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REVIEW ARTICLE

Thyroid cancer in children: a rare entity

Cáncer tiroideo en niños: una entidad poco frecuente

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ABSTRACT

Introduction: thyroid cancer in children is considered a rare disease due to its low incidence, representing less than 1% of pediatric tumors. However, it is the most prevalent childhood endocrinological tumor and its frequency has experienced a significant increase in recent years.

Objective: to highlight the differences that thyroid tumors present in children compared to adults.

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Methods: 30 articles were identified, of which 23 were included, more than 75 % from the last 3 years; coming from academic search engines such as PubMed, MedLine, Ovid, ResearchGate and Google Scholar.

Development: thyroid cancer in children is diagnosed in advanced stages, when lymph node involvement and lung metastases are more frequent than in adults. However, the prognosis is excellent, except in the most aggressive tumors, which present precisely.

Conclusions: thyroid cancer in pediatrics presents peculiarities that make it different from that which occurs in adults. It has a greater influence of genetics, a greater probability of locoregional extension and metastasis at diagnosis, but on the contrary the prognosis is usually good.

Keywords: Endocrinology; Thyroid Neoplasms; Child; Pediatrics

RESUMEN

Introducción: el cáncer de tiroides en niños se considera una enfermedad rara debido a su baja incidencia, representando menos del 1 % de los tumores pediátricos. Sin embargo, es el tumor endocrinológico infantil más prevalente y su frecuencia ha experimentado un importante aumento en los últimos años.

Objetivo: resaltar las diferencias que presentan los tumores de tiroides en niños con respecto a los adultos.

Métodos: se identificaron 30 artículos de los cuales se incluyeron 23, siendo más del 75 % de los últimos 3 años; provenientes de buscadores académicos como PubMed, MedLine, Ovid, ResearchGate y Google Scholar.

Desarrollo: el cáncer de tiroides en niños se diagnostica en estadios avanzados, cuando la afectación de los ganglios linfáticos y las metástasis pulmonares son más frecuentes que en los adultos. Sin embargo, el pronóstico es excelente, salvo en los tumores más agresivos, que se presentan con precisión.

Conclusiones: el cáncer de tiroides en pediatría presenta peculiaridades que le hacen distinto del que se presenta en adultos. Tiene una mayor influencia de la genética, una mayor probabilidad de extensión locoregional y metástasis al diagnóstico, pero por el contrario el pronóstico es bueno de forma habitual.

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Palabras clave: Endocrinología; Neoplasias de la Tiroides; Niño; Pediatría

INTRODUCTION

Thyroid cancer in children is considered a rare disease due to its low incidence, representing less than 1 % of tumors in children of this age. Its incidence in pediatric patients aged 0 to 19 years is low and is around 5 cases per million. However, it is the most prevalent childhood endocrinological tumor and its frequency has experienced a significant increase in recent years, especially among young people and girls. (1)

Because it is a tumor whose incidence increases with age and is the most common tumor among cancer survivors, many children with cancer are expected to develop a thyroid tumor in adulthood, especially if they have received radiation therapy. (1)

Since thyroid cancer occurs much more frequently in adults, it is common that an important part of the knowledge and treatment of this pathology in pediatrics is adapted to adults. However, it is important to know that childhood thyroid cancer differs from adult thyroid cancer in clinical presentation, pathophysiology, treatment, and long-term outcomes. (2)

The importance of these differences is so great that it is currently recommended to stratify thyroid cancer according to the time of onset into prepubertal, adolescent, and postpubertal. (2)

The purpose of this article is to highlight the differences that thyroid tumors present in children and adults in comparison with epidemiology, risk factors, clinical presentation, diagnostic evaluation, treatment and prognosis.

MATERIALS AND METHODS

A bibliographic review was carried out using the key words: endocrinology; thyroid neoplasms; child; pediatrics 30 articles were identified, of which 23 were included, more than 75 % from the last 3 years. All types of articles were selected from academic medical search engines such as PubMed, MedLine, Ovid, ResearchGate and Google Scholar, each of them allowing different aspects related to epidemiology, risk factors, clinical presentation, diagnostic evaluation, treatment to be analyzed and prognosis in this entity. The search was limited to English and Spanish.

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DEVELOPMENT

Epidemiology and risk factors

Despite the rare occurrence of thyroid tumors in children, their incidence increases with age and occurs more frequently in the second decade of life and more frequently in girls. Therefore, adolescent girls are the most affected group. Thyroid cancer is rarely diagnosed in children under 10 years of age, although incidence and prevalence have increased in recent years. The histological distribution is similar to that in adults, with differentiated thyroid cancers clearly outnumbering undifferentiated ones. (2)

Among differentiated tumors, the most common is papillary (almost 90 %), followed by follicular, which barely reaches 10 %. Other types of childhood thyroid cancer may be considered exceptional. In general, a follicular tumor is less aggressive than a papillary tumor because it is usually less advanced at the time of diagnosis, usually unifocal, and has a lower probability of metastasis and recurrence during follow-up. (3)

Spinal cord cancer is rare in children. Papillary thyroidectomy for medullary or high-risk thyroid cancer is one of the most common reasons, especially in children aged 0 to 4 years, which is why the Spanish series support that this operation extends beyond the papillary method. This increase is due to the increased availability of molecular genetic testing, which has led to prophylactic thyroidectomy in children with pathogenic RET gene variants described in the familial cascade by a parent with MEN2A or Hirschsprung disease. (3)

Advances in genetic engineering demonstrate the usefulness of molecular genetics in tumor characterization and therapy. A pediatric patient is generally a healthy organism that has received little radiation and usually has few other diseases. The early onset of thyroid cancer raises questions about the underlying trigger, especially when it appears before the age of 10 and even before the age of 5. It has been shown that sometimes this predisposition is genetic. (4)

An association has been found between papillary thyroid cancer and several genetic variants. This effect of genetics on thyroid cancer has been reported more frequently in children than in adults. The genetic changes observed are

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mostly copy number variations and, to a lesser extent, single nucleotide variations. (4)

The most frequently altered gene in thyroid cancer with a non-syndromic phenotype is BRAF. Genetic syndromes due to monogenic causes associated with tumor risk are increasingly diagnosed in pediatrics. The Carney complex, Werner syndrome or the APC, PTEN, RET, DICER1 variants stand out. Considering the rarity of these syndromes and the long latency period for tumor appearance, it is unusual for them to be diagnosed in children. Therefore, it is still necessary to plan a check-up or in some cases a preventive thyroidectomy before the first year of life. (4)

In addition to traditional factors, autoimmune thyroiditis, iodine deficiency, or thyroid irradiation are classic risk factors for pediatric thyroid cancer. In children, the risk of thyroid cancer is usually 0,02 %, but in people with hypothyroidism it is 3 %.

Thyroid exposure to chemical radiation is a well-studied risk factor, especially in children, who are particularly susceptible to the carcinogenic effects of radiation. These children should be monitored periodically using ultrasound. Because nodules form 15 years after exposure, adult endocrinologists often diagnose thyroid tumors in these children. (5,6)

Presentation and diagnostic evaluation

It is usually discovered accidentally during a wellness study or during follow-up ultrasounds in children with thyroid inflammation. Thyroid nodules in children are rare, and approximately 20 % of pediatric thyroid nodules have been reported to be malignant. Once found, a diagnostic protocol should be initiated that consists of thyroid function, ultrasound, scintigraphy, and fine needle aspiration (FNAC). Thyroid function, thyroid-stimulating hormone, and free T4 are usually normal. Ultrasound examination of the thyroid gland plays an even more important role in adults, so the radiologist's opinion about nodules is more cancer-specific than in adulthood. In any case, the criteria for malignancy on ultrasound are the same as in adults. (6)

These criteria are detailed in the TI-RADS classification, where they consider composition, echogenicity, shape, borders and foci. The scan will show whether it is a cold nodule, suspicious for malignancy requiring FNAC, or a

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warm nodule. Although there is no indication for FNA in hot nodules in adults, between 8 % and 29 % of these hot nodules in children are thyroid cancer and therefore require FNA. If thyroid cancer is suspected, fine-needle aspiration is performed and the risk of malignancy is determined based on the histopathologic findings of the Bethesda system in adults. (7)

Despite very high sensitivity and specificity, pediatric FNAC has limitations. Repeatedly indeterminate results are associated with a higher risk of malignancy (28-58 %) than in adults (6-40 %). If the FNA is benign, ultrasound monitoring of the nodule is necessary, and if it increases in size or shows signs of malignancy, the FNA should be repeated. In the event of a new indeterminate result, Bethesda III or IV, hemithyroidectomy, or thyroidectomy surgery should be considered, because there is a high probability that it is true thyroid cancer. (7)

More studies should be performed before surgery due to the possibility of local spread (nodes or laryngeal nerve) or metastasis, mainly to the lungs. Local involvement can be evaluated by an experienced radiologist who performs an ultrasound examination of all areas of the cervix. Chest radiography may not be sufficient to evaluate metastases, so it is necessary to include other more sensitive imaging techniques. If additional treatment with radioactive iodine is prescribed, do not forget that Computed Tomography with iodinated contrast is contraindicated. Younger age, male sex, multiple colonies, and size greater than 2 centimeters determine the possibility of wider spread. (8,9)

The purpose of this evaluation is to stratify the tumor based on symptoms, size, regional invasion, and metastasis. It is classified as low risk (limited to thyroid disease or microscopic lymph nodes), medium or high risk (metastasis or significant locoregional infiltration or metastasis). (8)

Compared with adults, larger tumors with multiple foci at diagnosis are common, with locoregional extension of up to 30-80 % and metastasis in 5-25 %. They are mainly detected at the lung level (10-25 %) and less frequently at the bone level (5 %). Also, thyroid nodules are less common in children than in adults, but have a higher risk of malignancy; in adults 5-10 %, while in children 22-26 %. Furthermore, decreasing age has a greater tendency to induce aggressive cancers with higher recurrence rates. (9)

Treatment

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Treatment should be performed in children's hospitals and an experienced thyroid surgeon is essential. These should include oncology, endocrinology, nuclear medicine, radiology, an intensive care unit, anesthesia and a genetics unit is recommended. The surgical approach depends on a preoperative evaluation that differentiates low, intermediate and high risk tumors. Given the recurrence rate of partial resections, as a general rule, total thyroidectomy is performed even when bilateral (30 %), multifocal (30-65 %), or metastatic (16 %) disease is not suspected. (10)

Advantages of total thyroidectomy include lower recurrence, easier follow-up (thyroglobulin), and the possibility of additional evaluation with radioactive iodine. The risk of regional recurrences has been reported to be higher than in adults, and central lymph node drainage is controversial in all children, regardless of tumor extension. (10)

Therapeutic dissection is generally recommended when metastases are suspected in the mid-neck or posterolateral region. Prophylactic drainage of the lymph nodes of the central compartment can be considered in all cases, without forgetting that in children it is associated with an increase in complications derived from surgery (recurrent paralysis, hypothyroidism). Given that survival in the first years is 100 %, the current trend is to be conservative and for large tumors (more than 4 cm) or extrathyroidal resection only in the central section. (11)

Lateral or posterolateral dissection is indicated for children diagnosed with metastatic disease preoperatively, but never routinely. The risks of thyroidectomy in children are the same as those described in adults: hematoma, infection, hypoparathyroidism, and temporary or permanent damage to the recurrent nerve. Although there is no difference in recurrent nerve damage, follow-up is an important recommendation. Because the surgical field in children is smaller and the disease is usually more extensive, surgical complications occur more frequently. The risk of transient damage to recurrent nerves is up to 3,8 % in younger children. (11)

The probability of transient hypocalcemia is greater than 50 %, although it is usually controlled by early calcium supplementation. The risk of long-term hypoparathyroidism is rare (2 %), but increases with the aggressiveness of the operations. If concentrations have decreased, it is recommended to

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perform a PTH measurement immediately after surgery to obtain calcium and calcitriol. If we have histological and molecular information about the tumor, it is necessary to perform a postoperative evaluation that divides the risk into low, medium and high. (12)

The objective is to evaluate the presence of local disease and local continuity of the disease and should be performed within the first 2-3 months after surgery: thyroglobulin determination is performed in all patients and thyroid remains are searched with iodine-123. In medium and high risk patients. (12)

Thyroglobulin below 0,5 ng/ml indicates absence of thyroid tissue and tumor remains. For small tumors without extrathyroidal extension and adequate thyroglobulin levels, an iodine-123 scan may be ruled out. A level greater than 2 ng/ml indicates residual disease. In patients with elevated thyroglobulin levels, a whole-body scan and/or other imaging studies (ultrasound, CT, MRI, or SPECT) will look for residual thyroid tissue to evaluate whether another operation is necessary to supplement with iodine-131. (13)

As already mentioned, the prevalence of thyroid cancer is usually higher in children than in adults. Despite this, the prognosis is very good. The same does not occur in the long term, which indicates an increase in mortality in other tumors. It is important to select patients to whom iodine-131 is administered.

As Orellana MJ et al., (14) children constitute a population group that is particularly sensitive to the effects of radiation. They are a growing organism with immature gonads and many years ahead. Special protocols should be created for children, explaining the postoperative risk and reserving the most aggressive treatments for those who need them.

Therefore, although the most important treatment after surgery is the administration of iodine-131, its administration must be decided on an individual basis. Low-risk tumors do not require iodine-131 administration, but patients with intermediate- or high-risk papillary tumors should. Furthermore, the administration of iodine-131 is indicated without discussion in patients with tumor remains, lymph node involvement or distant metastases. (14)

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According to Bauer A, [15] the administration of iodine-131 requires a high level of TSH, and it is sufficient to stop treatment with thyroxine 14 days before administration or treatment with Thyrogen®, which is generally not done, because it is accepted in the technical specifications only in exceptional cases. There are medications that can be considered.

The endothelial and platelet growth factor inhibitor SORAFENIB has already been used in adults and is currently showing good results in clinical trials in children, although it is not currently indicated in children. Another investigational drug is vemurafenib, a BRAF gene inhibitor, and may be used in adults with iodine-131-resistant papillary carcinoma that is metastatic or inoperable. [15]

In spinal cord cancer, the RET tyrosine kinase inhibitor vandetanib is indicated and can be used for more than five years if the disease is unresectable or metastatic. Considering the importance of genetics in childhood thyroid cancer and advances in molecular genetics and pharmacogenetics, it is expected that the pharmacological treatment of these patients will have a promising future with new therapies depending on the type of cancer and its molecular changes. [16]

Long-term monitoring and prognosis

Thyroid cancer in children is diagnosed in advanced stages, when lymph node involvement and lung metastases are more common than in adults. However, the prognosis is excellent, except in the most aggressive tumors, which present precisely. In any case, early diagnosis and adequate follow-up are important to reduce or even prevent morbidity and relapses related to treatment. [16]

After surgery and with a rest of at least two weeks before the administration of iodine-131, replacement therapy with levothyroxine is started. If iodine-131 is not needed, levothyroxine treatment is started immediately. Treatment is adjusted according to the risk of recurrence. A low-risk TSH level (0,5-1 µIU/ml) is sought in low-risk children, a lower level (0,1-0,5 µIU/ml) in medium-risk children, and undetectable in children high-risk. The role of a pediatric endocrinologist is to adjust medications to the desired TSH level and prevent symptoms of hyperthyroidism by monitoring growth, bones, heart rate, and school performance. [17,18]

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After changing the dose of levothyroxine, an ultrasound is initially performed every 6 months, after which time can be distributed according to individual risk. The risk of recurrence in the near future is very low. However, in the long term it will increase to 15-40 percent after 30 years. Therefore, monitoring must be extended over time. Survival is more likely in patients with earlier-onset tumors, those who required more aggressive surgery, and those whose TSH levels are not adequately controlled. (18)

In long-term follow-up, palpation, measurement of thyroglobulin (anti-thyroglobulin antibodies for correct interpretation) and ultrasound have proven to be useful in the diagnosis of relapse. Additionally, an iodine-123 scan should be included in patients at increased risk of recurrence, especially if they have received isotope therapy, to confirm negativity or determine indications for a new dose. (19,20)

Peculiarities of other types of non-papillary tumors

A follicular tumor is usually diagnosed after surgery, which in many cases is performed after two inconclusive FNAs. In the tumor stage, locoregional spread or metastases are very rare at the time of diagnosis of this type of tumors, but in such cases a total thyroidectomy is required if it has not been previously performed. (21) Long-term progress is good, as is the case with papillary cancer. Spinal cord cancer is characterized by a low incidence in pediatrics. The diagnosis of MEN2A occurs when C-cell hyperplasia, a confirmed malignancy, is detected during glandular analysis after a preventive thyroidectomy. (22)

These tumors do not respond to iodine-131. However, surgery is very effective if there is no metastasis. The type of variant described in the RET gene determines the timing of total thyroidectomy, which can be before one year of age, and this thyroidectomy is one of the most common reasons for thyroid surgery in MEN2A, thyroid surgery in pediatrics. As in adult age groups, vandetanib therapy can be used in children older than 5 years with unresectable tumors. (23)

CONCLUSIONS

Thyroid cancer in pediatrics presents peculiarities that make it different from that which occurs in adults. It has a greater influence of genetics, a greater

probability of locoregional extension and metastasis at diagnosis, but on the contrary the prognosis is usually good. We must move towards personalized medicine by establishing diagnostic protocols that correctly characterize the tumor and stratify the prognosis so that treatments with surgery, iodine-131 and new pharmacological treatments seek maximum effectiveness and minimize side effects.

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STATEMENT OF AUTHORSHIP

RMGV: Conceptualization, research, methodology, project administration, validation, original draft writing, review, editing.

CLVH: Conceptualization, research, methodology, project administration, validation, original draft writing, review, editing.

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CRP: Conceptualization, research, methodology, project administration, validation, original draft writing, review, editing.

CONFLICT OF INTERESTS

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