A Case of Turner’s Syndrome with Hyperthyroidism

KOICHI KAWAI, IKUKO KONDO, TARO TERASAKI AND ETSURO OGATA

The Institute of Clinical Medicine, the University of Tsukuba, Niihari-gun, Ibaraki-ken 300-31, Japan

Synopsis

A female patient with classical gonadal dysgenesis associated with Graves’ disease is reported. The karyotype was mosaicism of 45,X/46,X,i(Xq). The relationship among Graves’ disease, Hashimoto’s thyroiditis and Turner’s syndrome is discussed along with a review of the reported cases.

The association of gonadal dysgenesis with autoimmune thyroiditis is well established (Williams et al., 1964). In contrast, the association with Graves’ disease, allegedly another autoimmune thyroid morbidity, has been reported in only scattered cases (Grumbach and Morishima, 1964; Torizuka, 1969; Miyamoto et al., 1972; Chang and Burkle, 1973; Kondo and Sasaki, 1975; Brooks et al., 1977). In this communication a case of patient with Graves’ disease is presented who has the karyotype of 45,X/46,X,i(Xq) mosaicism. Then, relationships between Graves’ disease and Turner’s syndrome are discussed with special emphasis on the autoimmune phenomena.

Case Report

A 34-year-old Japanese female visited us because of palpitation and easy fatigability. She was the fifth product of healthy nonconsanguinous parents with normal pregnancy and delivery. The birth weight was 2,300 g. Tinnitus and a difficulty in hearing have been noticed since about 7 years. At 27, she presented herself at another hospital for amenorrhea, poor breast development and short stature, and treatment with estrogen and gestagens was instituted with a diagnosis of Turner’s syndrome. At 29, she got married and thereafter the medical control including the hormone treatment was interrupted. At 30, she began to notice a gradual increase in fatigability, palpitation and sweating. During the last two years she lost about 8 kg in weight. The family history was non-contributory.

Physical examination revealed a thin jittery female; height, 132 cm; weight, 28.0 kg. The pulse was regular and 120 per minute, the blood pressure, 120/70 mmHg. The thyroid gland was diffusely enlarged (about 30 g) with rubbery firm consistency. Fine finger tremor was detected. The skin was moist and generally dusky. Mal-demarcated depigmentation was present at the back, to which a diagnosis of nevus depigmentia was made by a dermatologist. She had a high arched palate, an increased carrying angle in the elbows, short fourth metacarpals, clinodactylyia in the right fifth
finger, prominent clavicle bones and "shield-like" chest. Webbing of the neck was very poor. Axillary and pubic hair was absent. Examination of the lungs, the cardiovascular system and the abdomen was negative. External genitalia was infantile and a small uterocervical body was felt. The eyes were negative for the symptoms of Graves' disease, but cataracta congenita was detected bilaterally. The IQ was low normal.

In X-ray examinations; bones were slightly osteoporotic. The skull was normal except for hypoplasia of mastoid cells. The Kosowicz's exostosis, short metacarpals (the fourth, bilaterally), and a deformity of the right fifth phalanx were detected. The chest, gastrointestinal tract and the urological system were normal roentgenologically.

Laboratory investigations revealed normal urinalyses and blood counts. Blood chemistry was normal except for high alkaline phosphatase, 22.7 K-A units (normal, 2.6–10.0 U). A 50 g oral glucose tolerance test was normal. The LH-RH provocative test (100 µg LH-RH iv) showed high base-line levels of LH and FSH (LH, 45.0 mIU/ml; FSH, 37.0 mIU/ml) and exaggerated responses (LH, 135.0 mIU/ml; FSH, 49 mIU/ml at 30 min).

Chromosome studies
The incidence of sex-chromatin in buccal smear samples was 7% (normal value for female, 20%; and normal value for male, less than 5%). The peripheral blood leukocytes and biopsied skin samples were cultured according to the standard methods (Moorhead et al., 1960).

Two cell lines were identified both in lymphocytes [35.7% (45, X) and 64.3% (46, X, i(Xq))] and in fibroblasts [26.0% (45, X) and 74.0% (46, X, i(Xq))], the karyotype being 45X/46X, i(Xq) according to the terminology recommended by Paris Conference (1971).

Dermatoglyphic studies revealed the axillary triradius t and increased total ridge counts.

Discussion
The present patient exhibited typical signs of Turner's syndrome. The karyotype was 45, X/46X, i(Xq) mosaicism. She had a diffuse goiter and thyrotoxicosis of about five years of duration. The fact that the thyroidal 131I-uptake rate was high and not suppressed by T₃ indicates that thyrotoxicosis of this case was due not to hyperthyroiditis but to Graves' disease.

In contrast to the well-recognized combination of Turner's syndrome with Hashimoto's thyroiditis, the combination with Graves' disease has been reported rather rarely. Only eight such patients including three in Japanese literatures have been published (Table 1).

In patients with Turner's syndrome increased incidence was also demonstrated with diabetes mellitus, ulcerative colitis and rheumatoid arthritis (Forbes and Engel, 1963; Williams et al., 1966; Elejalde et al., 1966). Because the pathogenesis of these diseases is being discussed on the basis of autoimmunity and Hashimoto's thyroiditis is considered to be a typical example
of autoimmune disease, the relationship between these diseases and gonadal dysgenesis has been explained from autoimmunity phenomena (Williams et al., 1966). Recently accumulating evidence indicates that Graves’ disease is also a disorder of immunity (Kriss et al., 1964; Volpe et al., 1972). Cases were reported in which Graves’ disease interchanged with Hashimoto’s thyroiditis (McConahey, 1972).

In the present thyrotoxic patient, the goiter was moderate in size and rubbery firm in consistency. Serum tests were strongly positive for thyroid antigens. Eye signs were negative. These findings are compatible with those for chronic thyroiditis. But, this possibility (hyperthyroiditis) was excluded by the T<sub>3</sub> suppression test. One likely interpretation is that hyperthyroidism of such patients has a pathogenetic autoimmune basis common to Hashimoto’s thyroiditis. Then the next question is why the Turner’s syndrome with hyperthyroidism was rare in contrast to that with Hashimoto’s thyroiditis. This may be explained if one assumes that different autoimmune processes are involved in typical Graves’ disease and Hashimoto’s thyroiditis. Then only a special type of chronic thyroiditis is to be associated with diffuse toxic goiter. It is of interest that two of the patients (No. 1 and No. 2) summarized in Table 1 were described either as being complicated with or being changed to Hashimoto’s thyroiditis.

In Table 1, the incidence of isochromosome was not high (2/9) in the patients with hyperthyroidism in contrast to those with chronic thyroiditis (Sparkers and Motulsky, 1967). The association between autoimmune susceptibility and several major human histocompatibility complexes has been established. The genes for the major histocompatibility antigens is located at

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>PBI (μg/dl)</th>
<th>T&lt;sub&gt;3&lt;/sub&gt; (μg/dl)</th>
<th>T&lt;sub&gt;4&lt;/sub&gt;RSU (%)</th>
<th>Test 24 hr</th>
<th>1&lt;sup&gt;3&lt;/sup&gt;-I-uptake (%)</th>
<th>Exophthalmos</th>
<th>Thyroid Test</th>
<th>Microsome Test</th>
<th>Chromosome Studies</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;*/1&lt;/sup&gt;</td>
<td>n.d.&lt;sup&gt;2&lt;/sup&gt;</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>not suppressed with T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>n.d.</td>
<td>n.d.</td>
<td>45X/46X, r(X)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Grumbach and Morishima. (1964)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>5.0</td>
<td>n.d.</td>
<td>37.0</td>
<td>78.9</td>
<td>(+)</td>
<td>1:10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>n.d.</td>
<td>46X, i(Xq)</td>
<td>Torizuka et al. (1969)</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;*/4&lt;/sup&gt;</td>
<td>15</td>
<td>n.d.</td>
<td>9.5</td>
<td>30.8</td>
<td>16.4</td>
<td>(+)</td>
<td>(−)</td>
<td>n.d.</td>
<td>45X</td>
<td>Miyamoto et al. (1972)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>17.1</td>
<td>15.8</td>
<td>59.8</td>
<td>66</td>
<td>(+)</td>
<td>1:25</td>
<td>n.d.</td>
<td>45X</td>
<td>Change and Burke (1973)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>reported as elevated</td>
<td>n.d.</td>
<td>(+)</td>
<td>n.d.</td>
<td>n.d.</td>
<td>45X/46X, r(X)</td>
<td>Kondo and Sasaki (1975)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>17</td>
<td>n.d.</td>
<td>n.d.</td>
<td>67</td>
<td>(+)</td>
<td>1:640</td>
<td>n.d.</td>
<td>45X/46XX</td>
<td>Brooks et al. (1977)</td>
<td></td>
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<tr>
<td>7</td>
<td>23</td>
<td>25.5</td>
<td>n.d.</td>
<td>n.d.</td>
<td>71</td>
<td>(+)</td>
<td>1:1024</td>
<td>n.d.</td>
<td>45X</td>
<td>Brooks et al. (1977)</td>
<td></td>
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<tr>
<td>8</td>
<td>15</td>
<td>n.d.</td>
<td>7.7&lt;sup&gt;5&lt;/sup&gt;</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>45X/46XX</td>
<td>Brooks et al. (1977)</td>
<td></td>
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<tr>
<td>9</td>
<td>34</td>
<td>n.d.</td>
<td>20</td>
<td>40</td>
<td>not&lt;sup&gt;6&lt;/sup&gt; suppressed with T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>(−)</td>
<td>1:10&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1:320&lt;sup&gt;2&lt;/sup&gt;</td>
<td>45X/46X, i(Xq)</td>
<td>present report</td>
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<sup>*/1</sup> Hashimoto’s thyroiditis with biopsy.
<sup>*/2</sup> n.d.; not described
<sup>*/3</sup> r(X); ring chromosome
<sup>*/4</sup> treated with radioactive iodine at 10 y.o.
<sup>*/5</sup> data under treatment with propylthiouracil for 18 months.
<sup>*/6</sup> 1<sup>3</sup>-I-uptake, 20 min.
the sixth chromosome in human. Because Turner's syndrome is a disorder of sex chromosome, the likelihood is remote that combination of two disorders is due to a single gene defect. Considering the high susceptibility to autoimmune disease in Turner's syndrome, analysis of the HLA genes still appears of consideral importance.

References