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Unusual Abnormal X Chromosome in Hyperthyroidism and Turner's Syndrome

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The concurrence of thyroiditis and Turner's syndrome was first described in 1961 by Engel and Forbes.[1] Since then, several additional reports have detailed clinical and cytogenetic studies in patients with Turner's syndrome and thyroid diseases, particularly Hashimoto's thyroiditis. The possible mechanisms of the relationship of the two diseases have been postulated and discussed.[2-6] The most frequently reported thyroid disease associated with Turner's syndrome is Hashimoto's thyroiditis. Other thyroid diseases have been reported.[2-4,7-9] Explanations of the relationship of these two distinct diseases employing theories of autoimmune mechanism and chromosomal aberration have been attempted.

Although there have been several reports of Hashimoto's thyroiditis associated with Turner's syndrome, only one case of associated hyperthyroidism has been reported.[4] In this study a patient with typical Turner's syndrome complicated by severe hyperthyroidism is described. The spectrum of thyroid diseases occurring in Turner's syndrome is reviewed and the possible pathogenesis discussed.

Case report

A twenty-year-old white female was admitted on December 17, 1969, with the chief complaint of ankle edema and productive cough of six weeks' duration. The present illness began three months prior to admission with ankle edema, which initially subsided with rest. The patient then noticed a slight continuous fever and chronic fatigue. Approximately six weeks prior to admission, she experienced chills and fever accompanied by nausea and vomiting. A cough productive of small amounts of white sputum developed. The ankle edema increased and persisted. Recently, she had frequent loose bowel movements one to three times a day. She consulted her family physician, who referred her to the hospital.

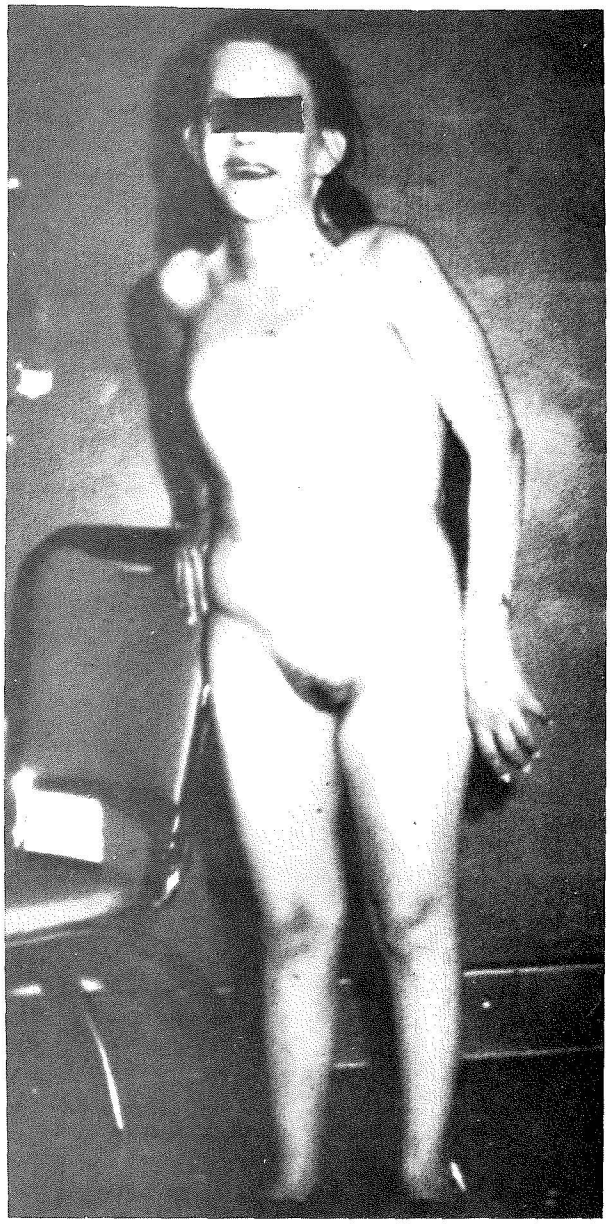

FIGURE 1. Patient with typical stigmata of Turner's syndrome. Note short stature with classical somatic anomalies.

The patient, who is the oldest of five siblings, was hospitalized shortly after birth for failure to thrive. Her growth was slow in comparison to her siblings. She had always been much smaller than her peers but had been able to participate nor-

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mally in childhood activities. According to her parents, she was found to have hypertension in 1967 and had been taking antihypertension drugs intermittently since. The patient had never menstruated. At age seventeen years this was evaluated by a physician, who assured the parents that "nothing was wrong." There was a history of diabetes in her paternal grandfather.

Physical examination revealed a height of 55 inches and a weight of 115 pounds. The temperature was 100° F., pulse rate 130 per minute, and blood pressure 200/90 in both arms and 140/90 in the left leg. She demonstrated the typical stigmata of Turner's syndrome, including webbed neck, low posterior hairline, and shield-like chest. Additional important features were typical facies, low-set malformed ears, wide-spread nipples, cubitus valgus, brachydactyly, and borderline mental retardation (Fig. 1).

Her skin was warm, moist, and velvety with fine sparse axillary and pubic hair in normal distribution. The eyelids showed slight proptosis. The thyroid was slightly enlarged with an estimated weight of 30 Gm. The heart revealed sinus tachycardia with Grade III to VI systolic murmur in the pulmonic area with radiation to the precordium, neck, and back. A fine tremor of the extended fingers was noted. There was massive pitting edema in both lower extremities. The deep tendon reflexes were slightly hyperactive.

Severe congestive heart failure was evident. Treatment with furosemide, ethacrynic acid, and rapid digitalization was instituted. On the second hospital day evidence of failure had subsided remarkably. The diagnosis of hyperthyroidism was clinically suspected and confirmed by thyroid function studies. Propranolol, 10 mg. three times a day, and propylthiouracil, 100 mg. every six hours, were instituted on the seventh hospital day. The blood pressure stabilized at 160/85, pulse rate 90 per minute, and temperature 98.0° F. after five days. Roentgenogram of the chest revealed notching of the ribs, highly suggestive of coarctation of aorta. Further evaluation and correction of cardiac anomalies await establishment of euthyroid state.

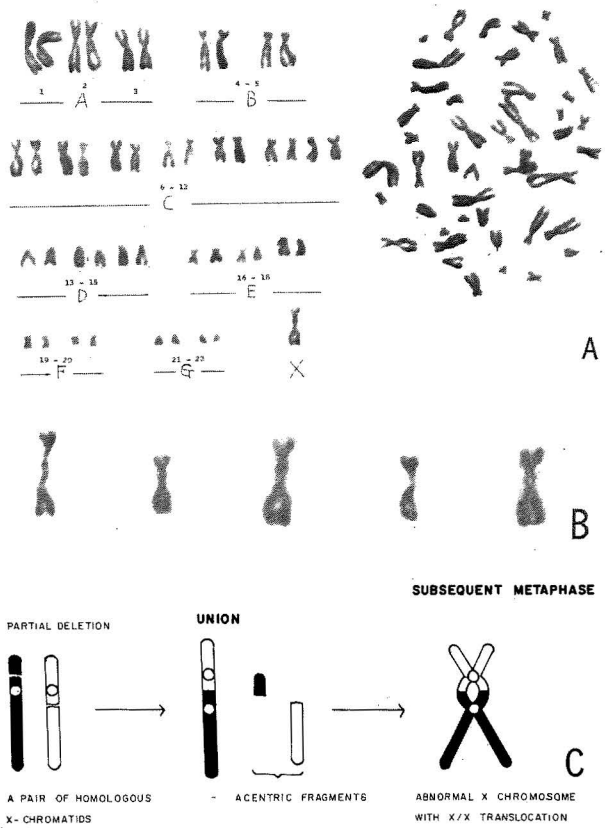

FIGURE 2. (A) Karyotype of patient arranged according to Denver classification. Note abnormal X chromosome. Metaphase plate also shown. (B) Series of abnormal X chromosome collected from five different metaphases. Note each X chromosome has same abnormal characteristic configuration with two centromeres. (C) Possible mechanism of partial deletion and X/X translocation to form abnormal X chromosome seen in patient.

Cytogenetic findings. Buccal smears showed 3 cells out of 100 with Barr bodies. Chromosome analysis of leukocytes was performed on peripheral blood using the kit technic (Difco). Fifty-five cells were examined at metaphase; all showed 45 XO chromosome pattern. This X chromosome was abnormal in most metaphase plates (Fig. 2A and 2B). Tentatively, we interpreted this as X/X translocation with partial deletion of two long arms of one X chromosome and of two short arms of the other. During early mitosis the partial deletion and translocation converted two homologous X chromatids into an abnormal X chromatid containing one short arm, one long arm, and partially deleted short and long arms each with two centromeres. In a subsequent metaphase the abnormal X chromosome was formed (Fig. 2C). Two fragments of the deleted long arm and short arm which do not contain a centromere are probably lost in later cell divisions. The possibility of secondary constriction of the long arms of X chromosome was considered but discounted by careful examination of the shape of several abnormal chromosomes. Autoradiography was attempted using ^{3}H-thymidine but did not show heavy labeling chromosome.

Thyroid function studies. Findings of thyroid-function studies confirmed the clinical impression of hyperthyroidism. The serum protein-bound iodine determination was done by the method of Technicon Autoanalyzer. The serum T_4-1 was determined by the modified method of competitive protein-binding analysis of Murphy and Pattee.[10] Both of these were above normal range. T_3 resin uptake was performed by the modified method of Sterling and Tabachnik.[11] In addition, the uptake and scan of the thyroid were

TABLE I. Thyroid function studies

Test	Normal	Patient
Protein bound iodine (micrograms per 100 ml.)	4.0 to 8.0	17.1
T_4-I (micrograms per 100 ml.)	3.5 to 8.5	15.8
T_3 resin uptake (per cent)	25.0 to 35.0	59.8
Iodine-131 uptake (per cent)		
Six hours	6.0 to 18.0	50.0
Twenty-four hours	9.0 to 32.0	66.0
Cholesterol (milligrams per 100 ml.)	150.0 to 300.0	110.0
Thyroid antibody titer*	none	1:25

* By tanned red cell agglutination test.

done using 20 microcurie iodine-131 in six and twenty-four hours. This revealed hyperthyroid range iodine uptake and a slightly enlarged thyroid with the radioactivity evenly distributed in both lobes (Table I).

Comment

This patient presents a typical clinical picture of Turner's syndrome with 40 XO karyotype and, in addition, has abnormal X chromosome. A variety of chromosomal aberrations, including XO/XX or XO/XXX mosaicism, XX isochromosome, and XX ring chromosome, has been described with Turner's syndrome. Also, there have been reports of so-called "male Turner's syndrome," or "Ullrich-Turner's syndrome." This latter syndrome usually occurs among males with XY karyotype or its mosaic. To our knowledge, this patient is the first report of a case of Turner's syndrome with a presumptive X/X translocation.

Recently, an unusual association of Hashimoto's thyroiditis in Turner's syndrome has been reported (Table II). Other presumed autoimmune diseases, including rheumatoid arthritis, diabetes, and ulcerative colitis, have been recorded with Turner's syndrome.[13-15] Because of these observations, it was speculated that autoimmune mechanism is an important factor in the pathogenesis of Turner's syndrome. This autoimmunity may produce a dysjunctive phenomenon during meiosis or early mitosis in the zygote and result in chromosomal aberration.[16] An alternative hypothesis proposes that isochromosome X seen in Turner's syndrome associated with Hashimoto's thyroiditis is inactivated. The uniform inactivation of isochromosome X is suggested by autoradiographic studies using tritiated thymidine.[17] Therefore, the body is not exposed to proteins coded by isochromosome X. In a patient with uniform inactivation of isochromosome X, tolerance will develop only to the protein coded by normal active X chromosome. In such a patient, if all or a part of isochromosome X acquired the property of coding protein synthesis by reactivation, such proteins would be recognized as foreign by the individual and could lead to the development of autoimmune phenomena observed in

TABLE II. Thyroid diseases associated with Turner's syndrome

Disease	Variation in X Chromosome
Thyroiditis[1]	Metacentric chromosome*
Myxedema[2,7-9]	XO, XY
Hashimoto's thyroiditis[2-6,12]	XX isochromosome, XY, XO
Hyperthyroidism[4]	XO/XX ring chromosome
Thyroid carcinoma[3]	XX isochromosome

* Probably isochromosome.

Hashimoto's thyroiditis.[3] These mechanisms do not always explain the concurrence of these two diseases. There have been reports of XY or XO sex chromosome in Turner's syndrome associated with Hashimoto's thyroiditis.[5,6]

A search of the literature, excluding those reports on Hashimoto's thyroiditis, revealed a few cases of thyroid diseases in Turner's syndrome. These include hypothyroidism, hyperthyroidism, and thyroid carcinoma.[2-4,7-9] These findings bring out some interesting points in relation to Turner's syndrome. First, it may be true that there is an interrelationship in the pathogenesis of thyroid disease and Turner's syndrome. It was suggested that perhaps a certain thyroid disease might be ascribed to a recessive gene on the short arm of the X chromosome.[2] XO, XY, or XX isochromosome is monosomic for the short arm. This may explain the increased incidence of thyroid diseases in these karyotypes of Turner's syndrome. If we assume that our patient has an abnormal X chromosome possessing two short arms and two partially deleted short arms, the gene for thyroid disease may be located in the terminal portion of the short arms. Second, a question regarding the natural history of hyperthyroidism arises. Accumulating evidence indicates that certain cases of Hashimoto's thyroiditis may present or be associated with typical clinical and laboratory findings of hyperthyroidism.[18,19] The presence of hyperthyroidism and Hashimoto's thyroiditis in identical twins is implicated as a common immunologic defect and a possible genetic factor in their etiology.[20] The pathogenesis of hyperthyroidism has long been controversial. However, there is some information for the theory of autoimmunity predisposed by genetic defect.[21-23] With this assumption, some cases of hyperthyroidism as an autoimmune process lead to Hashimoto's thyroiditis and eventually terminate as hypothyroidism. This concept implies that in certain instances hyperthyroidism, thyroiditis, and hypothyroidism may be a spectrum of thyroid disease. It is interesting to speculate whether this may occur in this patient.

Turner's syndrome is a rather rare disease entity. Although it is possible that the occurrence of thyroid disease in this syndrome might be essentially coincidental, the association of two diseases

seems to be unusually frequent. It seems likely that thyroid disease, autoimmune process, and chromosomal aberration are somehow interrelated in their pathogenesis. One may be the cause and the others the result. In this case of Turner's syndrome with an abnormal X chromosome, presumptive X/X translocation, we believe that there is an interrelationship between the hyperthyroidism, Turner's syndrome, and the abnormal X chromosome. The possibility that the abnormal X chromosome led to the occurrence of hyperthyroidism and Turner's syndrome and the possibility that parental antibodies affected gamete or zygote development to cause the chromosomal abnormality should be considered.

We speculate that this patient presents symptoms of hyperthyroidism as an early phase of thyroiditis that has a high probability of terminating with hypothyroidism. Because of this, we selected propylthiouracil as the treatment of choice at this time. We plan to follow this patient closely to determine changes in thyroid function studies and antithyroglobulin-antibody titer.

Summary

Hyperthyroidism occurring in a patient with Turner's syndrome is presented. Detailed clinical, cytogenetic, and thyroid function studies were performed. An abnormal X chromosome was detected with a karyotype of 45 XO. The possible mechanism of hyperthyroidism seen in Turner's syndrome is reviewed in the aspect of the interrelationship of autoimmune theory, chromosomal aberration, and natural history of thyroid diseases.

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