

# Juvenile Hypothyroidism: A Clinical Perspective from Eastern India

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## Abstract

**Introduction:** Juvenile hypothyroidism (JH) can have deleterious effects on growth, pubertal development, and scholastic performance of children. In India, there is a paucity of data on acquired hypothyroidism in children, in contrast to congenital hypothyroidism. Our objective was to assess the profile of JH in a referral clinic from eastern India. **Materials and Methods:** For this study, 100 patients with documented acquired hypothyroidism (subclinical and overt) (aged <18 years), from eastern India, were evaluated retrospectively. Evaluation included history as well as clinical, biochemical, and ultrasonography parameters. **Results:** Out of the 100 participants, 74% had overt hypothyroidism (OH), while 26% had subclinical hypothyroidism (SCH). The majority of the participants were females (66%). The mean age at detection was  $8.95 \pm 3.96$  years in the SCH group and  $8.38 \pm 3.29$  years in the OH group. A family history of thyroid disorder and/or goiter was present in 35% of the patients. Goiter was the most common presentation in both SCH and OH, with overall prevalence of 58%. Height below 3<sup>rd</sup> percentile was significantly higher (28%) in OH group compared to 4% in SCH group. Five percent of OH subjects were obese. Worsening school performance was reported in only 9% of subjects. Only 4% (all males) presented with delayed puberty, while one female (1%) presented with precocious puberty. Sixty-four percent of OH group were TPOAb positive compared to only 15% in SCH group. Five percent of our study population had type-1 diabetes mellitus (T1DM) and 7% had Down syndrome (DS). **Conclusion:** In our study, JH showed significantly higher female preponderance and TPOAb positivity in OH group, in comparison to SCH group. Family history of thyroid disorder and/or goiter was present in a significant proportion of patients. Goiter was the most common presentation of JH. Height deceleration, weight gain, and fatigue were the other common presentations. Prevalence of short stature was significantly higher in OH group. Interestingly, in contrast to prevalent notion, only 5% of OH were obese and worsening school performance was observed to be rare. Puberty disorders (both delayed and precocious) may occur in JH as seen here. Because of strong association, those with T1DM or DS should be screened for JH and vice versa in T1DM.

**Keywords:** Acquired juvenile hypothyroidism, clinical profile, eastern India

## INTRODUCTION

Hypothyroidism is the most common thyroid dysfunction among children. It may be due to congenital or acquired causes; the latter is generally referred to as juvenile hypothyroidism (JH). JH can be either subclinical hypothyroidism (SCH) or overt hypothyroidism (OH). Thyroid hormones are indispensable for fetal and postnatal growth, development, and also for neuropsychological functioning.<sup>[1]</sup> Whatever may be the cause, hypothyroidism in children can have deleterious effects on growth, pubertal development, and school performance.<sup>[2,3]</sup> Most cases of JH are sporadic, while only 10% to 15% of cases are due to congenital defects in thyroid gland. Hashimoto's thyroiditis (HT) is the commonest cause of acquired JH. A six-year survey in 5179 school children showed a 1.2%

prevalence of HT.<sup>[4,5]</sup> HT may be associated with other autoimmune disorders like T1DM, Addison's disease, and also Down syndrome or Turner syndrome.<sup>[6]</sup> Autoimmune markers like anti-TPO antibody (TPOAb) are strongly associated with HT.<sup>[7,8]</sup>

Other causes of JH include post-ablative hypothyroidism, iodine deficiency or excess, drugs, and central hypothyroidism.

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Iatrogenic hypothyroidism is comparatively less frequent among children. Although there is abundant data on congenital hypothyroidism from India, data on clinical profile of acquired JH is definitely sparse. Our objective was to assess the same from a referral clinic in eastern India in this cross-sectional retrospective study.

## MATERIALS AND METHODS

Children between the ages of 1 and 18 years with documented hypothyroidism (both subclinical and overt) due to acquired causes, attending a tertiary referral center, were evaluated retrospectively. To look for any differences in the clinical profile of SCH and OH patients, we distributed the subjects into two groups: CH if they had an elevated serum TSH and normal T4 concentrations and OH if they had an elevated serum TSH concentration associated with a decreased T4 concentration.

Exclusion criteria included causes of transient increase in TSH levels without intrinsic defects in thyroid such as those recovering from acute illness and on anticonvulsant therapy. For the same reason, SCH associated with obesity which normalizes with weight loss was also excluded. We also excluded subjects with congenital hypothyroidism including aplasia/hypoplasia/ectopia of thyroid gland by ultrasonography.

Age and gender of the patients, their complaints at the time of presentation, and family history of thyroid disease/goiter were retrieved from the prior medical records. The presence of associated comorbidities, particularly other autoimmune disorders and syndromes like Down and Turner, was recorded and diagnosis confirmed. School performance in school going children was assessed qualitatively on parents' observations of worsening school performance and memory and the overall academic performance including the percentage of marks obtained.

Height and weight at presentation were noted from the records. Those with height less than 3<sup>rd</sup> percentile and weight more than 95<sup>th</sup> percentile for age and sex according to IAP approved

charts were considered as short and obese, respectively. Where applicable, puberty was staged according to Tanner staging and goiter was graded according to WHO classification. Serum TSH, T4 as well as anti-TPO antibody (TPOAb) levels were recorded. USG of thyroid was done in those without goiter.

The prevalence estimates of acquired JH from a prior large observational study was 0.067%.<sup>[9]</sup> Based on this study, the recommended minimum sample size for the current study was calculated to be 96 subjects. Accordingly, we conducted the study on 100 subjects.

Laboratory analysis of T4 and TSH was done with commercial test kits (Roche Cobus R) using Elecsys 2010R. The corresponding normal values for the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of T4 and TSH were 4.6–11.2 µg/dL and 0.27–4.2 mIU/mL, respectively. TPOAb measurements were done using IMMULITE 2000R kits and SiemensR analyzer. The 95<sup>th</sup> percentile value for TPOAb levels was 35 IU/mL.<sup>[10]</sup>

Statistical analysis of data was performed using Chi-square and unpaired t-test. Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows (SPSS, Inc., Chicago, IL, USA) and Microsoft Word 2010 and Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, USA) have been used to generate graphs and tables.  $P < 0.05$  was considered statistically significant.

## RESULTS

### General characteristics of study participants

The mean age of the study cohort was 10.26±3.42 years. Two-thirds (66%) of the participants were females. Majority of patients (74%) were diagnosed with OH; the rest 26% had SCH [Table 1].

### Chief complaints at presentation in the SCH and OH groups

Goiter was the most common presenting complaint in the SCH group (38.6%). Other complaints at the presentation in SCH were fatigue (26.9%), poor height gain (11.5%), excessive weight gain (11.5%), and worsening school performance (11.5%). In the OH group, the commonest presenting complaint was once again goiter (50%). Other complaints at presentation in the OH study subjects were also similar, with fatigue (13.5%), poor height gain (12.16%), excessive weight gain (10.8%), and worsening school performance (8.1%) [Table 2]. In OH group, 4% (all males)

**Table 1: General characteristics of study participants**

Parameter	Values
Mean age (year)±SD	10.26±3.42
Gender	Male (34%); Female (66%)
Type of hypothyroidism	SCH (26%); OH (74%)

**Table 2: Comparison of parameters between SCH and OH groups**

Parameter	SCH	OH	OR, 95%CI	P
Mean age at presentation±SD	8.95±3.6	8.38±3.29		>0.05
Gender preponderance	Male (58%)	Female (70%)	3.22	<0.05*
Family History thyroid disease	27%	38%	0.6	>0.05
Height <3 <sup>rd</sup> percentile	4%	28%	1.49	<0.05*
Weight >95 <sup>th</sup> percentile	NA	5%		
Goiter	46%	62%	1.64	>0.05
TPOAb positivity	15%	64%	9.57	<0.05*

presented with delayed puberty, while one female (1%) presented with precocious puberty.

### Comparison of clinical features and laboratory parameters between SCH and OH groups

When we compared the SCH and OH groups, a male preponderance (58%) was noted in the SCH group and a female preponderance (70%) was noted in the OH group. This difference in gender distribution was statistically significant (Odds Ratio = 3.22;  $P < 0.05$ ). The mean age at detection was  $8.95 \pm 3.96$  years in SCH group and  $8.38 \pm 3.29$  years in the OH group. There was no statistical difference between the two groups ( $P > 0.05$ ). A family history of thyroid disorder and/or goiter was present in a large number of patients (35%). Twenty-seven percent of patients with SCH and 38% of patients of OH had a positive family history of thyroid disorder and/or goiter. The difference between these two groups was not statistically significant (OR = 0.6;  $P > 0.05$ ). In SCH cohort, T4 was  $7.74 \pm 2.29$  with TSH -  $7.77 \pm 2.01$ , while in OH cohort, T4 was  $2.52 \pm 2.10$ , with TSH -  $58.81 \pm 41.10$  ( $P < 0.05$ ).

Twenty-two percent of the study participants had height below the 3<sup>rd</sup> percentile (4% in the SCH and 28% in the OH group). The difference between SCH and OH groups was clinically significant. Only 5% of OH patients had obesity. The overall presence of goiter was 58%. Goiter was present in 46% of SCH. The majority were grade I (31%), with grade II goiter seen in only 15% of the patients. Goiter was more frequent in the OH group (62%) of patients with an almost equal prevalence of grade I goiter (32%) and grade II (30%). The difference again was not statistically significant (OR = 1.64;  $P > 0.05$ ).

TPOAb positivity was significantly higher in OH (64%) compared to SCH (15%).

### Association with other autoimmune disorders and Syndromes

JH was closely associated with T1DM in 5% of our study population. A close association was also noticed with Down syndrome present in 7% of the study participants.

## DISCUSSION

In the present study, the prevalence of hypothyroidism was seen to be higher in girls than in boys (2:1), similar to the results found in the previous studies reporting female to male ratio varying from 2:1.4 to 8:1.<sup>[4,7,11]</sup> HT can start as SCH, with possibility of progression to OH. In our study, SCH was more common in boys, while OH was more frequent in girls suggesting significant association of progression to overt disease and increased severity of disease in female gender (Odds ratio = 3.22;  $P < 0.05$ ) probably related to skewed X chromosome inactivation or estrogen and progesterone levels.

In the current study, the mean age of presentation was  $8.95 \pm 3.96$  years in SCH group and  $8.38 \pm 3.29$  years in OH

group ( $P > 0.05$ ). Several studies have noted that acquired JH frequently presents between 9 and 11 years and is rarely seen before 4 years of age.<sup>[7]</sup> In the present study, family history of thyroid disorder and/or goiter was present in 35% of patients. HT is the commonest cause of acquired JH and has a genetic basis with family history reported in 23% to 46% of children and adolescents.<sup>[4,9,12,13]</sup>

A total of 58% of our patients had goiter and it was also the commonest presentation. Goiter prevalence was numerically higher in OH compared to SCH. There was almost equal incidence of grade 1 and grade 2 goiter in the OH group highlighting that the degree of enlargement of the thyroid does not correlate with the severity of disease.

Chowdhury *et al.* reported 19% and 28% incidence of hypothyroidism in male and female patients, respectively, presenting with short stature.<sup>[14]</sup> On clinical evaluation, height  $< 3^{\text{rd}}$  percentile or short stature (22%) was the second most common clinical feature in our study and was significantly higher in OH (28%) compared to SCH (4%). Onset of JH is often subtle; height velocity is one of the earliest parameters to be affected and manifests later as short stature. Hence, growth evaluation is mandatory in JH. Conversely, children presenting with short stature should be evaluated for JH.

Only 5% of our OH patients were obese, suggesting that children with JH are essentially nonobese.<sup>[15]</sup> There is a deceleration of height gain, whereas weight gain is relatively preserved in children with JH. Obesity, though historically considered a criterion to establish the diagnosis of hypothyroidism, is rarely seen clinically and the metabolic feature is weight gain due to change in thermogenesis.<sup>[16]</sup> Even in severe thyroid dysfunction, less than 10% weight loss may occur with treatment.<sup>[16]</sup> Treatment of obesity-associated subclinical hypothyroidism has almost no influence on the body weight and lipid profile.<sup>[17]</sup>

We deliberately excluded SCH presenting with obesity as it may confound the diagnosis of HT-related SCH. For the same reason, we excluded other causes of SCH such as recovery from acute illness and anticonvulsant therapy. That could be one of the reasons for the lower prevalence of SCH compared to OH in our study population. One of the major reasons for lower prevalence of SCH in our real-world clinic-based study compared to population-based studies could be because of asymptomatic nature of SCH leading to lesser detection and referral to hospital.

Contrary to popular belief, worsening school performance was reported in only a small percentage of patients (9%) of the total study cohort. In fact, many JH patients are toppers in class. Paradoxically, the school performance is observed to worsen with the initiation of thyroxine.

Pubertal disorders may be seen in JH; it is usually delayed. However, rarely, in long-standing and severe hypothyroidism, we may get incomplete precocity.<sup>[18,19]</sup> In the present study,

puberty was delayed in 4% children with OH. One girl (1.4%) with OH presented with precocious puberty.

In our study, TPOAb positivity was significantly higher in OH (64%) compared to SCH (15%) reaffirming the correlation between TPOAb positivity with progression to OH. Only 10% to 15% of the general population with or without goiter is TPOAb positive, while 90% of patients with OH secondary to autoimmune thyroiditis are TPOAb positive indicating that TPOAb is the most sensitive screen for autoimmune thyroiditis in acquired JH.<sup>[20]</sup> Apart from the difference in TPO positivity and shorter height in children with OH, there were no significant differences in clinical profile between OH and SCH groups.

T1DM patients have a higher prevalence of HT, ranging from 15% to 30% with TPOAb positivity.<sup>[21]</sup> In the present study, 9% of JH patients had T1DM and all were TPOAb positive. Therefore, routine screening of all T1DM for JH is recommended and vice versa.

Patients with DS have a strong association with HT, with high rates of TPOAb positivity.<sup>[22-24]</sup> Seven percent of our patients had DS and all were TPOAb positive. Annual screening of DS patients with thyroid function tests may be helpful because the signs and symptoms of hypothyroidism may be mistaken for that of DS.<sup>[25]</sup>

## CONCLUSION

In our study, JH showed overall female preponderance and significantly higher TPOAb positivity in OH group in comparison to SCH group. Family history of thyroid disorder and/or goiter was present in a significant proportion of patients. Goiter was the commonest presentation of JH. Height deceleration, weight gain, and fatigue were the other common presentations. Short stature was significantly higher in OH group. Therefore, all children presenting with unexplained short stature should be screened for JH. Contrary to popular belief, only 5% of OH were obese and worsening school performance was observed to be rare. Puberty disorders both delayed and precocious may occur in JH as seen here. Because of strong association, those with T1DM or DS should be screened for JH. Similarly, those with JH should be screened for T1DM.

## Limitations of our study

This was a cross-sectional retrospective study; hence, we could not assess long-term effects of treatment on parameters such as growth and goiter size. The assessment of scholastic performance was qualitative as we could not do a psychometric analysis or follow a more precise quantitative scoring method. Future prospective longitudinal follow-up studies with larger sample sizes are needed to strengthen our observations.

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## Conflicts of interest

There are no conflicts of interest.

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