Journal of Thyroid Disorders and Therapy

OPEN ACCESS Freely available online

Research Article

Hashimoto's Thyroiditis-associated Thyroid Swelling among Female Adolescents Presenting with Benign Goiter in Lahore, Pakistan

Shan Elahi[1], Saira Shan[2], Nazish Saleem[3], Nayab Batool Rizvi[3*]

[1]Department of Nuclear Medicine, Mayo Hospital, Lahore, Pakistan;[2]Department of Anesthesia, Mayo Hospital, Lahore, Pakistan; [3]Department of Chemistry, New Campus, University of the Punjab, Lahore, Pakistan

ABSTRACT

Objectives: To determine frequency of Hashimoto's thyroiditis (HT) associated thyroid swelling among local adolescents presenting with benign goiter.

Methods: Newly referred adolescents (age range 10-19 year) presenting with benign goiter (euthyroidism or subclinical hypothyroidism) was enrolled consecutively. Serum FT4 (normal range: 11.5–23.0 pmol/L), FT3 (normal range: 2.8–5.8 pmol/L) and TSH (normal range: 0.3–4.0 pmol/L) were determined by radioimmunoassay (RIA) and TPO-Ab by ELISA technique. TPO-Ab titer >20.0 IU/ml was considered HT.

Results: A total of 277 goitrous adolescents (female 194, male 83) with were selected. Their mean (± SD) age was 15.8 + 2.5 years. Female and male adolescents were comparable in age, goiter size and serum thyroid hormone levels but mean TSH and percentage of TSH levels >3.0 mIU/L was significantly higher in male adolescents. HT was detected in 38 (13.7%) patients. The incidence of HT in female (16.5%) was higher than male adolescents (7.2%) but the difference was not statistically significant (p=0.120). Similarly goiter size (palpable or visible) or patient age (below or above 16 year) has no significant effect on HT frequency. However, compared to adolescents with TSH within normal laboratory range those with TSH level above the upper normal limit (4.0 mIU/L) had significantly more frequency of HT (10.4% versus 30.4%; p=0.001).

Conclusion: Among local goitrous adolescents 13.7% had HT-associated thyroid swelling.

Keywords: Adolescents; Thyroid gland; Goiter; Hashimoto's thyroiditis; Thyroid autoimmunity

INTRODUCTION

Goiter is a slowly developing diffuse or nodular enlargement of thyroid gland due to an excessive replication of follicular epithelium with subsequent generation of new follicles of widely differing structure and function [1]. The development of goiter is determined by interplay between genetic, environmental and gender factors [2]. Globally the major environmental factor for goiter development is iodine deficiency. However, in iodine sufficient areas inflammation due to autoimmune thyroiditis causes thyroid enlargement particularly in children and adolescents [3]. Such thyroid swelling is characterized by lymphocytic infiltration into thyroid gland and is termed chronic autoimmune thyroiditis or Hashimoto's Thyroiditis (HT) after Hakaru Hashimoto who in 1912 first described this condition [4].

Universal salt iodization have eliminated goiter in many parts of the world. However, in formerly iodine deficient areas emergence of HT in the form of residual goiter has been reported after iodine supplementation [5,6]. It has been suggested that in such areas sufficient or excess iodine intake precipitates the thyroid autoimmunity manifesting in the form of thyroid enlargement [7]. The role of thyroid autoimmunity may be suspected if there is derangement in thyroid function parameters particularly Thyroid Stimulating Hormone (TSH). However, in case of normal thyroid parameters HT is difficult to be distinguished from simple goiter, the latter being defined as thyroid enlargement not associated with thyrotoxicosis or hypothyroidism and not a result of an inflammatory or neoplastic process. Most cases of HT, particularly in its initial phase exhibit normal thyroid function parameters (euthyroid HT). Distinction of euthyroid HT from simple goiter

Correspondence to: Rizvi NB, Department of Chemistry, New Campus, University of the Punjab, Lahore, Pakistan, Tel:+042-9230988; Email: nayab.batool@gmail.com

Received: March 11, 2021; **Accepted:** March 25, 2021; **Published:** April 01, 2021

Citation: Elahi S, Shan S, Saleem N, Rizvi NB (2021) Hashimoto's Thyroiditis-associated Thyroid Swelling among Female Adolescents Presenting with Benign Goiter in Lahore, Pakistan. Thyroid Disorder Ther. 10:249.

is necessary because HT may lead progressively to worsening of thyroid function that had negative effects on growth and metabolic function in children and adolescents [8,9]. The HT is a complex disease and is associated with other autoimmune diseases [10] as well as papillary thyroid cancer [11]. Moreover, treatment options for simple goiter and HT are also different owing to their different etiology [12].

Pakistan is an iodine deficient country and Government of Pakistan is patronizing the ongoing iodine supplementation program since 1994. The results of this initiative are encouraging according to National Nutrition Survey 2011 [13]. A recent study conducted in Lahore found that 21.2% of the adolescent girls had thyroid enlargement and more than half of them (58.3%) were taking sufficient iodine [14]. Thus iodine deficiency is no more the sole cause of goiter and role of HT may be suspected in the development of thyroid enlargement. In a previous study of female adolescents referred to our Centre for thyroid hormone workup, we have found that 61% of them had goiter with 80% presenting as euthyroid goiter [15]. This study was planned to know frequency of HT, by determination of serum TPO-Ab titer, in goitrous adolescents with euthyroid or subclinical hypothyroid function status detected at Centre for Nuclear Medicine (CENUM), Mayo Hospital Lahore, Pakistan.

SUBJECTS AND METHODS

Centre for Nuclear Medicine (CENUM), Mayo Hospital is one of the major referral centers for testing thyroid related disorders in the city and surrounding areas. We collected data of all referred goitrous adolescents, aged 10-19 years, who had undergone clinical assessment and determination of serum FT4, FT3 and TSH during calendar year 2015 and 2016. From them such adolescents with normal serum FT4 and FT3 (serum TSH normal or <10.0 mIU/L) were initially selected for this study. Among them such adolescents who were already diagnosed for thyroid diseases and taking thyroid medications or had thyroid surgery were excluded. Similarly patients suffering from systematic diseases like DM, cardiac diseases and hepatitis were also excluded. Residual serum samples of finally selected adolescents, after testing thyroid related hormones were preserved at minus 20°C for TPO-Ab determination.

Serum FT4 and FT3 were estimated by Radioimmunoassay (RIA) and TSH was estimated by IRMA techniques using commercial kits of Immunotech Inc. (Beckman, Czech Republic) as described in detail elsewhere. Normal ranges for serum FT4, FT3 and TSH, as standardized in our laboratory were 11.5–23.0 pmol/L, 2.8–5.8 pmol/L and 0.3-4.0 mIU/L respectively. Serum TPO-Ab titer of residual serum sample was determined by ELISA method using commercial kit (IMMCO Diagnostics, Inc. NY, USA). The patients with TPO-Ab titer >20.0 IU/ml were considered positive according to instructions of kit manufacturer.

The analysis of data was carried out using Microsoft Excel program on a personal computer. Student T-Test and Chi-Square test was applied to test the significance of difference between two arbitrary groups. A value of $p<0.05$ was considered significant.

RESULTS

A total of 277 adolescents presenting with goiter fulfilled the selection criteria and were selected for this study. All of them had serum FT4 and FT3 within respective normal ranges and TSH levels ranging 0.3-9.1 mIU/L. Among them 194 were female and 83 were male patients with average age 15.8 ± 2.5 year and age range 10 to 19 year. The anthropometric and laboratory characteristics of these adolescents as well as a comparison between male and female adolescents are shown in Table 1. Mean age and goiter sizes were comparable in male and female adolescents. Similarly mean levels of serum FT4 and FT3 were not significantly different between male and female participants. However, mean TSH level as well as percentage of serum samples with TSH >3.0 mIU/L was significantly higher in male than female adolescents ($p<0.05$).

Table 1: Anthropometric and laboratory characteristics of adolescents presenting with goiter.

	All	Female	Male	P-value
No.	277	194	83	-
Age (year)	15.8 + 2.5	15.6 + 2.8	15.9 + 2.3	0.140
Grade 1 goiter, n (%)	153 (55.2)	100 (51.5)	53 (63.9)	0.165
Grade 2 goiter, n (%)	124 (44.8)	94 (48.5)	30 (36.1)	0.165
Mean FT4 (pmol/L)	16.5 + 2.9	16.6 + 2.9	16.4 ± 2.7	0.533
Mean FT3 (pmol/L)	4.5 + 0.7	4.6 + 0.8	4.7 + 0.7	0.727
Mean TSH (mIU/L)	2.4 + 1.9	2.2 + 1.9	2.8 ± 1.9	0.018
TSH ≥ 3.0 mIU/L, n (%)	70 (25.3)	39 (20.1)	31 (37.4)	0.008

Serum TPO-Ab titer above 10.0 IU/ml was detected in 46 adolescents ranging from 11.3 to 5904 IU/ml. Serum TPO-Ab titer higher than 20.0 IU/ml was detected in 38 (13.7%) adolescents. These adolescents were positive for TPO-Ab according to cutoff value provided by kit manufacturer. TPO-Ab positive adolescents as compared to TPO-Ab negative counterparts had comparable serum FT4 (16.0 ± 3.2 vs 16.6 ± 2.8; p=0.254) and FT3 (4.5 ± 0.6 vs 4.7 ± 0.8; p=0.457) but significantly higher TSH levels (3.7 ± 3.1 vs 2.2 ± 1.6; p=0.0062). The TPO-Ab positive adolescents covered the whole age range (10-19 year) and the youngest among them was 10 year old.

Table 2 shows the association of factors like gender, age, goiter size and serum TSH with positive TPO-Ab titer in adolescents. It was found that percentage of positive TPO-Ab titer was more than double in female than male adolescents but the difference was not significant (16.5% vs 7.2%; p=0.120). Similarly early to middle adolescent age group (age ≤ 16 year) had higher percentage of positive TPO-Ab cases than late adolescent group but difference was comparable (16.1% vs 10.7%; p=0.428). This difference remained same when only female adolescents were compared after same stratification (19.5% vs 12.3%; p=0.411). Also a non-significant difference was found between adolescents presenting with palpable and visible goiter. However, effect of serum TSH was decisive in this regard. The adolescents presenting with basal TSH level above upper limit of normal range (4.0 mIU/L) had significantly higher incidence of TPO-Ab positivity as compared to those with serum TSH within normal range (30.4% vs 10.4%; p=0.001). Further analysis showed that among subgroup of adolescents with normal TSH level female (n=155) and male (n=52) adolescents had non-significant difference of positive TPO-Ab titer (10.3% versus 5.8%; p=0.608) but this difference was significant between female and male adolescents with TSH level ≥ 3.0 mIU/L (41.0% versus 9.7%; p=0.014). Thus with overall HT incidence of 13.7%, female adolescents with TSH level above normal range had the highest

percentage of HT among local goitrous adolescents.

Table 2: Effect of gender, goiter size, age and basal serum TSH levels on HT incidence in goitrous adolescents

		TPO-Ab Positive, n (%)	P-Value
Gender	Female (n=194)	32 (16.5)	0.120
	Male (n=83)	06 (7.2)	
Goiter size	Palpable, G1 (n=153)	21 (13.7)	0.999
	Visible, G2 (n=124)	17 (13.7)	
Age	≤ 16 Year (n=155)	25 (16.1)	0.428
	>16 Year (n=122)	13 (10.7)	
TSH level (mIU/L)	Within NR (n=231)	24 (10.4)	0.001
	Above NR (n=46)	14 (30.4)	

NR: Normal Range

DISCUSSION

Sporadic benign goiter is an enigma and debate on role of genetic or environmental factor in its etiology is still continuing [16]. In contrast to endemic goiter, etiology of benign sporadic goiter is complex. Besides iodine deficiency, thyroid autoimmunity, goitrogen ingestion, certain medicine and various infections may be involved in its etiology. It is very difficult to establish on clinical grounds alone which single or multiple factor is operative [17]. This is particularly true for detection of HT, the hallmark of which is the presence of high titer of serum TPO-Ab. The elucidation of exact etiology of an adolescent goiter is imperative because in contrast to iodine deficiency goiter thyroid enlargement associated with HT is a distinct entity. The aim of this study was to know the prevalence of serum TPO-Ab in adolescents presenting with benign goiter so that contribution of autoimmune thyroiditis in etiology of thyroid enlargement may be documented. Our results showed that among male and female goitrous adolescents 13.7% have high serum TPO-Ab titer manifesting chronic autoimmune thyroiditis. Thus thyroid swelling (goiter) in these adolescents is not because of iodine deficiency but is a part of HT.

This is probably the first large study of its sort conducted in goitrous adolescents residing in study area. A previous small study has detected high serum TPO-Ab titer in 19.5% goitrous adolescents mostly female [18]. Recently Ahmed et al. reported HT in 9.7% of 73 thyroidectomy specimen collected from young goitrous patients (11-20 year) residing in hilly areas of Pakistan [19]. Thus ours and other local studies confirmed the emergence of HT as a cause of goiter in Pakistan. Our result is in accordance to Marwaha et al. that reported HT in 13.8% of adolescent girls in India. Comparable studies in other countries had reported 3-9% incidence of HT in children and adolescents presenting with goiter [20,21]. The variation in prevalence of HT among different studies may be due to racial difference or different patient selection method employed in these studies.

The major risk factors for development of HT in adolescents are family history of thyroid disorder [22] and high iodine intake status. Other contributory factors for HT are female gender [23,24], goiter size and serum TSH level at presentation. We found that HT incidence in this study was independent of patient gender, age and goiter size and was positively associated only with serum TSH particularly above upper limit of laboratory range. Thus serum TSH was the only decisive factor in suspecting HT in local adolescents. These observations are in contrast to other studies reporting high incidence of HT in female patients and among those presenting with large goiter. The reason for TPO-Ab positivity in our patients may either be thyroid autoimmunity per se due to genetic component [25], its induction after use of iodized salt for its treatment or both. Enhanced dietary iodine content after successful implementation of USI had been implicated to initiate or aggravate the thyroid autoimmunity that cause thyroid swelling in children and adolescents. Increased levels of autoantibodies against thyroglobulin (Tg) and/or TPO had been detected in serum sample of goitrous children and adolescents taking iodized salt. As information regarding iodine salt use in these adolescents is not available so no definite role of these factors may be ascertained for presence of high titer of TPO-Ab in these goitrous patients. However, a recently conducted study in female adolescents at our Centre revealed that 64.7% of HT patients were consuming iodized salt [26]. So role of excess iodine consumption in initiation or aggravation of autoimmune thyroiditis cannot be excluded.

Simple benign goiter is still a therapeutic challenge in medical practice. Use of iodized salt for goiter treatment may be beneficial to those having iodine deficiency induced goiter [27] but for HT patients it is of no benefit. The continued use of iodized salt for HT treatment may possibly cause harm and lead to development of hypothyroidism. The treatment of choice for HT is thyroxine [28]. Along with this a careful supplementation of selenium and vitamin D in case of their deficiency is also recommended. A recent study has found specific diets beneficial to HT patients taking thyroxine [29]. Thus differentiation of HT among adolescents presenting with benign goiter is necessary for proper treatment and follow up.

This study has many shortcomings. First, the number of male adolescents was low as compared to female. This has hampered the true comparison of relative incidence of HT in female and male adolescents. Second urinary iodine was not determined in adolescents to elucidate role of dietary iodine in HT. Moreover, data regarding family history of thyroid disorder was missing. A large study is warranted to investigate relative contribution of current iodine supplementation as well as family history of thyroid disorder in HT development in children and adolescents presenting with goiter.

CONCLUSION

This study reports a prevalence of 13.7% of HT among local adolescents presenting with benign goiter. It may be speculated that emergence of HT is a natural consequence of USI started more than two decade ago in Pakistan. Further studies are required to characterize HT in different age groups of population. At present, realization of the presence and proper determination and treatment of this entity is necessary for thyroid heath in Pakistan.

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