Curr Pediatr Res 2014; 18 (1): 33-37 *ISSN 0971-9032*
http://www.pediatricresearch.info

Prevalence of malignancy in thyroid nodules in children and adolescents.

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Abstract

This study aims to look at the prevalence of thyroid malignancy in previously healthy children and adolescents presented with multinodular goiter (MNG) and or solitary nodules for which they underwent thyroid surgery. Twenty one children and adolescents (13 males and 8 females) underwent partial or total thyroidectomy over a 10-year period. Papillary thyroid carcinoma was found in 4 (19%) patients. Three of them had metastasis to the cervical lymph nodes. Five year survival for all diagnosed cases having malignancy was 100%. Multinodular goiter as well as solitary nodules in children and adolescents may have a higher incidence of malignancy and should always be taken seriously. In absence of known environmental hazards and previously healthy individuals, a prevalence of malignancy (19%) in 21 cases is considered alarming.

Keywords: Malignancy, papillary, children, adolescents, thyroid, multinodular, goiter, nodules,

Accepted 11th February 2014

Introduction

Multinodular goiter (MNG) usually progresses from a diffuse enlargement of the thyroid gland in children and neonates with advancing age [1]. Children presenting with asymptomatic solitary or multiple nodules may harbor thyroid carcinoma. Clinical findings that increase the likelihood are male gender, history of external radiation to the head and neck or exposure to nuclear fallout, history of rapid growth, a firm or fixed thyroid mass, hoarseness or dysphagia, and presence of cervical lymphadenopathy [2].

Although thyroid cancer is a rare disease, in the United States it has an incidence of approximately 1.75/100,000 [3].

There have been no studies among children to record the magnitude and pattern of this disease in this particular area of Saudi Arabia. In a study done by Abu Eshy *et a*l in 1995 on adults operated for multinodular goiter in Southwest area of Saudi Arabia, the prevalence of thyroid In spite of lack of published data on this problem in the region, we observed an increase in the numbers of children being referred for evaluation of thyroid nodules. This could be a real increase in the disease of thyroid gland or due to improvement in the detection of thyroid lesions by the primary health care physicians.

Material and Methods

Aseer region is located in the southwest of Saudi Arabia with a population of 12,00,000. This region extends from the high mountains of Sarawat (with an altitude of 3,200 meters above the sea level) to the Red Sea, and lies few kilometers from the northern border of the neighboring Yemen. Primary health care services delivery in Asser region is provided through a widespread network of 238 primary health care centers (PHCC). Each PHCC has well-defined catchments' area and population. Secondary care services in the region are provided through a network of 15 hospitals scattered all over the region.

A retrospective cohort of all children and adolescents who underwent thyroidectomy (lobectomy, subtotal thyroidectomy and total thyroidectomy), at Aseer central Hospital (ACH) and Abha Private Hospital (APH) for the period July 2002 - May 2012 were included in the study.

The data collected from their charts include age of the patient at the time of diagnosis, area of residence, exposure to radiation, family history of thyroid disease, size of the gland by clinical examination, presence of cervical lymph nodes, thyroid function tests, presence of thyroid antibodies. The size of the gland on ultrasound (US) was recorded and the presences of cystic changes, calcification or thyroid nodules were noted. Follow up was recorded and the change in the gland size in response to thyroxin therapy if given was taken into account by the clinical examination and by measurement on US. The reason for surgical intervention was also extracted from the charts as well as the surgical procedure performed. Intra-operative and postoperative complications were also recorded.

Frequencies, arithmetic mean, standard deviations and medians were used to present data. Non-parametric tests

of significance (Mann-Whitney and Fisher's Exact Tests) were used at 5% level of significance.

Results

The present study included a total of 21 patients (13 males and 8 females) who had surgical treatment during the study period. Table 1 shows their demographic and clinical data in first presentation. Their age ranged from 10 to17 years with a mean of 12.75 (2.12) and a median of 12.5 years. No statistical significant age difference was found between males and females (P=0.189). The duration of symptoms ranged from 3 to 60 months with a mean of 23.63 (19.41) and a median of 18.0 months. The most common presenting complaint was neck mass noticed by the parents or by the doctor. None of these patients had pressure symptoms such as difficulties in swallowing or voice changes. None of those patients had radiation exposure to the head or neck area. Only one patient had a family history of thyroid disease. Two cases showed cysts by ultrasonography and 19 cases had nodules. Only 3 cases had an abnormal thyroid function tests on presentation.

Table 1. *Data on First Presentation – Demographic, Clinical, Ultrasonography, and Thyroid Function Tests*

No.	Age (Years)	Sex	Symptoms Duration	Family History	Ultrasonography		T4(ug/dL)/ TSH(mIU/L)
					Size (cm) Rt / Lt	Cysts/Nodules	
1	11	M	3M	No	5x4 / 6x4	Nodules	Normal
2	17	F	5Y	No	4x4 / 5x4	Nodules	Normal
3	12	M	1Y	Yes	2x2 / 3x3	Cysts	Normal
4	10	M	6M	No	3x3 / 2x2	Nodules	Normal
5	13	F	3Y	No	5x6 / 4x3	None	15.7/21.1
6	12	F	2Y	No	2x3 / 3x4	Not done	19.9/10.4
7	13	F	3Y	No	3x3 / 2x2	Cysts	11.2/61.4
8	14	M	1Y	No	5x5 / 3x4	Nodules	Normal
9	10	M	5M	No	3x3/3x5	Nodules	Normal
10	13	M	4M	No	4x3/4x4	Nodules	Normal
11	15	F	3M	No	4x4/2x3	Nodules	Normal
12	17	F	7 M	No	3x3 / 2x2	Nodules	Normal
13	12	M	1Y	No	4x4/2x3	Nodules	Normal
14	10	M	1Y	No	2x3 / 3x4	Nodules	Normal
15	11	F	3M	No	2X2/3X3	Nodules	Normal
16	13	M	6M	No	3x3/3x5	Nodules	Normal
17	15	F	3M	No	2X3/4X4	Nodules	Normal
18	10	M	8M	No	5x4 / 3x3	Nodules	Normal
19	11	M	9M	No	4X4/3X3	Nodules	Normal
20	12	M	2Y	No	2X2/4X3	Nodules	Normal
21	13	M	1Y	No	5X2/3X3	Nodules	Normal

Table 2. *Surgical intervention, results and follow-up data*

No.	Reason	Surgical Intervention		Pathology	Complica-tions	Referral For Iodine Therapy
		Type of Thyroidectomy	Lymph Nodes Metastasis			
1	Abnormal FNAC	Total	Positive	Papillary Carcinoma	Transient Hypocalcemia	Yes
2	Rapid Enlargement	Total	Negative	Micro-carcinoma Variant of Papillary Carcinoma	Permanent Hypocalcemia	Yes
3	Cosmetic	Lt. lobe + Isthmus	Positive	Moderately Differentiated Papillary Carcinoma	None	Yes
4	Firm to hard Consistency	Total	Positive	Papillary Carcinoma	Transient Hypocalcemia	Yes
5	Cystic and Nodular Changes	Total	Negative	Hashimotos Thyroiditis	None	No
6	Large size	Subtotal	Negative	MNG	None	No
7	Cystic Changes	Subtotal	Negative	Hashimotos Thyroiditis	None	No
8	Large size	Subtotal	Negative	MNG	None	No
9	Nodule enlargement	Rt. Lobectomy	Negative	MNG	None	No
10	Nodule enlargement	Lt. Lobectomy	Negative	MNG	None	No
11	Rapid Enlargement	Rt. Lobectomy	Negative	MNG	None	No
12	Nodule enlargement	Rt. Lobectomy	Negative	Solitary Nodule	None	No
13	Nodule enlargement	Rt. Lobectomy	Negative	Solitary Nodule	None	No
14	Nodule enlargement	Lt. Lobectomy	Negative	Solitary Nodule	None	No
15	Large size	Lt. Lobectomy	Negative	Solitary Nodule	None	No
16	Nodule enlargement	Lt. Lobectomy	Negative	Solitary Nodule	None	No
17	Nodule enlargement	Rt. Lobectomy	Negative	Solitary Nodule	None	No
18	Nodule enlargement	Rt. Lobectomy	Negative	MNG	None	No
19	Nodule enlargement	Lt. Lobectomy	Negative	Solitary Nodule	None	No
20	Large size	Rt. Lobectomy	Negative	Solitary Nodule	None	No
21	Nodule enlargement	Lt. Lobectomy	Negative	Solitary Nodule	None	No

The indications for surgical intervention were variable and included some clinical findings, cosmetic reasons, abnormal findings on ultrasonography, and abnormal histology on fine needle aspiration. Thyroid lobectomy was done in 15 cases, subtotal thyroidectomy in 3 cases, total thyroidectomy in 3 cases. After follow up of 5 years one patient developed MNG in his other lobe and subsequently went for the other side lobectomy. Four cases (19 %) had papillary carcinoma and two cases had Hashimotos thyroiditis (9%) and the rest were diagnosed as simple non-toxic multinodular goiter. Three patients had positive papillary carcinoma metastasis to the local lymph nodes. Permanent hypocalcemia were present only in two papillary carcinoma patients. All cases that had thyroid papillary cancer metastasis went for iodine ablation therapy and no recurrent laryngeal nerve injury was noted in any of the operated patients.

Discussion

Thyroid cancer is rare below the age of 15 years [5]. Papillary and follicular thyroid cancer in childhood and adolescence is more advanced upon presentation than in adults, as evident from a higher frequency of extrathyroidal spread. The recurrence rate is also higher. Nevertheless, the prognosis for survival in children and adolescents is better than in adults; the reason remains unclear [5,6]. An approximately 30-fold increase in the incidence of thyroid cancer has been observed in children exposed to the fallout of the Chernobyl accident, especially in the age group of less than one year at the time of the disease [6]. In the absence of known precipitating risk factors such as Hodgkin lymphoma or other tumors of the head and neck treated with irradiation or nuclear fallout, thyroid cancer is uncommon. In a study conducted in the southwestern United States, thyroid nodules were present in 1.8% of school children between the ages of 11 and 18 years [7]. The incidence of thyroid carcinoma in children is reported to be approximately 1.75 per 100,000 [1]. Although several studies suggest that most of the thyroid nodules in children are benign, it was found that in adults the tendency of the nodules to harbor malignancy is varying from 2% up to 40% [8,9,10].

In UK a significant increase in the incidence of thyroid cancer after the Chernobyl accident was noticed. These temporal and spatial changes in incidence are consistent with a casual association with the Chernobyl accident although a greater effect in the younger rather than the older age group would have been anticipated. However, factors including improvements in ascertainment and earlier detection of tumors may also have contributed to the increasing incidence [11].

In the present study, our patients did not report any exposure to radiation of the head and neck, did not suffer previous malignancies or being in an area with known environment risk factors.

In a study done by Lyshchik et al, Power Doppler (US) was a useful diagnostic tool to predict thyroid cancer in children with thyroid nodules. In their study, a nodules with diameter of 15 mm and smaller, the most reliable diagnostic criteria for malignancy were an irregular outline (sensitivity, 69.6%; specificity, 86.4%; $P< .001$), sub capsular location (sensitivity 65.2%; specificity 86.4%; $P< .001$), and increased intranodular vascularization (sensitivity 69.6%; specificity 87.9%; $P< .01$). For nodules larger than 15 mm in diameter, the accuracy of US diag-

nosis was much lower than that for smaller nodules. The only reliable criterion for this group was hypoechogenicity (sensitivity 60.0 %; specificity 84.0%; $P < .01$) [12].

In our study, there were no significant differences on the US findings between those having single nodule and those with multiple nodules. US were not helpful in predicting cancer in our cases. Prediction of malignancy in thyroid lesions remains directly related to the experience of the radiologists and the sensitivity of the machine used.

In the previous study done by Al-Fifi et al, the use of ^{99m} Tc pertechnetate thyroid scans was of only modest utility. It did not detect lesions, which are not clinically palpable or seen by ultrasound. The functional information about the nodules, in itself, did not seem to alter the decision for surgery or conservative management. Especially for the cold lesions, there were other features; unilateral pathology, presumed solitary in nature, size or consistency that apparently directed the way of management. All cold lesions were biopsied or excised and one was determined to be papillary carcinoma. There were no cases of malignancy in the warm or hot lesions. The existing literature is insufficient to provide strong evidence of malignancy risk depending on the uptake, unlike the case for solitary lesions in adults [13,14]. In our series we did not feel that ^{99m} Tc pertechnetate thyroid scans would add significantly to the evaluation or therapy.
Thyroid function (TSH and Free T4) seems to be also of limited value in the prediction of thyroid malignancy. This was evident in our study, as all the four patients with thyroid cancer had a normal function at the time of diagnosis while three of those were benign pathology had altered thyroid functions.

Fine needle aspiration (FNAC) especially if done by an expert is a helpful tool for the diagnosis of different thyroid pathologies. It is not commonly used in children at our center. Only one patient had FNAC and turned out to be suspicious for malignancy. From the histopathology point of view, approximately 90% of thyroid cancers in children are papillary carcinoma or the follicular variant of papillary carcinoma, 10 percent are follicular carcinomas, and 1- 2 % are medullary carcinomas [1]. Histopathological specimens of all the four patients we reported here revealed papillary thyroid carcinoma.

Children with thyroid carcinoma tend to have advanced disease at presentation as compared to adults. This was illustrated in a review of 540 children from nine large centers that found 71 to 90 percent of the children had spread to regional lymph nodes, 20 to 60 percent had extra capsular extension with invasion of the trachea, and 30 percent had involvement of the recurrent laryngeal nerve [8,9,14,15]. Distant metastases commonly occur in the lungs (10 - 28 %), followed by the bones and brain [15,16]. Three of our patients with thyroid cancer, had metastasis to the regional lymph nodes at the time of surgery and this similar to the world literature.

Guidelines taskforce released detailed management recommendations for differentiated thyroid cancer, which primarily addressed the approach for treating adult patients. Children with differentiated thyroid cancer present with more advanced disease and yet have a more favorable outcome than adults. Thus optimal treatment for younger patients with differentiated thyroid cancer may differ from that for adults. All available data regarding differentiated thyroid cancer treatment in children are retrospective. In the past year, several large case series have been published that strengthen the argument for total thyroidectomy at the time of diagnosis, followed by administration of radioactive iodine for remnant ablation. There have also been recent advances in understanding the genetic abnormalities associated with pediatric and adolescent's thyroid cancer. The optimal treatment of differentiated thyroid cancer in pediatric patients continues to be debated. Recent publications from institutions around the world provide useful data regarding current approaches to this unusual disease. Further collaborative studies are needed to further refine the surgical approach, particularly the extent of lymph-node dissection, radioactive iodine dosing, and the role of genetic analysis in diagnosis and clinical approach [16].

Conclusion

In conclusion, carcinoma of the thyroid should always be considered in children presenting with thyroid nodules. Surgical treatment remains the best method of therapy with excellent outcome. Close postoperative follow up for those treated with thyroid lobectomy and subtotal thyroidectomy is recommended. Radioactive iodine therapy is reserved for cases having papillary carcinoma metastasis. Prognosis is generally good.

Acknowledgment

We thank Professor Ahmad Mahfouz for his assistance in statistical analysis of the data.
Financial disclosure of authors and reviewers: None reported.

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