Brief Communication

Agenesis and not ectopia is common in North Indian children with thyroid dysgenesis

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ABSTRACT

Context: Ectopic Thyroid Gland (ETG) is known to be the most common form of thyroid dysgenesis in children with permanent congenital hypothyroidism (CH). Recent reports indicate that agenesis or hypoplasia of thyroid gland may be commoner as compared to ETG in thyroid dysgenesis (TD). There is limited information available on the proportion of different variants of TD in Indian children. **Aim:** To characterize the different TD variants in a cohort of North Indian children with TD. **Settings and Design:** Endocrinology Unit of a large Multispecialty Pediatrics Center located in North India. Retrospective review of clinical records of children with CH due to TD diagnosed between April 2004 and March 2014. **Results:** Diagnoses of TD in 94 children (48 boys and 46 girls) were based on combined scanning with high-resolution ultrasonography, and technetium-99m pertechnetate thyroid scintigraphy. Thyroid agenesis, ectopia and hypoplasia were diagnosed in 74 (78.7%), 14 (14.8%) and 6 (6.4%) patients respectively. The mean initial serum total T4 and thyroid stimulating hormone concentrations at diagnosis were 3.03 ± 2.88 μg/dL (range 0.01–8.9) and 284.52 ± 300.67 mIU/L (range 10.03–1159.0) respectively. Patients with ETG were older at the time of diagnosis as compared to patients with hypoplasia or ectopia. The mean duration of follow-up was 3.7 ± 2.85 years (range 3 months–10 years). **Conclusions**: Thyroid agenesis was the most common form of TD in our children with permanent CH. Hypoplasia and ectopia were uncommon. Female preponderance, noted in many previous reports, was not seen in our patients with TD.

Key words: Agenesis, congenital hypothyroidism, ectopic thyroid gland, thyroid dysgenesis

Introduction

Thyroid dysgenesis (TD) is the most common cause of permanent congenital hypothyroidism (CH), and includes athyreosis, hypoplasia, hemiagenesis and ectopic thyroid gland (ETG).[1]

Worldwide, ETG is the most common form of TD with a prevalence of about 1/100,000–300,000 persons and 1/4000–8000 patients with thyroid disease.[2-5] Some recent studies indicate that the predominant form of TD is agenesis or hypoplasia.[6,7] There is limited information on the proportion of each TD variant in Indian children with CH. A previous study suggested agenesis and/or hypoplasia to be more common as compared to ETG.[8] Another study has only reported the clinical spectrum of ETG.[9] We aimed to determine the spectrum of TD in children diagnosed with permanent CH at our center.

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Materials and Methods

A record review of children with permanent CH, who attended our hospital between April 2004 and March 2014, was performed. 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] Children with subclinical hypothyroidism, transient hypothyroidism, autoimmune thyroiditis or syndromic diagnoses were

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excluded. Serum total T4, TSH and anti-thyroid peroxidase antibodies concentrations were measured by Electrochemiluminescence immunoassay on Elecsys 2010 analyzer using specific kits (Roche Diagnostics, Germany).

The diagnosis of TD was based on findings of the technetium-99m (99mTc) pertechnetate thyroid scintiscan, and thyroid ultrasonograms done routinely at the time of the initial evaluation of CH. Scintigraphy was performed using a gamma camera fitted with low energy high-resolution collimator (Siemens, Germany). Static planar images of head, neck and chest region were acquired in the anterior projection 20 min after intravenous injection of 74-111 MBq of 99mTc pertechnetate. Thyroid agenesis was defined as the absence of tracer uptake in the normal gland location while visualization of a single lobe was regarded as hemiagenesis. Mild to moderate tracer uptake in small, ill-defined focus in the normal gland location was taken as hypoplasia, while any focal uptake in midline from tongue to the suprasternal notch in absence of the normal gland was identified as ETG.

Ultrasonography was performed 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). Images were obtained in transverse, and longitudinal planes; and anterior cervical area was systematically viewed for presence of ectopic thyroid tissue. Agenesis was defined as the absence of gland in the normal location. Absence of gland in the normal location and presence of some thyroid tissue in the midline was labeled as ETG. Hemiagenesis was defined as the absence of one lobe. Linear dimensions of lobes and isthmus were measured, and thyroid volume (Tvol) was calculated for each lobe using the algorithm: Cranio caudal*lateromedial*anteroposterior diameter*0.5. Total Tvol was calculated by adding the volumes of lobes and ignoring the isthmus volume. Hypoplasia was defined as Tvol <3rd percentiles of normative data in a reference population.[11]

Results

Complete information was available in 94 children (48 boys and 46 girls) with TD. Their mean age at diagnosis was 2.45 ± 2.69 years (range 2 months–11 years). Based on the results of combined scanning, majority (74 patients, 78.7%) were diagnosed as agenesis. Hypoplasia was noted in 6 (6.4%) while 14 (14.8%) patients were labeled as ETG. The mean initial serum total T4 and TSH concentrations at diagnosis were 3.03 ± 2.88 μg/dL (range 0.01–8.9) and 284.52 ± 300.67 mIU/L (range 10.03–1159.0) respectively. The mean duration of follow up was 3.7 ± 2.85 years (range 3 months–10 years).

The mean age of patients at diagnosis of agenesis was significantly, lower as compared to patients with hypoplasia or ectopia [Table 1]. The mean total T4 and TSH concentrations as well as a requirement of thyroxine dose were similar in the 3 TD variants.

Discussion

The predominant form of TD noted in our patients was agenesis similar to a recent study.[6] Another study from Turkey found an increased incidence of thyroid hypoplasia but attributed this to noninclusion of thyroid scintigraphy.[7] Indian data obtained during 1990s suggested that agenesis and/or hypoplasia was the predominant form of TD in children belonging to iodine deficient regions, and postulated that iodine deficiency may lead to TD.[8] Iodine deficiency contributing to TD seems unlikely, as our study population belongs to a nonendemic area.[12,13]

The reasons for a different spectrum of TD in our patients are presently unclear. Although mutations associated with TD are detected in only 2% of all cases, the candidate genes probably determine the TD form.[14] The transcription factors PAX8, NKX2-1, FOXE1, NKX2-5 and PAX9 are considered as candidate genes for ETG while TSH receptor (TSHR) gene mutations result in hypoplasia.[1,15] Probably our patients have TSHR mutations more than the other mutations but in the absence of molecular investigations, this is only a speculation. The younger age of our patients might also have decreased the percentage of ETG as this is more commonly diagnosed between 10 and 20 years of age.[2] Since, we had employed both scintigraphy and high-resolution ultrasonography, it is unlikely that the characterization of TD variants in our patients was not exact. Combined scanning is considered more informative than single scanning in CH.[3,16]

Table 1: Comparison of clinical and laboratory parameters in different TD variants

Variables	Agenesis (*n*=74)	Hypoplasia (*n*=6)	Ectopia (*n*=14)	*P* value
Mean age at diagnosis (year)	1.99±2.19	3.8±4.44	4.34±3.35	0.004
Gender (boys:girls)	39:35	4:2	5:9	0.4
Mean T4 (μg/dL)	3.19±2.85	3.2±4.75	2.12±1.94	0.4
Mean TSH (mIU/L)	272.87±274.83	107.8±76.92	421.84±429.91	0.07
Mean thyroxine dose (μg/day)	57.77±17.02	56.25±17.23	56.25±15.30	0.9

TD: Thyroid dysgenesis; T4: Thyroxine; TSH: Thyroid stimulating hormone

Similar to our findings, absence of hemiagenesis has been noted in previous large cohorts of TD.[3,5] Higher prevalence is attributed to genetic factors resulting from frequent parental consanguinity.[4,6,7]

Similar to a previous study, we did not find a higher prevalence of TD in girls.[7] This is in contrast with several reports that suggest female preponderance.[3,8,17-19] The low prevalence of ETG in our cohort might partly explain the observed sex ratio as female preponderance is commoner in ETG than athyreosis.[9,20]

Conclusion

Majority of our patients with TD had agenesis. Hypoplasia and ectopia were uncommon, and hemiagenesis was not noted in any patient. The prevalence of TD was similar in boys and girls. This is the first study from our country to document the morphological spectrum of TD based on combined scanning.

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