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Relationship between Hashimoto's thyroiditis and papillary thyroid carcinoma in children and adolescents

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Abstract. – OBJECTIVE: We investigated the relationship between Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC) in children and adolescents.

PATIENTS AND METHODS: We carried out a retrospective study of thyroidectomies performed from 2004 to 2017 at The First People's Hospital and the Tumor Hospital of Yunnan Province (Kunming, China). The occurrence and features of PTC and benign thyroid disease (BTD) in children and adolescents (age ≤ 20 years) were compared.

RESULTS: We evaluated 258 consecutive thyroidectomies. Among children and adolescents with PTC, 23 cases were histopathologically confirmed as HT. Mean tumor diameter was smaller in children and adolescents with PTC than in those with BTD. Thyroid-stimulating hormone (TSH) level was abnormally elevated in a greater proportion of children and adolescents with PTC as compared to those with BTD or youths with PTC. The proportion of thyroglobulin antibody (TGAb)- and thyroid peroxidase antibody (TpoAb)-positive children and adolescents was higher in the PTC than in the BTD group. Among children and adolescents with PTC, 23 had HT as compared to two in the BTD group. The proportion of children/adolescents with abnormally elevated TSH levels was higher for the PTC combined with HT group than for the PTC without HT group. A multivariate conditional logistic regression analysis showed that elevated TGAb was an independent risk factor for PTC in children and adolescents.

CONCLUSIONS: HT is associated with an increased occurrence of PTC in children and adolescents.

Key Words:
Papillary thyroid carcinoma, Hashimoto's thyroiditis, Thyroid autoimmunity antibody, Children, Adolescents.

Abbreviations

PTC = papillary thyroid carcinoma, DTC = differentiated thyroid carcinoma, BTD = benign thyroid tumor, ATD = autoimmune thyroid disease, HT = Hashimoto's thyroiditis, LT = lymphocytic thyroiditis, GD = Graves' disease, TG = thyroglobulin, TPOAb = thyroid peroxidase antibody, TGAb = thyroglobulin antibody, TGAb = thyroglobulin antibody, TRAb = thyrotrophin receptor, TSH = thyroid-stimulating hormone, CLNM = Central lymph nodes metastasis, LLNM = Lateral lymph nodes metastasis.

Introduction

Thyroid cancer is rare in children and adolescents, accounting for 0.5-3% of all thyroid cancer cases[1] and 1.5-3% of all childhood cancers in North America and Europe. It is the third leading type of childhood solid tumor[2]. In recent years, the occurrence of thyroid cancer among children and adolescents has been steadily rising. Data from the National Cancer Institute Surveil-

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lance, Epidemiology, and End Results Registry have shown that from 1984 to 2010, differentiated thyroid cancer occurrence increased among children, adolescents, and young adults under the age of 30 years in the U.S[3]. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer in both adults and children: in youths ≤ 20 years old, 80-95% of pathological cases are diagnosed as PTC[4,5].

Thyroid cancer can coexist with Hashimoto's thyroiditis (HT), adenoma, and nodular goiter. HT is the most common form of childhood thyroiditis[6] and the most frequent cause of pediatric thyroid disease in areas of the world where iodine is abundant[7]. HT is characterized by high serum thyroid auto-antibody titers and goiter, and is the most common manifestation of goiter with hypothyroidism. The coexistence of thyroid cancer and HT has been increasing in recent years, and an increase in the risk of developing papillary cancer has been reported for HT patients[8-10]. Many studies have reported the close relationship between HT and PTC in adults, but a few have investigated whether there is a similar link in children and adolescents. A research[11] identified thyroid nodular disease in 31.5% of pediatric patients with juvenile autoimmune thyroiditis, and found that cancer was present in at least 9.6% of these cases, with PTC being the most common histologic type. Due to the low occurrence of child and adolescent thyroid cancers, there have not been any retrospective case studies of this age group in the Chinese population. Yunnan Province is located in People's Republic of China's Yunnan-Guizhou plateau, where the watershed of the Yangtze River meets the Pearl River Highlands. The altitude of Yunnan Province is 1,500-2,000 m above sea level, with some of the mountain peaks reaching heights of >3,000 m. Various studies have investigated the prevalence of and factors associated with PTC in People's Republic of China and other countries, but the population living at moderate altitudes (1,500-2,500 m) on the Yunnan-Kweichow plateau in South-Western China has not been included in any surveys to date. So, the present investigation, which is part of a survey of PTC risk factors in the Yunnan plateau carried out by our research center[12], retrospectively analyzed 129 children and adolescents at the First People's Hospital and Tumor Hospital of Yunnan Province who were diagnosed with PTC between January 2004 and December 2017, as well as 129 patients with benign thyroid disease (BTD) as a control for analyzing the clinical manifestations and pathological characteristics of patients in order to evaluate the relationship between HT and PTC in children and adolescents in the Yunnan plateau region. We also investigated the relationship between Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC) in children and adolescents.

Patients and Methods

Patients

The study protocol was approved by the Institutional Review Board of Yunnan First People's Hospital. This was a cross-sectional study of patients with a cytological diagnosis of HT or lymphocytic thyroiditis (LT). A total of 258 patients (216 female and 42 male) with rapidly growing thyroid nodules – for whom malignancy was suspected based on ultrasonography results – or nodules fixed to adjacent structures, and who underwent initial thyroidectomy at The First People's Hospital and Tumor Hospital of Yunnan Province, were retrospectively recruited from January 2004 to December 2017. All patients met the following criteria: 1) they were not taking L-T4 or methimazole and did not have significant hyper- or hypothyroidism; 2) their thyroid-stimulating hormone (TSH), free thyroid hormone, and thyroidglobulin antibody levels, were measured within 1 week prior to thyroidectomy; 3) they had not previously undergone any type of thyroid surgery. Patients exhibiting diffuse lymphocytic and plasma cell infiltration in the thyroid parenchyma and stroma, oxyphilic cells, and lymphoid follicles with reactive germinal centers were defined as having HT. If there were no oxyphilic cells, then a diagnosis of LT was made.

Methods

Patient characteristics such as age, sex, marital status, fertility state, and presence of other BTDs as well as information on clinical presentation were noted. Thyroid functional tests measuring the levels of TSH (normal value: 0.3-5.5 IU/ml) and anti-thyroid antibodies – i.e., thyroid peroxidase (TPOAb), thyroglobulin (TGAb), and thyrotrophin receptor (TRAb) – were carried out. TGAb > 30%, TPOAb > 20%, and TRAb > 5 U/l were considered positive. TSH and anti-thyroid antibody levels were evaluated in the hospital laboratories using radioimmunoassay kits (Tianjin

Xiehe Medical Science Co., Tianjin, China) according to the manufacturer's instructions and a DF-96 Geiger counter (Zhongchen Mechanical and Electrical Co., Foshan, China).

Statistical Analysis

Data were analyzed using SPSS v.17.0 (SPSS Inc., Chicago, IL, USA) and were reported as mean ± SD. Differences in thyroid cancer characteristics between groups were assessed with the χ^2-test. A univariate analysis was used to screen factors related to thyroid cancer, and a multivariate logistic regression analysis was used to evaluate PTC risk. In all cases, $p < 0.05$ was considered statistically significant. All data were analyzed anonymously.

Results

Clinical Characteristics

Children and adolescents were defined as patients < 21 years old[13]. A total of 258 of children and adolescents were diagnosed with BTD and PTC respectively. The age range of children and adolescents with PTC was between 6 and 20 years old (mean: 17.31±3.21 years), and the female-to-male ratio was 4.6:1. Children and adolescents with BTD ranged from 6 to 20 years (mean: 16.91±3.25 years), and the female-to-male ratio was 5.8:1. There was no difference between the two groups with respect to age ($p = 0.33$). Tumor diameters were smaller in children and adolescents in the PTC as compared to the BTD group (2.56±1.36 *vs.* 3.27±1.35 cm) ($p < 0.01$) (Table I).

Clinicopathological Features of PTC and BTD Patients

The proportion of children and adolescents with tumor diameter < 2 cm was higher among those with PTC than with BTD ($p < 0.01$), indicating that tumor diameters were smaller for PTC. All patients underwent near-total or total thyroidectomy and central and/or lateral lymph node dissection. Among children and adolescents, 9 patients (9%) (four female and five male) developed lung metastases following a diagnosis of PTC. With regards to tumor-node-metastasis (TNM) staging, patients exhibited stage II or I lung metastasis, with no significant difference between children and adolescents. A greater proportion of children and adolescents in the PTC (16.7%) as compared to the BTD group (6.3%) had elevated TSH levels ($p = 0.02$ and $p = 0.049$, respectively). Among children and adolescents with PTC, 24 were TGAb-positive (21.4%) and 28 were TPOAb-positive (25.8%); this was significantly higher than the percentages of children and adolescents in the BTD group ($p < 0.001$) (Table II). These results suggest that higher thyroid autoimmune antibody levels are associated with PTC in children and adolescents.

Clinicopathological Features of Patients with PTC Combined with HT

Among children and adolescents with PTC, 23 (all female) had concurrent HT as compared to two patients with BTD (17.8% *vs.* 1.6%, $p < 0.01$). Eight PTC patients had concurrent LT as compared to only one BTD case (6.2% *vs.* 0.8%, $p < 0.01$). Among PTC patients with concurrent HT, 11 (70%) and 12 (80%) cases were positive for TGAb and TpoAb, respectively, which were higher than among PTC patients without HT ($p < 0.001$) (Table III), suggesting that thyroid autoantibodies are specific to HT-induced PTC. There were no differences between the two groups in terms of distant or LNM, local invasion, or TNM staging.

Table I. Demographic characteristics of 258 patients analyzed in this study.

Subgroups	PTC in children and adolescents (n=129)	BTD in children and adolescents (n=129)
Gender		
Male	23 (17.8)	19 (14.7)
Female	106 (82.2)	110 (85.3)
Age group, y		
0-95 (3.9)	6 (4.7)	
10-14	12 (9.3)	21 (16.3)
15-20112 (86.8)	102 (79.1)	
Age (year)	17.31±3.21	16.91±3.25
Tumor size (cm)	2.56±1.36	3.27±1.35

Table II. Final histopathology diagnosis after thyroidectomy in 256 patients involved in this study.

Subgroups		PTC in children and adolescents (n=129)	BTD in children and adolescents (n=129)	χ^2	p
Tumor Size (cm)	< 2 ≥ 2	38 (29.7) 90 (70.3)	18 (14.0) 111 (86.0)	9.33	0.002
TSH (mU/L)	< 0.3 0.3-5.5 > 5.5	6 (5.3) 89 (78.1) 19 (16.7)	7 (6.3) 98 (87.5) 7 (6.3)	6.03	0.049
TGAb (%)	≤ 30 > 30	92 (78.6) 25 (21.4)	109 (99.1) 1 (0.9)	23.40	<0.001
TPOAb (%)	≤ 20 > 20	72 (74.2) 25 (25.8)	91 (93.8) 6 (6.2)	13.86	<0.001
Hashimoto's thyroiditis	Without With	106 (82.2) 23 (17.8)	127 (98.4) 2 (1.6)	19.53	<0.001
Lymphocytic thyroiditis	Without With	121 (93.8) 8 (6.2)	128 (99.2) 1 (0.8)	4.41	0.042
Lymphatic metastasis	With Without	94 (72.9) 35 (27.1)	0 (0) 129 (100)	147.88	<0.001
Distance metastasis	With Without	9 (7.0) 120 (93.0)	0 (0) 129 (100)	7.37	0.007
Central lymph nodes metastasis (CLNM)	With without	83 (64.3) 46 (35.7)	0 (0) 129 (100)	122.37	<0.001
Lateral lymph nodes metastasis (LLNM)	With Without	60 (46.5) 69 (53.5)	0 (0) 129 (100)	78.18	<0.001
TNM staging	I II	121 (93.8) 8 (6.2)	0 (0) 0 (0)		

Independent Risk Factors for PTC in Children and Adolescents

Clinicopathological factors were evaluated in uni- and multivariate analyses in order to identify PTC risk factors in all 258 patients. The univariate analysis showed significant odds ratios (ORs) > 1 for PTC with elevated levels of TSH or TPOAb and HT or LT. In the multivariate analysis, nodule size > 1 cm had a significant OR of < 1 whereas increased TGAb level had significant ORs > 1 (Table IV).

Discussion

In general, the prognosis for PTC is excellent, especially among pediatric patients. Nonetheless, it is important to identify high-risk patients at the time of diagnosis, with cancer staging and risk assessment being essential aspects of patient management that provide accurate prognostic information and determine the extent of treatment that is necessary. The majority of thyroid cancers are papillary carcinomas in adults and in children. Diagnostic, therapeutic, and environmental radiation exposure are well-known risk factors for thyroid cancers [14-16], but a high occurrence has been reported in China despite the fact that no nuclear tests have been conducted [17]. Moreover, none of the cases in the present study had any history of radiation exposure, indicating that other risk factors should be taken into consideration.

Autoimmune thyroid disease (ATD) is the most common cause of thyroid dysfunction among children and adolescents with adequate iodine intake[18]. The prevalence of thyroid cancer in ATD patients is

unknown, but ranges from 1% to 30% in adults[19,20]. ATD may be a risk factor for pediatric thyroid cancer [21]. HT is a common organ-specific ATD with an annual occurrence of 0.3-1.5 cases per 1000 persons[22] that is closely associated with PTC[23-27]. HT affects 1.3% of children and is predominantly observed in females[22,28]. HT was previously diagnosed based on elevated TGAb and TPOAb levels, and papillary carcinoma has a higher occurrence in patients with positive as compared to negative thyroid autoantibody test results[29]. Data on children with autoimmune thyroiditis are scarce. PTC has been detected in 3.0%[11] and in 1.3%[7] of children with chronic thyroiditis. Although thyroid cancer is a relatively rare childhood malignancy with a reported occurrence of 0.5-1.2 cases per million, our data and those of other investigators suggest that PTC prevalence is higher among children with ATD, a finding that can influence the management and follow-up of ATD patients. A retrospective analysis of patients in the Changsha region of China revealed that 44% of children with PTC had concurrent HT[17]. Another research[30] which was conducted in India found that 7.5% of cases were associated with autoimmune thyroiditis, 5.6% with HT, and 1.0% with LT. Elevated TPOAb and TGAb levels were associated with thyroid nodules, while 67.4% of HT cases were TPOAb-positive. Of 129 children with PTC, we identified 23 (17.8%) with concurrent HT and 8 (6.2%) with concurrent LT, which was lower

Table III. Characteristics of children and adolescents patients about PTC with or without HT.

Subgroups		PTC with HT (n=23)	PTC without HT (n=106)	OR	CI (5-95%)	p-value
Gender	Male	0 (0)	23 (21.7)	1	--	
	Female	23 (100)	83 (78.3)	--	--	
Age (year)	< 15	3 (13.0)	14 (13.2)	1	--	
	15-20	20 (87.0)	92 (86.8)	1.01	0.27, 3.86	0.98
Tumor Size (cm)	< 2	13 (56.5)	25 (23.8)	1	--	
	≥ 2 cm	10 (43.5)	80 (76.2)	0.95		
TSH (mU/L)	< 0.3	1 (5.6)	5 (5.2)	2.76		
	0.3-5.5	10 (55.6)	79 (82.3)	1	--	
	>5.5	7 (38.9)	12 (12.5)	4.14		
TGAb (%)	≤30	6 (30.0)	86 (88.7)	1	--	
	>30	14 (70.0)	11 (11.3)	18.24	5.81,57.26	<0.01
TPOAb (%)	≤20	3 (20.0)	69 (84.1)	1	--	
	> 20	12 (80.0)	13 (15.9)	21.23	5.25, 85.84	<0.01
Lymphatic metastasis	With	16 (69.6)	78 (73.6)	1	--	
	Without	7 (30.4)	28 (26.4)	1.22	0.45, 3.27	0.70
Distance metastasis	With	0 (0)	9 (8.5)	1	--	
	Without	23 (100)	97 (91.5)	--		
Central lymph nodes metastasis	With	16 (69.6)	67 (63.2)	1	--	
	Without	7 (30.4)	39 (36.8)	1.33	0.50, 3.52	0.57
Lateral lymph nodes metastasis	With	10 (43.5)	50 (47.2)	1	--	
	Without	13 (56.5)	56 (52.8)	0.86	0.35, 2.14	0.75
Local invasion	Intrathyroidal extension	18 (78.3)	84 (79.2)	0.94	0.32, 2.82	0.92
	Extrathyroidal extension	5 (21.7)	22 (20.8)	1		
TNM staging	1	23 (100)	98 (92.5)	1	--	
	2	0 (0)	8(7.5)	--	--	

Table IV. Univariate and multivariate analysis for independent risk factors of children and adolescents PTC.

Factors	Odds ratio	95% CI	*p*-value
Univariate analysis			
TSH (+)	2.01	1.03, 3.94	0.041
TPOAb (+)	5.27	2.05, 13.52	<0.01
Hashimoto's thyroiditis (with *vs*. without)	13.78	3.18, 59.79	<0.01
Lymphocytic thyroiditis (with *vs*. without)	8.46	1.04, 68.67	0.046
Multivariate analysis			
Nodule Size > 2 cm	0.72	0.56, 0.92	<0.01
TGAb (+)	23.19	2.91, 184.44	<0.01

than the rates reported by Chang et al[17]. A possible reason for this discrepancy is that the previous study examined only 32 cases, which is far less than the number in our study. However, these percentages are much higher than those reported in European and American populations[7, 11] and of those observed in our previous investigation of adults living in the Yunnan plateau (12.1 and 3.6%, respectively)[12]. Nonetheless, patients with ATD with suspected thyroid nodules or significant gland asymmetry – especially in association with palpable cervical lymphadenopathy[31] – should be evaluated by an experienced thyroid ultrasonographer. On the other hand, the significance of circulating TGAb level in PTC patients remains controversial[9,26,32-35]; since TGAb concentrations change in response to the level of circulating TG antigen and indirectly represent changes in thyroid tissue mass, TGAb level can serve as a surrogate marker for DTC[36]. Several researches[37-39] have examined the association between PTC aggressiveness and circulating TGAb level, with most reporting the *de novo* appearance, persistence, or increase in TGAb concentrations during the postoperative period as a significant risk factor for persistent or recurrent disease[40]. The occurrence of positive TGAb and/or TPOAb titers is approximately two-fold higher in DTC patients than in the general population[23]; however, perioperative TGAb level is not an independent predictor of DTC prognosis[35]. Our findings suggest a close association between TGAb and PTC in children and adolescents, but the American Thyroid Association guidelines indicate that TG should be considered as a marker in the evaluation, treatment, and long-term follow up of DTC in children, even in those not previously treated with ^{131}I; however, TGAb levels should be concurrently measured in all samples since its presence will render the TG result uninterpretable[31]. Factors associated with thyroid function/autoimmunity – particularly TPOAb – can be used as diagnostic markers for predicting thyroid cancer risk[41]. It was previously reported[42] that positive results for serum TGAb or TPOAb are an independent predictor of PTC regardless of the presence of ATD. Moreover, the coexistence of TGAb and TPOAb confers a greater risk for PTC than TGAb or TPOAb alone, and is correlated with elevated TSH level and advanced PTC stage[42]. In our study, we found that TPOAb is not an independent risk factor for children and adolescents with PTC, although it is associated with pediatric cases. In summary, the TGAb and TPOAb are diagnostic antibodies for HT; in the present study, these were found to be risk factors for PTC in children and adolescents, leading us to conclude that in these patients, PTC is closely related to HT. TSH, also known as thyrotropin, is the main factor acting on thyroid tissue. TSH signaling has been implicated in DTC, in which malignant cells typically express TSH receptor[43]; moreover, DTC is characterized by hyperactivation of this receptor[44]. In animal models, TSH overexpression leads to thyroid hyperstimulation, resulting in hyperplasia and an increase in the rate of cancer development[45,46]. A diagnosis of pediatric thyroid carcinoma is significantly associated with elevated TSH levels[47], and serum TSH concentration was significantly higher in children and adolescents with thyroid cancer as compared to those with benign nodules, with cancer prevalence increasing as a function of serum TSH level[47]. TSH is an independent risk factor for PTC[48], although this has been contested by others; for example, it has been suggested that growth factors such as insulin-like growth factor 1 may play a more important role[49]. A research carried out on Turkish children with thyroid cancer found that TSH was not associated with PTC[50]. In our study, TSH was not found to be an independent risk factor for PTC in children and adolescents, but in the univariate analysis, an abnormal elevation in TSH level increased the risk of

PTC. PTC has different clinical manifestations in children and adults[51]; long-term morbidity and mortality are better in children than in adults with advanced local disease, lymph node involvement, and distant metastases[52], and the overall long-term prognosis of PTC in the pediatric population is excellent. A study in a North American population found that the presence of LT was associated with a 39% decrease in the risk of CLNM after adjusting for age, gender, tumor size, PTC histopathologic subtype, and presence of lymphovascular invasion[53]. In children and adolescents with DTC accompanied by chronic thyroiditis, the tumor is more aggressive than that without it[54]. In our study, lung metastasis, CLNM, and lateral LLNM occurred at higher rates in children and adolescents with PTC than in youth irrespective of the presence of HT. We speculate that HT in children and adolescents with PTC has no effect on lymph node and distant metastases, although this remains to be confirmed in future studies. The Yunnan plateau is located in South-Western China at an altitude of 1,500-2,500 m above sea level, occupying a unique geographical position. The mountainous area accounts for 84-98% of the plateau. Iodine deficiency is widespread in Yunnan Province, which comprises 16 prefectures (cities) and 129 counties (cities/districts) of 45.7 million inhabitants. In Yunnan, iodine content in water is low (150 μg/L)[55] and has been linked to the high occurrence of thyroid cancer in this region. Universal salt iodization (USI) has been carried out throughout People's Republic of China since 1996, and iodine intake has consequently increased nationwide. This, in conjunction with Yunnan iodine deficiency prevention measures, has led to a significant improvement in iodine nutritional status among residents. However, iodine excess resulting from overexposure to environmental iodine in addition to poor monitoring is now more frequently observed than iodine deficiency and is a precipitating environmental factor in the development of autoimmune thyroid disease, hypo- and hyperthyroidism, and cancer[56-60]. Too much iodine intake and thyroid disease are closely related. Excessive intake of iodine may lead to thyroid autoimmune diseases[61]. An increased frequency of TGAb and of HT was observed after the beginning of iodine prophylaxis[62]. We hypothesized that the occurrence of thyroid cancer in children and adolescents in the Yunnan Plateau may be related to the excess iodine in the area. A limitation of the study is that we did not evaluate the prognosis of pediatric PTC patients with and without HT, and focused instead on the influence of HT on local invasion and distant metastasis in PTC. In addition, there was no post-operative long-term follow-up, which would have provided additional information on survival rates.

Conclusions

HT is associated with an increased occurrence of PTC but has no effect on local invasion and distant lymph node metastasis in children and adolescents in the Yunnan Plateau of South-Western of China. The question of whether HT affects the prognosis of PTC patients awaits further study. We, therefore, recommend that thyroid nodules in children and adolescents should be treated seriously, especially when occurring in conjunction with HT, or associated with a tumor diameter < 1 cm or abnormal elevations in TGAb, TG, or TPOAb levels; in these cases, PTC should be suspected. We recommend using fine-needle aspiration to ascertain whether thyroid resection is necessary; if the lesion increases in size, or if LLNM is suspected, surgical excision under general anesthesia should be considered as a treatment option.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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