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Original Research Article

A RETROSPECTIVE STUDY ON ACQUIRED HYPOTHYROIDISM AMONG CHILDREN

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is a biochemical condition defined by mildly elevated serum Thyroid stimulating Hormone (TSH) concentrations associated with normal circulating levels of thyroid hormones. Data on SCH in the general pediatric population are scarce; it seems to be a relatively rare condition in children and adolescents (1.7–2.9%), usually characterized by a self-limiting and remitting process with spontaneous normalization or stabilization of TSH values in the majority of cases (up to 88%).

Materials and Methods: For this study, 90 Children between the ages of 1 to 18 years with documented hypothyroidism (both subclinical and overt) due to acquired causes, attending a tertiary referral center, were evaluated retrospectively. Evaluation included history as well as clinical, biochemical, and ultrasonography parameters. 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.

Results: In this study, out of 90 children, 82 (91.1%) were SCH and 8 (8.9%) were OH. The mean T3 level at start was 4.00±0.64; in the 6th month of follow-up, the mean was 1.88±0.44; in the 12th month of follow-up, the mean was 1.69±0.34 nmol/l. The mean T4 level at start was 11.8±1.99; in 6th month of follow-up, the mean was10.58±1.99; in 12th month of the follow-up, the mean was 9.58±4.18 µg/dl. The mean TSH level at start was 4.88±1.54 in 6th month of the follow-up, the mean was 4.4±1.44, and in 12th month of the following, up mean was 1.68±1.22 mIU/l. A gradual decrease in the levels at follow-up was statistically significant ($p<0.001$).

Conclusion: Subclinical hypothyroidism (SCH) was the most predominant hypothyroid dysfunction found in our studied population. Correction of thyroid dysfunction particularly SCH in early childhood is highly essential to prevent the impairment of psychomotor and cognitive development.

Keywords: Hypothyroidism, Subclinical hypothyroidism, Thyroid stimulating Hormone.

INTRODUCTION

Subclinical hypothyroidism (SCH) is a biochemical condition defined by mildly elevated serum TSH concentrations associated with normal circulating levels of thyroid hormones.[1]

Data on SCH in the general pediatric population are scarce; it seems to be a relatively rare condition in children and adolescents (1.7–2.9%), usually characterized by a self-limiting and remitting process with spontaneous normalization or stabilization of TSH values in the majority of cases (up to 88%).[2]

It has already been documented that underlying Hashimoto thyroiditis (HT) can negatively affect the natural course of SCH by increasing the risk of thyroid function deterioration over time. Moreover, the association with chromosomopathies such as Turner syndrome or Down syndrome (DS) may impair the outcome of HT-related SCH by further increasing the risk of progression to overt hypothyroidism. The abnormalities most frequently associated in the pediatric population are goiter, poor school performance, weight gain, increased cholesterol levels, impaired growth velocity, anemia, excessive sleepiness, weakness, and impaired psychomotor and cognitive development.[3] With respect to DS, it is well-known thyroid dysfunction which is much more prevalent and occurs earlier than in the general population. SCH is the most common thyroid abnormality in DS children, with prevalence ranging from 25.3% to 60% depending on studies.[4] The etiology of SCH in DS remains still not completely clarified. The most obvious and important hypothesis to explain early onset SCH is based on a generally mild and non-autoimmune thyroid dysfunction, probably caused by a congenital alteration in the regulation of the thyroid gland itself.[5] Autoimmunity is also among the hypothesized causes, appearing predominantly from school-age years onward.[6] The American Academy of Pediatrics (AAP) recommends that thyroid function should be evaluated at 6 and 12 months and then annually in all DS children, with increased frequency in SCH.

MATERIAL AND METHODS

Children between the ages of 1 to 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: SCH 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.

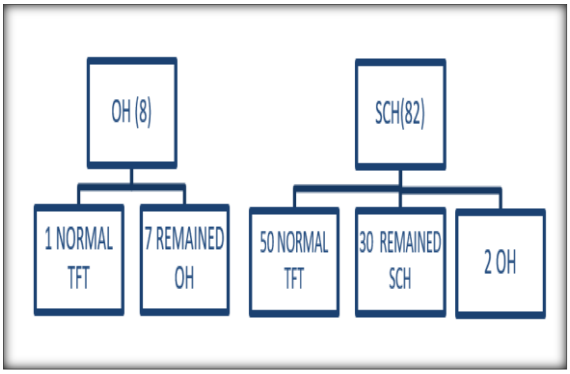
Height and weight at presentation were noted from the records. Those with height less than 3rd percentile and weight more than 95th percentile for age and sex according to IAP approved charts were considered as short and obese, respectively. Where applicable, puberty was staged according to Tanner staging and goiter was graded according to WHO classification. Serum TSH, T4 as well as T3 levels were recorded. USG of thyroid was done in those without goiter and patients were followed up.

Laboratory analysis of T3,T4 and TSH was done with commercial test kits (Roche Cobus R) using Elecsys 2010R. The corresponding normal values for the 2.5th and 97.5th percentiles of T3,T4 and TSH were 1.23-4.00 nmol/L, 4.2–14.9 µg/dl and 0.5–5.5 mIU/l, respectively.

Statistical Analysis

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



Flowchart 1: Progression of acquired hypothyroidism after 12 months of follow up

Table 1 shows the age distribution among the subjects. Total 31.1% were between 1-3 years, 32.2% were between 4-6 years, 11.1% were between 7-9 years, 8.9% were between 10-12 years and 16.7% were between 13-18 years. Maximum participants (29) belong to 4-6 years of age group (32%) followed by 1-3 years 28 participants (31.1%). The mean age in the study was 6.18±5.29 years. [Table 1]

The study consisted of 52 (57.8%) males and 38 (42.2%) females, with the sex ratio being 1.6: 1 [M: F], as shown in Table 2. [Table 2]

Family history was present in 3.3% (3), and the remaining 96.7% (87) had no relevant family history, as seen in Table 3. [Table 3]

The clinical signs and symptoms of hypothyroidism were present only in two subject (2.2%), and none of the remaining 88 had any signs and symptoms of hypothyroidism, as shown in Table 4. [Table 2]

Out of 90 subjects 82 (91.1%) were SCH and 8 (8.9%) were OH, as shown in Table 5. [Table 5]

The mean T3 level at start was 4.00±0.64; in the 6th month of follow-up, the mean was 1.88±0.44; in the 12th month of follow-up, the mean was 1.69±0.34 nmol/l. The mean T4 level at start was 11.8±1.99; in 6th month of follow-up, the mean was10.58±1.99; in 12th month of the follow-up, the mean was 9.58±4.18 µg/dl. The mean TSH level at start was 4.88±1.54 in 6th month of the follow-up, the mean was 4.4±1.44, and in 12th month of the follow up mean was 1.68±1.22 mIU/l, as shown in Table 6. A gradual decrease in the levels at follow-up was statistically significant (p<0.001). [Table 6]

Table 1: Distribution according to age

Age	Frequency	Percent
1-3 years	28	31.1
4- 6 years	29	32.2
7- 9 years	10	11.1
10-12 years	8	8.9
13-18 years	15	16.7
Total	90	100
Mean age: 6.18±5.29 years		

Table 2: Distribution according to gender

Gender	Frequency	Percent
Male	52	57.8
Female	38	42.2
Total	90	100
Sex ratio: 1.6: 1 [M: F]		

Table 3: Distribution according to family history

Family history	Frequency	Percent
Yes	3	3.3
No	87	96.7
Total	90	100

Table 4: Distribution according to the presence of signs and symptoms of hypothyroidism

Signs and symptoms of hypothyroidism	Frequency	Percent
Yes	2	2.2
No	88	97.8
Total	90	100

Table 5: Distribution of acquired hypothyroidism

Disease	Frequency	Percent
SCH	82	91.1
OH	08	8.9
Total	90	100

Table 6: Thyroid profile of the subjects

Thyroid profile	At start	At 6th month of follow up	At 12th month of follow up	P value
Mean T3 nmol/l	4.00±0.64	1.88±0.44	1.69±0.34	<0.001*
Mean T4 µg/dl	11.8±1.99	10.58±1.99	9.58±4.18	<0.001*
Mean TSH mIU/l	4.88±1.54	4.4±1.44	1.68±1.22	<0.001*

DISCUSSION

It is a well-known fact that thyroid hormone is essential for the growth and maturation of many target tissues, including the brain and skeleton. As a result, altered thyroid gland function in infancy and childhood affect not only in the metabolic consequences of thyroid dysfunction as in adult patients, but also in unique effects on the growth and or maturation of thyroid hormone dependent tissues. It has been observed from various studies that about 42 million people in India suffer from thyroid disease. [7]

In this retrospective study, 90 children were studied aged 1-18 yrs. Total 31.1% were between 1-3 years, 32.2% were between 4-6 years, 11.1% were between 7-9 years, 8.9% were between 10-12 years and 16.7% were between 13-18 years. Maximum participants (29) belong to 4-6 years of age group (32%) followed by 1-3 years 28 participants (31.1%). The mean age in the study was 6.18±5.29 years. [Table1] In a population-based study from India, it has been observed that 12% of children

aged 5-16 years were found to have thyroid dysfunction in which TSH levels above the reference range.[8] However, the prevalence of thyroid dysfunction in children and adolescents is lesser than adult population where the prevalence was found 19.6%.[9]

In our study consisted of 52 (57.8%) males and 38 (42.2%) females. According to Lakshminarayana GR the prevalence of thyroid dysfunction was found to be higher in female population (12%) as compared to males (7.4%) in children and adolescent's groups (12 % vs 7.4% and 10% vs 9.4% respectively).[10] Similar results were also explained by Marwaha RK et al., where the females have higher prevalence in both children and adolescent groups. The higher prevalence of thyroid dysfunction in young females can be attributed to the difference in sex hormones and pubertal growth pattern.[11] [Table 2].

In this study none of the children had developmental delay. The role of thyroid hormones in brain development has long been studied, and numerous studies have been published to date. Congenital hypothyroidism that is not diagnosed or not treated early causes developmental delay, is triggered by abnormalities in neural architecture during brain development.[12] Furthermore, Fisher RS et al. (2019),[13] reported that individuals with severe congenital hypothyroidism are at risk of developing white matter microstructural abnormalities, despite early detection and treatment.

In our study of 90 participants, microcephaly was present in none of the subjects. Research has shown that normal thyroid metabolism is necessary for human development, including the formation and functioning of the brain. However, abnormal thyroid metabolism is increasingly diagnosed in the spectrum of pediatric neurological disorders. [14] Moreover, in their literature review investigating neurological symptoms of impaired thyroid metabolism, Kurian and Jungbluth also point out the correlation between hypothyroidism and microcephaly.[15] A similar relationship was reported by Carré et al.[16] Nonetheless, the criteria for the diagnosis of microcephaly are often not included. In reviews of the literature considering the relationship between microcephaly, cerebral abnormalities and hypothyroidism.[17]

In current study, the clinical signs and symptoms of hypothyroidism were present only in two subjects (2.2%), and none of the remaining 88 had any signs and symptoms of hypothyroidism, as shown in Table 4. Most patients with SCH exhibit few or no signs or symptoms of hypothyroidism. It has been suggested that some patients have functional, clinical, or biochemical manifestations of hypothyroidism that are more common than age-matched controls.[18] Goiter is the most common manifestation.[19] The abnormalities found most commonly in the pediatric population include weight gain, increased cholesterol levels, impaired growth velocity, anemia, sleepiness, weakness, and impaired psychomotor and cognitive development.[3] Out of 90 subjects 82 (91.1%) were SCH and 8 (8.9%) were OH, as shown in Table 5. Redetti, et al. had done a prospective observational study (2006) out of 160 subjects 55 were SCH and rest were euthyroid. Gopalakrishnan et al. done a longitudinal study and out of 98, 32 had SCH. Wasniewska, et al. done a prospective observational study (2009) for 2 years, found 92 with SCH.

In this study the mean T3 level at start was 4.00±0.64; in the 6th month of follow-up, the mean was 1.88±0.44; in the 12th month of follow-up, the mean was 1.69±0.34 nmol/l. The mean T4 level at start was 11.8±1.99; in 6th month of follow-up, the mean was10.58±1.99; in 12th month of the follow-up, the mean was 9.58±4.18 µg/dl. The mean TSH level at start was 4.88±1.54 mIU/l in 6th month of the follow-up, the mean was 4.4±1.44, and in 12th month of the following, up mean was1.68±1.22, as shown in Table 6. A gradual decrease in the levels at follow-up was statistically significant ($p<0.001$).

In our study 82 were SCH and 8 were OH. After 12 months of follow up, out of 82 SCH subjects 50 ended up having normal thyroid function test (TSH/T3/T4), 2 progressed to OH and 30 remained as SCH and out of 8 overt hypothyroidism subjects 1 subject ended up having normal Thyroid function test and rest 7 subjects remained as OH. [Flowchart 1] According to research data, the natural course of SCH in adults seem to progress to overt hypothyroidism in proportions ranging from 1 up to 20%. [20] However, most recent longitudinal studies show that at about 1/3 of patients with SCH has normalization of TSH in due course of time whereas most of the rest have persistent mild TSH elevation, in which causes of SCH will be considered. In a recent prospective study, it has been observed that out of 92 children between 5-15 years of age with "idiopathic" SCH, 38 patients had normal TSH levels (none in the first 6 months, 16 between 6 and 12 months and 22 between 12 and 24 months).[21] Similarly, in another prospective study by Lazar et al. followed SCH children for 5 years and found that 73.6% of them normalized TSH. [22] On the contrary, none of the SCH children has developed overt hypothyroidism in another study.[23]

CONCLUSION

Subclinical hypothyroidism (SCH) was the most predominant acquired hypothyroid dysfunction found in our studied population. SCH is a biochemical entity commonly faced by practicing pediatricians. Several factors including clinical condition of the child and laboratory factors influencing TSH levels should be considered while interpreting the results. Majority of acquired hypothyroid patients has spontaneous normalization / stabilization of TSH values over a period of time. There is a need for large prospective studies for

longer duration, designed to conclude the outcome of acquired hypothyroidism in pediatric population.

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