

High Thyroid-stimulating Hormone Level in Down's Syndrome: A Mere Resetting of Hypothalamopituitary Axis in Subclinical Hypothyroidism?

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Abstract

Objective: Hyperthyrotropinemia (HT) or reduced thyroid function in Down syndrome (DS) is not uncommon, causes range from glandular dysgenesis to altered hypothalamopituitary axis. In the present study, we have compared hypothyroid Indian children with and without DS (NDS), especially focusing on family history, goiter, and biochemical features. **Methods:** We conducted this retrospective observational study from previous medical records of children with DS (1-17 years) having an elevated TSH (≥ 5 mIU/L) who were consecutively referred for with HT to Endocrinology OPD of a tertiary care hospital in India. Records from hypothyroid children (1-17 years) without Down Syndrome (NDS) were evaluated as controls. Free thyroxine (FT4), anti-thyroid peroxidase (TPO) antibody were measured and congenital hypothyroidism was excluded in all subjects. **Results:** Thirty-four DS cases [median age 8 years (IQR: 2-14), M: F = 13:21] and 34 controls [median age 10.5 years (IQR: 7-13.25), M: F = 13:21] were comparable in terms of age and sex, Median age of presentation was significantly earlier in case of DS vs NDS [7 years vs. 10 years]. DS children had significantly less family history of thyroid disorders compared to NDS [14.7% vs 64.7%]. Goiter was significantly less common in patients with DS [DS - 32.25% vs. NDS - 73.5%, $P = 0.001$]. Anti-TPO antibody positivity was significantly less common in patients with DS [DS - 41% vs. NDS - 73.5%, $P = 0.014$]. **Conclusion:** There is a significant difference in presentation in hypothyroid children with DS compared to NDS. DS children with hypothyroidism compared to NDS, had earlier presentation, lower incidence of traceable family history, goiter, and anti-TPO-antibody positivity.

Keywords: Children, down syndrome, hyperthyrotropinemia, hypothyroid

INTRODUCTION

Thyroid dysfunctions represent the commonest endocrine disorders in patients with Down syndrome (DS).^[1] Derangements in thyroid function in DS may present at any stage in life: congenitally, neonatally, in childhood or adulthood.^[1] An elevation in the thyroid-stimulating hormone (TSH) level or hyperthyrotropinemia (HT) is the most common thyroid disorder associated with Down's syndrome.^[2] The spectrum of thyroid dysfunction in children with DS include congenital hypothyroidism, subclinical hypothyroidism (SH), overt hypothyroidism (OH). Adult DS patients with hypothyroid have a greater percentage of cases positive for anti-thyroid antibodies^[3] but the etiological basis for hyperthyrotropinemia in the pediatric age group remains obscure. While some authors have implicated an autoimmune pathology similar to

Hashimoto's thyroiditis^[4,5] others have suggested that a delayed maturation of the hypothalamo-pituitary-thyroid axis might be responsible.^[6] Their theories include an over-secretion of TSH due to hyper-responsiveness to interferons or an erroneous dopaminergic control of the pituitary gland.^[7] While it was postulated that a mild elevation in TSH or SH can eventually lead to OH,^[8] this theory has been challenged by subsequent findings that many of these cases only show a transient rise

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in TSH^[9] and non-progression to OH, even on long-term follow up.^[10] The implication of the elevation of TSH has also been questioned based on its lack of association with clinical symptoms.^[9] From a therapeutic perspective, these add up to the vital question of the necessity of thyroid hormone replacement therapy in the pediatric DS patients with hyperthyrotropinemia, with some studies indicating effectiveness and others lack of any benefit of such treatment.^[11,12]

Identification of features specific to the presentation and biochemical manifestations of hyperthyrotropinemia in children with DS is essential to better understand the etiological basis as well as deciding upon screening and treatment strategies. Median age at presentation, family history of thyroid disease, baseline TSH level, presence of goitre, thyroid antibody positivity were found to be important determinants of outcome in hypothyroidism with DS.^[13-18] But there is very limited literature on Hypothyroidism in DS especially in children, accordingly, in the present study, we have investigated hypothyroid Indian children with and without DS (NDS), especially focusing on age at presentation, family history, goiter, and TPO antibody positivity.

The protocol was presented to the ethics committee of the KPC Medical College and Hospital. Given the retrospective nature of the study and collection of data from the electronic database, the ethics committee suggested that the formal approval process can be dispensed with.

MATERIALS AND METHODS

We conducted this retrospective observational study from previous medical records of children with DS patients (1–17 years) having an elevated TSH (≥ 5 mIU/L) who were consecutively referred for HT to Endocrinology specialty OPD of a tertiary care hospital in India. Records from hypothyroid children (1–17 years) without Down Syndrome (NDS) were evaluated as controls. We mainly focused on age at presentation, sex, family history of thyroid disease, presence of goiter, baseline TSH and TPO antibody positivity status between DS and NDS with hyperthyrotropinemia. Congenital hypothyroidism was excluded in both arms, as also patients taking medications that can affect thyroid status, like amiodarone, lithium, interferons. Recorded data of Thyroid-stimulating hormone (TSH), Free thyroxine (FT4), anti-thyroid peroxidase (TPO) antibody, were evaluated in the cases and controls. Serum FT4, TSH, and anti-TPO levels were measured by electrochemiluminescence immunoassay (Cobas e411 Analyser, Roche Diagnostics, GmbH Mannheim). Reference ranges after one month of age were TSH 0.5–5.0 uIU/ml and Free T4 0.9–1.7 ng/dl, while reference for anti-TPO antibody positivity was anti-TPO antibodies above 34 IU/ml. Based on thyroid function test results, participants were classified using the following definitions: overt hypothyroidism (OH) low serum FT4 (i.e., <0.9 ng/dL) and elevated TSH >10 μ U/ml; For subclinical hypothyroidism (SH), we considered a normal serum FT4 (0.9–1.7 ng/dL) along with elevated TSH ≥ 5 mIU/L.

Kolmogorov-Smirnov test was used to test the normality of the data. Comparisons between groups were performed by unpaired Student's t-test for continuous data and Fischer's exact test for categorical data. A P value < 0.05 was considered to be statistically significant. All analyses were performed on SPSS Version 16.0.1 (SPSS Inc., Chicago, 2007).

RESULTS

A total of 34 hypothyroid patients with DS and 34 with NDS were included. The characteristics of the hypothyroid study subjects with and without DS are tabulated [Table 1]. The groups were comparable in terms of age and gender. Hypothyroid subjects with DS had a significantly less positive family history of thyroid disorders compared to NDS children and goiter was significantly less common in hypothyroid children with DS compared to NDS. The rates of positivity of anti-TPO antibody significantly less in DS children with HT compared to NDS [Supplementary Table 1].

The characteristics of anti-TPO negative ($n = 20$) and anti-TPO positive ($n = 14$) subjects with and without DS are tabulated [Supplementary Table 1]. The anti-TPO negative group had earlier median age of presentation, but no significant difference in traceable family history and presence of goiter were seen. OH was significantly more common in TPO positive DS children, conversely SH was more common in TPO negative DS children.

DISCUSSION

A link between DS and hyperthyrotropinemia has been long documented.^[5] Thyroid dysfunction is the commonest endocrine disorders in DS, with elevated TSH level or HT being the commonest thyroid disorder in DS.^[1,2] Identification of features related to presentation and biochemical manifestations of hypothyroidism in children with DS may help in deciding upon screening, treatment, and follow-up strategies. In our study, hypothyroid children with DS compared to NDS had 1 significantly earlier median age of presentation, lower incidence of traceable family history of thyroid disorders. In the present study, hypothyroid children with and without DS were comparable in terms of gender., Goiter was significantly less common in hypothyroid children with DS compared to NDS. The rates of positivity of anti-TPO antibody were significantly lower in hypothyroid children with DS compared to NDS. TPO positive DS children had significantly more OH, conversely SH was more common in TPO negative DS children

Thyroid dysfunction in DS may present at any stage in life.^[1] In a retrospective records review by Pierce *et al.*, thyroid disease in DS was more common and occurred earlier than in the general population, but was often transient and was unrelated to gender, obesity, or other comorbidities.^[13] HT in DS is associated with a lack of clinical features.^[9] Amr reported that the main features of autoimmune hypothyroidism in DS versus the general population were equal sex distribution, earlier age of onset, lower antibody titer at diagnosis, lower rate of positive family history, and higher rate of progression to overt disease.^[15]

Table 1: Characteristics of the study participants

Parameter	Children with hyperthyrotropinemia with Down's Syndrome (n = 34)	Children with hyperthyrotropinemia without Down's Syndrome (n = 34)	P value
Median age, IQR (in years)	8.00 (2.00-14.00)	10.50 (7-13.25)	0.181
Median age at presentation, IQR (in years)	7.00 (1.00-11.00)	10.00 (5.75-13.25)	0.010
Sex (% female)	61.76	61.76	1.000
Family history (% present)	14.70	64.70	<0.0001
Thyroid status (% subclinical)	41.17	52.94	0.466
Median TSH, IQR	13.00 (7.80-22.47)	9.62 (8.00-40.58)	0.735
Median FT4, IQR	1.03 (0.75-1.308)	0.92 (0.65-1.24)	0.643
Median Anti-TPO, IQR	30.00 (16.43-89.50)	89.00 (34.00-120.00)	0.005
Goiter (% present)	41.17	73.52	0.014

King *et al.* reported anti-TPO antibody positivity of 7.5–31% in DS children, but not exclusively with hyperthyrotropinemia.^[7] Adult DS patients with hypothyroid have a greater percentage of cases positive for anti-thyroid antibodies.^[3] Pierce *et al.*, reported a higher likelihood of antibody positivity in DS with higher TSH levels.^[13] We found significantly lower (41%) anti-TPO positivity in hypothyroid children with DS compared to NDS (73.5%) children. The autoantibody positivity rate in the NDS group mirrors previous data and can thus be considered representative.^[18-20] Some reports suggest that autoantibodies appear in DS patients only after the age of 5 years or 8 years while other authors have reported detectable autoantibody levels even at infancy.^[21] In our cohort, antibody levels in DS patients were detected as early as 2 years of age. A recent 5-year prospective multicenter study in 101 DS subjects, aged 2–17 years, reported a higher risk of thyroid function deterioration over time was influenced by thyroid autoimmunity and higher baseline TSH.^[14]

In our study, hypothyroid children with DS had earlier presentation and lower rates of goiter, these are apparently contradictory as greater duration of exposure to an elevated TSH level could lead to a greater degree of goiter. However, goiter and OH were significantly more frequent in our DS children with elevated anti-TPO antibodies, whereas DS children with low anti-TPO antibodies had more SH. While overlaps are possible, as is also apparent in our cohort, such a distinction might be helpful in planning therapeutic interventions, follow-up schedules, and prognostication.

Limitations of the study were its retrospective nature, relatively small sample, nonrandom sampling, and differential detection due to bias for hypothyroidism in DS versus NDS, because of well-known risk of hypothyroidism in DS. Several clinical parameters like growth and developmental parameters were not documented. Longitudinal data including treatment outcomes were not assessed due to poor follow-up.

CONCLUSION

In conclusion, there is a significant difference in presentation in hypothyroid children with DS compared to NDS. In our study, hypothyroid children with DS compared to NDS, had an earlier age at presentation, but lower incidence of traceable family history of thyroid disease, anti TPO-antibody positivity and goiter.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Comparison between TPO positive and TPO negative study subjects

	Anti-TPO negative			Anti-TPO positive		
	DS (<i>n</i> = 20)	NDS (<i>n</i> = 9)	<i>P</i> value	DS (<i>n</i> = 14)	NDS (<i>n</i> = 25)	<i>P</i> value
Median age at presentation (years)	7.5	8	0.978	3	11	0.0005
Presence of family history (%)	20.00	77.77	0.010	28.57	72.00	0.017
Presence of goiter (%)	5.00	44.44	0.022	50.00	72.00	0.297
TSH levels	8.27	9.00	0.220	21.61	11.60	0.291