Autoimmune hypothyroidism and hyperthyroidism in patients with Turner's syndrome

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A high prevalence of autoimmune thyroid disease (AITD) has been described in Turner’s syndrome (TS) but the extent of this association is controversial for the prevalence of thyroid autoantibody and the clinical impact of thyroid dysfunction. In this study we searched for thyroid disease and thyroid autoantibodies in patients with TS. Seventy-five unselected TS patients (age range 3–30 years) were studied. Sera were tested for thyroid hormones, thyrotropin (TSH), thyroglobulin (TG-ab) and thyroperoxidase (TPO-ab) antibodies. The TSH-receptor antibodies with thyroid-stimulating (TS-ab) or TSH-blocking activity (TSHB-ab) were measured in the IgG fraction using a bioassay. Ten out of 75 (13.3%) TS patients had AITD; eight had autoimmune thyroiditis (AT) (six with subclinical and two with overt hypothyroidism and one with euthyroidism) and one had Graves’ disease. The prevalence of AITD increased significantly (p < 0.05) from the first (15%) to the third (30%) decade of life. The prevalence of TPO-ab and/or TG-ab (20%) was higher (p < 0.05) in TS than in age-matched female controls and increased from the first (15%) to the third (30%) decade of life. Clinical AITD was diagnosed in 46% of TS patients with TPO-ab and/or TG-ab. Thyroid-stimulating antibody was detected in the hyperthyroid patient, and TSHB-ab was found in one of eight patients with hyperthyroid AT. It was concluded that: TS patients are at higher than average risk of developing AITD not only in adolescence and adult age but also in childhood: hypothyroidism, mainly subclinical, is the most frequent thyroid dysfunction: elevated TPO-ab and/or TG-ab alone do not imply thyroid dysfunction: TS-ab or TSHB-ab are always associated with thyroid dysfunction although most cases of autoimmune hypothyroidism are not due to the latter antibody.

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A greater prevalence of autoimmune thyroiditis has been described in Turner’s syndrome, but the extent of this association is still controversial for both thyroid autoantibody prevalence and clinical impact of thyroid dysfunction. Figures from previous reports in Turner patients range from 3.9% to 87.5% for thyroid autoantibody prevalence and from 4.3% to 40% for laboratory or clinical evidence of thyroid dysfunction (1–11). An association between autoimmune thyroiditis and a particular karyotype (the X-isochromosome) responsible for Turner’s syndrome was also hypothesized (6–7, 12–13) but, with one exception (10), studies on this aspect concerned only a small number of patients with this karyotype.

An aspect of the association between thyroid autoimmunity and Turner’s syndrome is the low prevalence of Graves’ hyperthyroidism (1–11). In view of its etiopathogenetic relationship with autoimmune thyroiditis (14, 15), Graves’ disease should be expected to be more frequent in Turner’s syndrome, but this combination has been described only in anecdotal reports (3, 16–19). In this regard, TSH-receptor antibodies with thyroid-stimulating or TSH-blocking activity have not been investigated systematically in Turner’s syndrome. All previous studies in this syndrome were concerned with the prevalence of thyroid peroxidase (formerly defined as “microsomal”) and thyroglobulin antibodies. These antibodies, while being good markers of thyroid autoimmunity, probably do not exert a direct pathogenetic effect by themselves (14, 15, 20). On the other hand, antibodies to the TSH-receptor with thyroid-stimulating or TSH-blocking activity are directly involved in the pathogenesis of thyroid dysfunction in autoimmune thyroid diseases (21, 22). Thyroid-stimulating antibodies (TS-ab) are found in sera of hyperthyroid patients with Graves’ disease, while TSH-receptor antibodies with blocking activity (TSHB-ab) are present in variable percentages of patients with autoimmune thyroiditis, and contribute to the development of hypothyroidism (21, 22).

In this study we reviewed 75 unselected patients with Turner’s gonadal dysgenesis to exactly define the terms
of association between this syndrome and thyroid autoimmunity. To this purpose we searched for thyroid-stimulating, TSH-blocking, thyroid peroxidase and thyroglobulin antibodies in sera of these patients. Laboratory and clinical evaluation were carried out to identify thyroid diseases and to define the type and extent of thyroid dysfunction. The results obtained were related to the age of patients and to their karyotype, and were compared with those found in the literature.

Subjects and material

Seventy-five unselected and consecutive patients with Turner's syndrome (age range 3–30 years, mean age 13.8 ± 6 years) were studied. None of them had been evaluated for thyroid disorders before entering the study. The diagnosis of Turner's syndrome was based on clinical findings and on peripheral blood leukocyte karyotypes. The karyotype was: X-monomosomy (45,X) in 44 patients. X-isochromosome in 10 patients, other structural alterations of X chromosome in 12 patients (five with X ring and seven with deletion of short or long arm of X chromosome), mosaicism without structural abnormalities (45,X/46,XX) in seven patients and mosaicism with abnormalities of Y chromosome (45X/46XY-isochromosome) in two patients. At the time of the first observation, 13 patients were younger than 10 years, 49 had an age range between 10 and 19 years and in the remaining 13 the age varied from 20 to 30 years. Among 42 patients older than 12 years, four had spontaneous pubertal development and periods and 19 patients were on cyclic ethynyl estradiol and progesterone treatment when first examined. Nine patients were on GH treatment; among them, seven were younger and two were older than 12 years.

The control group included sera from 41 normal female subjects who shared with patients the same age range. Four adult patients with hyperthyroid Graves' disease (GD) were specifically selected for the presence in their serum of TS-ab. Sera from four patients with autoimmune atrophic thyroiditis (AAT) that contained TSHB-ab were used as positive controls in the TSH-dependent adenylate cyclase inhibition assay.

Methods

Clinical evaluation and diagnostic criteria

All Turner patients received a full clinical examination with particular regard to thyroid diseases and organ- or non-organ-specific autoimmune disorders. Laboratory evaluation of thyroid function included determinations of the following serum hormones: total T₄ (RIA-Coat T₄ Byk-Sangtec Diagnostica, Dietzenbach, Germany), total T₃ (RIA-Coat T₃ Byk-Sangtec Diagnostica, Dietzenbach, Germany) free T₄ (FT₄ RIA, Lyphoseph, Technogenetics SpA, Milan, Italy); free T₃ (FT₃ RIA, Lyphoseph, Technogenetics SpA, Milan, Italy). Thyrotropin was assessed in all patients by an ultrasensitive method (UltraseNSitive-TSH IRMA, Delfia, Wallac, Finland) (23). The diagnosis of Graves' disease was based on common clinical and laboratory criteria, including elevated serum levels of total and free thyroid hormones, undetectable TSH and a diffuse goiter at palpation, echography and scintiscan. The diagnosis of autoimmune thyroiditis was based on the finding of circulating thyroid peroxidase (TPO-ab) and/or thyroglobulin (TG-ab) antibody associated with subclinical or overt hypothyroidism. Subclinical hypothyroidism was defined by evidence of elevated serum TSH with normal total T₄ and T₃ and no clinical signs of hypothyroidism. In clinical or overt hypothyroidism, total and free T₄ and T₃ were low and TSH was high. In some patients with hypothyroidism, thyroid autoantibody tests were negative, but ultrasound examination of the gland showed a pattern typical of chronic autoimmune thyroiditis characterized by diffuse low echogenicity (24). A similar echographic pattern in the presence of circulating TPO-ab and/or TG-ab was considered indicative of autoimmune thyroiditis even when thyroid function was normal.

Immunoglobulin G (IgG) preparation

Immunoglobulins were prepared from sera by double anion-exchange chromatography on DEAE-Sephadex A50 and subsequent precipitation by ammonium sulfate. After extensive dialysis in TRIS-Sephadex buffer for 2 days, IgGs were centrifuged at 105 000g for 1 h to remove aggregates. The IgG concentration was determined by optical density at 280 nm using an extinction coefficient of 1.46. Immunelectrophoresis showed that IgG preparations were 90% pure, the remaining proteins being represented mostly by albumin.

Thyroid peroxidase (TPO-ab) and thyroglobulin (TG-ab) antibody

Thyroid peroxidase and thyroglobulin antibody were assessed by passive agglutination (SERODIA-AMC and SERODIA-ATG, Fujirebio, Tokyo, Japan).

TSH-binding inhibiting antibody (TBI-ab)

The presence of TBI-ab was detected by a radioreceptor assay based on the inhibition of the binding of T₂₁-labelled bovine TSH to solubilized porcine TSH receptor (TRAk assay, Henning, Berlin, Germany). Results were read off a standard curve obtained with a reference serum (normal values < 10 U/l).

Cell cultures

FRTL-5 cells were grown in Coon's modified Ham's F-12 medium supplemented with 5% adult calf serum and a six-hormone mixture (6H medium) containing insulin...
(1.6 \times 10^3 \text{ nmol/l}), hydrocortisone (1 \text{ nmol/l}), transferrin (62.5 \text{ nmol/l}), 1-glycyl-1-hystidyl-1-lysine (25 \text{ nmol/l}), somatostatin (6.25 \text{ nmol/l}) and TSH (500 \text{ mU/l}) (25, 26).

**Assay for TS-ab and TSHB-ab**

As described previously (25, 26), 50 000 cells were seeded in each well of a 96-well Costar (Cambridge, MA, USA) plate. After 3 days of culture in the presence of TSH, FRTL-5 cells were switched to a medium deprived of the hormone (5H medium) and maintained in this medium for 4 days before assay for TS-ab and TSHB-ab.

The bioassay for TS-ab and TSHB-ab was run following previously described procedures (25, 26). Before the assay, the culture medium was aspirated and cells were washed with Hank’s balanced salt solution. The IgGs were dialyzed in hypotonic buffer (27) and then diluted in the same buffer containing 4 g/l bovine serum albumin (BSA) and 0.5 mmol/l isobutylmethylxanthine (IBMX). A purified preparation of bovine TSH (kindly provided by Dr LD Kohn, NIDDK, Bethesda, MD) was diluted in hypotonic buffer–BSA–IBMX. Cell cultures were incubated with IgG alone (1 g/l), TSH alone (10 mU/l) or IgG plus TSH (at the same final concentrations) in a total volume of 100 \mu l of hypotonic buffer–BSA–IBMX. Hypotonic buffer–BSA–IBMX alone was added to some cultures in each experiment to measure basal cAMP production. After 1 h of incubation at 37°C in a 5% CO₂/95% air atmosphere, cAMP was measured in the extracellular medium by RIA.

All experiments were performed in triplicate, and the results (in pmol/well) were expressed as the average of these.

The results of TS-ab were expressed as a percentage increase of cAMP production with respect to the basal value (normal value < 140%); results of TSHB-ab were calculated according to the following formula (normal value < 30)

\[
\left[ \frac{1 - \frac{\text{cAMP (TSH + sample IgG) - cAMP (sample IgG)}}{\text{cAMP (TSH) - cAMP (control buffer)}}}{100} \right]
\]

**Organ-specific autoantibodies**

Organ-specific autoantibodies were detected by indirect immunofluorescence (IF) on cryostat sections by two observers. The intensity of staining was graded as negative (−), positive (+) or strongly positive (+++). Gastric parietal cell antibody, adrenocortical cell antibody and ovary cell antibody were measured by IF on cryostat sections of unfixed normal human stomach, monkey adrenal and ovary tissue, using undiluted serum. Islet cell antibody was determined by IF on cryostat sections of unfixed normal human group O pancreas.

**Non-organ-specific autoantibodies**

Antinuclear antibody, smooth-muscle antibody and reticulin antibody were measured by IF on cryostatic sections of rat liver and kidney using serum in a 1:10 dilution.

**Statistical analysis**

The chi-squared test with Yates correction when appropriate was used to analyze the frequency distribution of serum autoantibodies and thyroid abnormalities in different subgroups of patients.

**Results**

**Clinical and hormonal findings**

Ten out of 75 (13.3%) patients with Turner’s syndrome had thyroid disease. A 22-year-old patient had Graves’ disease with hyperthyroidism and required treatment with methimazole. Endocrine ophthalmopathy was not detected in this patient. Eight patients with Turner’s syndrome had autoimmune thyroiditis with variable degrees of thyroid hypofunction. Among them, six patients presented with subclinical hypothyroidism. The remaining two had overt hypothyroidism that required l-thyroxine therapy. Among patients with hypothyroidism, two were younger than 10 years, three were in the 10–19-year age range and the remaining three were older than 20 years. None of the hypothyroid patients had a typical firm Hashimoto’s goiter. In most cases the thyroid was apparently normal by palpation. One of the patients with overt hypothyroidism had a thyroid gland reduced in size at echography. Ultrasound examination showed in all cases, but one, a thyroid hypechogenic pattern. Four out of nine patients with thyroid dysfunction were on estrogen-progesterone treatment, and two also received growth hormone therapy. A 14-year-old girl was diagnosed as having autoimmune thyroiditis with euthyroidism based on the finding of high titers of serum TPO-ab and TG-ab and a thyroid hypechogenic pattern at ultrasound examination of the gland. Autoantibody findings in these patients are shown in Table 1.

None of the patients included in the study had clinical evidence of other organ-specific or non-organ-specific autoimmune diseases.

**Thyroid peroxidase, thyroglobulin and TSH-receptor antibodies**

Thyroid peroxidase antibodies and/or TG-ab were detected in 15 out of 75 (20%) Turner patients. This prevalence was significantly higher than in controls (4.8%; p < 0.05). Among them, six had both circulating TPO-ab and TG-ab, 14 had TPO-ab alone and one patient had TG-ab without TPO-ab. The TPO-ab titers ranged from 1:400 to 1:102 400 and TG-ab titers ranged from 1:400 to 1:1600. Among patients with
Table 1. Age, karyotype and thyroid antibody findings in patients with Turner’s syndrome and clinical evidence of thyroid disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Karyotype</th>
<th>TPO-ab (titers)</th>
<th>TG-ab (titers)</th>
<th>TBI-ab (U/ml)</th>
<th>TS-ab (% basal cAMP)</th>
<th>TSHB-ab</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>8</td>
<td>45,X ring</td>
<td>1:25 600</td>
<td>1:1600</td>
<td>0</td>
<td>59</td>
<td>38</td>
<td>AT-SH</td>
</tr>
<tr>
<td>CR</td>
<td>16</td>
<td>45,X</td>
<td>1:25 600</td>
<td>0</td>
<td>0</td>
<td>82</td>
<td>-18</td>
<td>AT-SH</td>
</tr>
<tr>
<td>GG</td>
<td>9</td>
<td>45,X</td>
<td>1:00</td>
<td>1:400</td>
<td>0</td>
<td>47</td>
<td>5</td>
<td>AT-SH</td>
</tr>
<tr>
<td>FA</td>
<td>10</td>
<td>45.X/47.X,i(Xq),i(Xq)</td>
<td>1:25 600</td>
<td>1:1600</td>
<td>0</td>
<td>79</td>
<td>-15</td>
<td>AT-SH</td>
</tr>
<tr>
<td>PT</td>
<td>24</td>
<td>45,X</td>
<td>1:1600</td>
<td>1:1600</td>
<td>0</td>
<td>120</td>
<td>12</td>
<td>AT-SH</td>
</tr>
<tr>
<td>MA</td>
<td>24</td>
<td>45,X</td>
<td>1:25 600</td>
<td>1:400</td>
<td>0</td>
<td>67</td>
<td>13</td>
<td>AT-SH</td>
</tr>
<tr>
<td>PI</td>
<td>13</td>
<td>45.X ring</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>70</td>
<td>5</td>
<td>AT-H</td>
</tr>
<tr>
<td>GL</td>
<td>21</td>
<td>45,X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>65</td>
<td>9</td>
<td>AT-H</td>
</tr>
<tr>
<td>FM</td>
<td>14</td>
<td>45.X ring</td>
<td>1:102 400</td>
<td>1:1600</td>
<td>0</td>
<td>87</td>
<td>-5</td>
<td>AT-E</td>
</tr>
<tr>
<td>OM</td>
<td>22</td>
<td>46.X,i(Xq)</td>
<td>1:25 600</td>
<td>0</td>
<td>59</td>
<td>236</td>
<td>-3</td>
<td>GD</td>
</tr>
</tbody>
</table>

*GD = Graves’ disease, AT = autoimmune thyroiditis, SH = subclinical hypothyroidism, H = overt hypothyroidism, E = euthyroidism.

circulating TPO-ab and/or TG-ab, seven (46%) had thyroid dysfunction (six with subclinical hypothyroidism, and one with Graves’ hyperthyroidism), and one had euthyroid Hashimoto’s thyroiditis. Both patients with overt hypothyroidism, who were treated with L-thyroxine for more than 1 year, were seronegative.

The TSH-receptor antibodies by radioassay (TBI-ab) were detected in the hyperthyroid patient with Graves’ disease, while negative results were obtained with sera from the remaining patients with Turner’s syndrome irrespective of their thyroid function. The results obtained in the bioassay for TS-ab are shown in Fig. 1. Activity of TS-ab was detected in the IgG obtained from the patient with Turner’s syndrome and Graves’ hyperthyroidism. When tested at different concentrations, this IgG produced a dose-dependent increase of cAMP accumulation in FRTL-5 cells (Fig. 2). None of other IgGs from Turner patients contained TS-ab; in particular, IgGs from euthyroid or hypothyroid patients with autoimmune thyroiditis did not modify the basal production of cAMP in FRTL-5 cells.

Figure 3 shows the results obtained in the bioassay of TSHB-ab; TSHB-ab were detected in one out of six patients with autoimmune thyroiditis and untreated subclinical hypothyroidism. When tested at graded concentrations this IgG produced a dose-dependent inhibition of cAMP accumulation induced by TSH in FRTL-5 cells. Negative results were obtained with all other IgGs from Turner patients. In particular, IgGs from patients with autoimmune thyroiditis and overt hypothyroidism, who were treated with L-thyroxine for more than 1 year, did not contain TSHB-ab.

All sera from normal controls gave negative results both in the radioreceptor assay and in bioassays for TSH-receptor antibodies.

**Thyroid autoantibodies, thyroid dysfunction and age**

Thyroid peroxidase antibodies and/or TG-ab were detected in 2/13 (15.4%) patients younger than 10 years, in 9/49 (18.3%) patients in the age range 10–19 years and in 4/13 (30.7%) of those aged 20 years or older. This trend towards an increased prevalence of circulating thyroid antibodies with age did not reach statistical significance. The frequency distribution of thyroid dysfunction (hypothyroidism and hyperthyroidism) was 15.4%, 6.1% and 30.7% in the 0–9, 10–19 and 20–30 years age ranges, respectively. Statistical analysis indicated a significant (p < 0.05) increase in the prevalence of thyroid dysfunction with age. By taking a cut-off at 14 years, TPO-ab and/or TG-ab were detected in 17.2% of patients in the age range 0–14
years and in 24.1% of those aged 15 years or older. In these age groups, the frequency distribution of thyroid dysfunction was 8.6% up to 14 years and 17.4% in patients older than 14 years.

Thyroid autoantibodies, thyroid dysfunction and karyotype

Thyroid peroxidase antibodies and/or TG-ab were detected in 7/44 (16.0%) patients with X-monosomy, in 4/10 (40.0%) with X-isochromosome, in 4/12 (33.3%) with other structural abnormalities of X chromosome and in none with mosaicism. The frequency distribution of thyroid dysfunction was 11.4%, 20.0% and 16.6% in patients with X-monosomy, X-isochromosome and other structural abnormalities of X chromosome, respectively. These differences did not reach statistical significance. No Turner patient with mosaicism was affected. Among patients with hypothyroidism, five had X-monosomy, one had X-isochromosome and two had other structural abnormalities of X chromosome. The patient with Graves’ disease had Turner’s syndrome with X-isochromosome.

Other organ-specific and non-organ-specific autoantibodies

Gastric parietal cell antibody was present in eight out of 75 (10.6%) patients with Turner’s syndrome, adrenocortical cell antibody in three (4.0%) and ovary cell antibody in one (1.3%). None of the patients had islet cell antibody. The prevalence of gastric parietal cell antibody in patients with Turner’s syndrome was significantly higher (p < 0.05) than in controls (2.4%). Adrenocortical cell antibody, islet cell antibody or ovary cell antibody were not found in the control group.

Antinuclear antibody was present in three out of 75 (4.0%) Turner patients. Two patients (2.6%) had
smooth-muscle antibody and four (5.3%) had reticulin antibody. In the control group, antinuclear antibody was present in 2/41 (4.8%) and smooth-muscle antibody in 2/41 (4.8%), while nobody had reticulin antibody. There was not statistical difference in the prevalence of non-organ-specific antibodies between patients and controls.

Discussion

The increased incidence of thyroid abnormalities in Turner’s syndrome has been documented (1–11), but the frequency of this association ranges from 4% to 40% in different series. Selection bias, inclusion of pediatric vs adult patients and differences in the karyotype responsible for Turner’s syndrome could explain the wide range of results reported in different studies. In our unselected series of children, adolescents and young adults with Turner’s syndrome, the percentage of patients with thyroid abnormalities was 13%. All patients with thyroid abnormalities had serological and/or ultrasonographic evidence of autoimmune thyroid disease. Among them the majority had autoimmune thyroiditis (90%) with subclinical thyroid failure (60%). Overt hypothyroidism was present in two patients and Graves’ disease with hyperthyroidism in one. Thus, our findings are in keeping with the previous literature indicating that Graves’ disease occurs rarely in combination with Turner’s syndrome (3, 16–19). The reason for this low incidence of Graves’ disease, despite its genetic and pathogenetic relationship with autoimmune thyroiditis (14, 15), is poorly understood, but probably reflects the higher frequency of asymptomatic autoimmune thyroiditis with respect to Graves’ disease in the general population (28). With specific regard to thyroid autoimmune diseases in Turner patients, it has been hypothesized that the X-isochromosome might play a role, because this chromosomal abnormality has been reported more frequently in patients with associated Hashimoto’s thyroiditis than in those with associated Graves’ disease (1, 6, 7, 10, 12, 13, 16). This does not appear to be the case in our series because the patient with Graves’ disease had the X-isochromosome Turner’s syndrome. The frequency of thyroid abnormalities (20%) and the prevalence of circulating thyroid antibodies (40%) was higher in Turner patients with X-isochromosome as compared to those with other karyotypes (11% and 16%, respectively), although these differences did not reach statistical significance. This observation is in keeping with previous studies indicating that patients with X-isochromosome Turner’s syndrome have an increased risk of developing autoimmune thyroid diseases (6, 7, 10).

The frequency of thyroid abnormalities significantly increased with the age of Turner patients, reaching a 30% prevalence in the third decade of life. Overt hypothyroidism or hyperthyroidism were detected only in patients older than 13 years. In the normal population the prevalence of autoimmune thyroid diseases also increases with age up to the sixth decade (29). Such age relation was observed in other studies of Turner patients (4, 6, 10), but in most series (4, 10) no thyroid abnormality was found before the age of 10 years. This was not the case in our study, because subclinical hypothyroidism was found in two out of 13 children younger than 10 years. This finding implies that the evaluation of thyroid status cannot be delayed until adolescence in patients with Turner’s syndrome.

Humoral evidence of thyroid autoimmunity, as assessed by circulating TPO-ab and/or TG-ab, was found in 20% of our unselected series of patients with Turner’s syndrome. This prevalence of circulating thyroid antibodies is lower as compared to the 27–80% rate of positive results reported in other series (1–11), but it is definitely higher than the 4% prevalence found in the large German UTS Multicenter Study (9). Even taking into account only patients younger than 14 years (as in the latter study), the prevalence of circulating thyroid antibodies in our series was 17%. This prevalence of thyroid antibodies in unselected Turner patients was significantly higher than that found in the internal control group, and was also higher as compared to the prevalence of thyroid antibodies found in the age-matched general population in the same geographical area (30). Thus, our data confirm that in Turner’s syndrome there is an increased rate of humoral thyroid autoimmunity. In agreement with previous studies (4, 6), the frequency of positive TPO-ab/TG-ab increased with age from 15% in patients younger than 10 years to 30% in those older than 20 years.

Thyrotropin-receptor antibodies were not detected in Turner patients with normal thyroid function irrespective to the presence of circulating TPO-ab and/or TG-ab. On the other hand, the presence of circulating TSH-receptor antibodies was always associated with thyroid dysfunction, confirming the direct pathogenetic role played by these antibodies (21, 22). Using the FRTL-5 cell culture system, TS-ab can be detected in more than 90% of untreated patients with Graves’ disease (21, 22). In the present series of patients with Turner’s syndrome, TS-ab was found in the one with Graves’ hyperthyroidism. Thyrotropin-receptor antibodies with blocking activity (TSHB-ab) were found in one out of eight Turner patients with hypothyroidism. TSHB-ab have been described in patients with autoimmune hypothyroidism (25), in particular in those with autoimmune atrophic thyroiditis (idiopathic myxedema) (25, 31). In different series of patients with AAT, the prevalence of TSHB-ab ranges from 14% to nearly 80% (32), but in our experience the prevalence of TSHB-ab in AAT is around 30% (33). Therefore, TSHB-ab are present in only a minority of patients with autoimmune hypothyroidism, while in most cases the accompanying lymphocytic destruction of the thyroid plays a major
pathogenetic role (14, 15). This appears to be the case also in thyroid autoimmune diseases associated with Turner’s syndrome, because only one out of eight hypothyroid patients was found positive for TSHB-ab.

With specific regard to the two Turner patients with autoimmune thyroiditis and overt hypothyroidism but negative results for all thyroid autoantibodies, it must be recalled that L-thyroxine therapy may reduce serum levels of TPO-ab, TG-ab (34) and TSHB-ab (35). On the other hand, negative antibody titers in Turner patients with thyroid abnormalities have been reported in other studies (5–7). The possibility of negative antibody tests in chronic juvenile autoimmune thyroiditis has also been described in the general population (7, 36).

Other endocrine autoimmune disorders, such as idiopathic Addison’s disease, have also been described in association with Turner’s syndrome (37–39). Similar to previous reports (5–6, 8), the percentage of patients with adrenocortical cell antibody in our series was low and was not different from that found in the control group. Similarly, there was no significant increase in the prevalence on non-organ specific antibodies. Therefore, obtaining adrenocortical cell and non-organ-specific antibodies does not appear worthwhile in patients with Turner’s syndrome in terms of potential benefit to their health and in terms of cost effectiveness. Gastric parietal cell antibody was more frequently observed in Turner patients than in controls. This finding implies that patients with Turner’s syndrome are particularly prone to develop both thyroid and gastric autoimmunity.

In conclusion, the main implications of the present study can be summarized as follows:

(i) patients with Turner’s syndrome are at higher than average risk of developing autoimmune thyroid diseases, not only in adolescence and adult age but also in childhood;

(ii) hypothyroidism, mainly subclinical, is the most frequent type of thyroid dysfunction, but Graves’ hyperthyroidism may also occur;

(iii) patients with X-isochromosome Turner’s syndrome are more prone to develop autoimmune thyroid diseases, including Graves’ disease;

(iv) the presence of TPO-ab and/or TG-ab alone does not imply thyroid dysfunction but indicates the need for careful, periodic evaluation of thyroid function;

(v) TS-ab or TSHB-ab are always associated with thyroid dysfunction, although most cases of autoimmune hypothyroidism are not due to the latter antibody.

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