Original Article

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Clinical and Biochemical Profile of Children on Follow-up with Autoimmune Thyroiditis

Paediatrics Section

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ABSTRACT

Introduction: Hashimotos Thyroiditis (HT) is the most common autoimmune thyroid disease and the most common cause of acquired hypothyroidism in children. Understanding the clinical profile in children with Autoimmune Thyroiditis (AIT) helps in follow-up and appropriate management of the condition.

Aim: To assess the clinical, biochemical profile and the course of disease in children with AIT.

Materials and Methods: This was a hospital-based longitudinal study done at a Paediatric endocrinology clinic, from January 2018 to June 2019, at southern India on all children with autoimmune thyroiditis on follow-up for at least three years, aged up to18 years, attending the clinic. Clinical examination for thyroid swelling, anthropometry of the child, Tanner staging for pubertal status, Thyroid Stimulating Hormone (TSH), and free Thyroxine (T4) were done at enrollment and also at follow-up after one year.

Results: A total of 33 children were enrolled into the study. Of this, girls constituted 85%, with a female to male ratio of 5.6:1. Mean age at diagnosis was 9.76±1.69 years; 25 (75.7%) were hypothyroid and 8 (24.2%) were euthyroid at presentation; 21 (64%) had a positive family history of thyroid illness. The most common presentation was goitre (88%), 32 (96.9%) of them had positive thyroid antibodies either Antithyroid Peroxidase (TPO) or anti thyroglobulin (Tg) antibody. Of the 32 children with positive antibodies, 26 (78.7%) had raised anti TPO and 17 (51%) had positive anti Tg; 12 (36.3%) were positive for both anti TPO and anti Tg; 29 patients(78.7%) required treatment with thyroxine. All were noted to be pubertal but with no significant growth impairment. On follow-up after 1 year, the percentage of hypothyroid patients increased from 75.7% to 97%, and 1(3%) became hyperthyroid. None of them had other autoimmune disorders during follow-up.

Conclusion: Children with AIT were mostly females and the majority had goitre. The prevalence of goitre was 88% and the majority were hypothyroid at presentation. A majority of children with autoimmune thyroiditis had a positive family history of thyroid disease. On follow-up after at 1 year, all the euthyroid patients had become hypothyroid. The thyroid status of children with autoimmune thyroiditis can change over time and needs regular clinical and biochemical follow-up.

Keywords: Antithyroid peroxidase, Goiter, Hypothyroidism

INTRODUCTION

Autoimmune thyroiditis is one of the most common cause of acquired thyroid disorder in the paediatric age group [1]. Hashimotos thyroiditis typically presents with hypothyroidism, painless enlargement of thyroid gland or both. Upto 90% of Hashimoto's patients have high anti-thyroid peroxidase and anti-thyroglobulin antibody [2]. Various studies on autoimmune thyroid disease in children globally have found that most of them are asymptomatic at the time of diagnosis and majority of them are females, pubertal and euthyroid [2,3]. A study by Skarpa V et al., in 2011 in Greece have shown a prevalence of goiter among children with autoimmune thyroiditis to be 28%, of thyroid nodules to be 14%, and of papillary thyroid cancer to be 1.3% [3]. Knowing the natural history and prognosis of AIT being an easily detectable and treatable cause of hypothyroidism is of prime importance. Timely follow-up is also mandatory as a euthyroid patient at initial stage can go for overt hypothyroidism later on.

Studies have shown varying prevalence of autoimmune thyroiditis according to the criteria used for diagnosis, the ethnicity, the iodine status, the age and the gender [2-4]. Also the epidemiological and clinical manifestations of AIT among children varies in different studies [5,6]. Most of the previous studies about autoimmune thyroiditis were conducted among adults. There are only a few studies on autoimmune thyroiditis in children [7,8]. Rajamanickam R et al., studied autoimmune thyroiditis in children from southern India. They reported a female preponderance, less familial clustering, higher paucity of clinical manifestations and quick progression to hypothyroidism [7].

This study was aimed to analyse the epidemiological, clinical and laboratory characteristics of autoimmune thyroiditis in children and the disease evolution over a period of time.

MATERIALS AND METHODS

A hospital-based longitudinal study was done in the Paediatric endocrinology clinic, Government Medical College, Thrissur, Kerala, India, after approval by the Ethical committee. (Letter No B5-8772/2016/MCTCR, dated 27/11/2017). The study was conducted from January 2018 to June 2019.

Inclusion criteria: Thirty-three children with autoimmune thyroiditis in the age group of 5-18 years, who attended the endocrinology Outpatient Department (OPD), during the study period, and had autoimmune thyroiditis for a minimum duration of three years were enrolled into study.

Exclusion criteria: Newly diagnosed cases of autoimmune thyroiditis were excluded from the study.

Sample size calculation: The sample size was estimated to be 47 as per the reference study which showed a prevalence of goitre of 68% in subjects of autoimmune thyroiditis [9], using the formula:

$N=Z^2P(1-P)/d^2$

where,Confidence Interval: 95% (Z), Precision of the study:0.1(d), Prevalence (P) of diffuse goitre in autoimmune thyroiditis 68% [9]

Final sample size=47.

Procedure

Their clinical and biochemical parameters were assessed at the time of study and at follow-up after 1 year. Growth was assessed by

measuring weight, height and Body Mass Index (BMI). The results were interpreted based on Indian Academy of Pediatrics (IAP) 2015 growth charts. Pubertal assessment was done using Tanner staging [10,11]. The World Health Organisation (WHO) grading of goitre [12], consistency, nodularity, presence of cervical lymph nodes were also done. The thyroid status of the children as analysed according to the titre of antithyroid antibodies at presentation i.e. >100 IU/L (high titres) and <100 IU/L (low titres) estimated by Enzyme Linked Immunosorbent Assay (ELISA) technique. A positive antibody titre was taken as >35 IU/L for Anti-Thyroid Peroxidase (Anti TPO) antibody and >20 IU/L for antithyroglobulin antibodies according to the available literature [13]. TSH and fT4 at diagnosis and at study were recorded and were classified as euthyroid (TSH <5 mIU/L), hypothyroid (TSH >5 mIU/L) or hyperthyroid (raised T4, low TSH) as per the age specific cut-offs [14]. Thyroid Function Test (TFT) and antithyroid antibodies were measured by chemiluminescence technique by Clinical Laboratory Improvement Amendments (CLIA) in all. In children who were started on thyroxine, the treatment, the dose was noted. The same clinical parameters and thyroid function tests were assessed at enrollment, and after a period of one year.

STATISTICAL ANALYSIS

All quantitative variables were summarised using percentage and appropriate measures of central tendency and dispersion. Quantitative data like age, duration of the disease, anthropometry etc. was analysed using mean and SD. Analysis was done by appropriate statistical methods like Chi-square test and for repeated measures Analysis of Variance (ANOVA) was used. Statistical software used was Statistical Package for Social Sciences(SPSS) version 16.0. A p-value of <0.05 was taken as significant.

RESULTS

Out of 33 children, the mean age of presentation was 9.76±1.69 years (range 8.07-11.45 years). All children were above 5 years of age. The majority (66.7%) presented after 9 years of age. The mean age at the time of enrollment was 14.82±2.35 years and average duration of the disease was 5±1.79 years. There were 28 (85%) females and 5 (15%) males. [Table/Fig-1]. The majority showed normal growth parameters with a mean weight of +0.29 Z score and that for height was +0.52 Z score at the time of enrollment [Table/Fig-2]. It was +0.24 Z score for weight and +0.24 Z score after 1 year. At enrollment, the mean BMI 18.98±3.36 kg/m^2, and after 1 year at follow-up, it was 20.12±3.28 kg/m^2. All children were pubertal.

Parameter	n (%)
Females	28 (85%)
Males	5 (15%)
Family history of thyroid illness	21(64%)
Goitre	29 (88.8%)
Increased sleep	20 (60.6%)
Fatigue	19 (57.5%)
Constipation	10 (30.3%)
Poor scholastic performance	9 (27.2%)
Reduced appetite	5 (15%)
Cold intolerance	5 (15%)
Hashimoto's encephalopathy	1 (3%)

[Table/Fig-1]: Demography and clinical features.

At diagnosis, 75.8 % children were hypothyroid and only 24.2% were euthyroid. At the time of enrollment to the study, 88% had become hypothyroid and 9% remained euthyroid. On follow-up, all euthyroid children had become hypothyroid and one of the hypothyroid child (3%) became hyperthyroid and was started on antithyroid medication carbimazole. Thus, at follow-up after 1 year, 97% of the children were hypothyroid and one was hyperthyroid [Table/Fig-3].

Parameter	N (%)
Age	
9-11 years	5 (15%)
12-15 years	15 (45%)
16-18 years	13 (39%)
Anthropometry	
Height Z score	+0.52±1.1
Weight Z score	+0.29±0.9
Types of Hashimoto Thyroiditis(HT)	
Goitrous	21 (64%)
Atrophic	12 (36 %)
Thyroid profile (Baseline)	
Euthyroid (TSH <5 mIU/L)	8 (2.2)
Hypothyroid (TSH >5 mIU/L)	25 (75.7)
Hyperthyroid	Nil
Antibody positivity	32 (97%)
Anti-TPO Ab positivity	26 (81.2%)
Anti Tg Ab positivity	17 (53.1%)
Both positive	12 (37.5%)
Antibody negative	1 (3%)

[Table/Fig-2]: Clinical and Biochemical profile of children with autoimmune thyroiditis. TPO: Thyroid peroxidase; Ab: Antibody; Tg: Thyroglobulin

Thyroid status	Onset of study	On follow-up (1 year)
Euthyroid (TSH <5 mIU/L)	3 (9.09%)	Nil
Hypothyroid (TSH >5 mIU/L)	29 (87.88%)	32 (96.97%)
Hyperthyroid	nil	1 (3.03%)

[Table/Fig-3]: Thyroid status at enrollment and after 1 year.

Overall, 88% of children presented with a goitre. The next common symptom was increased sleep (61%) and fatigue (58%). One of the children had features of Hashimoto's encephalopathy at presentation. At diagnosis, antithyroid antibodies were positive in 32 children (97%). One patient (3%) had both the antibodies negative and autoimmune thyroiditis was diagnosed by ultrasonography. Out of 32 patients, 26 (81.2%) were positive for antiTPO. Anti Tg alone was positive in 6 (18.7%) patients. Of the 21 children, who had low antibody titres, 71.4% were hypothyroid and 28.5% were euthyroid. Out of the 12 patients with high antibody titres, 83.3% were hypothyroid and 16.6% were euthyroid (p-value 0.22) [Table/Fig-4].

Thyroid status	Anti TPO Titre <100 IU/mL	Anti TPO Titre >100 IU/mL	p-value
Total (N=33)	21	12	0.22
Hypothyroid	15 (71.4%)	10 (83.3%)	
Euthyroid	6 (28.5%)	2 (16.6%)	

[Table/Fig-4]: AntiTPO titre and Thyroid status.

There were 3 children with very high anti TPO titre >1300 (U/mL). All of them were hypothyroid at presentation and one of them ultimately developed hyperthyroidism.

In the 21 patients with low anti TPO titre, 57.2% had a family history of hypothyroidism. Out of the 12 patients with high antibody titre, 75% had atleast one of their family members affected with hypothyroidism (p-value=0.45). It was found that those with high anti TPO titre were more symptomatic than those with low titre. They had more occurrence of goiter and hypothyroid features like constipation, reduced appetite, poor scholastic performance, fatigue and increased sleep. Constipation and decreased appetite had statistically significant association with high antibody titre. (p-values 0.01 and 0.05 respectively [Table/Fig-5].

The relationship between thyroid status and symptoms were assessed at disease onset. Most of the patients with TSH levels >5mIU/L were

symptomatic with more prevalence of goiter, constipation, reduced appetite, poor scholastic performance, fatigue and increased sleep as compared to those with TSH values <5 mIU/L i.e euthyroid patients. Of that poor scholastic had a significant association with high TSH value (p-value 0.03) [Table/Fig-6].

Clinical features	AntiTPO <100	AntiTPO >100	p-value
Goitre (29)	5 (17.24%)	24 (82.75%)	0.19
Constipation (10)	5 (50%)	5 (50%)	**0.01**
Reduced appetite (5)	3 (60%)	2 (40%)	**0.05**
Poor scholastic performance (9)	3 (33.3%)	6 (66.67%)	0.35
Fatigue (19)	3 (15.7%)	16 (84.2%)	0.42
Hashimoto's encephalopathy (1)	0	1 (100%)	1
Increased sleep (20)	6 (30%)	14 (70%)	0.2

[Table/Fig-5]: Association Between Anti TPO and Clinical Features.

Clinical features	Hypothyroid (TSH >5)	Euthyroid (TSH <5)	p-value
Goitre (29)	21 (72.4%)	8 (27.5%)	0.55
Constipation (10)	10 (100%)	0	0.07
Reduced appetite (5)	4 (80%)	1(20%)	1
Poor scholastic performance (9)	9 (100%)	0	**0.03**
Fatigue (19)	14 (73.6%)	5 (23.6%)	1
Hashimoto's encephalopathy (1)	1 (100%)	0	1
Increased sleep (20)	16 (80%)	4 (20%)	0.68

[Table/Fig-6]: Association between TSH and clinical features.

DISCUSSION

In this study of children with autoimmune thyroiditis, there was a female preponderance (85%) with a female to male ratio of 5.6:1. This is in agreement with the study conducted by Skarpa V et al., [3] in Greece which showed a female preponderance (83.8%) in children with autoimmune thyroiditis. Female to male ratio in a study of AIT in children conducted by Desai MP and Karandikar S, in Mumbai was 2.9:1 [2]. A high M:F ratio has been observed in studies conducted on adults [15-17].

The mean age at diagnosis was 9.76 years in this study. This is similar to other reported series by Skarpa V et al., [3] where the mean age of diagnosis of AIT was 10.25 years. Many studies have shown that the usual age at presentation is above 6 years, and rarely under the age of 3 years, [16,17] [Table/Fig-7].

	Skarpa V et al., (2007) [3]	Gopalakrishnan S et al., (2007) [5]	Rajamanickam R et al., (2016) [7]	Current study
Mean age (years)	10.2±2.5	13.2±2.6	9.9+1.76	9.76±1.69
Gender				
Females	83.8%	80.9%	84.5%	85%
Males	16.2 %	9.1%	15.5 %	15%
Family history of thyroid disorders	76%	18.4%	14%	64%
Goitre	28 %	100%	100%	88.8%

[Table/Fig-7]: Baseline characteristics of the present study compared to other studies [3,5,7].

As most of the children were diagnosed earlier and were under regular follow-up, treatment compliance was good and their pubertal status and growth parameters were normal on follow-up. This indicates the need for early detection and treatment of thyroid disorders in children as it might affect their growth, development and pubertal status. Although all the children in this study were pubertal, in similar studies by Corrias A et al., [18] and De Vries L et al., [19], children with hypothyroidism were mostly prepubertal and the majority of euthyroid children were pubertal.

In this study, 21 patients (64%) had a family history (first-degree relatives) of autoimmune thyroid diseases. This is in agreement with the observation in a study conducted by Desai MP and Karandikar S, where familial aggregation was noted in adult family member (33%) with positive thyroid antibodies in 65% of the mothers [2]. A study by Marwaha RK et al., revealed AIT in 42% of first degree relatives on Fine Needle Aspiration Cytology (FNAC) [20].

The majority of children in this study were hypothyroid (75.7%) at diagnosis as observed in other studies [16,21,22]. But in an Italian study by Corrias A et al., [18] in children and adolescents and a study of AIT in children conducted by Skarpa V et al., [3] most of them were euthyroid at presentation. This variability in results may be due to the small sample size and selection bias, as the present study was conducted in a referral centre.

Most of the children had an asymptomatic goitre at presentation (88%). It was observed in this study, that the prevalence of goitre in hypothyroid children was more (75%) compared to that in euthyroid children (24%), although this association had no statistical significance. But other studies have shown varying results. In the study conducted by De Vries L et al., the prevalence of goitre was significantly higher in euthyroid group (92%) compared to the prevalence in subclinical hypothyroid (66%) and hypothyroid (76%) group [19]. A study by Svensson BJ et al., also found a comparable prevalence of goitre among both euthyroid and hypothyroid patients which was assessed by Ultrasonography (USG) [23]. Discrepancies between the studies might be due to the different methods of assessing goiter as USG was used to diagnose autoimmune thyroiditis in the latter study.

The high prevalence of autoimmune thyroid antibodies (96.5%) among patients in the present study correlates with other similar studies. Thomas T et al., [9] found that 93 per cent of the study subjects with AIT were anti TPO positive and 92 per cent were antithyroglobulin antibodies positive. Pearce EN et al., found anti TPO antibodies in 90-95 per cent of AIT but anti-Tg antibody positivity in only 20-50 per cent [24]. It is suggested that both titres should be tested as it could detect approximately 95% of the patients. Usually the antibody titre levels are lower in children when compared to adults [1]. Upto 90% of hypothyroid patients are anti TPO positive in some studies [2,3]. Repeated measurements are indicated as antibody levels may increase later in the course of the disease.

On follow-up, all euthyroid children progressed to hypothyroidism and were started on thyroxine. A similar trend towards a spontaneous deterioration of thyroid function over time has been recently reported in series of children with HT initially presenting with subclinical hypothyroidism, even though the process is very slow and not predictable in the single case [5,6,25]. However other studies evaluating the thyroid status on follow-up show conflicting results [26]. A multicentric study by Radetti G et al., that investigated the outcome of euthyroid children with AIT, showed that 64.8% of them remained euthyroid, 9.5% progressed to subclinical hypothyroidism and 25.7% to overt hypothyroidism after 5 years [26]. Aversa T et al., in 5-year prospective evaluation of 234 children with HT, reported that the TSH values significantly increased during follow-up, whilst FT4 values decreased and the proportion of children with a thyroid dysfunction increased from 27.3 to 47.4% [27]. A study of AIT in children by De Vries L et al., [19] showed that there was no change in the thyroid status of nine untreated patients. The disparity between the present and other studies could be due to the small sample size in this study and referral bias. Also, the number of children with sub-clinical hypothyroidism was not assessed separately in the present study.

Limitation(s)

The prevalence of subclinical hypothyroidism was not studied. There was also probable referral bias to this tertiary care centre study as majority of children presented had hypothyroidism, contradictory to the earlier studies which showed predominantly

euthyroidism at presentation. Since most of the euthyroid children who were not started on treatment often fail to follow-up regularly, they were probably missed out in this study. Hence, the actual prevalence of euthyroidism on follow-up could not be demonstrated in this study.

CONCLUSION(S)

This study done in children with juvenile AIT in a tertiary care centre like ours is one of the very few studies done from South India. Children with AIT presented with asymptomatic goitre, mostly being females. The prevalence of goitre among these children was 88% and the majority were hypothyroid at presentation (75.8%). A vast majority of children with autoimmune thyroiditis (74%) had a positive family history of thyroid disease. On follow-up after 1 year, all the euthyroid patients had become hypothyroid. All hypothyroid patients remained the same except one child who developed Grave's disease. The thyroid status of children with autoimmune thyroiditis can change over time and needs regular clinical and biochemical follow-up.

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