Raised somatomedin associated with normal growth hormone

A cause of Beckwith-Wiedemann syndrome?

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SUMMARY A child with Beckwith-Wiedemann syndrome is described. Growth hormone levels were normal, but circulating somatomedin activity was increased. The role of somatomedins in this condition, and the possibility of a feedback mechanism controlling somatomedin production are discussed.

The Beckwith-Wiedemann syndrome is rare and is characterised by omphalocele, muscular macroglossia, visceromegaly, and gigantism.1-2 Pancreatic islet-cell hyperplasia has been described at necropsy, and the resultant hyperinsulinism is believed to be the reason for the hypoglycaemia observed in many of the patients.3 Growth hormone (GH) levels have been reported to be normal4 and there is no explanation yet for the excessive growth.

Somatomedin, as the active mediator of GH, and an insulin-like peptide5 could be important in the aetiology of this syndrome. We describe a child with Beckwith-Wiedemann syndrome in whom we measured a number of hormones, including GH and somatomedin.

Case report

This baby boy was the first child of healthy non-consanguineous parents. He was delivered normally, 10 days before term, after an uneventful pregnancy. Two hours after birth blood glucose was < 25 mg/100 ml (1·39 mmol/l). Body length was 58 cm and weight 4·55 kg, both > 90th centile; head circumference was 34·5 cm, 50th centile. There was pronounced macroglossia, typical furrowing of the ear lobes in the shape of an inverted Y, a broad thorax, diastasis of the rectus abdominus, and a large, skin-covered umbilicus. Enlarged kidneys could be felt on both sides and the liver was palpable 2 cm below the right costal margin. The spleen was not palpable. The right testis was descended but the left was not palpable. Musculature was well developed. X-rays showed typical signs of the syndrome: advanced bone age, microcephaly, hypoplasia of the maxilla and prognatia, a prominent occiput, thymus hyperplasia, and enlarged kidneys. Blood-gases and electrolytes, blood cell count, and urine amino-acids were normal.

The baby was fed calorie-enriched milk 4-hourly, but in the first 2 weeks twice became hypoglycaemic with blood glucose levels 23·2 and 29·8 mg/100 ml (1·29 and 1·65 mmol/l). On the 10th day there was a rise in blood glucose from 29·8 to 56·4 mg/100 ml (1·65 to 3·13 mmol/l) 60 minutes after oral glucose administration. Blood glucose fell to 33·1 and 29·8 mg/100 ml (1·84 and 1·65 mmol/l) after 120 and 180 minutes respectively. At the start of the third week, blood glucose levels were normal and after 2 months repeated oral administration of glucose produced a normal glucose response, but without any detectable immunoreactive insulin.

Methods

Somatomedin activity was measured independently in two laboratories against the same standard reference plasma, using a porcine costal cartilage bioassay.6 GH and insulin were measured by radioimmunoassay, and glucose by the glucose-hexokinase method. Bone age was determined according to the atlas of Greulich and Pyle.

Results

The tolbutamide test causes a release of insulin and produces hypoglycaemia in the normal, but not in the diabetic state. In this patient the hypoglycaemic response to tolbutamide was pronounced, however no immunoreactive insulin was detectable. Plasma GH level was high at 4 weeks, but was normal at all other times that it was measured (Table 1).

Table 2 shows the length, weight, head circumference, and bone age during the first 3 years, together with measurements of urinary corticosteroid excretion and plasma cortisol levels.

Somatomedin activity was 9·4 and 9·8 U/ml at 32 months, whereas in pooled plasma collected from normal adults somatomedin activity was 1·0 U/ml. Plasma somatomedin increases throughout childhood until adult levels are reached during
adolescence. The normal plasma level at age 2 years is about 0·6 U/ml.

Thyroid function and thyroxine levels were normal.

Discussion

This patient exhibiting the Beckwith-Wiedemann syndrome had an advanced bone age and gigantism, however basal GH levels were normal, except at 4 weeks of age. The response of GH to insulin was normal at all ages at which it was tested. The normal GH level under both stimulated and nonstimulated conditions suggests that the GH-hypophyseal system was not the aetiological factor for the gigantism in this patient. Plasma somatomedin was very high at 32 months, despite the normal GH levels, and could have been responsible for the excessive height and weight.

The Laron dwarfism is now well documented and is characterised by high immunoreactive GH but negligible plasma somatomedin activity. It has been suggested that there is a defect in the control of somatomedin production, rather than a defect in the GH molecule. It would seem that our patient exhibits the other end of the spectrum as there is normal GH but high somatomedin activity. This suggests a defect in the control of somatomedin production and indicates that circulating somatomedin may control somatomedin production by a direct autoregulatory mechanism, but does not regulate GH production.

The liver is probably the main site of somatomedin production and the visceromegaly associated with Beckwith-Wiedemann syndrome often includes a large liver. This could be a part of the cause of high somatomedin levels; however in some experimental conditions of increased liver size (for example, the obese-hyperglycaemic syndrome in mice), plasma somatomedin activity is not increased. It is also interesting to note that patients with Beckwith-Wiedemann syndrome often have adrenal hyperplasia, and the somewhat raised 17-ketosteroid levels suggest that this patient may also have adrenal hyperplasia. Paradoxically, low somatomedin levels have been associated with adrenal hyperplasia in Cushings syndrome when they are thought to be due to inhibition of the bioassay by increased levels of cortisol.

The tolbutamide test produced a strong hypoglycaemic response, but this was not accompanied by any detectable immunoreactive insulin. It has been established that most of the serum insulin activity is nonsuppressible immunoreactive insulin (NSILA). Somatomedin has a strong insulin-like activity, and somatomedin activity cannot be separated from NSILA during purification. It seems that NSILA is one of the family of somatomedins, and could be a factor in the hypoglycaemia associated with some cases of Beckwith-Wiedemann syndrome. However, the present knowledge of somatomedin response to tolbutamide is not sufficient to explain the decrease in glucose after a tolbutamide test, although the high NSILA of somatomedin may be implicated.

It would seem that in this patient the gigantism, macroglossia, and visceromegaly may be the result of a defect in the control of somatomedin production, leading to increased somatomedin levels in the plasma. If this patient is typical of patients with Beckwith-Wiedemann syndrome, the high somatomedin activity may be at least one of the causative factors of this condition.

References

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Recognition of bilateral neonatal testicular torsion

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SUMMARY Two cases of bilateral neonatal testicular torsion are reported and combined with 6 previously reported ones. These infants with bilateral testicular torsion are compared with neonates with unilateral torsion. Both have similar signs and symptoms: (1) a swollen bluish-red firm scrotum at birth, and (2) no evidence of spontaneous pain. Infants in neither group had any systemic symptoms. Immediate investigation with reduction is mandatory to prevent testicular atrophy.

Bilateral neonatal testicular torsion remained unrecognised until the reports of Frederick et al. and Papadatos and Moutsouris in 1967. Since then 4 more cases have been reported; yet, the clinical presentation has not been defined. The purpose of this report is to define the clinical features of bilateral neonatal testicular torsion and to correlate these findings with those of the more common unilateral testicular torsion.

Patients and methods

14 patients with unilateral testicular torsion were identified from the records over 100 years at the Hospital for Sick Children, of which 12 were sufficiently documented for analysis. The clinical

Table 100-year review of unilateral neonatal testicular torsion. Comparison with 8 cases of bilateral neonatal testicular torsion of which 6 are cited from the literature. All patients were aged <28 days. Bilateral torsion, under surgical procedures and findings, are recorded for each side

<table>
<thead>
<tr>
<th>Unilateral(%)</th>
<th>Bilateral(%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median gestation (weeks)</td>
<td>41 (n=11)</td>
<td>All term</td>
</tr>
<tr>
<td>Median weight (kg)</td>
<td>3.60</td>
<td>3.49</td>
</tr>
<tr>
<td>(n=12)</td>
<td>(n=6)</td>
<td></td>
</tr>
<tr>
<td>Side of involvement</td>
<td>8R:6L</td>
<td>8R:8L</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, firm</td>
<td>1/4/14</td>
<td>8/8</td>
</tr>
<tr>
<td>Discoloration</td>
<td>9/9</td>
<td>8/8</td>
</tr>
<tr>
<td>Blue</td>
<td>6/8 (75)</td>
<td>2/6 (33)</td>
</tr>
<tr>
<td>Red</td>
<td>2/8 (25)</td>
<td>4/6 (67)</td>
</tr>
<tr>
<td>Elicited scrotal pain</td>
<td>4/7 (57)</td>
<td>0/6</td>
</tr>
<tr>
<td>Spontaneous scrotal pain</td>
<td>0/7</td>
<td>0/5</td>
</tr>
<tr>
<td>Apparent abdominal pain</td>
<td>0/6</td>
<td>0/4*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0/8</td>
<td>0/4*</td>
</tr>
<tr>
<td>Surgical procedure and findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploration alone</td>
<td>± unilateral</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>Orchidectomy</td>
<td>or contralateral</td>
<td>7/14 (50)</td>
</tr>
<tr>
<td>orchidopexy</td>
<td>(10/14 (71)</td>
<td>7/14 (50)</td>
</tr>
<tr>
<td>No operation</td>
<td>1/14 (7)</td>
<td>0/14</td>
</tr>
<tr>
<td>Extravaginal torsion</td>
<td>7/9 (78)</td>
<td>12/14 (86)</td>
</tr>
</tbody>
</table>

*One patient excluded due to symptomatic Hirschsprung’s disease.
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