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Original Research Article

A CADAVERIC STUDY OF AGENESIS OF ISTHMUS OF THYROID GLAND WITH EMBRYOLOGICAL, GENETIC BASES AND CLINICAL SIGNIFICANCE

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ABSTRACT

Background: The thyroid is a highly vascular endocrine gland with two lateral lobes connected by a narrow, median isthmus**.** Morphological and developmental anomalies of thyroid gland such as hypoplasia, ectopic thyroid, persistence of pyramidal lobe, thyroglossal cyst are common. Agenesis of thyroid gland with or without the involvement of isthmus is a rare congenital anomaly. The incidence has been reported to vary from 5% to 10%. The absence can be explained, as an anomaly of embryological development. It can be associated with other types of dysorganogenesis, such as the absence of a lobe or the presence of ectopic thyroid tissue. Agenesis of isthmus does not cause clinical symptoms by itself, and diagnosis is secondary due to existence of other thyroid pathology.

Materials and Methods: The study was conducted on 30 adult human embalmed cadavers collected from Department of Anatomy, Sri Siddhartha Medical College, Tumkur, Karnataka, India by dissection method. The morphology of the thyroid gland was studied, and presence or absence of isthmus was noted. The length of the lobes and isthmus were noted. The specimens were photographed.

Results: Three out of the 30 cadavers dissected showed agenesis of isthmus of thyroid.The respective lateral lobes were positioned independently on either side of trachea. The average length of the lobe of the thyroid gland was 5 cm on the right side and 4.5 cm on the left side. The average height of the isthmus was 1.75 cm. There were no significant variations in neurovascular relations. No tissue or structures similar to thyroid tissue were noted along its developmental route.

Conclusion: Agenesis of isthmus is an uncommon presentation that is frequently asymptomatic and detected incidentally when imaging for another condition. The absence may be due to an error in development or due to mutations of genes associated with thyroid gland. In clinical practice, when an image of the absence of isthmus is found, it is necessary to perform a differential diagnosis against other pathologies such as autonomous thyroid nodule, thyroiditis, ectopic thyroid tissue etc Knowledge of thyroid isthmus agenesis assumes surgical significance, as this has relevance in the resection of thyroid, tumours and tracheostomy.

KEY WORDS: Thyroid Agenesis, Ectopic Thyroid, Tracheostomy, PAX8 Gene, TITF2 Gene, Thyroiditis.

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INTRODUCTION

The thyroid gland (TG) is one of the ductless glands, located in front and on the sides of the trachea, level with the fifth cervical to first thoracic vertebrae. It is ensheathed by the pretracheal layer of deep cervical fascia. The gland varies from H to U shape, and is formed by two elongated right and left lobes connected by a narrow median isthmus at the level of 2nd to 4th tracheal rings and protected by infrahyoid group of muscles. The normal size of each lobe of the TG has been described to be 5 cm long, its greatest transverse and anteroposterior extent being 3 cm and 2 cm respectively. The isthmus connects the lobes lower parts and measures about 1.25 cm transversely and vertically. It lies opposite the second and third tracheal cartilages though often its site and size vary greatly. TG is highly vascular. It is the largest endocrine gland and plays an important role in the maintenance of the basal metabolic rate of the body [1,2].

TG, being the first endocrine gland to develop in the embryo [3], is well known for its developmental anomalies. Common anomalies include persistence of pyramidal lobe and thyroglossal duct cyst. Rare anomalies are agenesis or hemi –agenesis of TG, agenesis of isthmus alone or aberrant thyroid tissue [4, 5]. Thyroid hemiagenesis was first described by Marshall in 1895 [4]. Hemiagenesis of left lobe, detected at surgery was reported from India by Das in 1962 [6]. The incidence of anomalies like hemiagenesis, agenesis of isthmus, aberrant TGs are difficult to determine, as the absence of one thyroid lobe/ isthmus does not cause clinical symptoms by itself. They are usually diagnosed in cohort of individuals presenting with other thyroid diseases like nodular goitre, thyroiditis or primary carcinoma. There are reports of thyroid developmental anomalies such as single lobe hemiagenesis accompanying Graves' disease [7]. The underlying developmental anomaly may or may not be contributing to the altered function or clinical symptoms.

Incidence of agenesis of thyroid isthmus has been reported to vary from 5% to 10% by Pastor et al., [8]. Marshal reported incidence to vary from 8 to 10% [4]. Ranade et al., in their study on anatomical variations of TG reported a 33% incidence of agenesis of isthmus [9]. Diagnosis of congenital anomalies of TG and their possible developmental bases can be made utilizing various techniques like gross dissection, histology, developmental anatomy, thyroid scans and scintigraphy [10]. When an image of absence of isthmus is observed, a differential diagnosis against autonomous thyroid nodule, thyroiditis, primary carcinoma, neoplastic metastasis and infiltrative diseases such as amyloidosis should be considered [8].

Knowledge of developmental anomalies of the gland, especially rare anomalies like isthmus agenesis, will aid the surgeons in planning safe and effective neck surgeries in resection of thyroid, tumors and tracheostomy.

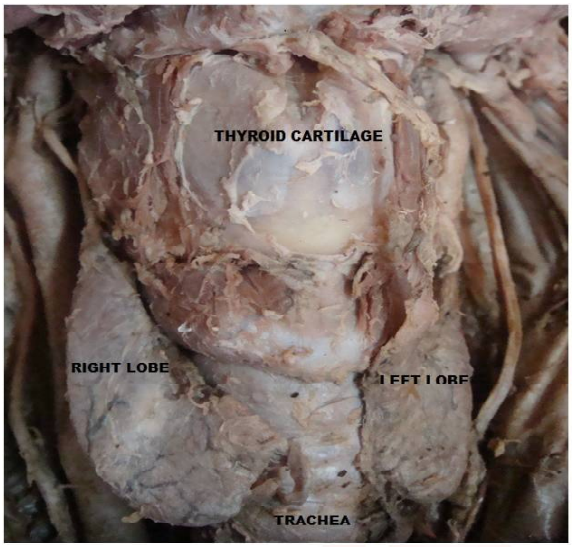
MATERIALS AND METHODS

The study was conducted on 30 apparently normal human adult cadavers of known age and sex in the dissection laboratory, Department of Anatomy, Sri Siddhartha Medical College, Tumkur, Karnataka, India.

Cadavers with no scars in the cervical region, suggesting that the patient have not undergone any surgery were included in the study. The midline of the neck was dissected to expose the thyroid gland.

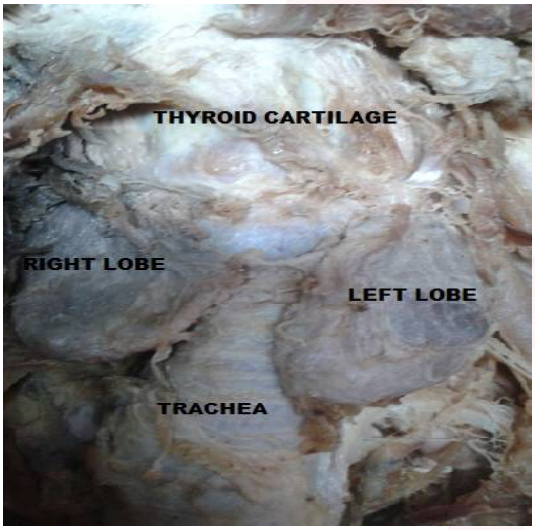
A skin incision was made from chin to sternum in midline. The flap of skin was reflected inferolaterally and platysma was reflected upwards. Deep fascia was incised immediately above the sternum and extended along anterior border of sternocleidomastoid. The fat and fascia was removed from the margins of the sternocleidomastoid. The sternocleidomastoid was retracted and the deep fascia removed from the anterior belly of digastric to expose the infrahyoid muscles. The muscles were separated in the midline to expose the pretracheal fascia and the isthmus of TG. The infrahyoid muscles were reflected upwards to expose the lobes of the thyroid gland. Various parameters like length of the lateral lobes, height of isthmus, presence of pyramidal lobe and levator thyroidae glandulae, arteries supplying, and termination of the veins draining the thyroid gland were recorded.

Fig. 1: Agenesis of isthmus of thyroid gland in a male cadaver.



We can see the two lateral lobes lying independently on either side of the trachea connected by a thin layer of pre tracheal fascia.

Fig. 2: Agenesis of isthmus of thyroid gland in a female cadaver.



RESULTS

In our study, the average length of the right lobe of TG was 5cm and that of the left lobe was 4.5cm. The average height of isthmus was 1.75cm.

In our study, 3 out of 30 cadavers dissected showed no glandular tissue in the region of isthmus of TG [Fig. 1, Fig.2]. Grossly only pre-tracheal fascia connecting the right and left lobes of the TG was observed. The respective lateral lobes were positioned independently on either side of trachea. The average length of the right and left lobes in these 3 cadavers were 4.75cm and 4.5cm respectively. There were no anastomoses between the arteries of right and left sides. There were no significant variations in neurovascular relations. No tissue or structures similar to thyroid tissue were noted along its developmental route.

The incidence of agenesis of isthmus of TG was noted to be 10%.

DISCUSSION

Agenesis of the thyroid isthmus is the complete and congenital absence of the thyroid isthmus as is defined by Pastor et al [8]. In their study, they had reported agenesis of isthmus of thyroid gland with enlarged lobes in a Caucasian cadaver. Marshall documented the variations in the gross structure of the thyroid gland in 60 children, varying in age from a few weeks to 10 years and the absence of the isthmus was reported to be 10% in this group [4]. Ranade et al reported absence of isthmus in 35 out of 105 cases (33%), of which 8 were female cadavers [9]. According to Gruber, the incidence of agenesis of isthmus is about 5% [5]. According to the study by Braun et al, the isthmus was missing in 4 cases of the 58 cadavers they studied [11] (Table 1).

Table 1: Comparison of incidence agenesis of isthmus of thyroid gland in various studies.

Author	Incidence of agenesis of isthmus of thyroid gland
Marshall CF 1895 [4]	10%
Gruber 1978 [5]	5%
Pastor et al 2006 [8]	5-10%
Ranade et al 2008 [9]	33%
Braun et al 2007 [11]	6.80%
Joshi SD et al 2010 [10]	16.66%
Daksha Dixit et al 2009 [13]	14.60%
Harjeet et al 2004 [12]	7.90%
Won & Chung 2002 [14]	3%
Alan [28]	3%
Anson [28]	7%
Present study	10%

Harjeet et al., reported the incidence of agenesis of isthmus of thyroid gland to be 7.9% in Northwest Indians [12]. Daksha Dixit et al reported the incidence to be 14.6% with a male

to female ratio of 5:1 [13]. Won and Chung have reported that in 3% of the cases studied, the isthmus was absent and the lateral lobes of the thyroid were separated [14]. In the present study incidence of agenesis of isthmus was 10% (Graph 1). In our study, the average length of the right lobe of TG was 5cm and that of the left lobe was 4.5cm. The average height of isthmus was 1.75cm (Table 2).

Graph 1: Comparison of incidence of agenesis of isthmus of thyroid gland in various studies.

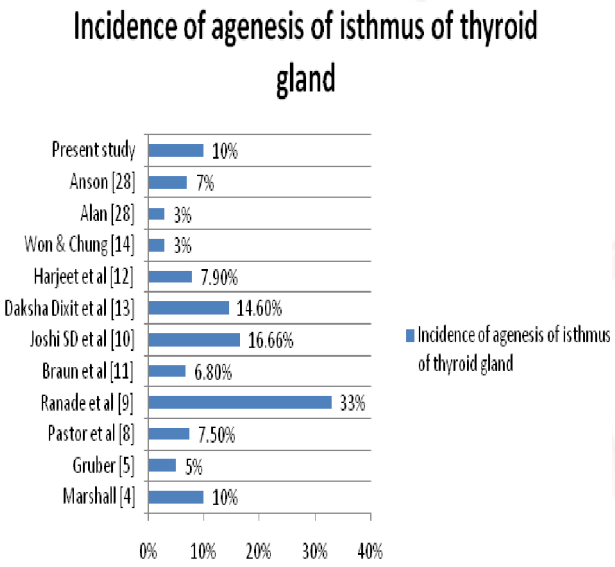


Table 2: Comparison of morphometric features of thyroid gland in various studies.

Author	Average length of right lobe in cm	Average length of left lobe in cm	Average height of isthmus in cm
Daksha Dixit et al 2009 [13]	5.29	4.95	2.25
Joshi SD et al 2010 [10]	4.32	4.22	1.6
Ranade AV et al 2008 [9]	5.1	4.7	1.8
Present study	5	4.5	1.75

The prevalence of agenesis of isthmus is ranging from 3% to 10 % in different studies, the true figure is uncertain, possibly because of the no-symptom population. This is diagnosed only when there is a symptom, such as nodular goiter, thyroiditis or primary carcinoma [15]. It can be diagnosed via scintigraphy, ultrasonography, Computerised tomomography and Magnetic resonance imaging [16]. Most common thyroid dysorganogenesis in cadavers is absence of isthmus followed by hemiagenesis of one of the thyroid lobe [17]. Studies carried out in symptomatic or in normal population had shown that the most common anomaly is absence of left lobe (80%) followed by absence of isthmus [18]. The etiology of agenesis of TG or isthmus is not clearly known and most of the isthmus agenesis is sporadic, familial or genetic predisposition [19]. Genetically the developmental agenesis may be associated with alterations in chromosome 22 [20], or in one of the three thyroid developmental genes (TITF1, PAX8, FOXE1/TITF2), especially TITF2, because these genes are more essential for the normal development of palate and TG [21, 22]. Phylogenetically the isthmus may be missing in amphibians, birds and among mammals – Monotremes, certain Marsupials, Cetaceans, Carnivores and Rodents. In Rhesus monkey, the thyroid glands are normal in position but there were no isthmus [8]. The morphological difference in the evolutionary origin does not result in any changes in thyroid function.

The agenesis of isthmus can be explained as an anomaly of embryological development. The adult TG has two types of endocrine cells, follicular and parafollicular cells or 'C' cells, which are derived from two different embryological cell families. The follicular cells come from endodermic cells of the primitive pharynx and the parafollicular cells come from the neural crest [23]. It has also been noted that the C cells are derived from caudo- pharyngeal endoderm complex of 4th and 5th pharyngeal pouches [24].

Embryologically the TG develops as a median thickening of the endoderm on the floor of pharynx between the first and second pharyngeal pouches a point later indicated by the foramen caecum. Subsequently, the area invaginates in front of the pharyngeal gut to form a bilobed diverticulum. This thyroid diverticulum grows in allometric proliferation, becoming a solid cellular cord called thyroglossal duct. The duct grows caudally and bifurcates to give rise to the thyroid lobes and the isthmus. As the caudal migration is taking place, the cephalic end of the duct degenerates [25]. Rarely, a high separation of the thyroglossal duct can engender two independent thyroid lobes and pyramidal lobes with the absence of isthmus [26]. Further developments, the TG descends in front of the hyoid bone and the laryngeal cartilages. It reaches its final position in front

of the trachea in the 7th week. By then it has acquired a small median isthmus and two lateral lobes. Small detached masses of thyroid tissue may occur above the lobes or isthmus as accessory thyroid glands. Vestiges of thyroglossal duct may persist between the isthmus and the foramen caecum of the tongue, sometimes as accessory nodules or cysts of thyroid tissue.

Clinically, the diagnosis of agenesis of the isthmus can be done with scintigraphy, which can also be performed with an overload of TSH or during a surgical procedure. In asymptomatic patients with nodular goitres fine-needle aspiration biopsies and eventually immunohistochemistry tests are useful to support the medical decision, but when agenesis is present the importance of pre-operative differentiation between benign and malignant lesions is critical, considering the surgical procedure , possibility of impairment of the thyroid function and to facilitate preservation if possible [27]. When an image of the absence of isthmus is observed, a differential diagnosis against autonomous thyroid nodule, thyroiditis, primary carcinoma, neoplastic metastasis and infiltrative diseases such as amyloidosis should be considered.

CONCLUSION

Thyroid isthmus agenesis is an uncommon presentation that is frequently asymptomatic and detected incidentally when imaging for another condition. The incidence varies from 5% to 10 %. In our study, the incidence was 10%. Etiology is uncertain, although various genetic and embryological factors have been associated with it. In clinical practice when such a condition is diagnosed, it is necessary to perform a differential diagnosis against other thyroid pathologies such as autonomous thyroid nodule, metastasis etc. The surgeon planning thyroidectomy must look for ectopic thyroid nodules around normally located thyroid gland when he encounters agenesis of isthmus preoperatively or postoperatively. Variations like agenesis of isthmus should be kept in mind during transthyroid tracheotomy procedures. Recognition of this rare congenital anomaly is important to avoid unnecessary contralateral neck exploration with its potential morbidity and to ensure that all patients receive careful follow-up and appropriate thyroid hormone therapy when necessary.

ABBREVIATIONS

TG - Thyroid gland

Conflicts of Interests: None

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