

## Short communication

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### Gonadal dysgenesis with Graves's disease<sup>1</sup>

**SUMMARY** Hashimoto's thyroiditis has previously been associated with gonadal dysgenesis. Recent evidence suggests that Graves's disease and Hashimoto's thyroiditis are disorders of cell-mediated immunity and may have a common genetic predisposition. However, patients with both Graves's disease and the Turner syndrome have been reported only rarely. Three such cases are presented and the relation among gonadal dysgenesis, Hashimoto's thyroiditis, and Graves's disease is discussed.

Chronic lymphocytic (Hashimoto's) thyroiditis is one of several autoimmune disorders associated with gonadal dysgenesis (Rimoin and Schimke, 1971). Recent evidence indicates that Graves's disease is also a disorder of cell-mediated immunity (Volpe *et al.*, 1972). Immunoclinical studies of families and twins suggest that these two thyroid diseases may have a common genetic predisposition (Fialkow, 1969). Since Hashimoto's thyroiditis has been reported with increased frequency in the Turner syndrome, one might also expect a higher incidence of Graves's disease in such patients. However, a review of the medical literature revealed only two previous case reports (Grumbach and Morishima, 1964; Chang and Burkle, 1973). We have seen three patients with this apparently unusual dual endocrinopathy.

#### Case reports

##### CASE 1

A 20-year-old woman presented with progressive enlargement of the thyroid gland accompanied by exophthalmos, nervousness, weight loss, fatigue, and frequent stools. She had a previous history of primary amenorrhea which responded to oestrogen therapy. There was no family history of thyroid

disease or chromosomal abnormality. Examination showed a short, tremulous woman who had a blood pressure of 160/60 mmHg. Her thyroid was diffusely enlarged with an audible bruit and she had non-infiltrative ophthalmopathy. Pelvic examination revealed infantile labia with a small midline uterus. The PBI was 17  $\mu\text{g}/\text{dl}$ , the 24-hour <sup>131</sup>I uptake was 67%, and the serum thyroglobulin antibody titre was 1:640. An intravenous pyelogram showed a horseshoe kidney. A peripheral blood karyotype showed XO/XX mosaicism.

##### CASE 2

A 23-year-old woman presented with complaints of increasing nervousness, a thirty-pound weight loss, photophobia, and a goitre. She had had primary amenorrhea and had undergone repair of an aortic coarctation. She was a short, white woman with a webbed neck, marked exophthalmos with periorbital oedema, and a diffusely enlarged goitre with an audible bruit. The serum thyroxine was 25.5  $\mu\text{g}/100\text{ ml}$  and the thyroglobulin antibody titre was 1:1024. Both the two- and eight-hour LATS responses were substantially raised. The 24-hour <sup>131</sup>I uptake was 71%. Chromosome analysis from peripheral blood lymphocytes showed a 45,X karyotype. The buccal smear was negative.

##### CASE 3

A 15-year-old girl was investigated because of short stature and primary amenorrhea. At the age of 9 she had been diagnosed as having Graves's disease and was placed on propylthiouracil for 18 months. Subsequent thyroid studies had been within normal limits. She was an alert white girl, 139 cm tall. She had multiple pigmented naevi, short fourth metacarpals bilaterally, and absent secondary sex characteristics. A serum thyroxine was 7.7  $\mu\text{g}/\text{dl}$ . A peripheral blood karyotype showed XO/XX mosaicism.

#### Comment

Patients with the Turner syndrome have an increased incidence of autoimmune endocrine disorders such as lymphocytic thyroiditis, diabetes mellitus, and idiopathic Addison's disease (Rimoin and

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Schimke, 1971). Recent surveys indicate that primary myxoedema and thyroid antibodies also occur more often in patients with the Turner syndrome than in a control, age-matched population (Fialkow, 1969). Though the thyroid antibodies were found with equal frequency in chromatin-positive and chromatin-negative patients, most patients who had clinical Hashimoto's disease were chromatin-positive and usually had an isochromosome. Graves's disease also shows several characteristics compatible with an autoimmune aetiology. Histologically the thyroid gland in this disease exhibits foci of plasma cells and lymphocytes and the serum contains both thyroid stimulating immunoglobulins such as LATS and 'LATS protector' along with antithyroglobulin and antimicrosomal antibodies. Patients with Graves's disease and with Hashimoto's thyroiditis both show a macrophage-inhibiting factor (MIF) response to thyroid antigen (Volpe *et al.*, 1972). Furthermore, an increased proportion of thymus-derived lymphocytes has been demonstrated in patients with both diseases (Farid *et al.*, 1973). Immunoclinical studies of twins and families also indicate that Graves's disease and Hashimoto's thyroiditis are aetiologically related and, indeed, have even been reported in the same individual (Fialkow, 1969).

Graves's disease as a complication of the Turner syndrome has been reported only rarely—a surprising finding in view of the genetic and aetiological relation between Graves's disease and Hashimoto's thyroiditis. One of these patients had an X/X translocation with partial deletion of both a short arm of one X and a long arm of the other; the other had XO/XXr mosaicism. Perhaps the coexistence of the two conditions is more common than is generally

recognized and mild degrees of thyrotoxicosis are clinically masked by the hypogonadal state or some other facet of the Turner syndrome. Since Graves's disease and Hashimoto's thyroiditis represent somewhat different aspects of the spectrum of autoimmune thyroid function conceivably the absent or altered X-chromosome in some fashion renders the thyroid more susceptible to a hypo- rather than hyperfunction. More detailed studies of the immune system in patients with the Turner syndrome may offer significant insight into the role of the X-chromosome in the immune response.

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#### References

- Chang, J. C., and Burkle, J. S. (1973). Unusual X chromosome in hyperthyroidism and Turner's syndrome. *New York State Journal of Medicine*, **73**, 1101-1104.
- Farid, N. R., Munro, R. E., Row, V. V., and Volpe, R. (1973). Peripheral thymus-dependent (T) lymphocytes in Graves' disease and Hashimoto's thyroiditis. *New England Journal of Medicine*, **288**, 1313-1317.
- Fialkow, P. J. (1969). Genetic aspects of autoimmunity. *Progress in Medical Genetics*, **6**, 117-167.
- Grumbach, M. M., and Morishima, A. (1964). X-chromosome abnormalities in gonadal dysgenesis. *Journal of Pediatrics*, **65**, 1087-1088.
- Rimoin, D. L., and Schimke, R. N. (1971). *Genetic Disorders of the Endocrine Glands*. C. V. Mosby, St. Louis.
- Volpe, R., Edmonds, M., Lamki, L., Clarke, P. V., and Row, V. V. (1972). The pathogenesis of Graves' disease. *Mayo Clinic Proceedings*, **47**, 824-834.