RESEARCH PAPER

Thyroid Stimulating Hormone Level at Diagnosis as a Predictor of Persistent Subclinical Hypothyroidism in Children with Down Syndrome

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Objective: To evaluate subclinical hypothyroidism in a cohort of children with Down syndrome and identify a TSH level at the time of diagnosis to predict persistent hypothyroidism. **Methods:** 192 children (age <3 years) with Down syndrome, registered in the Genetic Clinic of a referral tertiary care Hospital from 2010 to 2015 were evaluated with thyroid function test at initial visits and subsequently based on standard protocol. Children with subclinical hypothyroidism were evaluated at 3 years of age after discontinuation of thyroxine for 3 months. **Results:** 47 (24.5%) children had elevated TSH and among them 43 (91.5%) had subclinical hypothyroidism. Among the subclinical hypothyroidism group, 25 (73.5%) had transient hypothyroidism and 9 (26.5%) persistent hypothyroidism. Initial TSH level at the time of diagnosis was higher in persistent hypothyroidism group as compared to transient group (P= 0.003). The best cut-off level for prediction of persistent hypothyroidism for initial TSH level was 11.6 mIU/L. **Conclusion**: Subclinical hypothyroidism, especially transient, is the commonest form of thyroid dysfunction in children with Down syndrome. The initial TSH level may help to predict the possibility of persistence of hypothyroidism.

Keywords: *Congenital hypothyroidism, Hyperthyroxinemia, Thyroid dysgenesis.*

Children with Down syndrome are more prone to develop thyroid dysfunction. The spectrum of thyroid dysfunction includes congenital overt hypothyroidism (elevated plasma TSH with low plasma T4, usually detected at newborn screening), subclinical hypothyroidism (elevated plasma TSH with plasma T4 in the normal range, which can be congenital or acquired) and acquired autoimmune hypothyroidism [1]. The prevalence of congenital overt hypothyroidism and subclinical hypothyroidism (SCH) in children with Down syndrome is higher than that in the general pediatric population [2-6]. More than 70% of the subclinical hypothyroidism in children with Down syndrome is transient, whereas the rest progress to overt hypothyroidism or persist as subclinical hypothyroidism [7]. The decision to treat subclinical hypothyroidism in Down syndrome is controversial. There are studies demonstrating significant improvement in growth of these children after thyroxine therapy [8].

We analyzed a cohort of children with Down syndrome attending the Genetic clinic in a tertiary care hospital to evaluate the proportion of children with subclinical hypothyroidism, and to establish a TSH cut-off for prediction of persistent hypothyroidism.

METHODS

This cohort study was conducted in the Genetic clinic of Government Medical College, Thiruvananthapuram, India during 2010-2015. All cytogenetically proven children with Down syndrome, diagnosed before 3 years of age, and under regular follow-up were included in the study. Thyroid function tests (serum TSH and total T4) were done in all children at the time of initial visit. A repeat TSH and T4 measurement was done every 6 months in the first year of life and annually after one year of age as per the recommendations by American Academy of Pediatrics [9]. Total serum TSH and T4 levels were measured in venous blood by electrochemiluminescence immunoaasay. Elevated TSH level was defined as >5 mU/L; total T4 of 4.5-12.5 µg/dL was considered normal [10]. All children with TSH >5 mU/L received thyroxine supplementation at appropriate dose. Thyroxine supplementation was stopped at the age of 3 years in children with subclinical hypothyroidism and thyroid function test was repeated after 3 months. Children with persistent hypothyroidism were restarted on thyroxine supplementation. In all children with overt and persistent subclinical hypothyroidism, ultrasound thyroid, Anti-thyroid peroxidase (TPO) antibody and Anti-thyroglobulin (TG)

WHAT THIS STUDY ADDS?

- In children with Down syndrome, initial TSH level at the time of diagnosis is a good predictor of future persistence of hypothyroidism.

antibody testing was performed. Ethical clearance was obtained from Institutional Ethics committee.

The statistical significance of frequencies was done by Chi-squre test with *P* value significant level at 0.05. The comparison of mean value of TSH in various groups was tested by *t* test. ROC curve was plotted to identify the cutoff value of initial TSH for prediction of persistent hypothyroidism.

RESULTS

Of the 192 children with Down syndrome, 145 (75.5%) had normal TSH and 47 (24.5%) (27 males) had increased TSH. The initial diagnosis was made during infancy in 35 children, and mean (SD) age of initial diagnosis was 11.5 (4) months. Mean (SD) TSH value at the time of diagnosis was 13.2 (15.1) mU/L. The TSH level was 5-10 mU/L in 26 children, 10.1-20 mU/L in 17 children and more than 20 mU/L in 4 children. A history of maternal hypothyroidism was present in 2 children.

Among 47 hypothyroid children, 4 (8.5%) had overt hypothyroidism and 43 (91.5%) had subclinical hypothyroidism. Mean (SD) TSH level in children with overt hypothyroidism was significantly higher than that in subclinical hypothyroidism [46.5 (41.0) *vs.* 10.5 (3.8) mU/L; $P<0.001$]. For evaluation of persistence of subclinical hypothyroidism at the age of three years, nine cases were excluded as they were either aged less than three years (7 cases) or lost to follow-up (2 cases). Out of 34 cases with subclinical hypothyroidism, 25 (73.5%) were transient with normalization of TSH level. In 9 (26.5%) children, TSH at 3 years was high suggestive of persistent hypothyroidism.

TSH level at the time of diagnosis was significantly higher in persistent hypothyroidism group 25.1 (25.6) mU/L as compared to those with transient hypothyroidism 8.9 (1.8) mU/L ($P=0.003$). ROC curve suggested a TSH cut-off value of 11.6 mU/L to predict persistent hypothyroidism with a specificity of 92% and sensitivity of 77%.

Only 1 out of 4 patients with overt hypothyroidism showed agenesis of the thyroid gland on ultrasound examination. Anti-TPO antibody was elevated in 8 children (2 cases of overt and 6 cases of subclinical hypothyroidism) whereas Anti TG antibody was negative in all children.

DISCUSSION

This study documented that the commonest thyroid dysfunction in children with Down syndrome was subclinical hypothyroidism, which was transient in most of the cases. The TSH levels at diagnosis in children with persistent hypothyroidism was significantly higher than in children with transient hypothyroidism.

The prevalence of hypothyroidism in children with Down syndrome varies according to the study population and setting. However, in all these studies subclinical hypothyroidism is the major contributor which was also the major observation in our study. Studies from other parts of the world have shown that 65-70% of subclinical hypothyroidism in Down syndrome is transient in nature [5,6,11].

The reason for subclinical hypothyroidism in Down syndrome is not fully understood. It may be caused by thyroid autoimmunity. Some studies have hypothesized an inappropriate central secretion of TSH [12]. Resistance of the thyroid gland to TSH is another hypothesis; however, this has not been demonstrated [13]. Konnings, *et al*. [14] demonstrated that TSH bioactivity was normal compared to euthyroid non-Down syndrome children. Van Trotsenburg, *et al*. [15] observed that in children with Down syndrome, mean TSH is shifted to the right and mean T4 is shifted to the left compared to general population. These shifted plasma TSH and T4 values could be considered as a continuum with subclinical hypothyroidism. However, the reason for this shift in hormone levels has not been explained by a specific mechanism. All these information suggests that thyroid dysfunction in Down syndrome is thyroidal in origin.

The major limitation of this study was that the follow-up of these children was done only up to 3 years of age. Some of the children may develop autoimmune hypothyroidism later. The outcome of these children with and without treatment is to be studied for formulating recommendation regarding thyroxine therapy in children with Down syndrome.

We conclude that subclinical hypothyroidism is more common in children with Down syndrome and majority of these were transient in nature. An elevated initial TSH level of more than 11.6 mU/L will help predict the future possibility of persistence of hypothyroidism.

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