NATURAL COURSE OF AUTOIMMUNE THYROIDITIS IN THAI CHILDREN

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Abstract. Forty-seven pediatric patients with autoimmune thyroiditis were followed for an average of 5.18±2.89 years. The diagnosis was based on a firm goiter and a positive test for antithyroid antibodies. Initially, 23 patients had euthyroidism, 11 overt hypothyroidism, 6 compensated hypothyroidism and 7 with low TSH. All patients had clinical euthyroidism, except two who had overt hypothyroidism. The thyroid function tests, the size of the thyroid gland and the thyroid antibodies were regularly evaluated. After the follow-up, 26 patients had untreated euthyroidism, 12 with overt hypothyroidism received eltroxin for maintenance of euthyroidism, while 4 had compensated hypothyroidism and 5 low TSH levels. All had clinical euthyroid. The thyroid size was reduced in 12 patients (26%) while 4 (9%) had normal-sized gland. The goiter size in 35 patients (74%) remained unchanged. The antithyroglobulin and antimicrosomal antibody titers fluctuated higher in patients with overt hypothyroidism. Eltroxin was given only to those having overt hypothyroidism with diminished goiter size in 8 patients (73%).

INTRODUCTION

Autoimmune thyroiditis (Hashimoto, chronic lymphocytic thyroiditis) is the common cause of goiter and the most common cause of acquired hypothyroidism in many patients (Rallison *et al*, 1991; Jaksic *et al*, 1994). Five to 6.5 new cases per year per 1,000 children were reported in the United States (Rallison *et al*, 1975), however, the incidence in Thailand is unknown. Jaruratanasirikul *et al* (1995) demonstrated a prevalence of 8.4% of goiters in healthy schoolchildren in southern Thailand. Investigation for antithyroid antibodies is only available in advanced tertiary care hospitals so in general practice, euthyroid goiters are usually treated with thyroxine. Spontaneous diminution in the size of thyroid glands has frequently been reported in untreated patients with juvenile autoimmune thyroiditis (Rallison *et al*, 1975; Nilsson and Doniach, 1964; Rother *et al*, 1994). The objective of our study was to describe the natural course of autoimmune thyroiditis in children in order to devise proper management and long term follow-up protocols.

PATIENTS AND METHODS

Forty-seven patients, 46 girls and 1 boy, were followed-up in the Pediatric Endocrine Clinic at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand between 1990 and 2000. Only those patients followed-up for at least 12 months were included. The mean age ± SD at the time of diagnosis was 11.77 ± 2.33 years (range, 5 to 15 years). Follow-up averaged 5.18 ± 2.89 years (range, 1.0 to 10.3 years) (Table 1). Diagnosis of autoimmune thyroiditis was based on the finding of a firm goiter on palpation and the presence in plasma of significant antithyroglobulin and/or antimicrosomal antibody titers. Thyroid size was determined by measuring the length of both lobes and the height of the isthmus. A 2.5 to 4.0 cm length was defined as small-sized, whereas 4.0 to 5.5 cm moderate-sized and >6.0 cm large-sized. Twelve patients (25.5%) were referred from the district hospitals, and none had had thyroid antibodies determined, but all had been given thyroxine – this treatment was stopped at least 1 month prior to our initial thyroid studies.

Thyroid studies included measurements of serum total thyroxine (T_4), free thyroxine (FT_4) and thyrotropin (TSH) concentration. Serum T_4 and FT_4 were measured by standard radioimmunoassay techniques (RIA). TSH de-

terminations were made with a radioimmunological kit (RIA-gnost^{R} h TSH). Normal values are: T_4, 4.82 to 12.82 μg/dl, Free T_4, 0.86 to 1.87 ng/dl, and TSH 0.4 to 3.1 μIU/ml. Antithyroglobulin and antimicrosomal antibodies were titrated by passive hemagglutination. Results were considered significant if titers were >1:100.

The patients were divided into four groups based on the results of the initial thyroid function tests. Group 1 comprised euthyroid patients with normal serum T_4, FT_4 and TSH; Group 2 compensated hypothyroidism patients with normal T_4, FT_4 but serum TSH >5 μIU/ml; Group 3 overt hypothyroidism patients with subnormal serum T_4, FT_4 (T_4 <4.5 μg/dl; FT_4 <0.8 ng/dl and serum-TSH 75 μIU/ml and, Group 4 low TSH patients with normal T_4, and FT_4 but subnormal serum TSH (<0.3 μIU/ml). Goiter size and thyroid studies were completed once to twice per year.

RESULTS

Of the 47 patients in this study, 23 (49%) were euthyroid at diagnosis and 21 of them (91%) remained so during the 5.16 ± 2.78 years (range 1 to 10) of follow-up. One patient had compensated hypothyroidism and another low serum TSH at the end of the follow-up, both patients had small-sized goiters (Fig 1). Overall five patients had moderate-sized goiters and 18 had small-sized ones. The change in goiter sizes from moderate to small was documented in 2 patients (9%). Disappearance of goiters occurred in the 2%, 9% of the patients who had euthyroidism and small-sized goiters (Fig 2).

Eleven patients (23%) with overt hypothyroidism were given 2 to 3 μg of eltroxin/kg/day. Most of them were asymptomatic, and only 2 had mild hypothyroidism. Elevated T_4 and free T_4 with decreased TSH levels (< 0.125 μIU/ml) were found in 5 patients (46% of those with hypothyroidism) after eltroxin treatment of more than two months. Discontinuation of this therapy was tried in all 5 patients and overt hypothyroidism developed two to eight months following hormone discontinuation. So eltroxin was re-started (1 μg/kg/day) to maintain a euthyroid state (Fig 1). Eight patients presented with moderate-sized goiters and 3 with small-sized ones at the initial diagnosis. After treatment only 2 still had moderate-sized goiters, 7 were small and 2 were normal (Fig 2). One boy with Type 1 diabetes also had overt hypothyroidism with a small goiter. The follow-up period for this group averaged 6.38 ± 2.65 years (range, 1.5 to10.3 years).

Compensated hypothyroidism was documented in 6 (13%) patients including one pair of sisters. None received hormonal therapy after the initial diagnosis. Results of thyroid studies and goiter size evaluation were unaffected in 3 patients. One patient had overt hypothyroidism and the goiter size was unchanged so eltroxin was administered. Thyroid studies in 2 patients returned to normal

Table 1
Age at diagnosis and follow-up time of patients with autoimmune thyroiditis.

Year	Euthyroidism n = 23	Overt hypothyroidism n = 11	Compensated hypothyroidism n = 6	Low TSH n = 7	Total n = 47
Age at diagnosis (year)					
range	10-15	8-13.8	5-15	8-14.8	5-15
mean ± SD	12.35 ± 1.61	11.15 ± 1.75	9.65 ± 3.97	12.11 ± 2.55	11.77 ± 2.33
Follow-up time (year)					
range	1-10	1.5-10.3	2-10	1-6	1-10.3
mean ± SD	5.16 ± 2.78	6.38 ± 2.65	7.17 ± 3.13	2.94 ± 1.94	5.18 ± 2.89

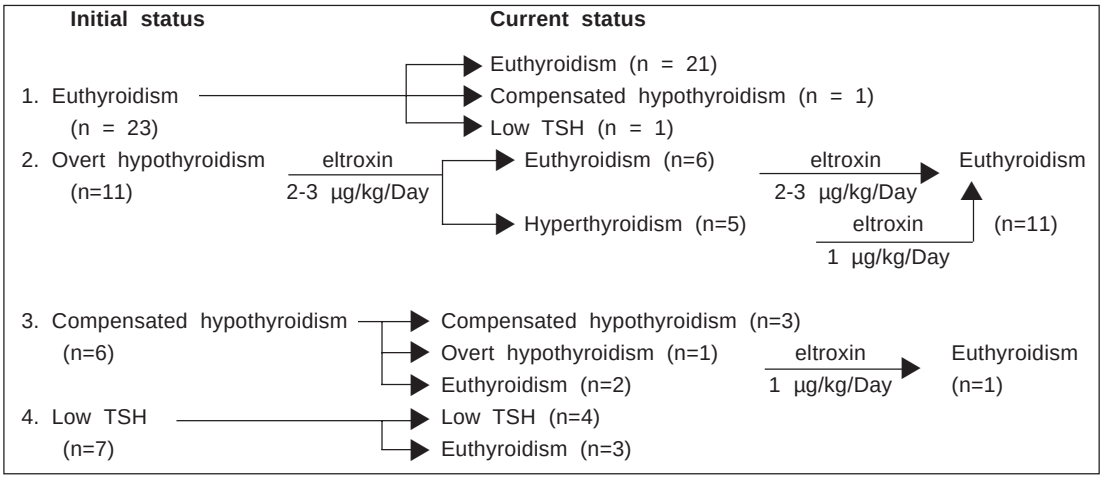

Fig 1–Natural course of thyroid function in 47 patients with autoimmune thyroiditis.

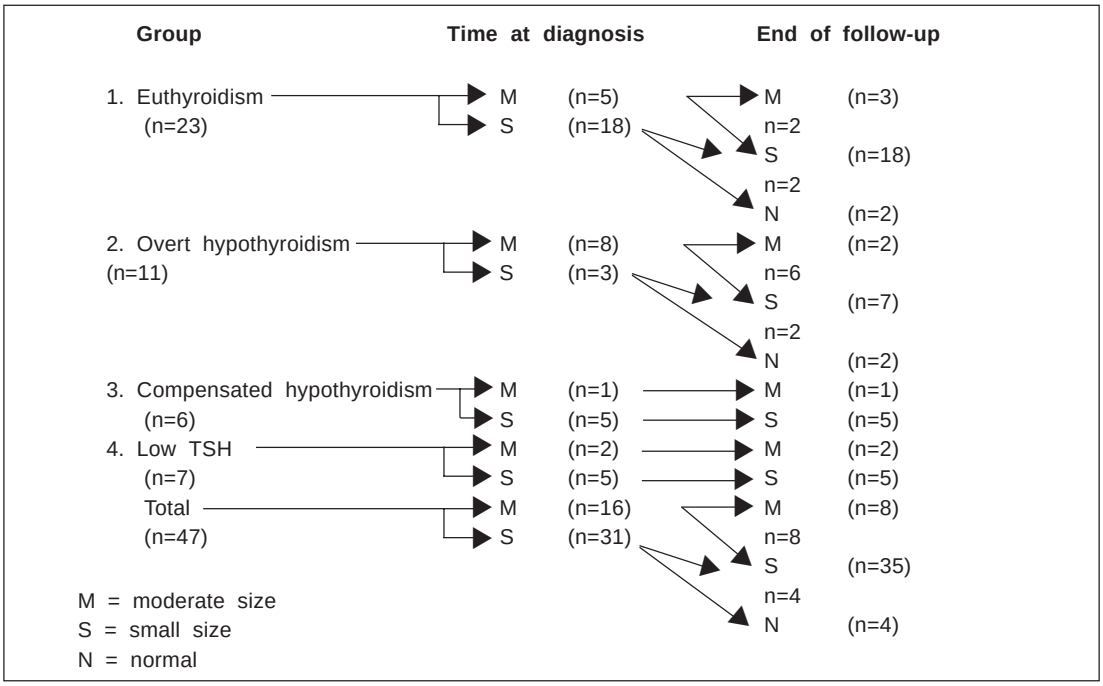

Fig 2–Changes in goiter size in patients with autoimmune thyroiditis.

at the end of the follow-up time (Figs 1, 2).

Seven patients (15%) had a low TSH level with clinical of euthyroidism and four remained so during the 2.94 ± 1.94 years of follow-up. The TSH levels in 3 patients increased to normal by the end of the study (Figs 1, 2).

The antithyroglobulin and antimicrosomal antibody titers in overt hypothyroidism fluctuated between 1:1,600 and 1:102,400. The antibody titers in the other three groups varied between 1:100 and 1:25,600. The titers did not correlate with either goiter size or thyroid function tests. A history of thyroid diseases in first degree relatives was obtained from 8 patients (17.0%).

DISCUSSION

Almost all of the children with goitrous autoimmune thyroiditis in our study had clinically defined euthyroidism, with a preponderance of females being affected. The initial thyroid function tests showed 49% with euthyroidism, about a quarter (23%) with overt hypothyroidism and the remaining quarter with compensated hypothyroidism and low TSH levels. It is believed that the thyroid function gradually decreases to hypothyroidism so eltroxin was given to all patients. (Winter *et al*, 1966; Papapetrou *et al*, 1972; Gordon and Lamberg, 1981). Children with euthyroid goiter in Thailand are commonly treated with eltroxin indefinitely.

From our study, 21 of the patients with euthyroidism (91%) remained clinically euthyroid and had normal thyroid function during the 5.16 ± 2.78 years of follow-up. A change in thyroid function was found in only 2 patients (9%), one patient showed compensated hypothyroidism. Spontaneous diminution of goiter sizes was observed in 4 patients with complete normalization in 2 of them (9%). Similar results have been reported in other untreated patients (Rallison *et al*, 1975; Nilsson *et al*. 1964; Sklar *et al*, 1986; DePapendieck *et al*, 1982). Because most of the children and adolescents with normal T_4 levels did not respond to thyroid hormone treatment, whether or not they had normal or elevated TSH levels (Rother *et al*, 1994). None of our patients in this group were given eltroxin treatment.

Almost all of the patients with overt hypothyroidism had clinical euthyroidism, except two patients who had mild symptoms of hypothyroidism. All of these patients received eltroxin therapy. About half of them developed hyperthyroidism with normal dosages of eltroxin. Discontinuation of the medication resulted in overt hypothyroidism again. These patients well tolerated low dose eltroxin (1 μg/kg/day). Seventy-three percent of patients responded well to the treatment: in 6 (55%) the goiter size reduced from a moderate to a small size and 2 patients (18%) gland size return to normal. High prevalence (7 to 38%) of Hashimoto thyroiditis among Type I diabetes individuals was reported (Riley *et al*, 1981; Maclaren *et al*, 1985). In one study with 42 years of follow-up of patients with Type I diabetes, the prevalence of Hashimoto thyroiditis was 26.6%; 42.0% of these individuals were euthyroid while 58.0% had hypothyroidism (McCanlies *et al*, 1998). From this study only one boy (9%) with Type I diabetes had overt hypothyroidism. These observations indicate that the longer the patient has Type I diabetes the higher the associated incidence of autoimmune thyroiditis. For the group with compensated hypothyroidism, 2 of 6 patients (33%) had normal thyroid function by the end of the study. Only one patient had overt hypothyroidism and thus eltroxin treatment. Because a third of the patients in this group had a spontaneous return to normal thyroid function, so the remaining 5 patients did not have eltroxin treatment. Since eltroxin treatment can reduce bone mineral density, increase heart rate and shorten the systolic time interval (Ross, 1988; 1991), its casual use was not justified.

The last group had clinical euthyroidism but low TSH levels (<0.3 μIU/ml). Rajatanavin *et al* (1988) showed that the lowest detectable value of serum TSH (IRMA) in euthyroid subjects was 0.3 μIU/ml and levels between 0.3 and 0.8 μIU/ml were overlapping values between euthyroid and some hyperthyroid patients. Three of the seven patients (43%) had a thyroid function test returned to normal by the end of the study. The follow-up time (2.94 ± 1.94 years) was shorter than the other groups. These patients may represent those who have an early stage of autoimmune thyroiditis with suppressed TSH-without overproduction of thyroid hormone and had TSH rising to normal later.

It is widely known that autoimmune thyroiditis occur in families. However, only about one-sixth (17%) had a family history of the disease in our study. Susceptibility to autoimmune thyroiditis depends on a complex interaction between multiple genetic and environmental factors. Cytokines are crucial in the regulation of both the immune and inflam-

matory responses and therefore are potential candidate genes for autoimmune thyroid disease. Recent studies have shown that interleukin-4 (IL-4) variant or a closely linked gene had a modest protective effect against the development of the disease (Hunt *et al*, 2000).

Our results suggest that the course of autoimmune thyroiditis may vary, most patients remaining in the same condition as indicated in the initial diagnosis. Spontaneous recovery from abnormal thyroid function with diminution of goiter size occurred in some patients. Treatment with eltroxin was recommended in overt hypothyroidism and produced a good response in those patients. It is appropriate for non-treated patients to be observed periodically (once or twice a year) although the incidence of developing hypothyroidism was not high.

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