Review Article

Maria Lucia Sur, Remus Gaga*, Călin Lazăr, Cecilia Lazea, Cornel Aldea and Daniel Sur

Papillary thyroid carcinoma in children with Hashimoto's thyroiditis – a review of the literature between 2000 and 2020

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Abstract

Objectives: Thyroid cancer is the most common pediatric endocrine neoplasm representing 3% of all malignancies in children. Hashimoto's thyroiditis (HT) is also a common disorder in the pediatric age range. Patients with HT frequently develop enlarged thyroid with nodules. We aimed to provide a literature review on the frequency of papillary thyroid carcinoma (PTC) in patients with HT.

Content: A literature search of the PubMed database between 2000 and 2020 was performed, using the relevant keywords "papillary thyroid carcinoma," "Hashimoto's thyroiditis" and "children". We followed the PRISMA statement guidelines during the preparation of this review. Six studies (n=2,065 patients with HT) were retained for the final analysis. The follow-up of the patients with HT was from 2 to 10 years. PTC was diagnosed in 0.67–7.87% of the HT patients included in these studies. In patients with HT and nodules, the percentage of PTC varied between 5.13 and 35%. The overall occurrence of PTC in patients with HT was 3.07%.

Summary and Outlook: The number of patients developing thyroid nodules in relation to HT was increased. The development of PTC in children with HT appeared to be higher than in the normal population.

Keywords: children; Hashimoto's thyroiditis; papillary thyroid carcinoma.

Background and aims

Thyroid cancer is an uncommon cancer in childhood. Fewer than one in 100,000 children develop thyroid cancer each year. Although it can occur at any age, childhood thyroid cancer is most common in the teenage years, and it is the second most common cancer among adolescents ages 15–19 [1].

Thyroid cancer is also the most common pediatric endocrine neoplasm representing 3% of all malignancies in children. Its prevalence is rising by 4.43% per year in the United States as was reported by Bernier et al. [2]. Although its incidence rates have progressively increased over the past 30 years [3–5], thyroid cancer remains rare in children and adolescents compared to adults. Only 2% of the approximately 60,000 cases annually diagnosed in the USA regard subjects younger than 19 years of age [6].

However, thyroid cancer plays a relevant role in pediatric oncology, as, in the USA, it is the eighth most common cancer diagnosed in patients aged 15–19 years and is the second most common cancer among adolescent girls [7].

The overall incidence of thyroid cancer in children is growing in Europe and America, being described in the literature as 0.5–1.2/million for children under 14 years of age and 4.4–11/million for children between 15 and 19 years of age [8].

There are several types of thyroid cancer, but they do not pertain to the present study [9].

Differentiated thyroid carcinoma includes two different types, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Both of these types of thyroid cancer develop from the thyroid cells that normally produce thyroid hormone. Papillary carcinoma (PTC) is the

All authors contributed equally to this work.

***Corresponding author: Remus Gaga**, Department of Pediatrics, Iuliu Haţieganu University of Medicine and Pharmacy, Victor Babeş 8, Cluj-Napoca, Romania; and Clinical Emergency Hospital for Children, Moţilor 68, Cluj-Napoca, Romania, E-mail: remusgaga@gmail.com. https://orcid.org/0000-0001-8326-5570

Maria Lucia Sur, Călin Lazăr, Cecilia Lazea and Cornel Aldea, Department of Pediatrics, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; Clinical Emergency Hospital for Children, Cluj-Napoca, Romania

Daniel Sur, Department of Medical Oncology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; The Oncology Institute "Prof. Dr. Ion Chiricuta", Cluj-Napoca, Romania

more common type and can occur at any age, but most often, it affects people aged 30–50 years [10]. Follicular carcinoma is less common and accounts for about 10% of cases. It also arises from the thyroid's follicular cells and it usually affects people older than 50 years. Hurthle cell cancer is a rare and potentially more aggressive type of follicular thyroid cancer [11].

Due to its increased incidence, papillary thyroid carcinoma (PTC) is the most extensively studied type of thyroid cancer, and it accounts for approximately 90% of the tumors. It is also the most common thyroid carcinoma found in pediatric patients. One of the supposed risk factors that has been linked to its development is autoimmune thyroiditis [6].

Hashimoto's thyroiditis (HT) is another common autoimmune disease with an estimated prevalence of 1–2% in children with variations according to genetic susceptibility, age and gender, ethnicity and iodine status. Currently, HT is being considered the most common cause of hypothyroidism in iodine sufficient areas in both the adult and pediatric patients. Although considered benign for many years, HT proved its unfavorable evolution being involved in altering the reproductive system, influencing mental and intellectual activity, influencing other autoimmune diseases and last but not least in the occurrence of malignant processes such as PTC [12, 13]. Potential causal associations between Hashimoto's thyroiditis and PTC have been studied previously and were first reported by Dailey et al. in 1955, linking chronic inflammation to neoplastic changes [14].

This issue is a continuing debate. Some studies have revealed a higher risk of PTC in patients with HT, while others did not demonstrate the increased risk. Lee et al. published a meta-analysis and found that PTC is significantly associated with pathologically confirmed HT [15]. Jankovic et al. found no statistically significant correlation between HT and PTC based on fine-needle aspiration (FNA) and thyroidectomy studies review. Other studies suggest a standardized incidence of 0.54 cases per 100,000 persons [16]. An explanation for these results is that both PTC and HT are precipitated by an interplay among the same genetic factors and environmental influences such as: female predominance, excess iodine intake and exposure to radiation [17].

In 2017, Lai et al. conducted a meta-analysis on 76,281 patients and finally showed that HT predisposed patients to the development of PTC [18]. However, a few studies focus on the link between HT and PTC in children. Some of them were conducted in the last years and were not analyzed in meta-analyses. We aimed to provide a literature review on the frequency of PTC in pediatric patients suffering from HT.

Methods

A literature search of the PubMed database between 2000 and 2020 was performed, using the relevant keywords "papillary thyroid carcinoma" and "Hashimoto's thyroiditis." We followed the PRISMA statement guidelines during the preparation of this review [19].

The quality appraisal and risk of bias of the studies were done by two individual reviewers (MLS and RG).This included the number of patients, year of publication, study period, study location and diagnostic procedure. With the retrieved information, the reviewers arrived at a decision. If the two reviewers had any disagreement, a third reviewer (CL) was consulted to reach a consensus.

Our initial intent was to do a meta-analysis. Because of the heterogeneity and inconsistency between the characteristics of the patients included in the studies, we could not perform the quantitative synthesis.

Results

The PubMed citations identified 85 articles, using the search terms "papillary thyroid carcinoma," "Hashimoto's thyroiditis" and "children," from inception to May 2020. In the period of interest, 2000–2020, a number of 59 articles were identified and 15 were retrieved for analysis. Six English language studies (n=2,065 patients with HT) were included in the final analysis (Figure 1).

All the six studies included in the final analysis were retrospective. The 11 studies included a total number of 2,065 patients with HT, with individual study cohorts counting from 89 to 904 children [20–25].

In 2008, Corrias et al. conducted one of the most important studies in the field. Its objective was to investigate the association between juvenile autoimmune thyroiditis (JAT) and thyroid cancer in pediatric patients. Data from six Italian pediatric endocrinology centers were collected in a retrospective study with 365 children and adolescents affected by JAT diagnosed at 3.6–17.0 years of age. All patients underwent clinical examination and thyroid function tests every 6–12 months and thyroid echography every 12–24 months. Fine-needle aspiration biopsy was performed in 39 patients. Thyroid nodules were found in 115 patients; 11 of these were confirmed to be papillary carcinoma at the cytology exam. The growth of nodules during levothyroxine sodium therapy (OR, 15.60; 95% CI, 1.87–181.90) and the finding of lymphadenopathy (OR, 5.44; 95% CI, 1.05–30.50) were statistically significantly associated with the presence of cancer, while uninodularity and hypoechogenicity were not [20].

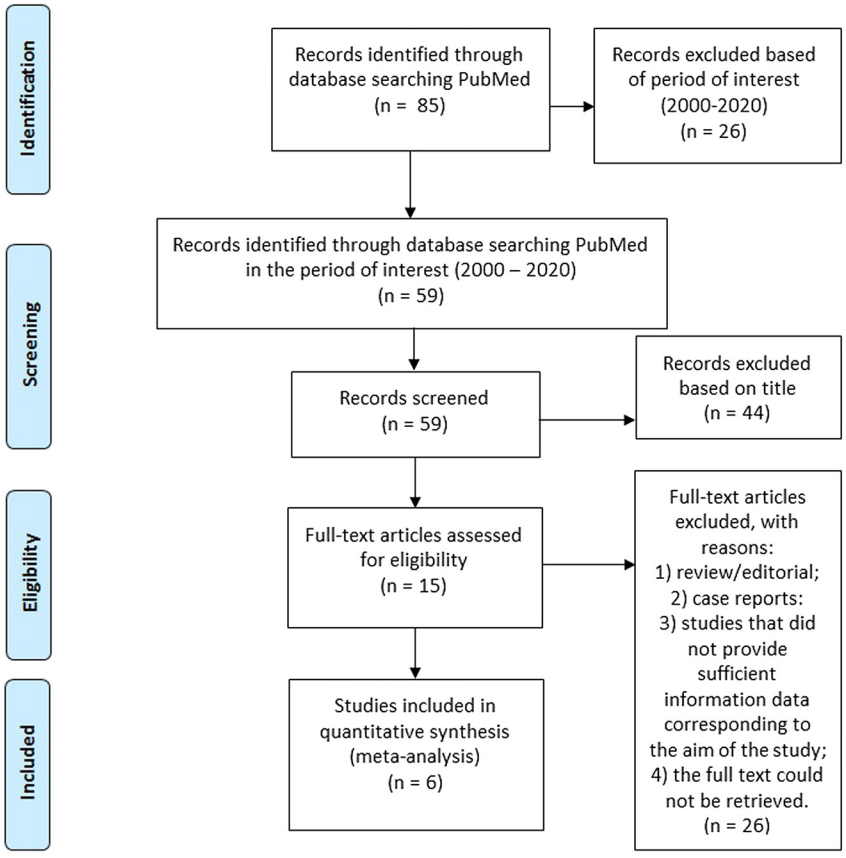

Figure 1: PRISMA flow diagram of studies screening and selection.

Skarpa et al. aimed to define the epidemiological, clinical and laboratory characteristics of children and adolescents with AIT. Various parameters including thyroid ultrasonography of 228 children and adolescents aged 10.2 ± 2.5 years (mean ± SD) with AIT, who attended the clinic during a 5-year period were retrospectively analyzed. From the total number of patients, 191 (83.8%) were female and 142 (62.3%) were pubertal. At AIT diagnosis, 130 children (57.0%) were euthyroid, 75 (32.9%) had subclinical hypothyroidism, 19 (8.3%) had hypothyroidism and 4 (1.8%) had hyperthyroidism. There was a positive correlation between thyroid stimulating hormone (TSH) levels and thyroid volume SDS (r=0.15, p=0.02). Sixty-three children (28%) had a goiter and 32 (14%) had thyroid nodules. Three children (1.3%) had PTC. Compared to euthyroid children, children with hypothyroidism were younger (9.2 ± 1.8 vs. 10.6 ± 2.4 years, p<0.05) and had higher thyroid volume SDS (3.1 ± 1.9 vs. 1.2 ± 1.2, p<0.05) and higher prevalence of goiter (11 [57.9%] vs. 29 [22.3%], p<0.05). The study concluded that children and adolescents with AIT were mostly asymptomatic; the majority were female, pubertal and euthyroid. There was an increase in thyroid volume, prevalence of goiter and antithyroid antibodies in the hypothyroid children [21].

Keskin et al. included in the study patients diagnosed with HT between 2004 and 2013. The HT diagnosis was made with a heterogeneous appearance on thyroid ultrasonography and the elevation of anti-TPO and/or anti-TG antibodies. Fine-needle aspiration biopsy (FNAB) was performed in cases with a nodule size >1 cm or in the cases in which findings were indicating malignancy. A total of 39 (13%) thyroid nodules were detected in 300 patients with a diagnosis of HT. Papillary thyroid carcinoma (PTC) was diagnosed in 2 of the 12 cases in whom FNAB was performed. In another 2 cases with malignancy, the thyroid nodule was detected at the same time as HT. The PTC diagnosis was made 2 years after the HT diagnosis in the first case and 3 years later in the second case. Keskin et al. concluded that the thyroid nodule rate on an HT background was 13%, and the thyroid malignancy rate was 0.67% [22].

In 2018, Janus et al. aimed to make a retrospective analysis of the ultrasound manifestation of AIT in relation to PTC development in pediatric patients. The study included 179 pediatric patients (133 females), mean (SD) age: 13.9 (3.03) years diagnosed with AIT and referred for ultrasound evaluation. Eight patients were diagnosed with PTC (6 females). The following results were observed in 179

patients: hypoechogenic background and normoechogenic parenchyma (35.2%), thyroiditis with irregular background (30.2%), nodular variant with normoechogenic background (18.9%), micronodulations (11.7%) and diffuse hypoechogenic background (3.9%). Janus et al. concluded that patients with AIT and nodular variant with normoechogenic irregular background of the thyroid gland on US scans are in the risk group of developing PTC and should be followed up with regular ultrasound investigations [23].

Won et al. retrospectively reviewed 89 pediatric and adolescent patients (age, 3–18.0 years) with HT who underwent thyroid ultrasonography (US) from February 2006 to July 2016 in Korea. Thyroid nodules were found in 20 of the 89 patients (22.4%). Eight of these 20 patients (40%) had colloid cysts, two (10%) had nodular hyperplasia, one (5%) had follicular adenoma, and two (10%) had lymphocytic thyroiditis. Seven of the 89 patients (7.9%) were confirmed to have a malignancy and in all of these cases PTC was confirmed; of those, five patients had diffuse sclerosing variant PTC, and two had conventional PTC on pathology. The study concluded that the prevalence of thyroid nodules in children and adolescents with HT was 22.4%, the malignancy rate of the same group was 7.9% and the malignancy rate among thyroid nodules was 35%, which is higher than the 26% rate generally reported for children with nodules. Therefore, using thyroid US to survey known or suspected thyroid nodules might be helpful in children and adolescents with HT and may provide further useful diagnostic information [24].

Radetti et al. made a retrospective survey of 904 children/adolescents with HT (709 females, 195 males) regularly followed in nine Italian centers of pediatric endocrinology was performed in order to assess the prevalence of thyroid nodules and/or cancer in patients with HT. Median period of follow-up was 4.5 years (1.2–12.8 years). The results indicated that 174 nodules were detected, with an annual incidence rate of 3.5%. About 10 nodules were malignant (8 papillary and 2 papillary follicular variant), giving a 5.7% prevalence of cancer among patients with nodules. The severity of hypoechogenity at ultrasound, anti-TPO antibodies and free T4 serum concentrations were predictive for the appearance of new nodules. Radetti et al. concluded that HT seems to influence the development of thyroid nodules, but not cancer in children and adolescents [25].

The summary of all the included studies and their results are shown in Table 1.

Discussions

In our clinical practice, we have encountered many cases of HT in children. Although considered benign for many years, HT has proven its influence on various other autoimmune diseases such as celiac disease, type 1 diabetes, autoimmune hepatitis, and last but not least, in the occurrence of malignant processes such as PTC. We have put a series of questions regarding the management of HT in pediatric patients such as: the timing of the introduction of treatment, the follow-up of patients to detect the appearance of nodules or thyroid papillary carcinoma, as well as other complications and associations of HT.

During a period of 5 years, we had 38 cases of HT with a higher prevalence in females and the appearance of nodules in 5 cases. We have not had any case of PTC in the HT patients so far but it should be mentioned that our service is a general pediatric service, not a center focused on thyroid pathology.

Research began to be more systematized after 2015, demonstrating the concern about the pathology of the thyroid and the association with HT.

We had consulted the data from the literature and found that there are different opinions about the moment

Table 1: Summary of the included studies and their results.

	HT cases (n)	HT and nodules at any time of surveillance (n)	PTC in HT cases (%)	PTC in HT (n)	PTC in HT and nodules at any time of surveillance (%)	Follow-up period (years)
Corrias et al. [20]	365	115	3.01	11	9.57	4.7 ± 3.9 (mean ± SD)
Skarpa et al. [21]	228	32	1.32	3	9.38	5
Keskin et al. [22]	300	39	0.67	2	5.13	9
Janus et al. [23]	179	34	4.47	8	23.53	2
Won et al. [24]	89	20	7.87	7	35.00	10
Radetti et al. [25]	904	174	1.11	10	5.75	4.5–1.2 to 12.8 (median – min to max)

when to start the treatment. Some recommend levothyroxine immediately after diagnosis or for at least two years after diagnosis, others recommend treatment only in forms with subclinical or overt hypothyroidism [26, 27]. In our service, we have adopted the first strategy and maybe the low prevalence of PTC in our cases with HT is linked to our management.

We questioned the evolution of these cases and found from literature studies that the frequency of PTC and thyroid nodules is constantly increasing [28]. This increase is also due to environmental factors that have increased in recent years. However, the literature shows no increased risk of thyroid cancer associated with living near nuclear plants [29, 30]. Results of a recent meta-analysis showed a similar finding.

Another element that can explain the frequency of PTC and thyroid nodules is the cytogenetic differentiation found in HT. Tamimi et al. found a significantly higher rate of lymphocytic infiltrate in patients with PTC, and the activated inflammatory response present in HT may create a favorable setting for malignant transformation [31]. The inflammatory response may cause DNA damage through the formation of reactive oxygen species, resulting in mutations that eventually lead to the development of PTC [16]. The relationship between inflammation and PTC is complex and still not completely understood.

Anti-TPO, anti-TG and TSH levels—we analyzed 2,571 patients after fine-needle aspiration biopsy of thyroid nodule. Totally, 91 patients with primary TC and 182 sex- and age-matched controls were included. Positive antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) antibodies were associated with TC (anti-TPO 44% in TC vs. 27% in controls, p=0.005, anti-TG 35% in TC group vs. 21% in controls, p=0.018), and the TC group had significantly higher TSH (median 1.88 mIU/L vs. 1.21 mIU/L, p<0.001). Using multiple logistic regression, positive anti-TPO was identified as an independent risk factor (OR 2.21, p=0.018), while spontaneously suppressed TSH<0.5 mIU/L was a protective factor (OR 0.3, p=0.01) against TC [32].

Most of the studies regarding the potential association between HT and thyroid cancer development have been carried out in adults [33]. With few exceptions [16], most have clearly demonstrated that the coexistence of HT and thyroid tumors, mainly PTC, is common and that the risk of development of thyroid cancer in patients with HT is significantly higher than that in patients without HT.

The possibility of transforming of the nodules is related to size, not number [34, 35]. According to the current pediatric guidelines neck US in children with autoimmune thyroid disease should be performed at least every 12 months [36].

Boi et al. [37] carried out a retrospective analysis on 2,053 patients with single/prevalent thyroid nodules submitted to TFNAC (thyroid fine-needle aspiration cytology) and found that a higher prevalence of suspicious/malignant or indeterminate cytological findings was detected in patients with positive TG-Ab and thyroid microsomal antibody (TM-Ab) than in those with benign cytology. Increased independent OR for malignancy was conferred by any antithyroid antibody (OR 2.21; 95% CI=1.49–3.29, p<0.0001), TPO-Ab (OR 2.15; CI=1.42–3.25, p<0.0001) and TG-Ab (OR 1.67; CI=1.05–2.67, p<0.05). The conclusion was that both thyroid autoimmunity and increased TSH represent independent risk factors for the malignancy of the nodules.

We have also found associations of HT with other autoimmune disorders such as: autoimmune hepatitis, JIA, DZ1 and vitiligo.

Autoimmune associations can be unpredictable which is why the medical literature handles multiple associations. Sometimes they can only be between two autoimmune diseases, sometimes several organs are involved. The more are the associations, the greater the severity of the case. In the literature, there was also a case describing a child with coexisting HT, vitiligo and autoimmune hepatitis [38–40].

Almost all the studies included in our research were retrospective. New prospective studies are needed to deepen research on the malignant transformation of the nodules that appear in HT.

Conclusions

- The number of pediatric patients suffering from HT, thyroid nodules and PTC is increasing;
- A careful follow-up of the HT patients is necessary;
- Studies in this area are few, so it is crucial to extend research in this area;
- Persistently elevated TSH levels play an independent role as predictors of malignant transformation in children with HT and nodules;
- HT and nodules increase the risk of PTC, which had a higher prevalence in all the six studies compared to the general population;
- Further prospective studies are needed in pediatric endocrinology and more specific in the evolution and malignant transformations found in HT.

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