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. 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.

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
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.[14,16]

| 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 | 421.8±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

Table 1: Comparison of clinical and laboratory parameters in different TD variants
Similar to our findings, absence of hemiagenesis has been noted in previous large cohorts of TD.\cite{5,6} Higher prevalence is attributed to genetic factors resulting from frequent parental consanguinity.\cite{4,6,7}

Similar to a previous study, we did not find a higher prevalence of TD in girls.\cite{7} This is in contrast with several reports that suggest female preponderance.\cite{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.\cite{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.

**REFERENCES**

1. Brown RS, Demmer LA. The etiology of thyroid dysgenesis-still an enigma after all these years. J Clin Endocrinol Metab 2002;87:4069-71.
2. Noussios G, Anagnostis P, Goulis DG, Lappas D, Natsis K. Ectopic thyroid tissue: Anatomical, clinical, and surgical implications of a rare entity. Eur J Endocrinol 2011;165:375-82.
3. Tamam M, Adalet I, Bakir B, Türkmen C, Darendeliler F, Bas F, et al. Diagnostic spectrum of congenital hypothyroidism in Turkish children. Pediatr Int 2009;51:464-8.
4. Ramos HE, Nesi-França S, Boldarine VT, Pereira RM, Chiamolera MI, Camacho CP, et al. Clinical and molecular analysis of thyroid hypoplasia: A population-based approach in southern Brazil. Thyroid 2009;19:61-8.
5. Belkhit OE, Yousef RM. Permanent and transient congenital hypothyroidism in Fayoum, Egypt: A descriptive retrospective study. PLoS One 2013;8:e68048.
6. Hashemipour M, Ghasemi M, Hovepayan S, Hejyrdari K, Sajadi A, Hadian R, et al. Etiology of congenital hypothyroidism in Isfahan: Does it different? Adv Biomed Res 2014;3:21.
7. Kirmizibekmez H, Güven A, Yıldız M, Cebeci AN, Dursun F. Developmental defects of the thyroid gland: Relationship with advanced maternal age. J Clin Res Pediatr Endocrinol 2012;4:72-5.
8. Shankar SM, Menon PS, Karmarkar MG, Gopinath PG. Dysgenesis of thyroid is the common type of childhood hypothyroidism in environmentally iodine deficient areas of north India. Acta Paediatr 1994;83:1047-51.
9. Gopal RA, Acharya SV, Bandgar T, Menon PS, Marfatia H, Shah NS. Clinical profile of ectopic thyroid in Asian Indians: A single-center experience. Endocr Pract 2009;15:322-5.
10. The Association of Clinical Biochemistry. 2006. UK guidelines for the use of thyroid function tests, from British thyroid association’s website. Available from: http://www.british-thyroid-association.org. [Last accessed on 2014 Aug 14].
11. Chanoine JP, Toppet V, Lagasse R, Spehl M, Delange F. Determination of thyroid volume by ultrasound from the neonatal period to late adolescence. Eur J Pediatr 1991;150:395-9.
12. Kapil U. Successful efforts toward elimination iodine deficiency disorders in India. Indian J Community Med 2010;35:455-68.
13. Das S, Bhansali A, Dutta P, Aggarwal A, Bansal MP, Garg D, et al. Persistence of goitre in the post-iodization phase: Micronutrient deficiency or thyroid autoimmunity? Indian J Med Res 2011;133:103-9.
14. Narumi S, Muroya K, Asakura Y, Adachi M, Hasegawa T. Transcription factor mutations and congenital hypothyroidism: Systematic genetic screening of a population-based cohort of Japanese patients. J Clin Endocrinol Metab 2010;95:1981-5.
15. Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J Med Genet 2005;42:379-89.
16. Perry RJ, Maroo S, Maclennan AC, Jones JH, Donaldson MD. Combined ultrasound and isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning. Arch Dis Child 2006;91:972-6.
17. Éugène D, Djemli A, Van Vliet G. Sexual dimorphism of thyroid function in newborns with congenital hypothyroidism. J Clin Endocrinol Metab 2005;90:2696-700.
18. Waller DK, Anderson JL, Lorey F, Cunningham GC. Risk factors for congenital hypothyroidism: An investigation of infant’s birth weight, ethnicity, and gender in California, 1990-1998. Teratology 2000;62:36-41.
19. Law WY, Bradley DM, Lazarus JH, John R, Gregory JW. Congenital hypothyroidism in Wales (1982-1993): Demographic features, clinical presentation and effects on early neurodevelopment. Clin Endocrinol (Oxf) 1998;48:201-7.
20. Devos H, Rood C, Gagné N, Laframboise R, Van Vliet G. A search for the possible molecular mechanisms of thyroid dysgenesis: Sex ratios and associated malformations. J Clin Endocrinol Metab 1999;84:2502-6.