RESEARCH BRIEF

Subclinical Hypothyroidism: A prospective observational study from Southern India

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ABSTRACT

Objective: To assess the natural history and progression of subclinical hypothyroidism and to study factors which help predict evolution of subclinical hypothyroidism into overt hypothyroidism. **Methods**: Longitudinal study in 40 children (2-16 yrs) presenting with subclinical hypothyroidism in a tertiary care unit in Chennai, India. Patients showing evidence of overt hypothyroidism or thyroid stimulating hormone ≥ 15 mIU/mL during follow-up were started on thyroxine. Others were followed up with 3 monthly thyroid function tests up to one year. **Results**: At the end of our study period 3 (7.5%) were overtly hypothyroid, 16 (40%) remained as subclinical hypothyroid, and 21 (52.5%) became euthyroid. Evidence of auto immunity at baseline was a significant (P<0.05) risk factor for progression to overt hypothyroidism. **Conclusions**: Subclinical hypothyroidism in children, with thyroid stimulating hormone upto 15 mIU/L and irrespective of thyroid autoimmunity, needs only periodic clinical and biochemical follow up. Thyroid autoimmunity may point to an increased probability of progression to overt hypothyroidism.

Keywords: *Children, Subclinical hypothyroidism, Thyroid autoimmunity.*

INTRODUCTION

Subclinical hypothyroidism (SCH) is a biochemical condition characterized by serum levels of thyroid stimulating hormone (TSH) above the statistically defined upper limit of reference range, with normal concentration of thyroid hormones and without clinical features of hypothyroidism [1]. SCH is a not an uncommon condition with incidence of about 2% in pediatric age group though large epidemiological studies are scarce [2,3]. SCH is often detected incidentally as patients exhibit few or no signs of thyroid dysfunction. There is a paucity of studies evaluating the natural history of SCH from India [4].

Clinicians often consider TSH abnormal when its value exceeds the upper reference range of the laboratory which may result in unnecessary long term thyroxine replacement. The aim of this prospective study was to assess the natural history and progression of SCH and evaluate factors that may help predict evolution to overt hypothyroidism (OH).

METHODS

This longitudinal study was done in a pediatric tertiary care hospital between January 2015 and April 2017. The study was approved by the Institutional Ethics Committee. The study protocol is depicted

in ***Fig.* 1**. After thorough history and clinical examination thyroid function testing (free T4 and TSH) was done. If TSH was elevated it was remeasured along with thyroid peroxidase (TPO) antibody titres on a subsequent visit. Children recovering from recent acute illness, or other comorbidities like seizure disorder, renal or hepatic dysfunction were excluded. All children who presented to our services between January 2015 to April 2016 and satisfied the above criteria were included based on time sampling principle. Thyroid function tests were repeated at 3, 6 and 12 months or earlier if worsening of symptoms noted. Based on existing published literature, thyroxine replacement in a SCH patient is usually considered when TSH is more than 10 mIU/L irrespective of autoimmunity [5]. Prior experience in our centre (unpublished**)** with SCH suggest that a higher cut-off of TSH up to 15mIU/L was well tolerated by children without clinical deterioration. Hence a cut-off of 15mIU/L was used to start treatment in this study. All thyroid function tests were conducted by chemiluminescence assay and the reference ranges used for inclusion in our study according to age is as follows: TSH: 2– 5 years: 0.4 - 6.0 mIU/L, 6 – 14 years: 0.4 – 5 mIU/L, 15 - 16 years: 0.4-4.2 mIU/L, normal range of free T4 for all the age groups was: 0.8-2 ng/dL. The thyroperoxidase (TPO) antibody test was done using chemiluminescent microparticle immunoassay (CMIA) and normal titres were <5.6 IU/L.

All categorical variables were expressed as percentages. Comparison of categorical variables was done by Chi-square or Fisher's exact test. Data analysis was done using SPSS version 16.0 and 'P' values <0.05 was considered statistically significant.

RESULTS

We enrolled 49 patients in this study. Nine patients were excluded either due to initiation of thyroxine therapy elsewhere or were lost to follow up. The complaints necessitating thyroid function evaluation were obesity in 28 (70%), constipation in 5 (12.5%), poor growth in 3 (7.5%), and menstrual issues, gynecomastia, dry skin and goiter in one patient each.

At the end of the study period 3/40 (7.5%) became overtly hypothyroid, 16/40 (40%) remained SCH and 21/40 (52.5%) became euthyroid respectively. Among 3 children with overt hypothyroidism (2 girls, 1 boy), 2 were obese and 1 had poor growth. All 3 had autoimmunity and did not have goitre. Serum TSH was between 5-10 mIU/L in one and between 10-15 mIU/L in other two. Goiter was seen in one child who had raised TPO levels and become euthyroid on follow-up.

For patients with TSH between 10-15mIU/L at presentation, the positive predictive value (PPV) was 20%, and the negative predictive value (NPV) was 96.7% for progression to overt hypothyroidism. Three out of 8 patients with positive TPO antibody titre became overtly hypothyroid. For patients with elevated TPO antibody titre, PPV was 37.5% and NPV was 100% for

progression to overt hypothyroidism. Patient profile at presentation and outcome at one year of follow up is shown in ***Table* I**.

Presence of thyroid autoimmunity was the most significant risk factor for progression to overt hypothyroidism. $P<0.005$. There was no statistically significant difference when comparing the sex distribution or family history of thyroid disease between those who became hypothyroid and SCH/euthyroid.

DISCUSSION

In this study we observed that in the absence of positive thyroid antibodies subclinical hypothyroidism in a child often runs a benign course as most of them either revert back to euthyroid state or remain in SCH state.

One of the limitations of our study was the relatively short duration of follow-up. Another limitation of our study was lack of urinary iodine levels due to financial and logistic reasons, a factor that might influence autoimmunity [6].

The proportion of children with SCH in the present study who progressed to overt hypothyroidism was similar to other studies [7-9]**.** In the other Indian study, among 32 children with autoimmune SCH and goitre, 12.5% children with SCH and goitre had developed overt hypothyrodism [4]. One third of children with SCH and autoimmunity in our study developed overt hypothyroidism on follow-up. Children without evidence of autoimmunity ran a benign course which was similar to observations made in other studies or reviews [10,11].

Majority of our children became euthyroid during the study. The reasons for reverting back to euthyroid state may include simple obesity, recovering phase of recent acute illness or subacute thyroiditis and relapsing and remitting condition like autoimmunity [5].

Obesity was the overwhelming reason for checking thyroid status in our cohort. It is increasingly recognized that TSH elevation may occur due to obesity per se. Although the exact mechanism of TSH elevation in obesity is unclear, the role of leptin has been postulated [12]. Studies with thyroxine replacement for marginal elevations of TSH in obesity had questionable benefits [13]**.**

The untreated children in our cohort did not have worsening of their presenting symptoms clinically. This study set up was not ideal to see whether a therapeutic trial with thyroxine would benefit improvement of symptoms. Previous studies on thyroxine replacement therapy in SCH have not shown any appreciable clinical benefits [13-15].

Our experience from this study adds to the increasing evidence for expectant management in SCH. Thyroid antibody positivity may point to an increased probability of conversion to overt hypothyroidism. However, even in the presence of autoimmunity, children often revert to

euthyroidism or remain as SCH. We conclude that subclinical hypothyroidism in children, even up to a TSH of 15 mIU/L, irrespective of autoimmunity may be periodically followed up clinically and biochemically. Longitudinal studies with a larger cohort and longer duration of follow-up are needed to further analyze the prognosis of SCH.

WHAT THIS STUDY ADDS?

- Subclinical hypothyroidism in children with TSH up to 15 mIU/L may be observed without treatment especially in the absence of thyroid autoimmunity.

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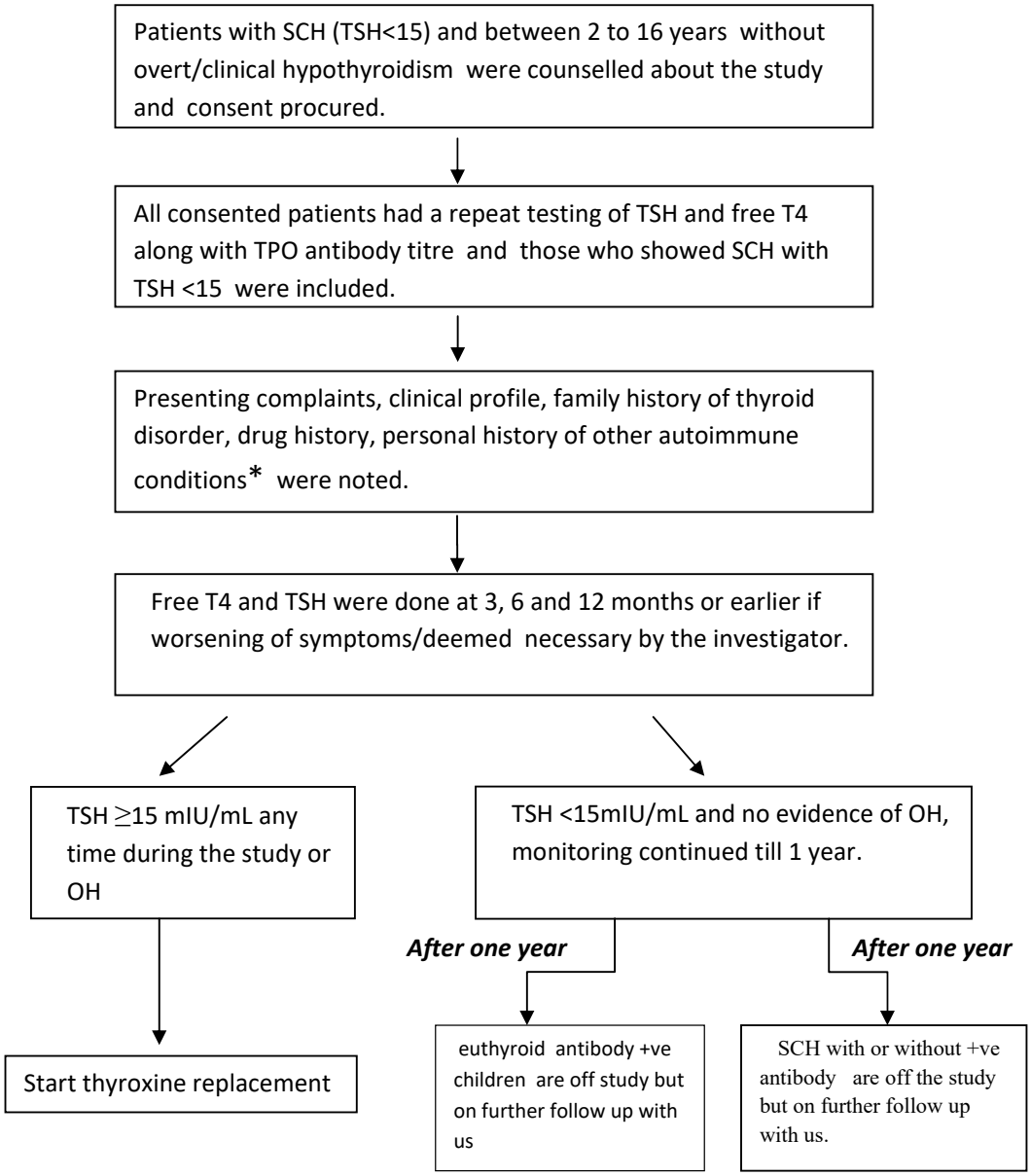
TABLE I PROFILE OF PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM AT PRESENTATION AND AT ONE-YEAR FOLLOW-UP

Parameters at enrolment	*(N=40)*	*Outcome*			*P Value*
		OH (n=3)	*SCH (n=16)*	*Euthyroid (n=21)*	
TSH at diagnosis between 5-10mIU/L	30	1	10	19	0.083
TSH at diagnosis between >10 and <15 mIU/L	10	2	6	2	
Male	22	1	10	11	0.433
Female	8	2	6	10	
Elevated TPO antibody titre	8	3	2	3	0.006*
Family history of thyroid disease	*16*	*2*	*6*	*8*	*0.327*

OH: Overt Hypothyroidism, SCH: subclinical hypothyroidism, TSH: thyroid stimulating hormone, TPO: thyroid peroxidase

Fig. 1. Flow chart of study protocol



OH: overt Hypothyroidism , TSH: thyroid stimulating hormone. , SCH: subclinical hypothyroidism, TPO: thyroid peroxidase, "∗": autoimmune condition like alopecia areata, vitiligo were asked for.