High Incidence of Chronic Lymphocytic Thyroiditis in Apparently Healthy School Children: Epidemiological and Clinical Study

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Synopsis

An epidemiological survey on the incidence of juvenile chronic lymphocytic thyroiditis was performed in 10,220 apparently healthy school children in Ishikawa district, Japan. The subject of present study included 6,244 school children (2,831 boys and 3,413 girls, ages 6-18 yrs.) in Kanazawa City and 3,976 children (2,055 boys and 1,921 girls, ages 6-18 yrs.) in Wajima City. The first group was selected as a representative of urban area and the second group as that of seaside area.

Children who have goiter or firm thyroid were selected for testing anti-thyroglobulin and anti-microsomal antibodies in sera. Final diagnosis of chronic lymphocytic thyroiditis was made on histological specimen obtained by needle biopsy on the antibody positive subjects.

The overall incidence of chronic lymphocytic thyroiditis in these children was 3.0 per 1,000, whereas the incidence in adolescent girls was as high as 8.2 per 1,000. There was a considerable sex difference in the prevalence, the ratio of female to male was 6.5:1, and the incidence increased with age. The incidence in seaside area was 5.3 per 1,000 that was significantly higher than in urban area, 1.4 per 1,000 (p<0.005).

Histologically, 26 of 30 cases (87%) were classified as focal thyroiditis and 4 cases (13%) were diffuse thyroiditis.

Serum T4-I and T3 values were within normal range in all patients, but resting TSH was elevated in 1 of 23 cases and TSH response to TRH was exaggerated in 3 of 23 cases. Impaired organification of iodide was observed in 6 of 32 cases by iodide-perchlorate discharge test.

The present study demonstrates that juvenile chronic lymphocytic thyroiditis is highly prevalent among apparently healthy school children and early recognition of the disease with preventive care for hypothyroidism in future should be stressed.

Recently it has been stressed that chronic lymphocytic thyroiditis of Hashimoto type, hereafter referred to as "chronic thyroiditis", is by no means rare in childhood and adolescence and that the disease might be the most common cause of childhood euthyroid goiters accounting for 30~60% of them (Hung et al., 1973; Nakajima, 1973). Some authors have also pointed out a real increase in morbidity of the disease during these decades (Mackstood et al., 1961; Hahn et al., 1965).

Nevertheless, there have been no definite studies so far, to our knowledge, concerning the incidence of chronic thyroiditis among general young populations except that of Rallison et al. (1974) in Southwestern USA.

The purpose of the present study is to determine the prevalence of the disease among the children and adolescents and to
find some characteristics in early subclinical stage of the disease, expecting to provide a clue to clarify the disease.

Materials and Methods

The survey was performed during the period of 1972 to 1975 and initially took place in schools of Kanazawa City and Wajima City, Ishikawa Prefecture, as a part of routine medical examination of the school children. Kanazawa was taken as a representative of urban area and Wajima as that of seaside area. The schools of each area were chosen at random and all children of the schools were subjected to the initial screening physical examinations of the thyroid gland. The children examined consisted of 3,413 girls and 2,831 boys of urban area and 1,921 girls and 2,055 boys residing in seaside area, all between the ages of 6 and 18 years (Table I and II).

1) Physical examinations were done, at the onset, on the thyroid glands of these 10,220 children in total to detect goiter and/or increased consistency, each time performed by at least two of the authors. For the criteria of goiter Shichijo's scheme (1958) was used and a thyroid gland of grade II-III or larger on inspection and palpation was considered to be enlarged (Table III).

2) Sera of all children who were considered to have goiter and/or abnormal consistency of the gland were tested for circulating antibodies to...
Table III Scheme for determination of goiter*

In sitting or standing position,

1. The thyroid gland palpable in the anterior neck with the head brawn backward when it would be most convenient to palpate the gland ...Grade 0
2. The thyroid gland palpable in the position described in (1) and its contour is
   a) not inspectable ..................Grade I
   b) barely inspectable .................Grade I-II
   c) obviously inspectable .............Grade II
3. With the head in normal position, the thyroid gland is
   a) barely inspectable .................Grade II-III
   b) clearly inspectable ...............Grade III
4. Enlargement of the thyroid gland so remarkable that it bulges forward giving the appearance of a tumor.................................Grade IV
5. The thyroid gland enormous ......Grade V

The contour of the gland is to be confirmed by the patient's swallowing movements.


thyroglobulin and to epithelial microsomal antigen of the thyroid by the tanned erythrocyte agglutination method utilizing commercially prepared test kits of Fuji Zoki Co., Japan.
3) On the subjects whose sera turned out positive for either of the antibodies percutaneous needle biopsy of the thyroid was performed with Franklin-Silverman's needle in one portion of each lobe. Histological classification was done according to Woolner's criteria (1959).
   Serum T<sub>4</sub>-I level was measured by Oxford column T<sub>4</sub> and T<sub>3</sub> by radioimmunoassay with T<sub>3</sub>-RIA kit of Dainabot RI Lab. Co., Tokyo.
   Serum TSH was determined by double antibody radioimmunoassay and serum TSH response to TRH was studied before and 30, 60 minutes after intravenous administration of 500 µg TRH as previously described (Sato et al., 1974). Iodide-perchlorate discharge test was carried out by the method described by Takeuchi et al (1970).

Results

Epidemiological observations

The details of the results are summarized in Table I and II, of the survey in Kanazawa City and Wajima City, respectively.

The prevalence of goiter was similar in the two areas (2.7% and 3.0%), although abnormality in consistency of the gland was more frequent in girls of seaside area than in urban girls.

In both areas there were no antibody positive subjects among 114 children under 11 years of age who were selected from 3,377 children of primary schools by physical examinations.

There were so many as 16 subjects (0.26%) with positive antibodies in Kanazawa and 27 subjects (0.68%) in Wajima.

Among the 43 subjects with positive sera 30 cases (0.3%) were histologically proved to have chronic thyroiditis. Of the remaining 13 children nine had colloid goiter, one had Basedow's disease and adequate specimens for histological diagnosis were not obtained in three.

A striking difference was noted in the incidence of chronic thyroiditis between Kanazawa and Wajima. The incidence among the children in Kanazawa was 1.4 per 1,000, while among those in Wajima it was 5.3 per 1,000. The difference is statistically significant (p<0.005), and the difference is more evident in girls (p<0.001) than in boys (p<0.05).

There was a considerable sex difference in the prevalence in both areas, the ratio of female to male being 6.5:1, and the prevalence increased with age. The prevalence in adolescent girls (16 to 18 years of age) was as high as 8.2 per 1,000.

Clinical observations

There were no past histories suggestive of thyroid diseases or autoimmune diseases in any of the 30 cases of chronic thyroiditis found in this survey, but family histories of chronic thyroiditis in three, Basedow's disease in one and diabetes mellitus in one were obtained.

The thirty patients had no characteristics in stature, as the values of their height and body weight were scattered in the ranges of -1.0SD to +1.6SD and -2.0SD to +1.8SD,
respectively from the mean of the Japanese children of their age.

In 26/30 cases (87%) slight to moderate increase in size of the thyroid gland (grade II–III to III) was noted and in 28/30 (93%) consistency of the gland was increased in the marginal areas of the lobes. However, firmness of the gland was not a remarkable finding in most cases, whereas only 5/30 (17%) showed pebbly nature of the surface.

26 of the 30 cases, which accounted for 87% of all, were histologically classified as focal thyroiditis and the remaining 4 cases (13%) were almost diffuse thyroiditis. The histological changes consisted of predominantly interfollicular infiltration of lymphocytes and plasma cells with lymph follicles, with various degree of follicular atrophy, while in none of the cases fibrosis and oxyphilic epithelial changes were remarkable.

No appreciable correlation was found between the findings of physical examination of the gland and the degree of histological changes.

T₄-I levels were within normal range in all cases as well as T₃. There was 1/23 cases of high basal serum TSH, and TSH response to TRH was excessive in 3/23 cases and hyporesponsive in 2/23 cases.

In all the cases of high basal TSH and excessive TSH response T₄-I was at low normal levels and the histological alternations were relatively advanced or almost diffuse. In two cases of low TSH response T₄-I was at high normal levels and in one of them hyperplastic epithelial changes were histologically demonstrated.

Abnormal ¹³¹I-discharge (more than 20% of administered dose) was noted in 6/23 cases. In these 6 cases two of the histologically diffuse thyroiditis were included.

The titers of antithyroglobulin and antimicrosomal antibodies of all the cases are shown in Fig. 1. The antimicrosomal antibody tended to be of relatively high titers in diffuse thyroiditis.

Routine laboratory data such as total serum protein, its fractions, thymol turbidity test, zinc sulfate test and serum cholesterol levels were within normal ranges in all 23 cases examined.

Discussion

Nakajima et al. (1972) has pointed out from their clinical observations that juvenile chronic thyroiditis has following characteristics; 1) Female predominance, the ratio of female to male being 11:1. 2) In most cases no apparent symptoms are present except goiter, which usually is unrecognized by the patient himself. However, this is a significant clinical sign to an experienced physician for a diagnostic clue. 3) Although a small number of goiters are of diffusely increased consistency as in adults' Hashimoto's disease, most of them have only portions of the lobes with increased consistency. 4) The most reliable and simple diagnostic test at present is thyroglobulin-
and thyroidal epithelial microsome-coated tanned red cell agglutination test, either of which turns out positive in about 93% of patients with biopsy proved chronic thyroiditis when performed with the commercially prepared kits of Fuji Zoki Co. 5) More than 90% of cases are of focal type.

Considering these characteristics the scheme of the field study was drawn up as follows:

1) Initial screening examinations by inspection and palpation of the thyroid gland.
2) To test the sera of all the subjects judged to have goiter and/or a portion of abnormal consistency for the circulating antibodies by tanned red cell agglutination test.
3) To perform needle biopsy of the gland on the cases whose sera turn out positive for the antibodies.

In order to give more objectivity to the screening method Shichijo's criteria for goiter was taken and each examination was carried out by at least two of the authors. Even the cases of chronic thyroiditis with normal consistency of the gland and those without significant goiter will not be overlooked in the initial physical examination when performed according to this scheme. Actually 5 cases with normal consistency and 3 cases without significant goiter were found in the present survey. Although cases of chronic thyroiditis with negative antibodies were neglected in this study, they are estimated to account for less than 10% of all chronic thyroiditis and therefore would give little influence upon the incidence of the disease.

In this survey the overall incidence of the disease was 3 per 1,000 and females it was 5.2 per 1,000. When limited to the adolescent girls it was as high as 8.2 per 1,000 among 1965 of them. Rallison et al. (1974) reported the prevalence of the disease among the children of Western USA and stated such a high incidence as 16 per 1,000 among the adolescent girls. In their study the means and the criteria for diagnosis were different from ours and not all of them were with histological confirmation, as their first aim was to detect thyroidal neoplasms.

It was surprising to find out such a striking difference in the prevalence between Kanazawa and Wajima. Although the reasons for the difference is open to question, we presume the first thing to consider as the difference in the two areas would be

Fig. 2. A case of chronic diffuse thyroiditis. Note extensive infiltration of mononuclear cells with minimal fibrosis. No intact thyroid follicles are seen in the field. (Hematoxylin and eosin, x40)

Fig. 3. A case of chronic focal thyroiditis. Note scattered areas of interfollicular aggregate of round cells and moderate follicular atrophy adjacent to infiltrates. (Hematoxylin and eosin, x40)
that the former is a representative of urban area and the latter is that of seaside area. One can suppose there would be a difference in the amount of iodine intake in the form of seaweeds. The increased prevalence of chronic thyroiditis after the administration of iodine for therapy and prophylaxis in the area of endemic goiter was reported by Weaver et al. (1969). Excessive iodine has also been observed to produce thyroiditis in experimental animals which were pretreated with iodine-deficient diets (Follis, 1964). Though we have not yet determined the iodine intake of our children, a direct effect of excessive iodine on the thyroid gland as one possible causal factor of chronic thyroiditis is suggested by these reports. The authors are now seeking for its possibility.

Another thing to consider is that Wajima has been famous for Japan industry for a long time and there have been many marriages within the people of the same area in order to bring up Japanners with the specific talent. This may have resulted in accumulation of certain genetic factor which composes the constitution of many people there with an increased susceptibility to the disease. Fukase (1975) pointed out that systemic lupus erythematosus and other autoimmune diseases were also highly prevalent in the area of Noto Peninsula including Wajima.

It also deserves mentioning that there were, though not many, cases who showed evidences for latent hypothyroidism in TSH response to TRH and for organification defect in iodide-perchlorate discharge test among such young patients most of whom were presumably in early stages of chronic thyroiditis.

As some of these cases are supposed to develop into classical Hashimoto's disease and overt hypothyroidism, we think our field study also has the meaning as the start of the follow-up study of chronic thyroiditis in children.

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