Graves’ disease associated with exophthalmos, cerebral ventricular dilatation and accelerated growth

Osamu Arisaka, Atsuto Hosaka, Hajime Arai, Sachi Fujiwara, Rieko Tadokoro, Keijiro Yabuta

Abstract
A report is presented of a girl with Graves’ disease, which was diagnosed at the age of 1.7 years. The mother had no thyroid disease. The patient developed signs of hyperthyroidism shortly before her first birthday, and the most prominent manifestations were accelerated skeletal maturation and linear growth, and dilatation of the brain ventricles. The latter manifestation, which has not been reported previously, was reversible upon normalisation of thyroid function with antithyroid treatment for three years.

Keywords: Graves’ disease; reversible ventriculomegaly; growth acceleration.

Hyperthyroidism during childhood is usually caused by Graves’ disease. Apart from the transient neonatal cases that develop in infants born to mothers with active Graves’ disease, the disease occurs infrequently in preschool children and rarely may begin in infancy. We describe the four year clinical course of a patient with Graves’ disease that was diagnosed at 1.7 years of age, although the disease had probably developed in late infancy. There were typical clinical signs of hyperthyroidism, but the patient’s growth and development were most affected.

Case report
A girl aged 1.7 years was referred because of bilateral exophthalmos (fig 1). She had been born normally (weight 2980 g) as the first child to a healthy mother. The family history did not suggest thyroid disease or other autoimmune diseases. The patient was 88.2 (+2.5 SD) cm tall, with a body weight of 12 kg and a head circumference of 46.5 (+0.2 SD) cm. She presented with restlessness, sweating, mild thyromegaly, tachycardia (130/min), and a systolic murmur (Levine 3/6). She had upper eyelid retraction and infrequent blinking. The anterior fontanelle was closed, and there was no frontal bossing or craniosynostosis. She had increased deep tendon reflexes, and her optic fundi were normal.

Further questioning revealed that these signs had developed shortly before 1 year of age. However, her milestones of motor and mental development up to the time of presentation had been normal except for linear growth acceler-
tion with advanced skeletal development (4.5 years by TW2 method for Japanese children) (fig 2). Also, a photograph taken at the age of 8 months revealed no exophthalmos (fig 1).

Thyroid function tests including immunological tests and biochemical tests are shown in table 1. The mother was euthyroid and had no detectable antithyroid antibodies including antimicrosomal antibody and thyrotrophin binding inhibitory immunoglobulins (TBII). Cardiomegaly (cardiothoracic ratio 60%) was recognised in a chest x-ray film, and mitral valve regurgitation was detected by colour Doppler echocardiography. Brain computed tomography had shown dilatation of the ventricular system (fig 3). This scan had been carried out at the referred hospital to rule out retro-orbital tumours.

A diagnosis of Graves’ disease was made and treatment was started with antithyroid drug (methimazole 10 mg daily) and a β-adrenergic blocker (propranolol 5 mg daily). Thyroid function became normal in several months. Propranolol was then withdrawn and the dose of methimazole was reduced (5–2.5 mg), but maintained thereafter. The systolic heart murmur and exophthalmos (fig 1) remained for two to three years and ventricular dilatation regressed over a four year period (fig 3).

Antithyroid treatment was stopped at the age of 4.5 years, when thyroid function (thyroxine 93.9 nmol/l; triiodothyronine 2.15 nmol/l; thyroid stimulating hormone 2.27 mU/l; TBII 2.9%) and the result of a triiodothyronine suppression test appeared normal. During the treatment, there were no complications.

On review at 5 years of age, the patient was within the normal ranges for social, motor, and communicative development. Her growth curve with skeletal ages are shown in fig 2. At present, sexual development is Tanner stage I.

Discussion

Occasionally, neonatal hyperthyroidism does not remit and persists into childhood. Such patients may have a family history of hyperthyroidism, although circulating thyroid antibodies are absent. It has recently been established that children with this disorder have a mutation of the thyroid stimulating hormone

### Table 1 Laboratory data of the patient at admission

<table>
<thead>
<tr>
<th>Endocrinological data</th>
<th>Value</th>
<th>Normal for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroxine (nmol/l)</td>
<td>463</td>
<td>90-180</td>
</tr>
<tr>
<td>Triiodothyronine (nmol/l)</td>
<td>7.9</td>
<td>1.3–3.8</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mU/l)</td>
<td>&lt; 0.05</td>
<td>2–8</td>
</tr>
<tr>
<td>TBII (%)</td>
<td>52.2</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Biological activity of thyroid stimulating hormone antibodies (%)*</td>
<td>500</td>
<td>&lt; 145</td>
</tr>
<tr>
<td>Antimicrosomal antibody (%)</td>
<td>&lt; 1:10</td>
<td>&lt; 1:10</td>
</tr>
<tr>
<td>Insulin-like growth factor I (U/l)</td>
<td>0.78</td>
<td>0.3–1.0</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Osteocalcin (nmol/ml)</td>
<td>10.5</td>
<td>1.6–3.2</td>
</tr>
<tr>
<td>Biochemical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>2.9</td>
<td>2.7–4.5</td>
</tr>
<tr>
<td>Creatine kinase (U/l)</td>
<td>125</td>
<td>50–150</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/l)</td>
<td>28</td>
<td>5–35</td>
</tr>
<tr>
<td>Alkaline phosphatase (KAU/l)</td>
<td>33</td>
<td>15–25</td>
</tr>
<tr>
<td>Urinary calcium/creatinine ratio</td>
<td>0.9</td>
<td>&lt; 0.15</td>
</tr>
</tbody>
</table>

*Cyclic AMP generation by rat thyroid cell line with patient's serum.
Arisaka, Hosaka, Arai, Fujisawa, Tadokoro, Yabuta

As Graves’ disease progresses insidiously, it is difficult to know when the hyperthyroidism in the present patient developed. It may not have occurred until mid-infancy, because exophthalmos, clinical signs of hyperthyroidism, and growth acceleration had not been evident until then. Furthermore, skull abnormalities, such as frontal bossing, craniosynostosis, and microcephalus, which are evidence of malformations, such as premature fusion of skull sutures, were not recognised in the present case. Therefore we suspect that the disease developed at a later stage of infancy.

In our patient, there were various typical manifestations of hyperthyroidism, some of which are usually seen in older patients. The most prominent manifestation was accelerated skeletal maturation and growth, although these phenomena have been reported to occur commonly in young children with Graves’ disease. The raised serum osteocalcin level and the increased urinary calcium/creatinine ratio would have indicated a bone metabolic status representative of increased bone turnover due to excess thyroid hormone.

The ventriculomegaly in the present case was an unexpected finding. This feature has been documented in only one report of twins with congenital hyperthyroidism. Pseudotumour cerebri (be

Markers of bone turnover in hyperthyroidism and the persistent form of Graves’ disease which develops in infancy, as described here, is very rare, but early recognition and antithyroid treatment are critical because a delay in the diagnosis of such young patients can have a marked effect on growth and development.

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