The Natural Clinical Course of Children with an Initial Diagnosis of Simple Goiter: A 5-Year Longitudinal Follow-up

The Natural Clinical Course of Children with an Initial Diagnosis of Simple Goiter: A 5-Year Longitudinal Follow-up

Somchit Jaruratanasirikul[1], Kalaya Leethanaporn[2] and Kalaya Suchat[1]

[1]Department of Pediatrics and [2]Department of Radiology,
Faculty of Medicine, Prince of Songkla University, Hat-Yai, Songkla, Thailand

ABSTRACT

A total of 154 children initially diagnosed as simple goiter were evaluated annually for 5 years. The mean age at diagnosis was 12.8 ± 1.8 years. The annual evaluation consisted of clinical assessment for height, weight, pubertal status, goiter size, and laboratory measurements for free thyroxine (FT_4), thyrotropin (TSH), anti-thyroglobulin and anti-microsomal antibodies. At initial diagnosis, goiter was grade I in 117 children (76%) and grade II in 37 children (24%). All children had normal FT_4, TSH and negative thyroid antibodies. After 5 years of follow-up, there were 6 children who later had positive thyroid antibodies in the 3rd and 4th year and the diagnosis was changed to chronic lymphocytic thyroiditis. In one patient TSH level was elevated in the third year and later increased which is strongly suggestive of compensated hypothyroidism. All children had normal growth as shown by the average final adult height of 2.67 ± 1.25 cm above the mid-parental height. In girls the average age at menarche was 12.5 ± 1.4 years which was not different from normal children. The goiter decreased in size in 36 children (23.4%) and remained the same size in 113 children (73.4%) without any medication. We concluded that 1) children who were initially diagnosed as simple goiter need to be followed annually for at least 5 years, and 2) the minimal annual laboratory evaluation should be TSH and thyroid antibodies to detect the early stage of chronic lymphocytic thyroiditis and compensated hypothyroidism.

KEY WORDS

adolescent goiter, chronic lymphocytic thyroiditis, colloid goiter, goiter, simple goiter, thyromegaly

INTRODUCTION

Simple goiter, also termed colloid goiter, is the most common cause of asymptomatic diffuse thyromegaly in iodine sufficient areas[1,2]. The diagnosis is made by exclusion of other causes of thyromegaly. It is a benign condition and data on the long term clinical course are limited.

Thailand is an endemic area of iodine deficiency goiter, particularly in the northern and northeastern regions[3,4]. After iodized salt was promoted in 1964, the prevalence of goiter markedly decreased. However, goiter is still prevalent in rural areas where goiter surveillance is not continuously monitored[5-7].

During 1993-1994, the prevalence of goiter was studied in the Hat-Yai municipality (located in southern Thailand). A total of 6,035 schoolchildren were examined[8]. The results showed that the prevalence of goiter was about 6%. All children with goiter had high urine iodine excretion above the level for diagnosis of iodine deficiency. The most common cause of goiter was found to be simple goiter (89.8%), followed by chronic lymphocytic thyroiditis (8.4%). Since then we have had the opportunity to follow these children for 5 years at our clinic. In this report, we focus only on children who were initially diagnosed as simple goiter. The objective was to study the clinical course of goiter, growth, pubertal status, and the final adult height of these children.

PATIENTS AND METHODS

The patients were recruited from the goiter survey in the Hat-Yai municipality during August 1993 - July 1994. Goiter was graded on the basis of adapted WHO criteria as follows: grade 0 - not palpable, grade I - palpable, visible only with neck extended, grade II - easily visible with neck in the normal position, and grade III - very large goiter. Of the total 6,035 schoolchildren examined, 355 children (6%) were found to have goiter[8]. Two hundred and fourteen children participated in the study and had blood drawn for measurement of free thyroxine (FT_4), thyrotropin (TSH), anti-thyroglobulin and anti-microsomal antibodies, and had urine collected for measurement of iodine excretion. The diagnosis of simple goiter was made on the basis of 1) presence of diffuse goiter, 2) no clinical signs and symptoms of hypo- or hyperthyroidism, 3) normal levels of FT_4, TSH, 4) negative for both anti-thyroglobulin and anti-microsomal antibodies, and 5) urinary iodine excretion greater than 10 μg/dl.

The methods of measurement were radio-immunoassay for FT_4 (Amersham, UK), immuno-radiometric assay for TSH (Cis-Biointernational, France), hemagglutination for anti-thyroglobulin and anti-microsomal antibodies (Murex Diagnostics, UK), and cerric ammonium sulfate for urinary iodine excretion.

Of the 214 children examined, 192 (129 girls, 63 boys) fit the criteria mentioned above. The mean age at initial diagnosis was 12.7 ± 1.8 years (range 9.4-15.5), mean FT_4 was 1.23 ± 0.22 ng/dl (range 0.81-1.69), and TSH was 2.18 ± 1.31 mIU/l (range 0.74-4.2). The mean level of urinary iodine excretion was 23 ± 9.6 μg/dl (range 10.5-66.5).

All children were invited for annual visits at our endocrine clinic. The annual evaluation consisted of clinical assessment of height, weight, pubertal status, goiter size and consistency, signs and symptoms of hypo- and hyperthyroidism, and laboratory measurement of FT_4, TSH, and anti-thyroglobulin and anti-microsomal antibodies. Height was measured in the standard standing position using a stadiometer. Weight was measured using a beam balance scale. Pubertal status was assessed according to Tanner staging. Age at menarche was recorded and determined in decimal fractions of years. The parents of the children were interviewed for family history of goiter and thyroid diseases. The parents' heights were measured for calculation of midparental height based on the formula[9]:
midparental height = [father's height + mother's height]/2 + 6.5 for boys, and - 6.5 for girls.

From the 192 children initially recruited, 154 (80.2%) completed the 5-year follow-up schedule. Of the 38 children (19.8%) lost to follow-up, 26 children moved out of the area and 12 children refused to have blood drawn. Therefore, the data of 154 children were used for analysis.

This study was approved by the Ethics Committee of Prince of Songkla University.

RESULTS

At the initial diagnosis, the mean age of the 154 patients was 12.8 ± 1.8 years (range 9.4-15.5). There were 123 females and 31 males. Goiter size was grade I in 117 children (76%) and grade II in 37 children (24%). Serum FT_4 and TSH levels displayed a bell-shaped distribution with FT_4 and TSH ranging from 0.74-1.74 ng/dl and 0.36-4.09 mIU/l, respectively. After 5 years of follow-up, the mean age of the patients was 17.9 ± 1.7 years (range 14.5-20.6).

For the 117 patients with grade I goiter, the goiter was still grade I in 86 patients (73.5%), decreased to grade 0 in 26 patients (22.2%), and increased to grade II in 5 patients (4.3%). Of the 37 patients with grade II goiter, 27 (73%) showed no change in size and in ten (27%) the goiter had decreased to grade I. Therefore, the goiter decreased in size in a total of 36 children (23.4%) and remained the same size in a total of 113 children (73.4%).

No patient had any signs or symptoms of hypo- or hyperthyroidism. Thyroid antibodies were positive in six patients (3.9%), three patients in the third year and three in the fourth year of follow-up. Of these six patients with positive thyroid antibodies, there were five whose thyroid size increased from grade I to grade II. Family history of thyroid disease was present in three out of the six patients (50%) who later developed positive thyroid antibodies, and in only 20 out of 148 patients (13.5%) who still had negative thyroid antibodies.

FT₄ and TSH values were all in the normal range, except for one patient who later had positive thyroid antibodies and compensated hypothyroidism (Table 1). In this patient TSH was elevated to 29.6 mIU/l at the 12-month follow-up and goiter size had increased from grade I to grade II, firm in consistency with smooth surface. Thyroxine was administered at the dosage of 75 µg/day, and goiter size decreased to grade I, and TSH declined to 2.18 mIU/l.

All 154 patients had normal physical growth as their heights and weights were along the normal percentile curves between the 25th and 90th percentiles of the Thai growth chart[10]. Their mean final height (as defined by height velocity less than 0.5 cm/year) was +0.62 SDS and was 2.67 ± 1.25 cm (range -3 to +5.6) above the midparental height. The mean age at menarche was 12.5 ± 1.4 years which was not statistically different from normal Thai girls (12.4 ± 1.1)[11].

DISCUSSION

Our results demonstrate that children with an initial diagnosis of simple goiter must be followed annually for at least 4-5 years. The annual follow-up schedule should include both clinical and laboratory evaluations, such as growth, pubertal status, size and consistency of the thyroid gland, thyroid function tests and thyroid antibody measurement.

All these evaluations are performed to distinguish between chronic lymphocytic thyroiditis and simple goiter, the two most common causes of goiter in adolescence in iodine sufficient areas[1,2]. In both conditions, the thyroid gland is symmetrically enlarged, but the consistency is soft and the surface is smooth in simple goiter whereas the consistency is firm and the surface feels pebbly in chronic lymphocytic thyroiditis. However, in the early stage of thyroiditis, the thyroid gland may be soft or have normal consistency with a smooth surface on palpation, so it is clinically difficult to distinguish from simple goiter. These two conditions, however, can be distinguished by measurement of thyroid antibodies. Serum anti-thyroglobulin and anti-microsomal antibodies are usually present in chronic lymphocytic thyroiditis and absent in simple goiter. A thyroid biopsy to distinguish histologically between chronic lymphocytic thyroiditis and simple goiter is not warranted since therapy for both conditions does not differ in situations of normal thyroid function[12]. It is generally accepted that the appropriate method to distinguish between the two conditions is long-term follow-up and the annual measurement of thyroid antibodies[2]. The presence of anti-thyroglobulin and anti-microsomal (or anti-peroxidase) antibodies is considered to be strong evidence for diagnosis of chronic lymphocytic thyroiditis in children with goiter. The distinction between these two conditions is of importance

TABLE 1

Details of patients who later had positive thyroid antibodies

Patient	Age (yr)	Year of follow-up	Anti-T	Anti-M	FT₄ (ng/dl)	TSH (mIU/l)	Family history of goiter
1	14.7	3rd	< 1 : 10	1 : 400	1.14	2.47	No
2	14.3	3rd	1 : 20	1 : 400	1.05	1.54	Yes
3	13.9	3rd	1 : 40	1 : 1,600	0.88	15.7	Yes
4	15.4	4th	1 : 20	1 : 400	0.98	1.94	No
5	14.9	4th	1 : 10	1 : 1,600	1.34	4.92	No
6	16.2	4th	1 : 20	1 : 400	0.92	2.14	Yes

Anti-T = anti-thyroglobulin antibody; Anti-M = anti-microsomal antibody.

since the long term consequences are totally different. The risks of acquired primary hypothyroidism and thyroid cancer are increased in chronic lymphocytic thyroiditis[13,14], whereas simple goiter has no long-term consequence.

The pathogenesis of simple goiter is not entirely verified. The histological finding is enlarged thyroid follicles filled with abundant colloid without evidence of inflammation, infection, or neoplasia[1,2]. The presence of thyroid growth-stimulating immunoglobulins (TGI) in many studies suggests an autoimmune process[15]. Recently, a population-based twin study has demonstrated that genetic influence is an important factor involved in the etiology of simple goiter[16]. The influence of environmental factors or autoimmunities in a genetically predisposed individual to develop clinically overt goiter is still being investigated.

In our study, the thyroid glands of children with simple goiter (excluding the patients who were later diagnosed as chronic lymphocytic thyroiditis) decreased in size or remained the same size during the 5-years of follow-up. The concentrations of FT_4 and TSH were all in the normal range. This observation indicates that thyroid replacement for the purpose of TSH suppression and reduction in goiter size is unnecessary. Furthermore, all children had normal physical growth and normal age of puberty, as shown by the final height of the patients greater than midparental height and normal age at menarche. The apparently normal growth and puberty are strong supporting evidence that the hormones influencing growth are normal in children affected with simple goiter. Therefore, thyroxine therapy is not recommended since long term thyroxine administration can cause adverse effects from a hyperthyroid state, such as tachycardia, increased bone turnover, decreased bone mineral density, mood lability and poor school performance[17,18]. In terms of risk-benefit ratio, thyroxine therapy in simple goiter is hazardous rather than beneficial.

The reduction of goiter size during the 5-year follow-up in our study can be clinically concluded as the natural course of simple goiter. However, the initial detection of goiter in our study was based on palpation, which may have led to the overdiagnosis of goiter grade I in some children[19]. Ultrasonography is a more precise method to measure thyroid volume and its echogenicity. However, thyroid measurement by this procedure should be done under experienced hands and the results must be adjusted for age, height, weight, and body surface area[19]. Moreover, this procedure takes more time, and the cost is relatively high. Therefore, thyroid assessment by palpation is still accepted as a practical method in clinical evaluation of goiter.

At the initial diagnosis, all the children had normal levels of FT_4 and TSH and had negative thyroid antibodies. After 5 years of follow-up, six patients had developed positive thyroid antibodies, and only one of the six patients had compensated hypothyroidism. All patients had normal levels of FT_4 and had no signs or symptoms of hypothyroidism. Our results indicate that annual evaluation of thyroid antibodies is of great importance to detect initially undiagnosed lymphocytic thyroiditis, particularly in children who have a family history of goiter or thyroid disease. Negative thyroid antibodies at the initial evaluation are possibly due to the very low or undetectable level of antibodies, or due to an insufficiently sensitive method of measurement. It is known that the recommended method of thyroid antibody measurement is radioimmunoassay[1,2]. However, the expense for radioimmunoassay is about three times as much as the hemagglutination method used in our study. Although radioimmunoassay is more sensitive in detecting low levels of thyroid antibodies, the level of these antibodies will increase and they can then be detected by hemagglutination 6-12 months later. In terms of cost-benefit, we decided to choose the hemagglutination method for thyroid antibody measurement.

All our patients had normal FT_4 and TSH levels throughout the 5 years of follow-up, except for one patient who had elevated TSH with normal FT_4. It is known that TSH is the first hormonal change responsible for primary hypothyroidism[20]. On the basis of our data, we suggest that initial evaluation in children presenting with diffuse goiter should include FT_4 or total T_4, TSH, and thyroid antibodies, and the annual follow-up evaluation should include only TSH and thyroid antibodies. FT_4 should be measured only when TSH is elevated to assess the severity of hypothyroidism. Elevated TSH with normal FT_4 is consistent with compen-

sated hypothyroidism, which is thought to be a transitional stage before the eventual progression to overt hypothyroidism[21,22].

In summary, children with an initial diagnosis of simple goiter need to be followed annually for at least 4-5 years. The clinical characteristics of the goiter (consistency and surface palpation) cannot distinguish between simple goiter and lymphocytic thyroiditis. The initial laboratory evaluation should include FT_4 (or total T_4), TSH and thyroid antibodies, and the annual follow-up should include only TSH and thyroid antibodies. The importance of thyroid antibody measurement is to detect the early stage of chronic lymphocytic thyroiditis, and that of the TSH measurement is to detect compensated hypothyroidism. Children with simple goiter grow normally and enter puberty at the same age as normal children. The thyroid size decreases with time or remains at the same size, and thyroxine therapy is not indicated.

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