Hypopituitarism in a Patient With Beckwith-Wiedemann Syndrome Due to Hypomethylation of KvDMR1

abstract

Beckwith-Wiedemann syndrome (BWS) is caused by dysregulation of imprinted genes on chromosome 11p15.5. The syndrome includes overgrowth, macroglossia, organomegaly, abdominal wall defects, hy- poglycemia, and long-term malignancy risk. No patient who has BWS has been reported with hypopituitarism. We describe a patient who presented at birth with macrosomia, macroglossia, respiratory distress, jaundice, and hypoglycemia, and who was followed for 4.5 years. Genetic test for BWS was performed, which detected loss of maternal methylation on region KvDMR1 (11p15.5). The hypoglycemia was attributable to hyperinsulinism and was treated with diazoxide and chlorothiazide. She responded well, but the hypoglycemia returned after reducing the diazoxide. It was possible to stop the diazoxide after 2.5 years. On routine follow-up she was noted to be developing short stature. Baseline pituitary and growth hormone (GH) stimulation tests detected GH deficiency and secondary hypothyroidism. A brain MRI showed a small anterior pituitary gland. Thereafter, thyroxine and replacement therapy with GH were started, which resulted in a remarkable improvement in growth velocity. This is the first patient to be reported as having hypopituitarism and BWS. It is unclear if the BWS and the hypopituitarism are somehow connected; however, further investigations are necessary. Hypopituitarism explains the protracted hypoglycemia and the short stature. In our patient, GH therapy seems to be safe, but strict follow-up is required given the increased cancer risk related to BWS. Pediatrics 2014;133:e1082–e1086

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KEY WORDS
Beckwith-Wiedemann syndrome, short stature, hypopituitarism, growth hormone deficiency, secondary hypothyroidism

ABBREVIATIONS
BWS—Beckwith-Wiedemann syndrome
GH—growth hormone
HH—hyperinsulinemic hypoglycemia
IGF-1—insulin growth factor-1

Dr Baiocchi conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Yousuf drafted the initial manuscript and reviewed and revised the manuscript; Dr Hussain supervised the study and critically reviewed and wrote the manuscript, and all authors approved the final manuscript as submitted.

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Beckwith-Wiedemann syndrome (BWS) has an incidence of 1 in 12,000 to 13,700 live births and is the most common overgrowth syndrome. In the United Kingdom, the prevalence is 1% of all live births. The phenotype is heterogeneous and the genetic alterations are complex. More commonly, deletion/mutations of imprinted genes within the chromosome 11p15.5 region are implicated. These modifications have been associated with the fetal-growth factor gene IGF-2 and the tumor suppressor gene H19. Most cases of BWS occur sporadically; ~10% to 15% are transmitted as an autosomal-dominant disease. Diagnosed primarily on physical examination after birth, BWS is established on the fulfillment of either 3 major criteria (anterior abdominal wall defects, macroglossia, and pre- or postnatal overgrowth) or 2 major features along with 3 minor ones (ear creases, post-auricular pits, prominent facial nevus flammeus, hypoglycemia, nephromegaly, or hemihyperplasia). Intra-abdominal embryonal malignancies such as Wilms tumor, hepatoblastoma, and adrenal cortical carcinoma may develop in 5% to 10% of the patients, whereas gonadoblastoma, rhabdomyosarcoma, and neuroblastoma are uncommon. We report a unique case of a patient who has BWS attributable to hypomethylation of KvDMR1, who exhibited a progressive decrease in growth velocity resulting in short stature. This was found to be related to hypopituitarism with resulting growth hormone (GH) deficiency and secondary hypothyroidism. To the best of our knowledge, hypopituitarism has never been reported in patients who have BWS.

**CASE PRESENTATION**

This patient was born by normal vaginal delivery at 36 weeks of gestation with a birth weight of 3.34 kg (91st to 98th percentile for United Kingdom, World Health System growth charts). She was conceived naturally from a non-consanguineous marriage. After birth the infant became plerotic and presented with unconjugated hyperbilirubinemia, for which she received phototherapy. At birth, macroglossia, an umbilical hernia, and persistent hypoglycemia were noted.

In view of the clinical features, BWS was suspected and methylation status analysis of KvDMR and H19 were done and showed a loss of maternal methylation of the differentially methylated region KvDMR1 on chromosome 11p15.5. The blood glucose levels were persistently low despite an intravenous glucose infusion rate of >8.0 mg/kg/min. The hypoglycemia screen confirmed the hyperinsulinemic hypoglycemia (HH) (glucose 43 mg/dL with simultaneous insulin of 20 pmol/L) associated with low non-esterified fatty acids and ketone bodies (Table 1). Interestingly, the GH level and the cortisol response during hypoglycemia were in the lower normal range (Table 1). The patient was started on oral diazoxide (15 mg/kg/day in 3 daily doses) and chlorothiazide (7.5 mg/kg/day in 2 daily doses). A good response to the therapy was observed and it was planned to let the infant outgrow the dose of diazoxide, but at a dose of 8.5 mg/kg/day, the infant started to re-experience hypoglycemic episodes, for which the diazoxide dose was readjusted.

At 1 year of age, the glucose homeostasis was reassessed after the medications were temporarily stopped. The 24-hour blood glucose profile showed low blood glucose (54 mg/dL) levels, with a fast tolerance of only 5.5 hours. Although the insulin concentration was undetectable at the end of the fast, the fatty acid and ketone body response was poor, suggesting the presence of insulin-like action. In view of these results the patient was restarted on diazoxide and chlorothiazide. In the next months the HH became milder and the medications were stopped at the age of 2.5 years. When she was 18 months old, the patient underwent a surgical tongue reduction with good aesthetic and functional outcome.

From a development point of view the patient presented with mild speech delay, probably related to the macroglossia. After the tongue-reduction surgery there were no other development concerns and the developmental screening was normal for her age. During the first 2 years of life, her growth rate was appropriate. Her length was between the 2nd and 9th percentile and her weight was between the 9th and 25th percentile. At 3 years of age it was noticed that she was growing slowly and had fallen off to the 0.4th

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Glucose (45–100 mg/dL)</td>
<td>43.6</td>
<td></td>
</tr>
<tr>
<td>Cortisol (200–700 nmol/L)</td>
<td>177</td>
<td>Cortisol response to hypoglycemia appears inadequate</td>
</tr>
<tr>
<td>Insulin (&lt;12.0 pmol/L)</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>GH (5.7–57.8 µmol/L)</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Ammonia (&lt;68.0 µg/dL)</td>
<td>50 (48.0 umol/L vn &lt;40)</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood spot free and acyl carnitine profile</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Nonesterified fatty acids (mmol/L)</td>
<td>0.2</td>
<td>Inappropriately low free fatty acids for hypoglycemia</td>
</tr>
<tr>
<td>β-Hydroxybutyrate (mmol/L)</td>
<td>&lt;0.05</td>
<td>Inappropriately low 3-hydroxybutyrate for hypoglycemia</td>
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<tr>
<td>Urine ketones</td>
<td>Negative</td>
<td></td>
</tr>
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percentile for length, with the growth velocity at that time being 2.1 cm/year. The reduction in the growth rate prompted baseline pituitary function tests and a GH stimulation test (glucagon test), which showed GH deficiency and secondary hypothyroidism (Table 2). The serum insulin growth factor-1 (IGF-1) level was undetectable, and serum insulin growth factor binding protein-3 concentration was low. The cortisol response to hypoglycemia, the celiac screen, and the skeletal survey were normal.

The patient was started on replacement therapy with thyroxine at a dose of 12.5 mcg/day (1 mcg/kg/day). In view of the GH deficiency and the known increased risk for cancer associated with BWS, the possibility of GH therapy was carefully evaluated. From a malignancy surveillance point of view, the patient was having surveillance screening for BWS with abdominal ultrasound and serum α-fetoprotein checked every 3 months. Overall it was thought that the benefits of the GH treatment outweighed the risks. The family agreed, and at the age of 3 years and 9 months the patient was started on replacement therapy with recombinant GH at a dose of 3.7 mg/m²/w (11.0 IU/m²/w). A brain MRI showed small anterior pituitary with thin corpus callosum and slightly enlarged lateral ventricles (Fig 1).

RESULTS

After GH therapy, the growth velocity increased and the child’s height increased from the 0.4th percentile to the 2nd to 9th percentile (Fig 2). The hypoglycemic episodes completely ceased, and at her last visit at 4.6 years of age, her height was 98.2 cm (2nd to 9th percentile) with a growth velocity of 10 cm/year, and her weight was 14.9 kg (9th to 25th percentile). Because the serum IGF-1 level was low, the GH dose was increased to 4.4 mg/m²/w (13.5 IU/m²/w). The thyroid function tests were normal. To date, the patient has been on GH therapy for 1 year, with good compliance and no problems with the injections. She is well and the parents don’t have any concerns. She is being followed every 4 to 6 months and the surveillance screening for malignancy so far is normal.

DISCUSSION

BWS has been associated with a number of molecular alterations. One mechanism includes paternal uniparental disomy of a segment of chromosome 11 that involves both domains of chromosome 11p15.5.2 Occurring in ~20% of the patients,2,13,14 these genetic changes result in the over-expression of paternally expressed genes and a reduction in the expression of maternally expressed genes.2 In another 5% to 10% of patients who have BWS, sporadic gain of methylation of the H19 DMR maternal allele in domain 1 results in BWS.2 In contrast, 50% of patients who have BWS exhibit a sporadic loss of methylation of the KCNQ1OT1 DMR (KvDMR1) in domain 2 of chromosome 11p15.5,2,13 Moreover, mutations involving the CDKN1C gene have been shown in both autosomal dominant (25%) and sporadic cases (5%) of BWS.2 In our patient, BWS was diagnosed on the clinical features.11 The diagnosis was then confirmed by the genetic test for BWS. To the best of our knowledge, this is the first patient who has BWS who was found to have structural and functional defects in the pituitary gland. Brain abnormalities such as posterior fossa defects (Dandy-Walker variant, Dandy-Walker malformation, Blake pouch cyst, vermian hypoplasia), corpus callosum dysgenesis, and nasal encephalocele have been described in the past in patients who have BWS,15–17 but to date there are no reports of hypopituitarism in these patients. It’s known that on chromosome 11p15.5, in the imprinted domain 2 there are genes that are involved in the normal development of midline organs.15 This could potentially explain the association between BWS and midline defects. The abnormalities in the pituitary gland described in our patient could be independent from the BWS, but the established presence of other midline defects in patients who have BWS may lead us to the hypothesis that this may not be a mere incidental finding and an association between BWS and hypopituitarism may actually exist.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Results of the Glucagon Stimulation Test Showing Low GH Peak, Concomitant With GH Deficiency</th>
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<tbody>
<tr>
<td>Time</td>
<td>0</td>
</tr>
<tr>
<td>Glucose (60–100 mg/dL)</td>
<td>55.8</td>
</tr>
<tr>
<td>GH (&gt;21.0 mU/L)</td>
<td>7.2</td>
</tr>
<tr>
<td>Cortisol (200–700 nmol/L)</td>
<td>356</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (&lt;0.6 mU/L)</td>
<td>1186</td>
</tr>
<tr>
<td>Free thyroxine (10.8–19.0 pmol/L)</td>
<td>9.1</td>
</tr>
</tbody>
</table>

The thyroid function tests detected secondary hypothyroidism. The cortisol levels were normal.

FIGURE 1
The brain MRI showed small anterior pituitary with thinning of the corpus callosum and slightly reduced white matter bulk. The posterior pituitary is present in the normal position and it has normal size.
The hypopituitarism in our patient could have influenced her phenotype; at birth, the presence of macroglossia, umbilical hernia, protracted jaundice with unconjugated hyperbilirubinemia, feeding problems, and respiratory distress could also have been associated with congenital hypothyroidism, in addition to BWS. Furthermore, it’s known that jaundice is an important feature of congenital hypopituitarism in a high percentage of newborns. The mechanism is not yet completely clear; but GH and cortisol deficiency, as well as secondary hypothyroidism, could have a role. Jaundice related to congenital hypopituitarism is usually cholestatic, whereas in our patient it was mostly unconjugated. Specific tests to detect possible hypopituitarism were not performed in the first few days of life. Only TSH level as screening for congenital hypothyroidism was measured, which by itself is not sufficient for diagnosing secondary hypothyroidism.

2HH in the newborn period is a feature of different syndromes, with BWS being the most common one. Approximately 50% of patients who have BWS experience HH, but usually it is transitory and settles spontaneously within a few days. In cases in which hypoglycemia persists, medical therapy or even subtotal pancreatectomy is used as a last resort to control the hypoglycemia. In our proband the hypoglycemia lasted for a longer period and the child was on medical therapy with diazoxide for 2.5 years. It could be argued that the hypoglycemia may have been attributable to a combination of HH as well as GH deficiency. The hypoglycemic episodes completely resolved only after commencement of GH therapy.

The main issue about using GH therapy in a patient who has BWS is the known increased risk for cancer development related to the syndrome. This risk was carefully weighed and was abated by the fact that GH was being used as a replacement therapy in our patient, who was GH deficient. Moreover, our patient’s genetic basis for the BWS (KvDMR1 hypomethylation) is known to be associated with a minimal risk for developing malignancies. A study of 29 patients who have BWS with loss of methylation of KvDMR1 showed that none developed embryonal tumors. In BWS there is a correlation between genotype and phenotype; the patients who develop embryonal cancers usually have uniparental disomy or other defects such as defects in a distal 11p15.5 imprinting control element (BWSIC1), but generally they don’t have loss of methylation of KvDMR1. The child is on a low GH dose and is followed closely. Her serum IGF-1 levels are checked every 4 to 6 months to ensure that they remain within the normal range for the patient’s age. To date, the patient has responded well and the growth velocity has remarkably increased, despite the low GH dose and low serum IGF-1 level.

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