Thyroid dysfunction and developmental anomalies in first degree relatives of children with thyroid dysgenesis

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Background: **Familial clustering in patients with permanent congenital hypothyroidism (CH) caused by thyroid dysgenesis (TD) has been reported in developed countries. There is no information on familial TD from developing countries.**

Methods: **A total of 312 first degree relatives belonging to 80 families of children with TD (group 1) and 40 families of age-matched normal children (group 2) were screened by thyroid ultrasonography, serum total thyroxine (T4) and thyroid stimulating hormone (TSH).**

Results: **Thyroid scintigraphy revealed agenesis in 78.7% of the patients, ectopic gland in 15%, and hypoplasia in 6.2%. The mean thyroid volumes were similar in parents and siblings of both groups. Eight (10.6%) mothers in group 1 were identified to have thyroid hypoplasia as compared with none in group 2 (*P*=0.03). Serum TSH was significantly higher in group 1 than in group 2 (*P*=0.004). Sixteen (7.8%) subjects (6 mothers, 5 fathers, and 5 siblings) in group 1 were found to have subclinical hypothyroidism as compared to none in group 2 (*P*<0.05). Four families were identified to have thyroid developmental anomalies and abnormal thyroid functions accounting for 5% of cases of familial TD in our cohort.**

Conclusions: **Thyroid developmental anomalies and thyroid function abnormalities are more frequent in first degree relatives of children with TD as compared with a control population. These findings suggest that possibly there is a genetic component of TD in Indian patients.**

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Introduction

Thyroid dysgenesis (TD) accounts for 80%-85% of all cases of permanent congenital hypothyroidism (CH) in iodine sufficient regions and includes athyreosis, hypoplasia, hemiagenesis and ectopic thyroid gland.[1] Most cases of TD occur sporadically and their etiology remains obscure. The familial occurrence and the higher prevalence in certain ethnic groups like Hispanics and Caucasians and in babies with Down syndrome suggest a role of genetic factors.[2] However, gene mutations associated with TD are detected in only 2% of all cases.[3] Probable roles of factors like parental consanguinity, gender and maternal age have also been suggested.[3-5] Recent studies[6-9] have demonstrated an increased prevalence of developmental anomalies as well as thyroid dysfunction in first degree relatives of children with TD as compared with the normal population. The familial prevalence of TD in these studies ranged from 2% to 12%.[2,6-9] Systematic screening for thyroid developmental anomalies and associated thyroid dysfunction in family members is recommended because they may otherwise remain asymptomatic.[8,9] The data of family studies in TD from the Indian subcontinent are lacking. We therefore aimed to investigate the presence of thyroid developmental anomalies and associated thyroid dysfunction in first degree relatives of our cohort of children with TD.

Methods

A cross-sectional study was conducted between January 2013 and June 2014 in the Pediatric Endocrinology Clinic of our hospital which is a large tertiary care center located in North India. First degree relatives of 80 children with permanent CH caused by TD (group 1) were included

in the study. The diagnosis of TD in the patients was based on the findings of Technetium-99m pertechnetate thyroid scintiscan and thyroid ultrasonography done routinely at the time of initial evaluation of CH. The diagnosis of hypothyroidism was based on low serum total thyroxine (T4) and elevated serum thyroid stimulating hormone (TSH) levels according to reference ranges.[10] Those having subclinical hypothyroidism (SH), transient hypothyroidism, autoimmune thyroiditis or syndromic diagnosis like Down syndrome (DS) were excluded. First degree relatives of 40 children without known thyroid disorder (group 2) who visited the outpatient department for minor illnesses were recruited as controls. A pre-designed structured proforma was used to record all the clinical and laboratory data. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all parents and assent from children wherever appropriate.

Thyroid ultrasound was performed in the Pediatric Radiology Unit of the hospital by an experienced radiologist (SKS) and with the same ultrasound equipment for all subjects. During sonography, the subjects were examined in supine position with hyperextended neck using ultrasound machine equipped with a 3-12 MHz high frequency linear transducer, 3-8 MHz sector array and 2-5 MHz convex array probes (Philips HD11XE, Philips Healthcare, DA Best, The Netherlands). Images were obtained in transverse and longitudinal planes and anterior cervical area was viewed through suprasternal area for ectopic thyroid tissue and echogenicity of the gland. All measurements were performed with electronic callipers on the frozen B-scan image. If normal thyroid gland was not found in the cervical location, this was defined as agenesis. Ectopia was defined as some thyroid tissue in the midline of the neck and no thyroid gland in the normal location. The anterior cervical area was also explored for presence of the pyramidal lobe representing the persistence of the caudal portion of the thyroglossal duct from the foramen cecum to the normal anatomic position of the thyroid gland and even lower above the manubrium sterni. Agenesis, hemiagenesis, hypoplasia and ectopia were labeled as "developmental" whereas goiter, nodule, colloid cyst and thyroiditis were taken as "non-developmental" thyroid anomalies.

Maximal linear dimensions of each lobe as well as isthmus were measured, and thyroid volume was calculated for the right and left lobes separately using the ellipsoid algorithm: craniocaudal diameter×lateromedial diameter×anteroposterior diameter×0.5. Total thyroid volume was calculated by adding the volumes of the right and left lobes. Isthmus volume was not taken into account for calculating the total volume. To identify hypoplasia, thyroid volumes in mothers of both groups were compared with the thyroid volumes of a reference Indian population of normal adult females.[11] Thyroid volume of less than the 3rd centile of the reference population i.e. 4.58 mL was labelled as hypoplasia.[11]

Total serum T3, T4, TSH and anti-thyroid peroxidase (anti-TPO) antibodies concentrations in both groups were measured by electrochemiluminescence immunoassay on an Elecsys 2010 analyzer using specific kits (Roche Diagnostics, Germany). The concentrations of total T4 below the reference ranges for age with elevated TSH were defined as overt hypothyroidism.[10] Subclinical hypothyroidism was considered with TSH level between 5-10 mU/L and normal total T4 level (4.5-12.5 μg/dL).[10] Total T3 and T4 concentrations above the reference range and decreased TSH concentration were taken as hyperthyroidism.[10] Anti-TPO concentration of >34 IU/mL was considered as elevated.

Statistical analysis

The data were coded and analyzed with SPSS Version 22.0 for Windows. Levene's test was used to assess the equality of variances. Quantitative data were presented as mean±SD and range, and mean values were compared using Student's *t* test. Ratios were compared with the Chi-square test. A *P* value of less than 0.05 was considered statistically significant.

Results

The study population comprised a total of 312 first degree relatives belonging to 80 families in group 1 and 40 families in group 2. The mean age of the patients (40 boys and 40 girls) at the time of diagnosis of TD was 2.65±2.81 years (range: 2 months-11 years). Thyroid scintigraphy revealed agenesis in 78.7% of the patients, ectopic gland in 15%, and hypoplasia in 6.2%. Ultrasound showed agenesis in 87.5% of the patients, ectopic location in 6.2%, and hypoplasia in 6.3%. The mean initial total T4 and TSH concentrations in these children were 2.705±2.384 μg/dL (range: 0.01-8.9) and 293.48±289.81 mIU/L (range: 10.03-1159.0) respectively. The mean duration of follow-up was 3.62±2.75 years (range: 3 months-14 years).

Group 1 included 143 parents (68 males and 75 females) and 60 siblings (23 boys and 37 girls) of 80 patients. Group 2 had 76 parents (37 males and 39 females) and 33 siblings (14 boys and 19 girls) of 40 healthy children. None of the first relatives had any symptoms suggestive of thyroid dysfunction. Only 1 of 203 (0.5%) subjects in group 1 had goiter on examination. Anthropometric parameters and the results of clinical examination were normal in the rest.

The baseline characteristics of the two groups were similar (Table 1). Thyroid gland was normally located in all the subjects. The calculated mean thyroid

Table 1. Baseline characteristics, thyroid volumes and developmental anomalies of the study groups

Parameters	Parents			Siblings		
	Group 1 (*n*=143)	Group 2 (*n*=76)	*P* value	Group 1 (*n*=60)	Group 2 (*n*=33)	*P* value
Age (y) (mean±SD, range)	33.58±6.29 (22-50)	34.09±5.48 (25-49)	0.5	8.48±5.02 (0.5-18)	8.81±5.03 (1-19)	0.7
Gender (Male:Female)	68:75	37:39	0.7	23:37	14:19	0.8
Total T4 (μg/dL) (mean±SD, range)	7.51±1.54 (4.85-13.73)	7.38±1.61 (4.98-10.92)	0.5	8.12±1.89 (5.13-12)	7.39±1.47 (4.91-10.37)	0.06
Serum TSH (mIU/L) (mean±SD, range)	2.82±2.21 (0.16-21.77)	2.04±0.85 (0.84-4.01)	0.004	3.04±3.03 (0.29-22.7)	2.31±0.81 (1.06-3.97)	0.08
Mean Tvol (mm^3) (mean±SD, range)	8.74±3.24 (2.65-17.34)	8.01±4.35 (5.67-18.64)	0.2	2.67±1.94 (0.2-8.81)	2.16±1.58 (0.2-6.98)	0.2
Developmental anomalies	8/75 (mothers)	0	0.03	-	-	-
Non-developmental anomalies	2	0	0.5	1	0	0.4

TSH: thyroid stimulating hormone; T4: thyroxine; Tvol: thyroid volume. "-": negative.

Table 2. Comparison of thyroid volumes according to age groups of the study subjects

Age group (y)	Group 1		Group 2		*P* value
	No.	Thyroid volume (mean±SD), mm^3	No.	Thyroid volume (mean±SD), mm^3	
<5	20	1.17±0.94	10	0.94±0.73	0.48
6-10	20	2.90±1.98	14	2.13±1.69	0.25
11-20	21	3.96±1.65	10	3.85±1.18	0.85
21-30	53	8.18±2.73	24	10.13±2.43	0.004
31-40	70	8.73±3.24	43	9.65±2.95	0.20
41-50	19	10.15±3.66	8	11.11±3.46	0.53
Total	203	6.91±3.97	109	7.57±4.38	0.21

volume was similar among parents and siblings of both groups (Table 1). Eight (10.6%) mothers in group 1 were identified to have thyroid hypoplasia as compared to group 2 (*P*=0.03). Four of these 8 mothers with hypoplasia had SH. Other developmental anomalies like agenesis, hemiagenesis and ectopia were not found in any subject. Non-developmental anomalies were found in 3 subjects in group 1: hypoechoic lesions (3×3 mm) in both lobes of one subject, hypoechoic lesion (2×2 mm) in the right lobe of another subject and colloid nodule (1.3×0.8 cm) in the right lobe of the other subject. Thyroid volumes were significantly lower in subjects of group 1 than those of group 2 in the age group of 21-30 years (Table 2).

Serum T4 levels were similar among parents and siblings in the two groups. However, serum TSH was significantly higher in parents of group 1 than in those of group 2 (Table 1). Sixteen (7.8%) subjects (6 mothers, 5 fathers, and 5 siblings) in group 1 were found to have SH in contrast to none in group 2 (*P*<0.05). The 16 subjects belonged to 14 families (2 families each had two members affected) of children with TD. Four of the six mothers with SH had thyroid hypoplasia. The mean (SD) anti-TPO level in subjects with SH was 5.0 (2.48) IU/mL. Mild hyperthyroidism (T3 2.16 nmol/L, T4 13.76 μg/dL, and TSH 0.16 mIU/L) was noted in an asymptomatic patient (48 years old female) in group 1. Her anti-TPO titre was 22 IU/mL and thyroid volume was 11.63 mm^3. In all, 4 families (with more than one affected family member) were identified to have thyroid developmental anomalies along with thyroid function abnormalities, with a true familial incidence of 5% for symptomatic TD.

Discussion

The familial incidence of TD has been reported to range from 2% to 12%.[2,6-9] The lower incidence of 2% from a 19-year national survey in France was due to exclusion of hypoplasia as a form of TD.[2] But the higher incidence attributed to higher rates of parental consanguinity in some patient populations.[8] In the present study, the familial incidence of TD was 5%, which is similar to that of some previous studies although we could not define hypoplasia in male adults because of lack of reference thyroid volume in the Indian population.[2,11] Researchers[2,6] have concluded that although familial cases represent a minority of cases of CH caused by TD, they appeared in a significantly higher proportion (>15-fold) than expected.

The proportion of subjects with hypoplasia in our study (10.6%) was similar to that reported previously.[6,8] However, the absence of development anomalies other than hypoplasia was in contrast to other studies showing higher rates (7.9%) of ectopic thyroid, hemiagenesis and thyroglossal cyst in first relatives.[6] This difference may be related to ethnic variations, a larger number of families enrolled, additional use of thyroid scintigraphy and differences in rates of parental consanguinity.[6,7] Thyroid hemiagenesis, in particular, is considered to be a rare form of TD which can occur as a familial disorder and can be associated with any form of TD. The high prevalence of hemiagenesis in previous studies attributed to genetic factors resulting from frequent parental consanguinity in some regions.[2,6,7,12] The characterization of TD in our study was, however, based on ultrasonography only and additional scintigraphy was not performed. It is possible that we may have missed some cases of developmental anomalies other than aplasia/hypoplasia. Combined scanning with ultrasound and scintiscan is considered more informative than single scanning.[13]

Similar to the results of a previous study from Iran, the presence of non-developmental thyroid abnormalities, such as goiter, nodule, colloid cyst, etc was not different among the two study groups.[7] Other studies[14,15] have reported different results. In a study on newborn infants born to goitrous and non-goitrous mothers, two infants born to goitrous mothers were found to have CH.[14] In another study,[15] thyroid function in newborns from mothers with non-developmental thyroid abnormalities

was normal and similar to that of controls. Further research is needed to study the rate of autoimmunity and thyroid disorders in relation with the causes of CH as goiter and other non-developmental abnormalities are also related to environmental and autoimmune factors.[16,17]

It is noteworthy that the developmental anomalies in our study population have remained asymptomatic. The detection of SH in 7.8% of the subjects of group 1 indicates the presence of mild TD where the gland may fail to supply adequate thyroxine with increasing age or during the period of increased demand like pregnancy. Systematic screening of thyroid dysfunction should therefore be undertaken in asymptomatic first relatives of children with TD.[6-9]

Familial clustering of CH due to TD suggests the involvement of genetic factors.[2,18] Mutations in several genes that encode thyroid transcription factors or TSH receptor have been characterized in familial TD but genetic heterogeneity suggests the involvement of unidentified novel genes.[3,18] It is likely that the subjects with familial TD in our cohort are carrying the genetic mutations. Our study confirmed the presence of familial TD in the Indian population and investigated the need of systematic screening for thyroid developmental anomalies and thyroid dysfunction in the asymptomatic first degree relatives of children with CH caused by TD.

In conclusion, thyroid developmental anomalies are more prevalent in the first relatives of children with TD than in the control population. Thyroid function abnormalities are present in a significant number of the asymptomatic first relatives of children with TD. Larger population based studies are needed to confirm our findings and to identify families with TD to further study the molecular mechanisms underlying TD.

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