postnatal period.

KEY WORD

Beckwith-Wiedemann, Sotos, Kabuki, neonatal hyperinsulinemia, hypoglycemia

INTRODUCTION

Neonatal hypoglycemia is a critically important complication because it can lead to neurologic injury. Hyperinsulinism is one of the essential causes of hypoglycemia for infants and recurrent episodes of hyperinsulinemic hypoglycemia (HH) might render high risk of permanent brain damage for infants. The severity and pathogenesis of HH vary widely from life-threatening and refractory against medical treatment to transient and asymptomatic [Arnoux et al., 2010]. Many genetic causes of HH have been identified and classified according to the type of functional category: the subunits of K channels on β-cells, such as ABCC8 and KCNJ11; transcriptional factors for insulin gene expression, such as HNF1A, HNF4A; and glucose metabolizing enzymes, such as glucokinase, glutamate dehydrogenase 1 (GLUD1) or uncoupling protein 2 (UCP2) [Arnoux et al., 2011; Mohamed et al., 2012; Yorifuji, 2014]. Transient HH is occasionally recognized in infants born from diabetic mothers, and the prolonged HH is one of responsible causes for hypoglycemia in small for gestational age infants or asphyxiated newborns. Dysmorphic syndromes are also known to present transient hyperinsulinism in infancy, especially, Beckwith-Wiedemann syndrome (BWS, OMIM 130650) is well recognized as one of major genetic diseases causing hyperinsulinism [Munns and Batch, 2001; Weksberg et al., 2010]. Sotos syndrome (SS, OMIM 117550)

and Kabuki syndrome (KS, OMIM 147920) are other malformation syndromes occasionally accompanied with hyperinsulinism, but are less recognized, and detailed clinical characteristics of HH in SS and KS has remained unclear [Genevieve et al., 2004; Kapoor et al., 2009; Matsuo et al., 2013; Subbarayan and Hussain, 2014]. We herein conducted a nationwide questionnaire survey in Japan of 347 institutions with maternal/perinatal intensive care units to investigate the clinical characteristics of the patients with dysmorphic syndromes; BWS, SS and KS, who present HH in the neonatal period. In addition, we compared the clinical characteristics of infants suffering from transient HH with and without dysmorphic syndromes.

SUBJECTS AND METHODS

We sent primary questionnaires to 347 Japanese institutions that have core maternal/perinatal intensive care unit and asked the neonatologists who cared for the infants in neonatal intensive care unit (NICU) and then followed them for evaluation their growth and development regularly at their out-patient clinic. The questionnaire asked for the clinical experience of patients with either BWS, SS or KS complicated with HH in infancy during January 2002 to December 2011. We then sent secondary questionnaires to the institutions that experienced BWS, SS or KS cases with HH, asking for the clinical

manifestations including the following items: <data at birth> duration of pregnancy, weight, length, head circumference, Apgar score, complications during pregnancy; <characteristic findings at birth> congenital anomalies, facial dysmorphism, chromosome abnormalities; <symptom of hypoglycemia in the neonatal period> onset of hypoglycemia, minimum blood glucose level, and <therapy for hypoglycemia> duration and maximum glucose rate of intravenous glucose infusion (IVG), treatment with diazoxide or octreotide, estimated duration of hyperinsulinemia. In addition, we retrospectively collected the clinical data of neonates complicated with transient HH without any dysmorphic syndromes for a comparison with the clinical characteristics of those with dysmorphic syndromes.

The study was approved by the Institutional Review Board of Kyushu University Hospital.

Statistical analysis

All data were entered and analyzed using the statistical analysis software (SAS) JMP version 10 (SAS Institute Inc., Cary, NC, USA).

The differences between the group of syndromic infants and the group of non-syndromic infants were analyzed by chi-squared test for the items of maternal complications during pregnancy, asphyxia and use of diazoxide. The others were evaluated by Mann-Whitney's

U test for quantitative variables.

Results were regarded statistically significant if P was <0.05.

RESULTS

<The results of the first survey>

For the primary questionnaire, 222 departments or hospitals returned the questionnaires with a response rate of 64%. Approximately half of the institutions, 112, answered the experience of the care for patients with any of these syndromes; the numbers of patients were 113 for BWS, 88 for SS and 51 for KS. We sent secondary questionnaires to 31 institutions where patients with any of these syndromes presented with HH during infancy. The secondary questionnaires were returned from the institutions with the numbers of 16 for BWS, 9 for SS, and 3 patients for KS, respectively. The clinical data were collected from medical records of 13 neonates who were admitted to the NICU in Kyushu University Hospital from 2012-2015 and suffered from transient HH in the neonatal period without any dysmorphic syndromes. Every parameter was compared between infants with and without dysmorphic syndromes.

< Comparison of clinical and laboratory data between infants with and without dysmorphic syndrome>

Each of the clinical and laboratory data was compared between infants with and without dysmorphic syndromes.(Table I) As a result, we found that dysmorphic patients were significantly larger body size (birth weight, birth length, birth head circumstance) than non-dysmorphic patients. And the 1-min Apgar scores of the dysmorphic patients were significantly lower than those of non-dysmorphic patients. The insulin level at HH was higher and the duration of HH was shorter in infants with dysmorphic syndromes than in those without.

<Clinical characteristics of HH for BWS, SS or KS>

1. Data at birth

The data of the duration of pregnancy, birth weight, length, and head circumstance, the Apgar scores and complications during pregnancy are presented in Tables II-VI. The medians (ranges) of the birth weights and weight-SD scores were 3245 g (1294-4272 g) and 2.8 SD (-0.5- +7.8) for BWS; 3470 g (2330-4756 g) and 1.1 SD (-1.4 - +4.0) for SS; and 3194 g (2438-3539 g) and 2.0 SD (-1.5- +2.3) for KS, respectively.

Asphyxia was complicated in 25% of BWS, 33% of SS and 33% of KS cases whereas it comprised 0% of non-dysmorphic infants. Maternal complications during pregnancy, such as pregnancy-induced hypertension (PIH), premature rupture of

membranes (PROM), or a non-reassuring fetal status, were found in 69% of BWS, 33% of SS and 33% of KS cases, respectively (Tables III-V). These complications were observed at a similar frequency in patients without dysmorphic syndromes (46%; Table VI). There were no apparent differences among the three syndromes regarding the birth weight and length or complication of neonatal asphyxia.

2. Characteristic findings at birth

The three major clinical features for BWS, i.e., gigantism, macroglossia and exomphalos, were observed in most of BWS patients, with the ratios of 68.8%, 81.3%, 43.8%, respectively. Macrocephaly and large hands and feet were frequently noted in SS patients, and 70% of SS patients had major cardiovascular or central nervous system anomalies. All KS cases had specific facial features, such as long palpebral fissures, ectropion of the lateral third of the lower eyelid, flat nasal tip and large ears.

3. Cytogenetic data

Chromosome abnormalities by G-banding of peripheral lymphocytes were not found in the analyzed cases, including 9 for BWS, 6 for SS, and 2 for KS. The cytogenetic data are shown in Tables III-V. One BWS case had chromosome 11p15 paternal UPD. Seven SS cases were identified as having a microdeletion at chromosome 5q35 detected by fluorescence in situ hybridization, whereas one SS case had no deletion of 5q35 but had

a *NSD1* mutation. *MLL2* mutations were detected in 2 of 3 KS cases.

4. Hypoglycemia

The onset time and blood insulin level during hypoglycemia, duration of IVG, maximum rate of GIR, introduction of diazoxide and estimated duration of hyperinsulinemia are presented in Tables III-VI. Twelve of the 16 BWS cases suffered from hypoglycemia as early as within 2 hr after birth, and the blood insulin level during hypoglycemia range from 2.8 - 49 μIU/ml. All patients were treated with IVG at a maximum rate of 5.9 - 15 mg/kg/min for 6 - 67 days. Six cases received medical treatment with diazoxide with a maximum dose of 3 - 18 mg/kg/day. Most cases recovered from HH within 1 month, however, one case (case 6) had persistent HH and was treated for three months.

As for SS, 7 of 9 patients presented with hypoglycemia within 3 hr after birth, and the blood insulin level during hypoglycemia ranged from 3.15 to 19.6 μIU/ml. All cases were treated with IVG at a maximum rate of 4.6 - 11.0 mg/kg/min for 9 - 49 days. Two of 9 cases were treated with diazoxide at a maximum dose of 5-6 mg/kg/day. Most of the cases finished the IVG or diazoxide treatment within 3 weeks, although one case (case 7) required the treatments for two months. Regarding KS, only 3 cases were evaluated from the questionnaires. Two of three cases had hypoglycemia within 3 hr after birth. In one case (case 1), HH occurred 25 days after birth and was treated with

diazoxide. The median onset-times of HH after birth were 1 hr (immediately after birth - two days) for BWS, 1 hr (30 min - one day) for SS and 3 hr (30 min - 25 days) for KS. The rates of patients treated with diazoxide were 38% in BWS, 22% in SS, and 33% in KS, respectively. There were no apparent differences among the three syndromes regarding the glucose levels at HH.

DISCUSSION

Beckwith-Wiedemann syndrome (BWS) is a well-known congenital overgrowth syndrome associated with hyperinsulinemic hypoglycemia (HH) in the neonatal period [Munns and Batch, 2001; Weksberg et al., 2010]. Recent reports have demonstrated that infants with SS or KS also present with HH in infancy, although the detailed clinical characteristics of HH have not been well characterized [Genevieve et al., 2004; Matsuo et al., 2013; Subbarayan and Hussain, 2014]. One reason might be that characteristic features for SS and KS, such as facial anomaly or overgrowth, appeared gradually during their early childhood and then most of the patients were diagnosed by pediatric neurologists or dysmorphologists. Therefore, transient HH in neonatal period would not be essentially important for the diagnosis of SS or KS. We herein conducted the first nationwide survey in Japan to determine whether there were any characteristic

manifestations in patients with dysmorphic syndromes, BWS, SS or KS, who present HH in their neonatal period. On this purpose, we asked the neonatologists who cared for sick infants and followed them for a while. As a result, we found that severity of HH was clinically variable and no particular trend was observed in their neonatal period. When we compared the clinical or laboratory data, dysmorphic patients showed significantly larger body size, lower Apgar scores, higher insulin levels at HH and shorter durations of HH than non-dysmorphic infants with transient HH. It might be possible that normal to overweight status accompanied with asphyxia and severe but short-duration HH is a clue to diagnose underlying dysmorphic syndromes. Although we could not find specific clinical findings or biochemical data suggestive of SS or KS, particular symptoms such as accompanying major anomalies, feeding disability or developmental delay would suggest the diagnosis of these syndromes.

There are some limitations associated with this study. First, we did not recruit the patients by referral from pediatric neurologists or dysmorphologists; therefore, the total number of patients and characteristic features of the Japanese patients with these syndromes remained unclear from this study, and we did not evaluate the clinical differences between infants with HH and those without HH. Second, we performed this survey in institutions with NICUs; consequently, we might miss a small number of

patients who were treated outside the NICUs, such as in pediatric departments or obstetrics hospitals.

CONCLUSIONS

Transient HH is an important complication occasionally observed in patients with SS and KS during the neonatal period. We propose that a careful observation for the signs of hypoglycemia and diagnosis of HH would be helpful for an early diagnosis of patients with BWS, SS and KS.

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DISCLOSURE

The authors declare that they have no potential conflicts of interest associated with this study.

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