Original Article

Clinical, diagnostic, and follow-up characteristics of children with ectopic thyroid: An 11-year tertiary referral center experience

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ABSTRACT

Background: Information on the clinical data and follow-up of ectopic thyroid (ET) in pediatric population in India is scanty; hence, this study aims to add more information on this entity. **Objective:** This study was undertaken to analyze the clinical, biochemical characteristics, and scintigraphy findings at diagnosis and follow-up response to thyroxine (T4) replacement in children with ET. **Methods:** This study was conducted at the Paediatric Endocrinology Department of Tertiary Center from January 2005 to March 2016. In children with abnormal thyroid function, scintigraphy was done before T4 replacement to establish the diagnosis of permanent congenital hypothyroidism. Thyroid dose modification, growth monitoring was done on follow-up. In infants and children without an etiological diagnosis, at ≥3 years of age, thyroid function test, scintigraphy was done after stopping treatment for 4 weeks. The initial clinical, biochemical parameters, follow-up data were analyzed. **Results:** Among 54 children with ET, 39 (72.2%) were girls. The mean age of presentation was 3.3 years and the average age at diagnosis on the basis of presentation with isolated short stature was 7.3 years. Developmental delay was the predominant symptom (24.9%) in children between age 1 month and 5 years. Among them, 78.5% had initial thyroid-stimulating hormone (TSH) >60 mIU/ml. During the first follow-up visit, high TSH >10 mIU/ml and >60 mIU/ml with normal levels of T4 were found in 29.6% and 7.4%, respectively, who were treatment compliant. TSH levels regressed gradually in the subsequent visits without any increase in T4 dose. Neck masses and externally visible lingual thyroids regressed with oral T4 without any surgical intervention. **Conclusions:** The assessment of adequacy of T4 replacement at follow-up needs both TSH and T4 levels. The prompt identification, early, and adequate treatment of children with ET can prevent possible surgical intervention.

Key words: Developmental delay, Ectopic thyroid, Thyroid-stimulating hormone

Thyroid dysgenesis is the most common cause of permanent congenital hypothyroidism (CH) and it comprises ectopia, hypoplasia, agenesis, or hemi-agenesis of the thyroid gland [1]. Ectopic thyroid (ET) is an aberrancy of the thyroid embryogenesis during its passage from the floor of the primitive foregut to the final anatomical position in the pre-tracheal position and accounts for 49–61% of the thyroid dysgenesis [2,3]. The prevalence of ET in other populations is 1 in 100,000 to 300,000 [3-5]. The clinical information on the spectrum of manifestations of ET in South Indian children is scanty [1]. Understanding the clinical profile of the various types of ET and the response to treatment helps the optimization of the clinician's approach to the patient. Hence, this study was undertaken to analyze the clinical, biochemical, and scintigraphy characteristics among children presenting with ET and their clinical and biochemical response to treatment.

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METHODS

This retrospective observational study was conducted in a single tertiary hospital. The case records of all infants and children diagnosed with ET and treated between January 2005 and March 2016 in the department of Pediatric Endocrinology at our center were studied. Most of the cases were referred to the specialist center seeking treatment, while a few were infants diagnosed at birth in this hospital. Physical examination of thyroid gland included search in its normal position or in the known ectopic sites-front of the neck or lingual. All infants and children with abnormal thyroid function tests (TFTs) at initial presentation had scintigraphy done before initiation of thyroxine (T4) therapy to establish the etiology and to confirm permanent hypothyroidism.

Gamma camera was used for nuclear scan to obtain static planar images of head and neck regions in anterior projection

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20 min after intravenous injection of 1 mci of 99mTc pertechnetate. Any focal tracer uptake along the midline from the tongue to the suprasternal notch, either isolated or in addition to the normal gland, was identified as ET. In infants and children in whom an etiological diagnosis was not possible/not available before initiation of T4 replacement, a re-evaluation with TFT followed by thyroid scintigraphy was undertaken ≥3 years of age by stopping T4 therapy for 4 weeks [6]. As thyroid ultrasonography does not locate ectopic gland as precisely as scintigraphy, the former was not used in the diagnosis of ET in our study [7].

Counseling of parents included diagnosis, need for lifelong replacement, regular follow-up for growth and development assessment, and T4 dosage modification as needed. Infants had a monthly follow-up, toddlers every 3 months, older children every 6 months till puberty, then on it was yearly until 18 years of age. The details of age at presentation, presenting symptoms, clinical examination, TFT, thyroid scan tracer uptake, and follow-up response to treatment were extracted from the records and analyzed.

Data were collected and entered into Microsoft Excel Sheet. Arithmetic mean was calculated and percentage frequency was also obtained for each set of variables from the data. The analyses of data were done by descriptive statistics, percentages, and proportions. As this was a retrospective study, the requirement of informed consent was waived off. The approval for the retrospective study was obtained from the Institutional Ethics Committee (2020/IEC/006).

RESULTS

There were 54 children with ET, 39 (72.2%) of them were females versus 15 (27.8%) males. The ratio of female-to-male was 2.6:1, indicating that there was a clear female preponderance. The mean age of presentation was 3.3 years (range: 2 days to 12.5 years). 11 (20.3%) were diagnosed in the neonatal period; 6 of the 11 were diagnosed by newborn screening (NBS) program for CH. One child with lingual thyroid had normal cord blood thyroid-stimulating hormone (TSH) – 11 mIU/L (normal <20 mIU/L) but was diagnosed only after 1 year of age on evaluation for developmental delay. There were 7 children (12.9%) who presented and diagnosed later in life after 10 years of age.

Tracer uptake in the lingual region was found in the majority of children, 46 (85.2%). Only 2 (4.3%) of the 46 had visible lingual thyroids (LT) in the posterior third of the tongue. The other ectopic position was the upper part of the neck above the normal anatomical location found in 11.1%. Two children had double ET – one each in the normal and just above the normal anatomical location. Symptoms and complications manifested in children of all groups are listed in Table 1. On subgroup analysis of children presenting with short stature alone, the average age at diagnosis was 7.3 years which was later than any other symptom of presentation. Children who underwent treatment early had normal growth.

Twenty-nine (53.75%) of 54 children had an elevated serum TSH >60 mIU/L when diagnosed. In children with developmental delay, it was found that 11 (78.5%) of 14 had TSH >60 mIU/L on presentation, while the remaining TSH ranged between 10 mIU/L and 60 mIU/L. The range of TSH on diagnosis of all the children in the study ranged from 0.06 mIU/L to 3616 mIU/L. On follow-up, there were some children with normal T4 levels and clinical improvement but with persistently elevated TSH. TSH >10 mIU/L was found in 16 (29.6%) and 4 (7.4%) of children had TSH >60 mIU/L. Compliance was confirmed, T4 replacement was not increased, and they were kept in close follow-up. During the subsequent visits, the TSH levels normalized slowly. The neck masses and visible LT regressed with oral T4 replacement alone, none required surgical intervention. One child developed idiopathic central precocious puberty, which was confirmed by GnRH analog stimulation test and was later treated with GnRH analog. Progression of puberty was normal in other children on follow-up.

Table 1: Predominant manifestations noted at diagnosis – all age groups

Clinical manifestations	Number (%)
Developmental delay	14 (25.9)
Poor growth and short stature	7 (13)
Neck swelling	7 (13)
Prolonged neonatal jaundice	6 (11.1)
Neonatal screening	6 (11.1)
Posterior tongue mass	4 (7.4)
Others (constipation, dry skin, obesity, lethargy, dysmorphism), evaluation of babies born to mothers with thyroid dysfunction (out-born)	10 (18.5)

DISCUSSION

Thyroid disorders are well known to be more common among females of all age groups [8,9]. Male:female sex ratio of CH has been reported in many studies to be 1:2 [10]. The sex ratio for ET in our study was 1:2.6, which is higher than previous reports (1:1.5, 1:1.8) from northern India [10,11]. However, a study from Quebec by Devos *et al*., also found ET to be significantly higher in girls (1:2.8) [12].

Arrest of thyroid tissue migration along the tract of thyroglossal duct from the tongue (junction of two-third and posterior one-third) to the final position in the anterior aspect of the neck leads to majority of the ectopic glands getting lodged in the midline of the neck [13,14]. Lingual region is the most common site of ET in 85.2% of our subjects, the incidence being similar to two earlier studies [15,16]. However, two other studies from central India and Korea have described LT in only 47% [4,11]. Foxe 1 gene plays a pivotal role in the migration of the thyroid gland. The variations in the expression in different population groups of the Foxe1 gene could explain the varied rates in different studies [13]. The other ectopic location of the thyroid tissue in our study was in the upper part of the neck in the sub-hyoid region in 11.1% of the subjects which is lower than the reported incidence of 53% from central India [11]. Double ET glands were seen in 3.7%. Other sites such as in the head and neck region, including the trachea, lateral

cervical regions, axilla, palatine tonsil, and carotid bifurcation have also been reported in the literature [17-19].

The mean age at presentation in our study (3.3 years) is nearly similar to 4.3 years reported from northern India, but data from Nigeria and central India reported the mean age to be 12.5 years and 14.3 years, respectively, the latter two reports being included age groups up to 40 years [1,11,17]. The average age at diagnosis for children with short alone was 7.3 years which was later than any other symptom as parents presumed that growth would eventually occur. As there is no national program in India for diagnosis of CH at present, neonatal detection of ET in the community is not easy [20].

Asymptomatic and undiagnosed ET enlarge during puberty as there is an increased physiological demand for thyroid hormones due to rapid somatic growth. This results in the detection of the mass for the first time in the ectopic sites [4]. Saul *et al*., in his study, have reported that about 7–10% of ET gland are asymptomatic [17,21]. The most common presentation in our study was a developmental delay (24.9%) followed by short stature (12.9%) and prolonged neonatal jaundice (11.1%). One child presented with neck swelling and referred as thyroglossal cyst. On evaluation, he was found to have ET. Various studies have listed cough, pain, dysphagia, dyspnea, and hemorrhage as other symptoms for diagnosis [11,17,22,23].

The variation in the spectrum of presentation and onset of clinical manifestations could be speculated to be due to the varying amount of hormone produced by the residual tissue and the associated iodine organification defect in 30% of ET [24,25]. Even after normal NBS result, regular follow-up is required for at least 6–12 months for detection of late-onset of hypothyroidism, as seen in one of our ET case.

Persistently elevated TSH on follow-up in children with adequate T4 replacement was found in 29.6% children, which is similar to Raza and Hulse *et al*., who reported similar elevation in 28% and 34% of their patients with ET, respectively [26,27]. Raza *et al*., in his study, did not find the etiology of CH (ectopic, agenesis, dyshormonogenesis of the gland) or the initial hormonal levels to have made a difference to the rate of fall of TSH [26]. The pituitary sub-responsiveness to TSH, long-standing thyrotrophic hyperplasia with variation in the maturation of the pituitary threshold for regulation of TSH release by T4 are the possible mechanisms postulated [28,29]. Hence, TSH should not be considered as the sole criterion for assessing the adequacy of thyroid hormone treatment [29].

All children in our study improved well with medical management alone as compared to 86% reported in a study from northern India where 14% required surgical intervention [11]. None of the children in this series required surgical management. Surgical intervention may be required when ET causes obstructive symptoms, bleeding, ulceration, cystic degeneration, or malignant transformation [17].

Our study has some limitations, —. it was a retrospective hospital record-based study. Some of the children were referred later in life and the clinical response to early treatment could not be accurately assessed. Ours being a tertiary referral center, a proportion (27.7%) of our patients have been lost to follow-up.

CONCLUSIONS

ET should be considered in evaluating any child with a midline mass in the neck or a mass in the posterior part of the tongue irrespective of the presence or absence of the various manifestations of hypothyroidism. TSH should not be used as a sole criterion for the adequacy of assessment of T4 replacement as a high percentage of children on regular appropriate doses of T4 replacement have persistent elevated levels with normal blood levels of thyroid hormone. The prompt and adequate treatment of children with ET can prevent the possible surgical intervention of the enlarging gland and restore normal function in all areas of growth and development.

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