



# Thyroid disease in children and adolescents

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## ULTRASONOGRAPHY

### PERSPECTIVE

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### Introduction

Thyroid imaging in pediatric patients is indicated for the evaluation of congenital hypothyroidism (CH) during newborn screening or for a palpable thyroid mass. The primary imaging modalities for newborn screening are ultrasonography (US) and radionuclide scintigraphy. US is useful as a first-line test for the diagnosis of thyroid abnormalities and lymphadenopathy in pediatric patients. In addition, US can be used to guide the aspiration of detected nodules and to support the evaluation of the lymph nodes [1–3].

### Embryology

The thyroid gland develops from the median and paired lateral anlagen during the first trimester of pregnancy. It consists of two distinct cell types: thyroid follicular cells and parafollicular cells (C cells). Thyroid follicular cells originate as the median thyroid anlage, an endodermal thickening in the floor of the primordial pharynx, between the first and second pharyngeal arches during the fourth to fifth gestational week. The thickening rapidly forms a small outpouch, referred to as the thyroid primordium. The thyroid primordium then elongates into a bilobed diverticulum and descends caudally. The thyroglossal duct, which disappears by the seventh week of gestation, is a connection between the tongue and the caudal migration of the thyroid primordium. The thyroid primordium first courses anteriorly to the primordial hyoid bone and laryngeal cartilage, and then loops inferiorly and posteriorly to the hyoid bone before continuing its descent into the infrahyoid portion of the neck, anterior to the thyrohyoid membrane, thyroid cartilage, and trachea. By the seventh week, the gland attains its normal final position anterior to the second and third tracheal rings. The thyroglossal duct has usually degenerated and disappeared by this time. Lateral anlagen arise from ultimobranchial bodies that are derived from the fourth and fifth pharyngeal pouches and give rise to parafollicular C cells that are thought to derive from the neural crest. These parafollicular cells secrete calcitonin. By the 10th week *in utero*, the right and left lateral anlagen fuse with the medial anlage, thus completing the development of the thyroid gland [4].

### Congenital Disorders

CH is a relatively common endocrine disorder, with a prevalence in Korea of one in every 3,981 live births [2]. Following the introduction of newborn screening and early treatment, children with CH who have severe growth retardation and mental handicaps are no longer seen in clinical practice. It is important to determine the etiology of CH because considerable differences exist in the inheritance and prognosis of the condition [1,2]. CH is classified according to the site, whether any associated conditions are present, and the duration of disease. When the gland itself

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is affected, the condition is described as primary, whereas when the defect lies in the hypothalamic-pituitary axis, it is described as central. Most cases of CH are due to a developmental defect known as dysgenesis (aplasia, ectopy, or hypoplasia) or defective thyroxine synthesis within a structurally normal thyroid gland-dyshormonogenesis-which is caused by various autosomal recessive mutations. Thyroid-stimulating hormone (TSH) and its receptors play a role in maturation and differentiation in the late stage of thyroid development [1,2,5]. Most cases of CH are permanent and arise from dysgenesis [2]. There appears to be wide molecular heterogeneity involving several causative genes. Among them, the TSH receptor (*TSHR*) gene and thyroid peroxidase (*TPO*) genes account for the majority of mutation-positive cases of dysgenesis and dyshormonogenesis, respectively [5]. Patients with *TSHR* mutations show decreased technetium ( $Tc^{99m}$  pertechnetate) uptake, and patients with *TPO* mutations show increased  $Tc^{99m}$  uptake on scintigraphy [5]. Dyshormonogenesis causes goitrous CH. Syndromic cases are associated with a variety of syndromes. Pendren syndrome, for example, involves deafness and goiter. Diagnosis of the transient form is important to avoid unnecessary lifelong therapy [2]. The prevalence of transient CH has been reported to be around 9.8% in Korea [6]. It is caused by maternal antibodies, perinatal illness, or congenital abnormalities. Rarely, a central form of the disease, such as panhypopituitarism, causes CH. Central CH is almost always associated with other anterior pituitary hormone deficiencies.

Thyroid aplasia is defined as the failure to detect thyroid tissue on US and scintigraphy. However, the total absence of the thyroid gland is rare. If the thyroid gland is not visible in the normal position, an attempt is made to locate the ectopic thyroid by examining the thyroid migration pathway. In such cases, US reveals a hyperechoic structure, reflecting remnants of the ultimobranchial body. A  $Tc^{99m}$  scan can confirm the absence of detectable thyroid activity using only visible background soft tissue and the salivary gland. Ectopic thyroid tissue can be found anywhere along the migration course of the thyroid primordium. A complete failure of descent of the thyroid results in a lingual thyroid at the base of the tongue, the most common type of functioning ectopic thyroid tissue. The appearance of the lingual thyroid on US scans is diverse, although the tissue is generally located close to the hyoid bone. Some ectopic thyroids are oval, with an irregular surface, whereas others resemble a normal thyroid. An ectopic gland typically appears as a round or oval area of uptake in the midline of the upper neck on scintigraphy. The ectopic gland may also occupy a sublingual or prelaryngeal location. Scintigraphy is more sensitive than US for detecting an ectopic thyroid. Overdescent may result in an ectopic thyroid in the lower neck or mediastinum. Mediastinal or lateral cervical ectopic glands are, however, rare.

In patients with thyroid hypoplasia, the thyroid gland appears normal or slightly smaller in size on US. However, scintigraphy reveals decreased isotope uptake.

Transient CH is diagnosed by the presence of normal thyroid function, a thyrotropin-releasing hormone study, and scintigraphy performed during a trial off therapy. Scintigraphy cannot detect thyroid tissue in neonates with a *TSHR* defect, an iodine transport defect, or maternal transfer of thyrotropin receptor-blocking antibodies, while in such cases US reveals a normal gland.

Thyroid hemiapsia is generally discovered incidentally, and thyroid function may be decreased during puberty when the need for thyroid hormone is high.

Dyshormonogenesis involves an inborn error in thyroxine synthesis. The most common defect is *TPO* deficiency, which results in a failure to oxidize iodide to iodine. Iodide becomes trapped in the gland and cannot be organified. In this case, US shows an enlarged gland. Scintigraphy also shows increased uptake. The most common pitfall in isotope scanning is a lack of uptake despite the presence of thyroid tissue, leading to the spurious diagnosis of aplasia. This condition may occur for several reasons: a scan delayed beyond 4–5 days of  $T_4$  treatment; iodine exposure; transient hypothyroidism caused by blocking *TSHR* antibodies; and, rarely, defects affecting iodide uptake. Concurrent US is helpful in avoiding this misdiagnosis.

The anatomical course of the embryonic thyroid primordium provides a road map of potential locations for thyroglossal duct cysts (TGDCs) and ectopic thyroid tissue, since these masses typically manifest in the tongue base, adjacent to the hyoid bone, in the infrahyoid neck, or, rarely, in the lateral part of the neck. Aberrant caudal descent of the thyroid gland results in a spectrum of anomalies. Incomplete degeneration of the thyroglossal duct may result in a persistent fistulous tract, or in a TGDC, which accounts for approximately 70% of congenital abnormalities in the neck along the path of migration from the foramen cecum at the tongue base to the anterior lower neck. TGDCs form an anterior midline neck mass when they occur at or above the hyoid bone, and tend to be paramedian in location, particularly when located below the hyoid bone; 65% of TGDCs are infrahyoid, approximately 20% are suprahyoid (at the tongue base, floor of the mouth), and 15% are at the hyoid level. On US, a classic TGDC exhibits a cystic lesion with a well-defined margin and thin walls. A ruptured cyst may result in a thyroglossal duct sinus that opens through the skin. TGDC can be associated with malignancy. Papillary thyroid cancer (PTC) is the most common type of malignancy. If the cyst has calcifications, a soft tissue component, or invasion of the surrounding tissue without a history of infection, an associated malignancy should be suspected [2,3,5–7]. Although TGDCs can often be diagnosed clinically,

preoperative imaging can determine the anatomical extent of the cyst, detect ectopic thyroid tissue, and evaluate the potential for malignancy within the cyst.

## Diffuse Thyroid Disease

Diffuse thyroid disease (DTD) encompasses several relatively common thyroid disorders. Diffusely enlarged thyroid glands with a heterogeneous echotexture, diffuse hypoechogenicity, and inhomogeneity or an irregular echo pattern have been described as common US findings [8,9]. Furthermore, the presence of hypoechoic micronodules with a surrounding echogenic rim is considered to have a relatively high positive predictive value for Hashimoto thyroiditis (HT) [10]. There are no differences in US findings in children compared with adults in general, although diffuse atrophy is uncommon in pediatric patients. A wide spectrum of diffuse diseases may affect the thyroid gland. The most common cause of DTD is autoimmune thyroid disease. HT and Graves disease are the most common autoimmune diseases. US is not generally required to diagnose DTD. However, US can detect these patients when typical US findings are present. US can also be used to exclude a focal thyroid nodule, assess the size of the gland, and detect diffuse infiltrating tumors.

Acute suppurative thyroiditis is rare and results from microbial infection. Patients present with a palpable mass with erythema and tenderness. US shows an enlarged and ill-defined hypoechoic lesion in the left lobe of the thyroid gland, as well as surrounding inflammation. An esophagogram shows a pyriform sinus fistula, reflecting the third pharyngeal pouch remnant.

Hyperthyroidism is rare in children and is most commonly caused by Graves disease. It affects 1 in 5,000 children. The peak incidence occurs from 11 to 15 years of age, with a female predominance [8]. A positive family history is common. It is characterized by hyperplasia and hyperfunction of the thyroid gland. Lymphocytes and plasma cells infiltrate the thyroid gland and retro-orbital tissue. The patient presents with an enlarged thyroid gland, exophthalmos, and thyrotoxicosis. US shows a markedly enlarged and inhomogeneous decrease in echogenicity. Color Doppler imaging reveals a hypervascular pattern, referred to as a "thyroid inferno." During remission, the gland shows normal echogenicity, and during relapse, hypoechogenicity and high-flow vessels are seen. On scintigraphy, the gland shows a markedly increased uptake. In patients with HT, in addition to antibodies and a thyrotropin binding inhibiting immunoglobulins test, scintigraphy is used for differential diagnosis. HT is the most common DTD and is characterized by diffuse lymphocytic infiltration on histopathology. Patients present with painless enlargement of the thyroid gland, resulting from diffuse

lymphocytic infiltration, and growth retardation. The condition may be associated with Turner syndrome, Noonan syndrome, Down syndrome, phenytoin therapy, juvenile diabetes, or treated Hodgkin disease. The diagnosis is made by detecting antithyroid antibodies. It affects 1.3% of children and has a female predominance. US shows an enlarged gland with a diffusely heterogeneous coarse echotexture. There may be discrete hypoechoic micronodules or coarse septation. In the chronic stage, the gland shows atrophy. HT can be associated with benign and malignant nodules [8–12].

According to the American Thyroid Association (ATA) management guidelines for children, US should be performed in any patient with a suspicious thyroid examination, such as a suspected nodule or significant gland asymmetry, particularly palpable cervical lymphadenopathy [13].

## Thyroid Nodules

Thyroid nodules are less common among children than in adults, but are more likely to be malignant in children referred for the evaluation of nodular thyroid disease (22%–26% in children versus approximately 5% in adults). Estimates from US and postmortem examinations suggest that 1%–1.5% of children, and up to 13% of older adolescents or young adults, have thyroid nodules [13]. With each 1-year increase in age, the incidence of thyroid abnormalities increases by 9% in children [14].

US scans of thyroid nodules should be carefully evaluated for nodule size, internal texture, shape, echogenicity, margin, the presence of calcification, and invasion of adjacent structures. The Korean Society of Thyroid Radiology revised the imaging reporting system from the previous 3-tier system to the Korean Thyroid Imaging Reporting and Data System (K-TIRADS), based on the solidity and echogenicity of the thyroid nodule [15]. A solid hypoechoic nodule with any suspicious US features is now categorized as K-TIRADS 5, corresponding to high suspicion. A non-parallel shape, ill-defined, spiculated margin, and microcalcifications are considered suspicious US features. Solid hypoechoic nodules have been found to show a high malignancy rate of about 79%, and partially cystic or iso/hyperechoic nodules have been found to be associated with an intermediate risk (25%). A partially cystic or iso/hyperechoic nodule without any suspicious US features is categorized as K-TIRADS 3, corresponding to low suspicion. A solid hypoechoic nodule without any suspicious US features, or a partially cystic, iso/hyperechoic nodule with any suspicious US feature, is categorized as K-TIRADS 4, corresponding to intermediate suspicion. The presence of intranodular vascularity might increase the risk of malignancy, but no consistent results have been reported regarding the potential association of intranodular vascularity patterns with

the risk of malignancy.

The majority of incidentally detected thyroid lesions in children are cysts, other benign nodules such as nodular hyperplasia, and intrathyroidal thymus [14]. Intrathyroid thymus has been reported in 17.3% of incidentally detected thyroid nodules. US shows similar results to a normal thymus and linear echogenic lines and dots. These lesions are more common in males than females, in contrast to the higher incidence of incidental thyroid lesions in adult females. Thyroid nodules are uncommon in children. However, nodules in children carry a greater risk of malignancy than those in adults (22%–26% vs. 5%–10% in most series).

PTC accounts for 90% or more of all childhood thyroid malignancies. Follicular thyroid cancer is uncommon, while medullary thyroid cancer, poorly differentiated tumors, and anaplastic thyroid carcinomas are rare in young patients. Children with PTC are more likely than adults to have regional lymph node involvement, extrathyroidal extension, and pulmonary metastasis. Despite extensive disease at clinical presentation, children are much less likely to die from the disease ( $\leq 2\%$  of long-term cases lead to specific mortality) than adults [13]. Thyroid cancer is the 11th most frequently diagnosed cancer in Korean boys under the age of 14 years and the fifth most common cancer in girls [6]. In the United States, among 15- to 19-year-old adolescents, thyroid cancer is the eighth most frequently diagnosed cancer and the second most common cancer among girls. Thyroid cancer presents with a high-suspicion nodule or a diffuse infiltrating tumor, and there are no differences in the US features between children and adults. Compared with adult PTC, childhood PTC is characterized by a higher prevalence of gene rearrangement and a lower frequency of point mutations in the proto-oncogenes. The *BRAF* mutation is rare in children. This may be important because point mutations of *RAS* and *BRAF* lead to genomic instability and dedifferentiation, as manifested by decreased expression of the sodium-iodide symporter. In contrast, *RET/PTC* rearrangements are more common in PTC in children and do not lead to genomic instability. These molecular differences might be one of the reasons for the better response to radioactive iodine treatment in children and could partially explain their low mortality and rare progression to less differentiated tumors [13].

According to the ATA management guidelines for adults, fine needle aspiration (FNA) is not warranted for the evaluation of nodules less than 1 cm in size unless the patient is considered high-risk. Because the thyroid volume changes with age, the size of the nodule alone does not predict malignant histology. Therefore, US characteristics and the clinical context should be used preferentially to identify nodules that warrant FNA. The ATA adult guidelines suggest that repeated FNA is an option for adults

with indeterminate cytopathology. However, due to the apparent increased probability of malignancy among these indeterminate categories in children, definitive surgery (lobectomy and isthmusectomy) is recommended for indeterminate FNA. In adults, the risk of malignancy in indeterminate nodules ranges from 5% to 15% in the atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) category, to 15%–30% in nodules that are a follicular neoplasm or suggestive of a neoplasm. The limited data available suggest these indeterminate FNA categories account for up to 35% of pediatric FNA procedures and that, in children, 28% of AUS/FLUS lesions and 58% of lesions that are suggestive of follicular or Hürthle cell neoplasms are malignant. For hyperfunctioning nodules, surgical resection, most commonly lobectomy, is recommended. The mutagenic effect of low-activity radioiodine on normal thyroid tissue is an important factor, and up to one-third of patients may harbor an incidentally discovered differentiated thyroid cancer associated with an autonomous nodule. The diffuse infiltrative form of PTC may occur in children and should be considered in a clinically suspicious gland. For the majority of patients with PTC, total thyroidectomy is recommended as an initial surgical approach because of the increased incidence of bilaterality and multifocality (30% and 65%, respectively). In long-term analysis, bilateral lobar resection has been shown to decrease the risk of persistent/recurrent disease compared with lobectomy. Central neck dissection is recommended for children with gross extrathyroidal invasion and/or locoregional metastasis on preoperative staging or intraoperative findings. Treatment is individualized based on staging and continuous risk stratification.

## Conclusion

In summary, dual imaging with US and scintigraphy increases the diagnostic yield for CH. Thyroid malignancies present as a nodule suspicious for malignancy or as a diffusely-infiltrating carcinoma that can mimic thyroiditis. Additional genetic studies have a limited role in children. Follicular carcinoma is diagnosed by capsular or vascular invasion on pathology. In light of the apparent increased probability of malignancy among indeterminate categories and hyperfunctioning nodules in children, definitive surgery is recommended for cases that show indeterminate cytology on FNA. US is the most sensitive diagnostic modality for evaluating thyroid nodules, and for the diagnosis of thyroid cancer. Moreover, US enables FNA and can be used in lymph node evaluation.

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**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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