# PREVALENCE OF AUTOANTIBODIES TO THYROID PEROXIDASE AND AUTOIMMUNE THYROID DISEASE IN GIRLS WITH TURNER'S SYNDROME

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**Abstract-** Patients with Turner's syndrome (TS) are at an increased risk of developing autoimmune thyroid disease (ATD). The aim of this study was to determine the frequency of anti-thyroid peroxidase (anti-Tpo) antibodies and ATD in children and adolescent girls with TS. It also assessed the influence of karyotype on the development of thyroid disease. Sixty eight patients with TS were compared with 68 age matched healthy unrelated girls in this study. They were screened for anti-Tpo antibodies, free T4 and TSH levels. Sign and symptoms of hypothyroidism and hyperthyroidism and the presence of goiter were also investigated. Anti-Tpo antibodies were found in 18 (26.4%) TS patients and 1 (1.4%) patient in the control group ($P < 0.001$), evenly distributed between the karyotypes 45X, 46X, isoXq and mosaicism. Out of 68 TS patients, 8 (11.7%) had visible goiter. Subclinical hypothyroidism and hypothyroidism both occurred in 2 patients (5.9%). These patients were characterized by higher levels of anti-Tpo antibodies. Visible goiter was found in 3 (4.4%) subjects of the control group, but all of them were euthyroid. We found that younger patients were more likely to be anti-Tpo negative ($P < 0.001$). Our data demonstrated a high frequency of ATD in a representative sample of Iranian girls with TS which is in accordance with previous observations. Regular follow up assessment of thyroid autoantibodies and thyroid function in patients with TS is recommended for timely diagnosis of thyroid dysfunction and treatment.

*Acta Medica Iranica*, 44(3): 191-195; 2006



**Key words:** Autoimmune thyroid disease, anti-peroxidase antibody, Turner's syndrome

## INTRODUCTION

Turner's syndrome (TS) is the most common sex chromosome abnormality in females, resulting from the absence of X chromosome or the presence of a structurally abnormal X chromosome. Short stature and ovarian failure are the most consistent clinical features (1-3).

Received: 9 May 2005, Revised: 22 Jun. 2005, Accepted: 16 July 2005

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There is epidemiological evidence of a high incidence of coronary heart disease was observed in females with TS (4). One possible explanation for the increased risk of cardiovascular disease is Hyperlipidemia (4). Other options would be hypothyroidism or subclinical hypothyroidism (5).

The relationship between thyroid disease and TS was first described by Atria *et al.* in 1948. At that time, they reported the postmortem findings of a small thyroid gland with lymphocytic infiltration in a young TS woman (6). During the last decades several screening studies were published on the prevalence of thyroid autoantibodies and ATD among patients with TS (6-18). In some reports these

were most common in patients with 45X or an iso-chromosome (14-16).

The diagnosis of thyroid dysfunction is often made late in TS population. Up to now, there is no consensus about the monitoring of ATD and the time point of therapeutic intervention in patients with TS. Thyroid auto-antibodies against microsomes (AMA) tend to have more correlation with thyroid dysfunction than the antibodies against thyroglobulin (ATA) (19).

In recent years, detection of antibodies against thyroid peroxidase (anti-Tpo), a major antigen for microsomal auto-antibody, appear to obviate the need for AMA and ATA measurements because of the improvement in specificity and sensitivity of the method (20). To date, no study focusing on the prevalence of ATD in patients with TS have been conducted in Iran. The aim of the present study was to evaluate the prevalence of anti-Tpo auto-antibodies and ATD in TS patients and furthermore to assess the influence of karyotype on the development of ATD.

## MATERIALS AND METHODS

Sera were collected from 68 girls aged 3-19 years (mean age; 13.9 ± 4.5 years) with TS attending a single Pediatrics Endocrine Clinic of Tehran University of Medical Sciences. They were diagnosed as having TS on the basis of chromosomal analysis and characteristic physical features.

These girls were compared with 68 randomly selected healthy girls, aged 3-19 years, (mean age 12.8 ± 4.7years). All the individuals recruited in this study were living in Tehran. The control subjects included in the study were based on the following inclusion criteria: 1) female, 2) normal growth and development, and 3) lacking any known systemic disease and any symptoms compatible with thyroid dysfunction.

Having explained our goals, the subjects were asked to participate in the study. They could interrupt their cooperation whenever they desired. Each patient and control was asked to answer questions about family history of thyroid disease. We excluded subjects with positive history of thyroid disease. At the time of enrolment, the subjects were requested to complete a questionnaire specific for thyroid symptoms by answering yes or no to a set of 25 questions regarding hypo and hyperthyroidism.

Physical examination for signs of thyroid dysfunction and estimation of thyroid size by using palpation were then performed. Thyroid size was classified according to the WHO classification in to grade 0, not palpable, 1, palpable but not visible and 2, visible goiter. All data were processed by a single supervisor.

Free T4 was measured by radioimmunoassay (RIA) (Zentech S.A Kit, Belgium), TSH by immunoradiometric assay (IRMA) (Spectra, Feniz, Finland) and anti-Tpo by enzyme linked immunosorbent assay (Radim, Rome, Italy). Free T3 was measured by RIA (Zentech, S.A Kit, Belgium) on samples with TSH level lower than normal range.

The normal (reference) levels were: Free T4, 8-20 pg/mL (10.3-25.7 pmol/L); TSH, 0.3-4.5 mu/L; anti-Tpo, up to 100 IU/mL; Free T3, 2.2-4.7 pg/mL (3.4-7.2 pmol/L). The chromosomal findings were based on medical records.

In patients with significant anti-Tpo titers (>100 IU/mL), subclinical hypothyroidism was defined as TSH elevation >10 mU/L with normal FT4 values.

Hypothyroidism was diagnosed in patients with FT4 values < 8 pg/mL and TSH values > 20 mU/L and hyperthyroidism was diagnosed in patients with FT4 > 20 pg/mL or FT3 > 4.7 pg/mL and TSH < 0.3 mU/L.

All data were presented as mean ± SD. Differences between patients and controls were compared with Student's *t* test. The Chi square test was used to assess the association between karyotype and thyroid autoimmunity among TS patients. A *P* value less than 0.05 was considered as statistically significant.

## RESULTS

Frequency of anti-Tpo antibodies among 68 patients with TS was 26.4% (18:68) as compared to 1.4(1:68) in the controls ($P < 0.001$). Frequencies and titers of anti-Tpo antibodies in TS patients and normal controls are shown in Table 1.

**Table 1.** Frequencies and titers of anti-Tpo antibodies in patients with TS and normal controls*

| | Anti-Tpo titers (IU/mL) | | | |
|---|---|---|---|---|
| **Subjects** | **< 100** | **100-200** | **200-500** | **> 500** |
| TS (n=68) | 50(73.5) | 8 (11.8) | 5 (7.3) | 5 (7.4) |
| Normal (n=68) | 67 (98.6) | 1 (1.4) | 0 (0) | 0 (0) |

Abbreviations: Tpo, Thyroid peroxidase, TS, Turner's syndrome.
* Data are given as number (percent).

The anti-Tpo antibody titer varied widely (range 0-3600 IU/mL). Visible goiter was detected in 8 out of 68 girls (11.7%) with TS but subclinical hypothyroidism and hypothyroidism both occurred in 2 (5.9%). These cases were characterized by higher levels of anti-Tpo antibodies. We failed to find any cases of hyperthyroidism. Visible goiter was found in 3 (4.4%) out of the 68 normal controls but none of them had thyroid disease. We found that younger patients with TS were more likely to be anti-Tpo negative than older patients; frequency of anti-Tpo antibodies was significantly higher in older patients (83.9% in the age group above 10 years compared to 16.6% in the age group less than 10 years, $P < 0.001$). The karyotype pattern is given in table 2.

The majority of girls (56 percent) had a 45X karyotype, while a mosaic karyotype was found in 44%. Patients with isochromosome (46Xi, Xq) were studied as a subgroup. There was no correlation between the 45X cells or isochromosome in an individual and serum Tpo, free T4 and TSH concentrations.

Elevated TPO concentrations were even between the karyotype 45X, mosaicism and the isochromosome (Table 2).

**Table 2.** Frequencies of positive anti-Tpo antibodies and ATD in patients with TS according to karyotype*

| **Karyotype** | **No (%)** | **Elevated anti-Tpo** | **ATD** |
|---|---|---|---|
| 45X | 38 (56) | 10 (26.3) | 3 (7.9) |
| 46Xi/Xq | 12 (17.6) | 3 (25) | 1 (8.3) |
| 45X/46XX | 11 (16.2) | 3 (27.2) | 0 (0) |
| Others | 7 (10.2) | 2 (28.5) | 0 (0) |

Abbreviations: Tpo, Thyroid peroxidase, ATD, autoimmune thyroid disease, TS, Turner's syndrome.
* Data are given as number (percent).

# DISCUSSION

ATD whether defined as the presence of antithyroid auto-antibodies alone or combined with thyroid dysfunction (nearly always hypothyroidism) as in this study, is known to be common in patients with TS (6-18).

The considered prevalence of anti-thyroid auto-antibodies in patients with TS varies between 25-60% (6-18) in contrast to 1-2% of thyroid autoimmunity in the general population (17). The frequency of thyroid auto-antibodies in this disease is employee of the age and increases around 16 years (8). The incidence of clinical hypothyroidism is low, but it is increased with age and is developed in 10-20% of all patients with TS (17). The first report of the prevalence of anti-thyroid auto-antibodies in TS patients was published in 1964 by Williams and co-workers who found that 13 out of 25 children (52%) with TS were positive for anti-thyroid auto-antibodies (17).

In Ivarrson *et al.* study anti-thyroid auto-antibodies were detected in 46 of 89 girls with TS aged 3-16 years (52%) as compared with 34 of 199 age matched normal girls (17%) (14). Chang and colleagues conduced a study on 77 children (mean age 10 ± 4.7 years) and showed anti-Tpo auto-antibodies and hypothyroidism in 21 (27%) and 3 (4%) of TS patients, respectively (13).

A high incidence of thyroid auto-antibodies has been described in both adults and children with TS (16-18). In a study on 145 women, mean age 26 years (16-52 yrs), with TS, Elsheikh and co-workers demonstrated that 60 (41%) had positive test for anti-thyroid auto-antibodies, 22 (15%) overt or subclinical hypothyroidism and 1 (0.7%) Graves hyperthyroidism (2).

In a multi-center study on 91 women (mean age 37.7 years) with TS, Mansoury and colleagues demonstrated that 25 (27.4%) of TS patients had an elevated anti-Tpo antibodies and 23 (25%) of them had hypothyroidism which developed in the five years follow up to 23 (37%) TS women with hypothyroidism (with an annual incidence of 3.2%). According to this report, hypothyroidism increased with aging (18). However, the present prevalence of

ATD among TS girls is similar to the prevalence of previous reports from studies of TS patients (13, 18).

The wide range of prevalence in various reports may be due to difference in ethnic groups, geographic area, age or the methodology of the study and population size. In line with earlier studies, we found that elevated anti-Tpo antibody concentrations are more frequently associated with hypothyroidism than hyperthyroidism, and older patients with TS were more likely to be anti-Tpo positive than younger patients. The Tpo concentrations correlated positively with serum TSH in the present study.

Studies assessing the influence of karyotype on thyroid autoimmunity (14-16, 18) and some congenital malformation have yielded conflicting results but have been limited by small numbers (21, 22). Based on some studies, patients with 45X or 46X, iso Xq are most likely to have autoimmune thyroid disease (14-16). However, in line with Mansoury and co-workers study (18) we failed to show any significant correlation between thyroid autoimmunity and a special cell line in TS. In the literature review, the clinical symptoms of hypothyroidism seldom led the TS patients to seek medical attention (23, 24).

In conclusion, the current study was in line with previous observations placing patients with TS at an increased risk for developing ATD and so determination of thyroid auto-antibodies, particularly anti-Tpo antibody, should be a part of health assessment in patients with TS and in cases with antibody positive, thyroid function tests are recommended in order to minimize the risk of undiagnosed ATD especially hypothyroidism in these patients.

## Conflict of interests

We have no conflict of interests.

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