Approach to thyroid nodules in children and adolescents

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Thyroid nodule prevalence is about 1.8% in healthy children; however, malignancy frequency is higher than in adults. Approximately 26.4% of thyroid nodules generate thyroid cancer in childhood. Coexisting thyroid disease, history of irradiation of the neck, post-pubertal age, female sex, and thyroid malignancy in the family are risk factors for developing nodules. After evaluation of the medical history and detailed physical examination, the second step is assessment of thyroid function and measurement of calcitonin level. Thyroid stimulating hormone (TSH) value in the upper range seems to be correlated with cancer. Calcitonin levels must be evaluated, especially if medullary cancer is suspected. Ultrasonography (USG) is the first-line imaging tool in the diagnosis of thyroid nodules. It gives information about the nodule size, echogenicity and location. Hypoechogenicity, microcalcifications, undefined margins, high internodular vascular flow, and subcapsular localization are clues of malignant lesions. Scintigraphy is only recommended in a solid nodule with the presence of suppressed TSH. Fine-needle aspiration biopsy (FNAB) has 90% accuracy and is very useful in the selection of patients for surgery. It must be applied to all nodules ≥1 cm and nodules ≤1 cm suspicious for malignancy. The other diagnostic tools are elastography, immunocytochemical markers and genetic evaluation. In the management of thyroid nodules, surgery is advised, especially if there is difficulty in distinguishing benign lesions from carcinoma.

Key words: thyroid nodule, children, adolescents.

Although thyroid nodules are less frequent in children than in adults, they have importance because of the high rate of malignancy. The probability of malignancy in thyroid nodules is reported to be 5% in adults and 25% in children[1-3]. The possibility of malignancy in one of every four children diagnosed with a thyroid nodule increases the importance of the issue and requires a rigorous and accurate approach.

Epidemiological studies report the prevalence of a palpable thyroid nodule in children as 1.8%, with a range of 0.2-5.1% in ultrasonography (USG)-guided studies[4]. These nodules can be benign or malignant. The history of the patient should be interpreted together with the results of the clinical evaluation, laboratory tests and imaging methods. Cysts, adenomas, multinodular goiter, and pseudonodules developing on a background of lymphocytic thyroiditis are among the benign thyroid nodules. Malignant thyroid nodules consist of papillary, follicular, medullary, and anaplastic carcinomas, primary thyroid lymphomas, and metastatic thyroid cancers[1]. Thyroglossal duct cysts, ectopic thymus tissue, inflammatory changes, unilateral thyroid agenesis, thyroid abscess, and teratomas should be taken into account in the differential diagnosis of thyroid nodules[2]. Accurate interpretation of imaging techniques, and ultrasound in particular, is therefore very important. The benign/malignant differentiation of thyroid nodules can be verified by pathology results while the other diagnostic methods only present probabilities. The malignancy potential of thyroid nodules is high in children, with rates of 9.7-50% reported in various studies[5]. The risk factors play a role in this difference. Male sex, postpubertal age, positive family history, radiotherapy history, large nodule size, hypoechogenicity, contour irregularity, and presence of microcalcifications increase the likelihood of malignancy. Thyroid

cancer is the third most common solid tumor in children, and its annual incidence has been reported as 1.75 per 100,000[6]. Most of the thyroid malignancies in the pediatric period are well differentiated (80-95% papillary, 5-15% follicular cancer)[2,7].

In this review, we aimed to discuss the medical history, physical examination and laboratory and imaging methods with the holistic diagnosis/treatment approaches for pediatric thyroid nodules.

Diagnostic Approach to Thyroid Nodules in Childhood

The most important point in the diagnostic approach to thyroid nodules in children and adolescents is to look for clues indicating malignancy in the findings obtained through the patient's history, physical examination, laboratory tests, and imaging techniques. Therefore, a checklist should be used to query and evaluate all possibilities without skipping any detail. A complete and accurate evaluation will ensure correct management and reduce the likelihood of an error. We discuss below the approach, starting with the patient's medical history and using clinical, laboratory and imaging methods.

Medical History

Other concomitant thyroid diseases (autoimmune thyroid disease, thyroid dysgenesis, dyshormonogenesis), the environment (iodine deficiency region), previous cancer, neck radiation therapy, and family history of thyroid cancer should be questioned in the history[7].

Corrias et al.[8] followed-up 365 pediatric patients with autoimmune thyroid disease (age 3.6-17 years) for an average of 4.7 years, and found a thyroid nodule in 115 (31.5%) patients, with a malignancy rate of 3% (all papillary carcinoma). Autoantibody positivity was found in 46 (41%) of 111 children with a thyroid nodule in a study in our country[3], and two were diagnosed with malignancy. There is a possibility of malignancy during the long-term follow-up of Graves' disease with anti-thyroid drugs in the presence of an enlarged thyroid gland. A nodule/malignancy (usually follicular carcinoma) has been reported in cases of congenital hypothyroidism that developed on a background of dyshormonogenesis, especially when prolonged thyroid stimulating hormone (TSH) elevation is present and proper treatment is not given[5,9]. Baş et al.[3] reported dyshormonogenesis in 10 of 111 children with a thyroid nodule. It should be noted that iodine deficiency can also play a role in the development of thyroid cancer. The follicular thyroid cancer prevalence is high in areas with iodine deficiency[2].

History of radiotherapy to the neck and previous cancers are also risk factors for the development of malignancy. The high division rate of thyrocytes during childhood increases the susceptibility to radiation. High-dose radiation (>30 Gy) seems less risky than low-dose radiation as it leads to cell death[7]. The risk of developing thyroid nodule was found to be increased 27 times compared to the normal population in 1791 Hodgkin lymphoma patients (1414 had a history of radiotherapy to the neck) whose age at diagnosis ranged from 2-20 years, with a follow-up of at least five years. A thyroid nodule was observed 14 (0-27) years after the primary disease was diagnosed. Risk factors for the development of thyroid nodules included a duration of >10 years after the diagnosis, female gender and administration of ≥2500 cGy radiotherapy. Malignancy was reported in 20 (11.5%) of 146 nodules in the same study. The risk of thyroid cancer increases 6-7 years after the primary cancer is diagnosed, and the radiation-related thyroid cancer risk remains high for 20 years[7].

When evaluated in terms of family history, 28.1% of 32 patients with a thyroid nodule (mean age: 10.9 years) were reported to have a history of Graves' disease in the family[10]. Roy et al.[11] reported a positive history of thyroid cancer in the family in 26.4% of the cases with malignancy in a retrospective analysis of 207 children who underwent total thyroidectomy, and such a positive history increased the risk of malignancy 1.4 times. A family history of thyroid cancer was present in 3.6% of children with thyroid nodules (2 of these children had papillary carcinoma) in a study from our country[3].

The relationship of certain genetic syndromes and hereditary diseases with thyroid nodules/cancer should be known and queried in the history (Table I).

Physical Examination

The nodule boundaries, fixation to surrounding tissue, sensitivity, and regional lymph nodes should be evaluated in detail on the physical examination. The probability of malignancy is higher in nodules that are painless, have irregular borders, are fixed to the surrounding tissue, and are accompanied by regional lymphadenopathy[2]. Malignancy can be detected in a single solid nodule as well as in multinodular goiter. The multinodular goiter rate in childhood thyroid cancers has been reported as 29.7-53%[5,12]. The nodule size on examination is not associated with the risk of cancer[5]. In addition, thyroid cancers can be diagnosed clinically only with regional lymphadenopathy, and there may be no palpable nodules[2].

Laboratory Evaluation

When a thyroid nodule is encountered, thyroid function tests should be evaluated first. Most of these patients are known to be euthyroid[13,14]. Approximately 5% of cases with nodules are hypothyroid and 5% hyperthyroid. Nodule size is reported to be greater in the presence of hyperthyroidism, and hence, compression signs are more common[7]. However, thyroid function tests are not helpful in benign/malignant lesion differentiation. TSH suppression can indicate a hyperfunctioning nodule[2]. It should be noted that 5% of hot nodules are papillary carcinomas[7]. Autoimmune thyroid diseases provide a background for malignancy, so it is necessary to check anti-thyroglobulin and anti-thyroid peroxidase antibody levels in addition to TSH receptor antibody levels when hyperthyroidism is present. The routine measurement of thyroglobulin in the diagnosis is not recommended[5]. Serum calcitonin levels should be checked if medullary thyroid cancer is suspected. It should be noted that calcitonin values change according to age, sex and weight, and are affected by the presence of neuroendocrine diseases, smoking and alcohol, autoimmune thyroid disease, sepsis, hypergastrinemia, and calcitonin autoantibodies. A basal calcitonin level over 100 pg/ml is considered significant for medullary thyroid cancer. Pentagastrin stimulation test may also be requested to improve specificity if necessary. Routine calcitonin measurement for all thyroid nodules is still controversial. Corrias et al.[7] recommended routine calcitonin measurement, but there are dissenting publications[15,16]. Measuring carcinoembryonic antigen (CEA) together with calcitonin can provide some guidance. In the presence of medullary carcinoma, catecholamine levels must be measured to check for pheochromocytoma[5].

Radiological Evaluation (Ultrasonography, Elastography, Scintigraphy)

Ultrasonography (USG) is an easily applicable, noninvasive method that provides maximum benefit in the diagnostic and management approach. USG provides information such as size, edge regularity, location, echogenicity, cystic and solid components, and neck lymph nodes, and can also distinguish non-thyroid conditions (abscess, thyroglossal cyst, ectopic thymus, lymphatic or vascular malformations, etc.). It can also detect changes in findings during follow-up and guide fine-needle aspiration biopsy (FNAB) (1). The USG report should include information on the location, composition (solid, cystic, mixed), echogenicity, halo sign of the nodule(s), calcification (microcalcification, macrocalcification, peripheral (eggshell) calcification), boundaries (regular, irregular), length/width ratio, and Doppler findings (blood flow within the nodules). The clinician should ask for incomplete reports to be completed to ensure that all the above characteristics have been evaluated. The lack of a finding in the report does not mean that it is absent; rather, it just may not have been evaluated. All possible findings related to the nodule should therefore be reported as present or absent.

A solid nodule, hypoechogenicity, microcalcifications, irregular contours, subcapsular localization, invasive growth, multifocal lesions, increased nodule blood flow on Doppler (when TSH is normal), and suspicious regional lymph node presence on USG indicate malignancy[5]. A ratio of the anteroposterior diameter of the nodule to the transverse diameter (AP/T) >1 indicates malignancy[17]. Table II presents USG findings indicating malignancy. Growth in nodule size during treatment for autoimmune diseases also indicates malignancy. A fine, regular halo around the nodule is considered benign, but a thicker and more irregular halo may indicate a neoplasm (follicular or Hürthle cell carcinoma or adenoma, encapsulated papillary carcinoma). Nodules that are cystic, isoechoic, have regular

boundaries, lack calcification, and show no invasive growth are usually considered benign[5].

Hypoechogenicity seems to be the feature most often associated with malignancy. It is a sensitive but nonspecific marker[7]. The risk of malignancy was found to show a positive correlation with nodule size and a negative correlation with cystic content in a study conducted on 136 children with a thyroid nodule who underwent FNAB/surgery[18]. No USG finding indicating malignancy was found to be superior to the others in 35 pediatric thyroid nodule cases with FNAB and postoperative evaluations (19). For benign lesions on FNAB, the USG sensitivity was 80%, specificity 50%, accuracy rate 57%, negative predictive value 90%, and positive predictive value 36% in that study. In addition to the thyroid, regional lymph nodes should also be examined in detail during USG. A lymph node longitudinal/transverse arch ratio <1.5, absence of the hilum, presence of cortical thickening, non-homogeneous appearance, and increased vascular flow can be considered in favor of malignancy[7].

Elastography is a new method that has become popular recently in adult patients and is based on the evaluation of nodule flexibility. Its principle is that stiffness of a malignant lesion is more than that of the surrounding tissue. It can provide guidance in the differentiation of malignant and benign lesions. The sensitivity was 94.9%, specificity 90.3% and accuracy rate 91.3% in a study evaluating 176 thyroid nodules (with non-diagnostic or suspicious findings) with elastography[20]. There are no data regarding the use of elastography in childhood nodules.

Scintigraphy should be performed in the presence of solid and/or mixed lesions together with suppressed TSH. While the rate of malignancy is 5% in the presence of classic hot nodules, this rate rises to 57.1% if a non-classical hot nodule is detected (if there is a minimal radioactive involvement on the outer side of the lesion)[5].

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) is very important in the approach to thyroid nodules. It is a fast, cost-effective and accurate diagnostic method. No false-positive or false-negative FNAB results were obtained in a center in which 21 of 206 cases underwent surgery[21]. Sensitivity was 100% and specificity 65% in another study that evaluated 218 FNAB samples[22]. A meta-analysis evaluating 12 studies reported a FNAB sensitivity of 100%, specificity of 81%, accuracy rate of 83.6%, positive predictive value of 55.3%, and negative predictive value of 98.2%[23]. About 9-20% of FNAB evaluations are not diagnostic[24]. Smith et al.[25] found a malignancy rate of 48% after surgery in 68 pediatric FNAB procedures, which had been reported as atypia of unknown significance, follicular-oncocytic-neoplasm suspicion or malignancy. It should be noted that FNAB cannot differentiate between follicular adenoma and carcinoma. Surgery should be performed and capsule invasion should be evaluated in such cases[2].

There is no consensus regarding indications for FNAB. Since the malignancy risk of thyroid nodules is higher in children and adolescents, FNAB indications should be individualized and carefully evaluated. Biopsy is suggested as a general approach for pediatric nodules >1 cm in diameter that grow slowly, especially under L-thyroxine therapy. However, biopsy must be performed for nodules <1 cm in diameter, if a family history of thyroid carcinoma is present, if there is a history of radiotherapy to the head and neck, and in the presence of fast nodule growth, accompanying cervical lymph nodes, and suspicious ultrasound findings

Table I. Syndromes and Conditions Associated with Thyroid Nodule/Cancer[7]

- Cowden syndrome
- Bannayan-Riley-Ruvalcaba syndrome
- Gardner syndrome
- Carney complex
- Familial adenomatous polyposis
- Multiple endocrine neoplasia type 2-A
- Multiple endocrine neoplasia type 2-B
- McCune-Albright syndrome
- Peutz-Jeghers syndrome

Table II. Ultrasonography Findings Indicating Malignancy[5]

- Solitary solid lesion
- Hypoechogenicity
- Subcapsular localization
- Irregular margins of the lesion
- Invasive growth (no compression of adjacent tissues)
- Heterogenous nature of the lesion
- Multifocal lesions within an otherwise clinically solitary nodule
- Microcalcifications
- High intranodular flow by Doppler (with normal TSH)
- Suspicious regional lymph nodes accompanying thyroid nodule

indicating malignancy[7]. Malignancy has been reported in solid and hypoechoic nodules, but can also be present in multinodular goiter and cystic nodules. It has been reported that 5-14% of papillary carcinomas develop in cystic nodules[26,27].

One of the practical problems in pediatric endocrinology is the indication for repeating FNAB and its timing. The biopsy should be repeated when the FNAB result is non-diagnostic and the clinical and USG findings are suspicious for malignancy. Furthermore, biopsy should be repeated when the FNAB result is reported as 'suspicious'. In conclusion, performing and repeating FNAB should be evaluated individually based on the risk for each child. Papillary carcinoma has been reported at a rate of 1.3% in patients with 'benign' FNAB results[28]. When repeating the biopsy is required, an interval of at least three months is suggested to prevent any misleading influence (due to the possibility of incorrect evaluation secondary to complications).

Many immunocytochemical examinations have been performed previously in thyroid nodules. The most significant indicators in terms of thyroid cancer seem to be galectin-3, HBME-1, CK-19, CD44v6, and telomerase[7,29-31].

Genetic Evaluation

In terms of genetic evaluation, some mutations commonly seen in certain types of thyroid cancer and which warrant investigation are known. BRAF mutations are the most common genetic changes in papillary thyroid cancer and in all thyroid cancers. Other common mutations seen in papillary carcinoma are RAS and RET/PTC mutations[32]. Recombination of the PAX8/PPAR-γ genes is the cause of 20-50% of follicular carcinomas. RAS mutations should be investigated in follicular cancers that do not carry this recombination[5]. RET mutation analysis must be performed in medullary thyroid cancers. Germline RET mutations in >95% of hereditary medullary thyroid cancers and somatic RET mutations in 50-80% of sporadic type have been reported[31]. Furthermore, specific mutational analyses can be planned (PTEN, GNAS, APC, STK11, PRKAR1-α) if there are findings of genetic syndromes concomitant with thyroid malignancies[7].

Approach to Thyroid Nodules, Follow-up and Treatment

For thyroid nodules detected by palpation or USG, risk factors (family history of thyroid carcinoma and radiotherapy) should first be queried in the history, and the size and structure of the nodule should be evaluated on USG. Thyroid functions, thyroid autoantibodies and, if necessary, the serum calcitonin level should be checked and evaluated together with other data. Thyroid scintigraphy should be used to determine whether hyperfunction is present.

Fine-needle aspiration biopsy (FNAB) should be performed for all nodules ≥1 cm that are not autonomous and not fully cystic on scintigraphy[18]. Lesions reported as benign on FNAB should undergo clinical follow-up[7]. Levothyroxine therapy has been reported to be effective for benign nodules, leading to a reduction in size. A study of 78 children with benign thyroid nodules reported more than 50% reduction in nodule size in 30.6% of the group receiving treatment, and this was a significant difference when compared to the non-treatment group[33]. Thyroid function tests are usually euthyroid in patients with a nodule. FNAB should be performed for euthyroid/hypothyroid nodules if there is a family history of thyroid cancer and neck radiotherapy and also when a solid, hypoechoic nodule with microcalcifications, increased

blood flow, accompanying lymphadenopathy, or slow growth under L-thyroxine therapy is present on USG. There is no need for all of the above-mentioned findings to be present together. Each of these findings is a clue indicating the malignancy potential of the nodule. An increase in the number of these findings also increases the malignancy risk. Therefore, detailed evaluation of findings indicating a low or high risk of malignancy will provide a more accurate approach to thyroid nodules. If the FNAB result is benign, the patient should be monitored, and especially any findings changing towards malignancy should be carefully followed up and interpreted. If the FNAB result is suspicious or undetermined, the biopsy can be repeated[34].The time interval between repeated FNAB evaluations does not affect the diagnostic yield or the accuracy rate[35]. Surgery is recommended for all nodules of 1 cm with a cytological suspicion of malignancy and cystic nodules persisting during follow-up[18,34]. One of the major difficulties is the problems encountered during the determination of surgical boundaries. All USG findings, FNAB results and risk factors should be evaluated together to make the correct decision. If the FNAB result is malignant, total thyroidectomy should be performed, and total or near-total thyroidectomy should be performed for nodules suspicious for malignancy[18]. Lobectomy can be performed for unilateral nodules, nodules with uncertain diagnosis and micropapillary carcinomas with a diameter <1 cm[18,34].

In conclusion, although thyroid nodules are less frequent in children and adolescents than in adults, it is important to approach them correctly due to the high malignancy potential of nodules detected in this period. A comprehensive evaluation that considers all findings obtained with a detailed medical history, detailed physical examination, laboratory tests, USG, and FNAB will facilitate the appropriate approach to these lesions.

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