Age-related Anti-thyroid Antibodies and Thyroid Abnormalities in Turner Syndrome

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One hundred pediatric patients with Turner syndrome were studied to determine the correlation between the presence of anti-thyroid antibodies with age and karyotype, and the value of anti-thyroid antibody titers as predictors of subsequent thyroid abnormalities. (54 patients = 45,X; 46 = other karyotypes.) The frequency of positive titers of anti-thyroid antibodies increased linearly with cumulative age. Anti-parietal cell and anti-adrenocortical cell antibodies were not increased in these patients (1.3 and 2.6% respectively). The ability to use positive anti-thyroid antibody titers to predict the development of thyroid abnormalities increased from age 10 years and became statistically significant at ages 13–17 years for the whole group as well as 45,X patients. None of the patients had clinical symptoms of thyroid dysfunction although 22% developed thyroid abnormalities, which included elevated TSH, low T4, and/or goiter. Key words: Turner syndrome, anti-thyroid antibodies, thyroid abnormalities.

The association of Turner syndrome with an increased incidence of anti-thyroid antibodies and an increased incidence of thyroid dysfunction has been documented (1–4) and has been shown to occur both in patients with a 45,X karyotype and in those with a mosaic or variant form of the syndrome. Two studies which have specifically examined the incidence of thyroid antibodies in children with Turner syndrome have shown an increased incidence of elevated anti-thyroid antibodies especially over age 10 years in 20 patients with Turner syndrome (5) and an 87.5% incidence of positive anti-thyroid antibodies in 24 children with Turner syndrome (6).

The current study of 100 pediatric patients with Turner syndrome was carried out to determine a possible correlation with age and karyotype of patients with positive anti-thyroid antibody titers in a large population, to evaluate the potential usefulness of anti-thyroid antibody measurements as predictors of the subsequent development of thyroid abnormalities and to confirm, in a large population, the high frequency of patients with positive anti-thyroid antibody titers. Concurrently, the percentage of patients with positive anti-parietal cell and anti-adrenocortical cell antibody titers was determined.

PATIENTS AND METHODS

We reviewed the medical records of 100 consecutive patients with Turner syndrome who were evaluated at the Pediatric Endocrinology Clinic of the Johns Hopkins Hospital between January 1964 and January 1984, and who also had determinations of thyroid antibodies. The majority of the patients were followed and had data evaluated over a long-term basis. At the time of their initial visit, their ages ranged from 15 weeks to 19 years, with a mean age of approximately 12 years. Peripheral blood leukocyte karyotypes were obtained on all patients, except one who was diagnosed by buccal smear analysis. Of the 100 patients studied, 54 had a 45,X pattern and 46 had other karyotypes (16 mos45,X/46,XX; 7 46,X,i(Xq); 4 mos45,X/46,X,i(Xq); 4 46,X,del(Xp); 1 46,X,del(Xp) with piece of long arm attached to short arm; 5 mos45,X/46,X,r(X); 1 mos45,X/46,X,r(X)/46,XX; 2 mos45,X/46,XY; 1 mos45,X/46,X,i(Yq); 1 mos45,X/46,X,del(X); 1 mos45,X/46,X,del(Xq11); 1 mos46,XX/46,X,del(Xp11 or pl3); 1 45,X/
The patients were divided into 2 groups for purposes of data analysis: those with 45,X and those with all other karyotypes.

Determination of anti-thyroid antibodies (anti-thyroglobulin and anti-microsomal antibodies) was carried out at least once in all patients. 85 of these patients had at least 1 set of thyroid function studies which included 1 or more of the following: TSH, T4RIA, T3RU, Free T4, PBI (Protein Bound Iodine), BEI (Butanol Extractable Iodine). Anti-parietal cell and anti-adrenocortical cell antibody titers were measured in 76 of the 100 patients. All auto-antibodies were measured in the Pediatric Endocrinology laboratory of the Johns Hopkins Hospital.

Anti-thyroglobulin antibodies were measured by a modification of the tanned-red-cell agglutination technique (7). Positive titers for anti-thyroglobulin antibodies were considered 1:4 or greater. Anti-microsomal antibodies were measured by a modification of the original method of Coons et al. (8, 9). Positive titers for anti-microsomal antibodies were considered significant if greater or equal to 2-3+ for undiluted plasma and 3+ for plasma diluted 1:4. Anti-parietal cell and anti-adrenocortical cell antibodies were also measured by a modification of the original Coons method (8, 9).

Thyroid function tests were done by routine methods at the Pediatric Endocrinology or Nuclear Medicine laboratories of the Johns Hopkins Hospital. Thyroid abnormalities were defined as development of a goiter (defined as a diffusely enlarged thyroid gland found in 4 of the patients), elevated TSH and/or low T4 (as determined by the methods previously stated).

Data were analyzed in relation to cumulative age, i.e. all ages up to and including that specific age. For example, age 10 represents all ages up to and including age 10. For each cumulative age, the percentage of patients with positive anti-thyroid antibodies (anti-thyroglobulin and/or anti-microsomal) was calculated by the number of patients who had at least one positive antibody titer divided by the total number of patients. The percentage of patients with positive anti-adrenocortical and anti-parietal cell antibodies was also determined. The ability of positive anti-thyroid antibodies to predict future thyroid abnormalities was analyzed for each cumulative age using the chi-square method with the Yates Correction. Relative risk was also determined for each age.

RESULTS

The relationship of percent positive anti-thyroid antibodies and cumulative age is shown in Fig. 1. There is a significant linear correlation between percent positive anti-thyroid antibody titers and cumulative age ($r=0.964, p<0.001$) from ages 7 to 16 years after which there is a plateau. Thus, as the age of a patient increases, the likelihood that she will have had at least one positive anti-thyroid antibody titer increases.

Fig. 2 shows these data grouped according to the patients' karyotypes. Data for 54 patients with 45,X karyotype are shown in Fig. 2 A and the 46 other karyotypes in Fig. 2 B. For these patients with 45,X karyotype there is a significant linear correlation ($r=0.985, p<0.001$) from ages 7 to 18 years, after which the curve plateaus. The patients with the other karyotypes also show a significant linear correlation ($r=0.976, p<0.001$) from 8 to 11 years after which the curve levels off.
Fig. 2. Percent of patients with positive anti-thyroid antibody titers vs. cumulative age. (A) 45,X patients (total=54). Data points represent the following numbers of patients: age 7=9; age 8=11; age 9=15; age 10=23; age 11=27; age 12=32; age 13=37; age 14=41; age 15=45; age 16=47; age 17=50; age 18=53; ages 19, 20, 21=54. (B) Other karyotypes (total=46). Data points represent the following numbers of patients: age 8=5; age 9=8; age 10=14; age 11=18; age 12=28; age 13=32; age 14=38; age 15=41; age 16=43; age 17=45; age 18=46.

The percentage of patients with positive antibody titers for parietal cells and adrenocortical cells is very low. One positive test out of 76 patients (or 185 total tests) was found for anti-parietal cell antibodies. No patients had associated clinical or laboratory findings. Two patients out of 76 (or 175 total tests) had positive anti-adrenocortical antibody titers, but had normal ACTH stimulation tests. All 3 of these patients also had positive anti-thyroid antibody titers and did not have a 45,X karyotype. Two of the 3 had a thyroid function abnormality: one had goiter; one had elevated TSH.

Positive anti-thyroid antibodies can be used as a predictor of the development of thyroid abnormalities for all karyotypes (n=85) as well as for the 45,X group at ages 13 through 17 years (chi-square = 3.83-4.67, p<0.05). Fig. 3 shows the percentage of patients with positive anti-thyroid antibodies who developed thyroid abnormalities (upper curve) and the percentage of patients with negative anti-thyroid antibodies who developed thyroid abnormalities (lower curve). If a patient's anti-thyroid antibody titer up to age 10 remained negative, then her probability of developing a thyroid abnormality was equal to that of a patient

Fig. 3. Anti-thyroid antibodies as predictors of development of thyroid abnormalities vs. cumulative age for all karyotypes (total number of patients=85). ■ Percent of patients with positive anti-thyroid antibody titers and subsequent development of thyroid abnormalities. △ Percent of patients with negative anti-thyroid antibody titers and subsequent development of thyroid abnormalities.
with 1 or more positive antibody titers at the same age. Beginning at age 11, the predictability of positive antibody titers for subsequent development of thyroid abnormalities became increasingly stronger, and reached significance at age 13. Relative risk was significant for ages 13–15 with the highest at age 15 years. For the 45,X patients the relative risk was also significant for ages 13–15 with the highest at age 15. Relative risks for the other karyotype group were not significant.

Of the 85 patients who had thyroid function studies done, 18 (22%) subsequently developed thyroid abnormalities (either elevated TSH, low T₄ and/or goiter). No patients had clinical symptoms of thyroid dysfunction, and only 4 had signs (goiter only). Four of the patients who developed thyroid abnormalities did not have positive anti-thyroid antibodies. Finally, four of the seven 46,X,i(Xq) patients (57%) developed positive anti-thyroid antibody titers.

DISCUSSION

In our population of 100 pediatric patients with Turner syndrome the percentage of patients with positive anti-thyroid antibody titers was greater than in the general population (10). This percentage increases with age. This has not been shown before with as large a group as our study. This confirms Pai's study of 20 patients (5). The percentage with positive anti-thyroid antibody titers peaks at 50% which is much higher than controls. A control population of 114 females between 0–50 years of age from the local area (Baltimore) showed that none had positive anti-thyroid antibody titers (R. M. Blizzard, unpublished results and personal communication). Another study of 105 female controls showed that 1% had positive titers (11). Finally, in 290 non-Turner control children (both male and female), 4.7% had elevated anti-thyroid antibody titers (12). These control populations show much lower titers than our population.

The percentage of our patients with positive anti-parietal cell and anti-adrenocortical cell antibodies was very low (1.3% and 2.6% respectively). The 3 patients with positive titers had no manifestations of disease. Previous smaller studies of normal children (10) and patients with Turner syndrome (6) found positive anti-parietal cell antibody titers among 2% and none, respectively. Thus, our results are consistent with previous studies. It is interesting to note that the 3 patients with the positive titers also had positive anti-thyroid antibody titers. We propose, therefore, that obtaining routine anti-parietal and anti-adrenocortical antibody titers is not worthwhile in patients with Turner syndrome both in terms of the potential benefit to the health of the patient and in terms of cost effectiveness.

On the other hand, the measurement of anti-thyroid antibodies is an excellent predictor of the development of thyroid dysfunction at certain ages for the population of patients with Turner syndrome as a whole, as well as for the group with the 45,X karyotype. This is important since most of our patients with thyroid abnormalities had no clinical signs or symptoms.

Our results show that patients under 10 years of age who had a positive anti-thyroid antibody titer were not at higher risk of developing a thyroid abnormality than patients less than 10 years of age with negative anti-thyroid antibody titers. Thus, a negative antibody titer before the age of 10 does not decrease the likelihood that a patient with Turner syndrome will subsequently develop a thyroid abnormality and means that it is necessary to measure antibody titers periodically thereafter.

A high percentage (57%) of patients with 46,X,i(Xq) karyotype had positive anti-thyroid antibody titers and thyroid abnormalities. However, the number of patients studied was small (7 patients). This high incidence has been suggested by several authors (1, 2, 4, 13, 14). From chi-square analysis of this small group, positive anti-thyroid antibody titers cannot be used as predictors of the subsequent development of thyroid abnormalities.
Since 22% of our patients with Turner syndrome developed a thyroid abnormality by mid-adolescence without clinical symptoms, it is clearly important to assess thyroid status in patients with Turner syndrome. Because of the difficulty in monitoring hypothyroidism by diminished growth velocity in already growth-retarded Turner patients, we believe it is worth the cost to monitor anti-thyroid antibodies or TSH values in order not to miss hypothyroidism. We propose that anti-thyroid antibodies be measured regularly in Turner patients from age 10 years onward because the percentage of patients with positive anti-thyroid antibody titers increases linearly with cumulative age, and the predictability of developing thyroid abnormalities also increases during the adolescent years. Once anti-thyroid antibodies become positive, there is no need to repeat measurements. Thyroid function at this point can be assessed by regular determinations of TSH levels.

Alternatively, it is satisfactory to evaluate thyroid status in patients with Turner syndrome by TSH determinations on a regular basis, since this is a sensitive indicator of the development of hypothyroidism at any age. If a patient has an elevated TSH, then anti-thyroid antibody determinations can be obtained to define the etiology of the thyroid dysfunction.

We believe it is well worth the cost of the tests discussed in order not to miss hypothyroidism. Currently, physician interventions to increase the growth of patients with Turner syndrome (e.g., human growth hormone and/or anabolic steroids) may be quite costly. The undetected occurrence of hypothyroidism could negate the growth-promoting effects of these agents. This issue will be of even greater importance with the advent of biosynthetic human growth hormone and its resultant increased availability.

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