Biochemical Markers in Nodular Goiter in Children
Indications, methods and outcome of the Surgical Treatment

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Nodular goiter is a rare condition in children and adolescents and compared with adults, thyroid nodules are more frequent malignant in pediatric population. We have investigated the prevalence of thyroid carcinoma among the thyroid disorder emphasizing on the surgical treatment in term of indication, methods and complications. Retrospective study of 35 children and adolescents with nodular goiter. Demographic data, thyroid ultrasonographic features, fine needle biopsy aspiration, hormonal profile, surgical treatment procedure as well as histological aspects were recorded. Study included 26 (74%) girls and 9 (26%) boys with a mean age of 11.66 years. Fine needle aspiration biopsy was performed in 10 cases due to the TIRADS score ≥4 with Bethesda II in 3 cases, Bethesda III in 4 cases and Bethesda V in 3 cases. The surgical treatment was performed in 16 (45.7%) cases due to fine needle aspiration biopsy results or due to the relapse after medical treatment. Lobectomy was performed in 7 (43.7%) cases while total thyroidectomy was the final option for the rest of 9 (56.3%) patients. As a result of pathological examination in 8 cases the thyroid carcinoma has been found. The rest of 8 patients presented benign thyroid findings (follicular adenoma, toxic adenoma and Graves' disease with follicular adenoma). The prevalence of thyroid carcinoma among the pediatric population with thyroid nodules was 22.8% most affected being the female gender.

Keywords: thyroid cancer, children, surgery

Nodular goiter is a rare condition in pediatric populations, occurring in only 0.2%–5% of this category. Compared with adults, thyroid nodules are more frequent malignant in children and the incidence of this malignancy seems to be increasing [1].

Thyroid nodular disease contains a large spectrum of disorders including: unique nodular goiter, multinodular goiter, Hashimoto thyroiditis with nodularisation, Graves' disease with nodularisation. In children with thyroid autoimmune disorders we should beware because a neoplastic lesion may be small and undetectable at clinical examination. The diagnostic circumstances of thyroid nodules are different; they may be discovered during a physical examination or during the ultrasound of the neck [2].

New cases of thyroid cancer in people under the age of 20 represent 1.8% of all thyroid malignancies diagnosed in the United States. In adolescents between 15 and 19-year old, thyroid cancer is the eighth most frequently diagnosed cancer and the second most common cancer among girls. The adolescents have a 10-fold greater incidence than younger children to present thyroid cancer and the most affected are the girls (female to male ratio is 5:1) [3].

In children clinical findings that increase the likelihood of thyroid cancer are: male gender, history of external radiation to the head and neck or exposure to nuclear irradiance, rapid growth of goiter, a firm or fixed thyroid nodule, hoarseness or dysphagia [4].

Papillary and follicular thyroid cancer in childhood and adolescence is more advanced upon presentation than in adults. The recurrence rate is also higher in the young age. The survival in children and adolescents is better than in adults. An increase in the incidence of thyroid cancer has been observed in children exposed to the fallout of the Chernobyl accident [5] especially in the age group of less than one year at the time of the explosion [4].

The pathological classification of differentiated thyroid cancer in children is based on standard definitions set by the World Health Organization (WHO). Papillary thyroid carcinoma accounts for 90% or more of all childhood case. Follicular thyroid cancer is uncommon like as medullary thyroid carcinoma or anaplastic thyroid carcinomas which are very rare in pediatric population. There are many histological variants of pediatric papillary thyroid carcinoma all having a distinctive set of nuclear characteristics. Subtypes of papillary thyroid carcinoma are: classic, solid, follicular, and diffuse sclerosing [3].

Factors suggesting the malignant thyroid nodule in children and adolescents are: prior exposure to internal radiation, ultrasound features of malignancy, cold nodule on scintigraphy, malignant cytology on fine needle biopsy aspiration and positive biomarkers of malignancy in aspirates (BRAF mutation, ret/PTC, RAS mutation) [2].

Considering the particularities of thyroid carcinoma in children and adolescents we have investigated the prevalence of thyroid carcinoma among the thyroid disorder emphasizing on the surgical treatment in terms of indication, methods and complications.

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Experimental part

Patients and methods

We investigated the medical records of 35 patients (children and adolescents) admitted with diagnosis of nodular goiter at Endocrinological and Surgical Departments, St. Spiridon Hospital, Iasi, Romania, between 2011-2018. Demographic data (sex/age), thyroid ultrasonographic features, fine needle biopsy aspiration, hormonal profile, surgical treatment procedure as well as histological aspects were recorded.

Thyroid ultrasound and fine needle aspiration biopsy (performed only in patients with Thyroid imaging reporting and data system TIRADS score of 4 or 5) were done by well-trained endocrinologists and fine needle aspiration biopsy specimens were reviewed by qualified pathologists. The results of fine needle biopsy aspirations were recorded in compliance with Bethesda classification. The surgical treatment was performed by experienced surgeons in the field of thyroid nodular disorders.

Serum thyroid stimulating hormone (TSH), free T4 (fT4), calcitonin, Serum anti-thyroid peroxidase antibody (TPOAb) and thyroid stimulating hormone receptor antibody (TRAb) were measured. The reference values were as follows: TSH 0.51-4.30 µIU/mL, fT4 0.97-1.67ng/dL, TPOAb <20 mUI/mL, TRAb<1.75 UI/L, calcitonin 9.82pg/mL.

Each medical record contain written informed consent of the parents or legal guardian.

Results and discussions

The retrospective study included the medical records of 26 (74%) girls and 9 (26%) boys (fig.1) with a mean age of 11.66 years, most patients being in age group of 11 (6 patients), 15 (7 patients) and 16 (8 patients) years old (fig.2).

The thyroid ultrasound examination revealed: unique micronodule (< 1cm) of the left lobe in 3 patients, unique micronodule of the right lobe in 2 patients, multiple micronodules in both lobes in 3 patients, unique macronodule (> 1cm) of the left lobe in 4 patients, unique macronodule of the right lobe in 5 patients, multiple macronodules in both lobes in 3 patients, unique microcyst of the left lobe in 4 patients, unique macrocyst of the left lobe in one patient, nodules with suspicious features of malignancy (TIRADS 4 or 5) in 7 patients, multiple micronodules in large, hypoechogenic thyroid with hypervascularisation in Doppler mode in 3 cases.

Fine needle aspiration biopsy was performed in 10 cases due to the TIRADS score ≥ 4 with Bethesda II in 3 cases, Bethesda III in 4 cases and Bethesda V in 3 cases.

The thyroid function was normal (euthyroidism) in 29 cases (82.8%), abnormal in 6 cases (17.2%), thyrotoxicosis in 4 cases and hypothyroidism in 2 cases. All patients with one exception had normal values of calcitonin. The presence of TPOAb in high titers was mentioned in 2 patients (Hashimoto thyroiditis) and of TRAb in two patients (Graves’ disease).

The surgical treatment was performed in 16 (45.7%) cases due to fine needle aspiration biopsy results or due to the relapse after medical treatment in cases with hyperthyroidism. Lobectomy was performed in 7 (43.7%) cases while total thyroidectomy was the final option for the rest of 9 (56.3%) patients (fig. 3).

The prevalence of thyroid carcinoma among the pediatric population with thyroid nodules was 22.8% (fig. 4) most affected being the female gender. In our study

| TREATMENT   | HYPERTHYROIDISM | HYPOTHYROIDISM | EUTHYROIDISM |
|-------------|-----------------|----------------|--------------|
| SURGERY     | 3 cases (total thyroidectomy) | - | 6 cases (total thyroidectomy) |
| DRUGS       | - | 2 cases (L-thyroxine) | - |
| NO TREATMENT| - | - | 16 cases |
| OTHER       | 1 case (ethanol sclerosis) | - | - |

| THERAPEUTICAL OPTIONS | ACCORDING WITH THE THYROID FUNCTION |
|-----------------------|-----------------------------------|
| SURGERY               | Lobectomy                        |
| DRUGS                 |                                  |
| NO TREATMENT          |                                  |
| OTHER                 |                                  |
group no complication after surgical treatment was present. The post-surgical evolution was normal with discharge in 2-3 days after the procedure.

Our results show a prevalence of 22% of thyroid malignancy among pediatric population with thyroid nodular disorders. This incidence is comparable to the reported prevalence of thyroid cancer in pediatric thyroid nodules of 20%-26% [1]. In Korea, the childhood thyroid cancer prevalence is 18% and the incidence increased 3 fold from 1999 to 2012 (0.5/100,000 to 1.7/100,000) and in the United States and the United Kingdom, the incidence of thyroid cancer in pediatric populations also appears to be increasing [1]. In fact, thyroid cancer is the most common pediatric endocrine cancer of all childhood malignancies.

The mean incidence of thyroid carcinomas in childhood thyroid nodules which were operated shows an overall 26.4% risk of cancer. If in adults, women to men ratio is 4:1, in children below 15 the ratio of girls to boys is 1.5:1 and in patients aged between 15-20 years the female to male ratio is 3:1. Males and children under 10 years are at higher risk of cancer. Age is also the major determinant of recurrence in pediatric differentiated thyroid carcinoma, particularly in those younger than 10 years [2].

In a study conducted in the United States, thyroid nodules were present in 1.8% of school children between the ages of 11 and 18 years. The incidence of thyroid carcinoma in children is reported to be approximately 1.75 per 100,000 [4].

Well-differentiated thyroid cancers are the most common endocrine tumors in children and adolescents. A significant increase in the incidence of thyroid cancers was observed in children following the nuclear reactor meltdown in Ukraine and those exposed to the atomic blasts in Japan [5, 6].

Screening for papillary thyroid carcinoma in children at risk is, however, an issue of debate. It is important to mention that thyroid nodules in children are five times more likely to be malignant than in adults. Pediatric and adolescent papillary thyroid carcinoma is possible to have no relationship with gender in prepubertal children, while after puberty; girls are 4-5 times more prone to have thyroid cancer than boys [7].

The incidence of thyroid cancer is higher in children presenting with nodular goiter compared with adults. In children, thyroid nodules have been reported to be malignant between 9.2% and 50% whereas in adults, the incidence of thyroid cancer is between 5% and 15% [8].

The majority of malignant nodules are found in a uninodeular goiter. Follicular adenoma is the most frequent nonmalignant diagnosis in children with thyroid nodules. The distribution of malignancy in pediatric goiter is similar to that seen in adults. Papillary thyroid carcinoma is the most frequent malignancy among children with nodular thyroid disorders [8].

Risk factors for developing thyroid nodules in pediatric population include: female gender, iodine deficiency, head and neck irradiation, age of puberty, and family or personal history of thyroid disease. Several diseases as: abscesses, lymphatic or vascular malformations, ectopic thymus, thyroglossal duct cysts, and tumors can mimic thyroid nodules in children [8]. The risk of thyroid neoplasia in children is elevated at any radiation dose [9]. Another risk factor for thyroid malignancy in pediatric population is the Hashimoto thyroiditis. In children this autoimmune disorder can be accompanied by important thyroid structural alterations [10]. In time period benign thyroid nodules, carcinoma and, rarely, primary non-Hodgkin lymphoma can develop. However, the relationships between HT and neoplasm are poorly defined. The frequency of papillary thyroid carcinoma in children and adolescents with Hashimoto thyroiditis was found from 0.67 to 3% [11].

Papillary thyroid cancer and follicular thyroid carcinoma present major clinical differences in terms of uni- or multinodular presentation, lymph nodes metastasis and hematogenous metastases. Hematogenous metastases to the lungs occurs in up to 25% of cases and generally occur only with significant regional lymph node metastases in papillary forms. A unifocal tumor and hematogenous metastases to lungs and bones are specific for the follicular type [3].

In order to decide the necessity of surgery multiple modalities are employed to help characterize thyroid nodules (ultrasound, radionuclide scans, fine needle aspiration biopsy, and thyroid function tests). Even all these tests are also performed in the pediatric population; these patients frequently undergo partial or total thyroidectomy for diagnosis [12]. An ultrasound examination to determine the main characteristics in term of: volume, structure, vascularisation is always necessary. Some authors have tried to define a set of characteristics that identify nodules at a higher risk of malignancy: the ultrasound evaluation of thyroid nodules- the Thyroid Imaging Reporting and Data System (TIRADS) [13].

If feasible, given the patients age and anxiety level, a fine needle aspiration biopsy should be performed [12, 14]. As biomarkers, circulating tumor cells from solid tumors can predict metastases and prognoses are helpful after the surgical treatment in order to monitor the treatment efficacy [15].

The surgical excision is the only option in those patients who have an inadequate or malignant fine needle biopsy aspiration or in cases when this procedure was not performed. Total thyroidectomy remains the procedure of choice for those lesions identified preoperatively as cancer, while lobectomy should be employed for those lesions in which the diagnosis is uncertain [12, 16].
Because most pediatric patients with thyroid pathology are adolescents, they are frequently operated on by general surgeons or endocrine surgeons in medical centers for adults as well. The approach varies from country to country and depends on the general principles of the medical care system in a given region [17].

Surgical resection remains the gold standard of management for all children and adolescent with thyroid carcinoma [16, 18] but there is still controversy regarding the extent of resection. Pediatric population with papillary thyroid carcinoma, not undergoing a total thyroidectomy, is at a higher risk for developing recurrences. The relative high incidence of multifocal disease is an argument for a total thyroidectomy in pediatric papillary thyroid carcinoma.

A central neck dissection should be performed when there is evidence of central and/or lateral neck metastasis or gross extra thyroidal invasion [7]. The post-surgical complication rate according different authors is 22%, including permanent recurrent nerve damage in 6.2% and permanent hypoparathyroidism in 12.3%. Complications can be minimized by the surgeons who perform thyroid surgeries at the high-volume centers [7].

The thyroid cancer in pediatric population is a challenge for the endocrinologist as well for the surgeon. The majority of pediatric patients with nodular goiter who have the indication of surgical treatment are operated by the general surgeon who must have a great experience in the field of thyroid surgery. The expertise in thyroid surgery is necessary in order to have a curative treatment and to avoid postoperative complications. A close collaboration is needed between pediatrician, endocrinologist and surgeon for children with thyroid cancer in order to receive proper and effective treatment.

Conclusions
Surgical treatment of nodular disorders in children must be performed after a careful clinical examination and tests that accurately establish the existence of a possible malignant proliferative process. Even the nodular goiter is a rare event in pediatric population the risk of thyroid carcinoma is increased that way the extent of surgical removal of the thyroid is very important. The total thyroidectomy and radical neck dissection must be performed only in specific cases when the results of fine needle biopsy aspiration are illustrative for malignancy.

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