ORIGINAL ARTICLE

Thyroid Cancer in Children of Eastern Anatolia

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ABSTRACT

Introduction: *The incidence of thyroid cancer has been increasing in recent years. In this study, the clinical and laboratory findings of 14 patients with thyroid cancer were analysed retrospectively. They were admitted to our clinic with complaints of swelling of the neck.*

Methods: *This study was performed in the Paediatric Endocrinology Polyclinics of Ataturk University Faculty of Medicine between 2008 and 2013. Patients with a diagnosis of thyroid cancer/hyperplasia were included. Patients' age and gender, a family history of goitre and thyroid cancer, and exposure to radiation were elicited. Free thyroxine (T4), thyroid stimulating hormone, thyroglobulin and urinary iodine levels were measured. Ultrasonographic characteristics of nodules were determined. Fine-needle aspiration biopsy was performed if nodules were ≥ 10 mm in diameter.*

Results: *The number of males and females was equal. There was no history of neck radiation. Grade 4 and grade 3 goitres were detected in four (28.5%) and 10 (71.4%) of 14 patients, respectively. The use of rock and iodized salt was determined in nine (64.2%) and three (21.4%) patients, respectively, while two (14.2%) patients have been using both forms of salt. According to biopsy findings, benign thyroid tissue was present in three (21.4%) patients, while papillary cancer, follicular carcinoma and hyperplasia were determined in six (42.8%), three (21.4%) and five (35.7%) patients, respectively.*

Conclusion: *Even if the biopsy findings are normal, surgery must be done in the presence of a history of bleeding in a nodule, fixation of a nodule and cervical lymphadenopathy. Iodine deficiency is an important risk factor for thyroid cancer. People should be informed about iodine deficiency and iodized products should be provided to those who live in areas with endemic iodine deficiency.*

Keywords: Cancer, child, iodine, thyroid, Turkey

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INTRODUCTION

Although thyroid cancer is thought to be uncommon in childhood, it is in fact widespread (1). The incidence in children under 15 years of age is two in 100 000 (2). However, thyroid cancers have been increasing in recent years. The majority (n = 3081) of cases with thyroid cancer were reported between 1990 and 2004 compared to the period 1969 to 1989 [n = 1106] (3). Thyroid cancers in the childhood age group are most common in adolescents, but are rare in infancy and early childhood. They are two to three times more common in females than in males. The incidence of thyroid cancer in the childhood and adolescent age has been determined to be between 0.54 and 1.75 in 100 000, the third highest among all solid tumours (4, 5). Iodine is a trace element for the human body. Average daily iodine requirement is 40 µg/day in babies aged less than 1 year, 60–100 µg/day in children aged 1–10 years, 50–100 µg/day in adolescents and adults, and about 150 µg/day for pregnant women and breastfeeding mothers (6). Iodine deficiency is an agent in cancer development. One study in animals showed that prolonged iodine deficiency caused a significant increase in thyroid epithelial cell cancers (7). A combination of congenital hypothyroidism and thyroid cancer has even been reported (8).

Cancer cases in children have increased, especially in the last five years in eastern Anatolia. Our cases include the last five years. There could be several unknown reasons. The aetiology of thyroid cancers was focussed on radiation and iodine deficiency. This study is a retrospective evaluation of the clinical and laboratory findings of 14 patients diagnosed with thyroid cancer.

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SUBJECTS AND METHODS

In this retrospective study, data on 14 patients diagnosed with thyroid cancer/hyperplasia during the 2008–2013 period at the Pediatric Endocrinology Clinic, Ataturk University Department of Pediatric Endocrinology, were reviewed. Data including patients' age and gender, a family history for goitre and thyroid cancer, exposure to radiation and the final diagnosis were obtained from the patients' files. Free thyroxine [FT4] (n: 0.9–1.7 ng/dL), thyroid stimulating hormone [TSH] (n: 0.6–5.8 μIU/mL) and thyroglobulin [TG] (n: 0–72 ng/mL) levels were measured by immunoassay method (DXI 800 Immunoassay System; Beckman Coulter, Inc., USA). Urinary iodine levels (n: 10–20 μg/dL) were determined by the spectrophotometric method. Serum antimicrosomal and antithyroid antibodies were measured by indirect haemagglutination.

Thyroid ultrasound and scintigraphy were performed in all cases. The sonographic features of thyroid nodules with respect to size, number, echogenicity, solid/cystic status, increased haemorrhage and presence or absence of calcification were analysed. Thyroid gland homogeneity and cervical lymphadenopathy characteristics were also noted. Nodule was present in all patients, thus scintigraphy and fine-needle aspiration biopsy (FNAB) was performed on all of them. The scintigraphic features of thyroid nodules were termed hot or cold based on increased or decreased radiotracer uptake. Criterion for an FNAB was the largest nodule, diameter ≥ 10 mm; FNABs were performed by a radiologist under ultrasound guidance. Following application of a local anaesthetic (lidocaine HCl 20 mg/mL + epinephrine HCl 0.0125 mg/mL), 20G size needle attached to 20 mL syringes was used to obtain the samples. An average of six (4–8 samples) separate aspirates was collected in each case. The cytological material was smeared onto slides. Approximately half of the slides were immediately fixed with 95% ethyl-alcohol and stained with Papanicolaou stain. The other slides were air-dried to be stained with Wright-Giemsa. The adequacy and classification of thyroid aspirates were analysed and evaluated using the Bethesda System for Reporting Thyroid Cytopathology. The cases with hypothyroidism at admission and those exposed to surgery were started on thyroid hormone therapy at 100 microgram/m^2 per day. Results are given as percentages.

RESULTS

The mean patient age was 13.3 years (range 10–16 years). The number of males and females was equal: seven patients (50%) were female and seven (50%) male. Although none of the patients had a history of radiation exposure to the neck area, four (28.5%) patients had chest X-rays previously. Only one (7.1%) patient had a positive family history for thyroid cancer (papillary cancer), while five (35.7%) patients had a family history of goitre. The use of rock and iodized salt was determined in nine (64.2%) and three (21.4%) of 14 patients, respectively, while two (14.2%) patients have been using both forms of salt. Grade 4 and grade 3 goitres were detected in four (28.5%) and 10 (71.4%) patients, respectively. Hypothyroidism was determined in nine patients (64.2%). Hyperthyroidism was determined in one patient (7.1%) who was treated with methimazole and propranolol. Three (21.4%) patients had normal urinary iodine level, while eight (57.1%) patients had urinary iodine level lower than normal. Urinary iodine levels could not be investigated in three (21.4%) patients. Antimicrosomal and antithyroid antibodies were negative in all cases. At scintigraphy, seven (50%) hypoactive nodules, five (35.7%) hyperactive nodules and two (14.2%) hypo-hyperactive nodules were identified. A single nodule was present in four (28.5%) patients, while multiple nodules were determined in 10 (71.4%) patients. The nodules were cystic in nine (64.2%) patients and solid in three (21.4%) patients. Bleeding within nodule was observed in all cases except for three (21.4%) patients with unavailable data. The thyroid gland was homogeneous in seven (50%) and heterogeneous in six (42.8%) patients, while there was no information for one (7.1%) patient. Calcification was determined in four (28.5%) of 14 patients. Eight (57.1%) patients had cervical lymphadenopathy. According to biopsy findings, benign thyroid tissue was detected in three (21.4%) patients, while papillary cancer, follicular carcinoma and hyperplasia were determined in six (42.8%), three (21.4%) and five (35.7%) of the patients, respectively. Three patients with normal histopathologic findings were operated on due to increased bleeding, fixation of a nodule and presence of cervical lymphadenopathy. The patients had a total or subtotal thyroidectomy and then 100 μg/m^2/day L-thyroxine was given. The patients remained on follow-up at outpatient clinics. Thyroid hormone and TG levels were checked every three months. Thyroid ultrasound was performed every three months and total body scintigraphy was done initially. When a residual or metastatic tissue was determined, radioactive iodine 131 therapy was given (cases 7 and 13). All the patients are apparently healthy and none of them has died. The patients' clinical and laboratory findings are shown in Table 1. Clinical characteristics of nodules are presented in Table 2.

DISCUSSION

Modest differences in iodine intake do not affect thyroid cancer incidence or the distribution of subtypes (9). Endemic iodine deficiency has been described in many parts of Turkey and particularly in mountainous regions. The eastern Anatolia region is also mountainous and one of the most common iodine-deficient regions in Turkey. Iodine prophylaxis has been provided in Turkey since 1998 with the iodination of salt. Urinary iodine clearance is a direct marker of nutritional intake. A correlation has been determined between endemic goitre formation and urinary iodine clearance (10, 11). Eight patients had urinary iodine levels lower than normal. There were only three patients using iodized salt. Two patients have been using both rock and iodized salt. This situation

Table 1: Clinical and laboratory characteristics of patients

Cases	Age (years)/ Gender	History of radiation	Goitre in the family	Goitre grade	Salt	FT4 (0.9–1.7 ng/dL)	TSH (0.6–5.8 μIU/mL)	TG (0–72 ng/mL)	Urinary iodine levels (10-20 μg/dL)	Scintigraphy	FNAB	Pathology	Recurrence
Case 1	15/M	+ (chest X-ray)	–	4	rock salt	0.8*	13.8*	37	7.8*	Hypoactive/ Hyperactive	Normal	Papillary cancer	No
Case 2	11/M	–	+	4	iodized salt/rock salt	0.5*	5.3	1000*	11.2	Hyperactive	Hyperplasia	Papillary cancer	No
Case 3	10/M	–	+	3	iodized salt	1.4	2.6	300*	8.6*	Hypoactive	Normal	Follicular carcinoma	No
Case 4	11/F	–	–	3	rock salt	0.7*	2.7	1000*	5.4*	Hypoactive/ Hyperactive	Hyperplasia	Follicular carcinoma	No
Case 5	12/F	–	+	3	rock salt	0.8*	6.7*	34.4	14.3	Hyperactive	Hyperplasia	Hyperplasia	No
Case 6	14/F	+ (chest X-ray)	–	3	rock salt	0.5*	3.1	1000*	3.6*	Hyperactive	Hyperplasia	Hyperplasia	No
Case 7	16/M	–	–	4	rock salt	1.1	2.2	149*	4.2*	Hypoactive	Normal	Papillary cancer	Yes
Case 8	15/M	–	–	3	rock salt	0.9	18.3*	175*	5.9*	Hyperactive	Hyperplasia	Papillary cancer	No
Case 9	15/F	–	+	4	iodized salt/rock salt	0.9	3.8	83*	12.6	Hypoactive	Hyperplasia	Follicular carcinoma	No
Case 10	13/M	–	–	3	rock salt	0.8*	6.9*	32.7	9.5*	Hypoactive	Hyperplasia	Papillary cancer	No
Case 11	16/M	+ (chest X-ray)	–	3	iodized salt	1.1	7.2*	1000*	8.2*	Hypoactive	Hyperplasia	Hyperplasia	No
Case 12	12/F	–	–	3	rock salt	2.1*	0.04*	1000*	–	Hyperactive	Hyperplasia	Hyperplasia	No
Case 13	13/F	+ (chest X-ray)	–	3	iodized salt	1.51	2.15	205*	–	Hypoactive	Hyperplasia	Papillary cancer	Yes
Case 14	14/F	–	+	3	rock salt	0.8*	0.8	1000*	–	Hypoactive	Hyperplasia	Hyperplasia	No

*: out of range
FT4: free thyroxine; TSH: thyroid stimulating hormone; TG: thyroglobulin; FNAB: fine-needle aspiration biopsy

Table 2: Clinical features of thyroid nodules

Case	Largest diameter of a thyroid nodule (mm)	Single/ Multiple	Echogenicity	Solid/ Cystic	Hyperaemia	Homogeneous/ Heterogeneous	Calcification	Cervical lymphadenopathy	Pathology
Case 1	22 x 31	Multiple	Hyperechogen	Solid	Yes	Heterogeneous	–	No	Papillary cancer
Case 2	17 x 27	Multiple	Isoechoic	Cystic	Yes	Heterogeneous	-	No	Papillary cancer
Case 3	25 x 14	Single	Hypoechogen	Cystic	Yes	Homogeneous	-	No	Follicular carcinoma
Case 4	23 x 17	Multiple	Isoechoic/ Hypoechogen	Cystic	Yes	Homogeneous	-	No	Follicular carcinoma
Case 5	14 x 8	Multiple	Isoechoic	Cystic	Yes	Homogeneous	-	Yes	Hyperplasia
Case 6	12 x 11	Multiple	Isoechoic	Solid	Yes	Heterogeneous	-	Yes	Hyperplasia
Case 7	38 x 25	Multiple	Isoechoic	Solid	Yes	Homogeneous	-	Yes	Papillary cancer
Case 8	21 x 17	Multiple	Isoechoic	Cystic	Yes	Heterogeneous	-	Yes	Papillary cancer
Case 9	41 x 54	Single	?	?	No	Heterogeneous	-	Yes	Follicular carcinoma
Case 10	34 x 35	Multiple	Isoechoic/ Hyperechogen	Cystic	Yes	Heterogeneous	+	Yes	Papillary cancer
Case 11	29 x 22	Multiple	Hyperechogen	?	No	?	-	Yes	Hyperplasia
Case 12	34 x 30	Multiple	Isoechoic/ Hypoechogen	Cystic	Yes	Homogeneous	+	No	Hyperplasia
Case 13	28 x 28	Single	Hypoechogen	Cystic	Yes	Homogeneous	+	Yes	Papillary cancer
Case 14	36 x 43	single	Isoechoic/	Cystic	No	Homogeneous	+	No	Hyperplasia

may result from the lower income of people who live in this region. People usually prefer using rock salt in spite of all warnings, because it is ten times cheaper than iodized salt. Additionally, iodine deficiency in some patients using the iodized salt suggests that the iodized salt is used in sub-optimal amounts or is stored improperly at home. Indeed, moisture plays a critical role in the stability of iodine in the iodized salt. In particular, when salt is stored at a temperature characteristic of storage and distribution conditions in many developing countries, moisture absorbed by hygroscopic impurities is the major contributor to the rapid loss of iodine. Furthermore, a salt jar at home should be kept closed and in dark places. Otherwise sunlight may cause a decrease in bioefficiency of iodine in the iodized salt (12).

Although goitre is four times more frequent in women, thyroid cancer is more common in men (13). The female: male ratio was 1:1 in our study.

Presence of thyroid cancer in the family increases the risk of exposure to neck radiation in childhood (14). There was no exposure to radiation in the neck region in our cases. However, four patients had taken chest X-rays previously. A family history of goitre and papillary thyroid cancer was positive in four and one of the patients, respectively. None of the patients had Hashimoto's thyroiditis. Apart from iodine deficiency, any obvious risk factor for thyroid cancer in our cases was not determined. Family history of patients could be a risk factor; a goitre could also be a sign of iodine deficiency.

Thyroid cancers might be accompanied with hypothyroidism, euthyroidism or hyperthyroidism. Hypothyroidism was present in nine patients, euthyroidism in four and hyperthyroidism in one.

Ultrasound is the imaging technique of choice in thyroid pathologies. No radiological technique is as sensitive or specific in showing malignancy as an ultrasound (15, 16). Fine-needle aspiration biopsy should be performed in thyroid nodules with a diameter larger than 10 mm. This was the case in all patients. Nodules are very important in thyroid cancer development. The primary objective in cases of goitre must be to detect thyroid nodules. Risk of nodule development increases with age, iodine deficiency and a history of radiotherapy to the neck (17). Compared to adults, children with thyroid cancers are more likely to have a thyroid nodule (18). The risk of cancer development in a single nodule is 10–25% and 1–7% in multiple nodules (19). An ultrasound is the most appropriate technique for detecting nodules. Fine-needle aspiration biopsy is an economical, reliable, easily performed technique with a low risk of complication; in other words, the most efficient technique in distinguishing whether a nodule is benign or malignant in cases with a diameter ≥ 10 mm (20). There is a significant difference between solid and cystic nodules in terms of the risk of developing cancer. The risk of malignancy is 8% in solid nodules and 15%–25% in cystic nodules (21, 22). However, another study reported that there was no difference in these two nodule forms in terms of frequency of malignancy (23). In our study, nine patients (64.2%) had cystic nodules, while three (21.4%) had solid nodules.

Fine-needle aspiration biopsy sensitivity and specificity range from 65%–98% and 72%–100%, respectively and diagnostic accuracy of 95% has been reported (24, 25). Grade 3 goitre was present in ten patients and grade 4 in four. This may indicate that families lack sufficient information regarding the importance of goitres. Nodules were identified

at ultrasound in all our cases. Fine-needle aspiration biopsy was performed from nodules, and cases identified as hyperplasia were also operated on. Hyperplasia was described in five of these patients. Bearing in mind the transition from hyperplasia to cancer, it is important that these patients were identified as early stage thyroid cancer.

In another study, 41% of children with nodules in the thyroid gland subsequently developed cancer (26). Nodules adhering to surrounding tissue, growing rapidly, and painless cervical lymphadenopathy are the main criteria for malignancy (27, 28). Fine-needle aspiration biopsy negativity in children is not as reliable as that in adults in terms of absence of cancer. In addition, children with a precancerous thyroid nodule like hyperplasia are shown to have a greater risk of getting thyroid cancer compared to adults (26). In this series, cases with normal FNABs were operated on due to increased bleeding, fixation of a nodule and presence of cervical lymphadenopathy. Pathology results were compatible with papillary cancer in two and follicular cancer in one. Three patients had a normal biopsy, but this does not exclude malignancy. Thyroid cancer is not ruled out by a negative FNAB. This finding suggests that clinical and radiological findings in children with thyroid cancer are more reliable than FNAB. Similarly, previous studies have reported cancer in cases with normal FNAB at surgery (29, 30).

Furthermore, increased bleeding is correlated with malignancy in thyroid nodules (31). Bleeding in nodules was determined in 11 (84.7%) of our cases. Data were unavail-able for three cases.

Thyroid scintigraphy is routinely used to evaluate thyroid nodules. It has been proven that cold or hypofunctional thyroid nodules are associated with malignancy more than hot or hyperfunctional ones (32). In our study, scintigraphic analysis of the patients revealed seven hypoactive nodules, five hyperactive nodules and two hypohyperactive nodules (17). In our patients with papillary cancers, two had hyperactive nodules, while four had nodular hyperplasia.

Thyroglobulin is the tumour marker of differentiated thyroid cancer after total thyroidectomy and radioiodine ablation (33). Differentiated thyroid cancer is known to have an excellent prognosis after initial treatment with surgery and radioactive iodine 131 systemic therapy (34). If TSH serum levels are more than 30 mU/L, thyroid tissue can optimize radioiodine intake (35). All of the patients underwent subtotal and total thyroidectomy by a paediatric surgical team. After total thyroidectomy, L-thyroxine 100 $\mu g/m^2$/day was given as a single oral dose. We used TG for tumour marker during the polyclinic control examination. Thyroglobulin levels in these cases were high, and residual thyroid tissue was determined on ultrasound and at thyroid scintigraphy. Four to six weeks after surgery, L-thyroxine treatment was stopped for 14 days. Total body scintigraphy was performed on patients with TSH levels over 30 µIU/mL. In case of residual/recurrence/metastastic conditions seen in total body scintigraphy, radioactive iodine 131 therapy was given. Recurrence was seen in two cases (cases 7, 13). All our cases are still being monitored.

Although thyroid cancers exhibit a rapid course in children, they do not affect life span (36). Papillary carcinoma is the most commonly seen thyroid cancer (85%), followed by the follicular type (10%). Anaplastic and medullary carcinomas are seen at a level of 5%. The giant cell type of anaplastic carcinoma is the most malignant. Papillary cancer and follicular carcinoma were determined in six (42.8%) and three (21.4%) of our cases. None of the patients had medullar or anaplastic type carcinoma. Five patients had nodular hyperplasia. Surgery is the primary treatment in thyroid cancers. There is no statistically significant difference in complications among total, near total or subtotal thyroidectomy cases (37).

The prevalence of thyroid cancer in Turkey, like other countries, is rising. Childhood thyroid cancer was very rare previously. The incidence of thyroid cancer in the adult population in the east of Turkey was reported to increase after the Chernobyl accident in 1986. Our region is very close to Chernobyl. Additionally, our region is bordered by countries such as Armenia, Georgia and Iran that have nuclear power plants. We think that a radiation leakage might contribute to the increasing incidence. Furthermore, iodine tablets are known to protect the thyroid gland from radioactive pollution. This finding, together with a probable radiation leakage, may explain the rise in thyroid cancer incidence in our region.

In conclusion, iodine deficiency is likely to play a role in thyroid cancer and prevention is important. The thyroid glands of children coming from areas of endemic iodine deficiency must be examined by ultrasound. Cases with thyroid nodule must be monitored closely. A FNAB must be performed when a nodule diameter is $\geq$ 10 mm. Even if the biopsy findings are normal, surgery must be done in the presence of bleeding in a nodule, fixation of a nodule and cervical lymphadenopathy. People should be informed about iodine deficiency. The use of iodized products such as salt, water and bread should be provided to people who live in areas with endemic iodine deficiency.

Authors' note

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Authors' contributions

A Kaya: manuscript preparation, patient's doctor, data acquisition, literature research; A Çayır: manuscript preparation, patient's doctor, data acquisition; Z Orbak: patient's doctor, manuscript review; A Oral: patient's doctor, data acquisition; B Demir: patient's doctor, data acquisition, literature research; H Döneray: patient's doctor, manuscript

preparation, manuscript editing; B Özkan: patient's doctor, manuscript review

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