



ALEXANDRE CAIXETA GUIMARÃES

AVALIAÇÃO DA RELAÇÃO DA ASSIMETRIA DAS TONSILAS PALATINAS COM
O LINFOMA TONSILAR EM CRIANÇAS

*EVALUATION OF THE RELATIONSHIP BETWEEN TONSILAR ASYMMETRY
AND TONSILAR LYMPHOMA IN CHILDREN*

CAMPINAS

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Tese apresentada à Faculdade de Ciências Médicas da
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área de concentração em otorrinolaringologia.

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RESUMO

O linfoma é a terceira neoplasia mais frequente da infância correspondendo a cerca de 12% de todas neoplasias em indivíduos com menos de 15 anos, e é a neoplasia maligna mais frequente em cabeça e pescoço. Aproximadamente 15% dos linfomas de cabeça e pescoço em crianças acometem o anel de Waldeyer. O diagnóstico e o tratamento precoce têm grande importância no prognóstico dos pacientes com linfoma de tonsilas palatinas. Os objetivos deste trabalho são avaliar a prevalência das manifestações clínicas de crianças com linfoma de tonsila palatina e identificar a associação entre a assimetria tonsilar e o linfoma de tonsila palatina em crianças. Foram realizadas revisões sistemáticas da literatura com artigos que incluíam crianças até os 18 anos com linfoma de tonsila palatina ou assimetria tonsilar. Foram encontrados 66 casos de crianças com linfoma; a assimetria tonsilar foi a manifestação clínica mais frequente, presente em 72,7% dos casos, seguida pela alteração na aparência da tonsila palatina em 45,4% e linfonodomegalia cervical em 30,3% dos casos. O linfoma de Burkitt foi o tipo mais frequente. A principal causa de assimetria tonsilar foi a hiperplasia linfóide seguida pelo linfoma e por alterações benignas inespecíficas. Foi encontrada associação entre a assimetria tonsilar e o linfoma de tonsilas palatina, sendo a razão de verossimilhança de 43,5 para crianças com assimetria de tonsilas e de 8938,4 para crianças com assimetria de tonsilas e outros sinais de suspeição para malignidade.

Palavras- Chave: Linfoma; Criança; Tonsila Palatina; Neoplasias Tonsilares.

ABSTRACT

Lymphoma is the third most common malignancy of childhood, accounting for approximately 12% of all cancers in individuals under 15 years of age and is the most common malignancy in the head and neck. About 15% of head and neck lymphomas in children affect the Waldeyer's ring. The early diagnosis and early treatment are very important in the prognosis of patients with palatine tonsils lymphoma. The objectives of this thesis are to evaluate the prevalence of the clinical manifestations of children with tonsillar lymphoma and identify the association between the tonsillar asymmetry and the tonsillar lymphoma in children. Systematic reviews of the literature were conducted with articles that included children up to 18 years with tonsillar lymphoma or tonsillar asymmetry. 66 cases of children with lymphoma were included; the tonsillar asymmetry was the most common clinical manifestation, present in 72.7% of cases, followed by the change in appearance of the palatine tonsil in 45.4% and cervical lymphadenopathy in 30.3% of cases. Burkitt's lymphoma was the most common type. The most frequent cause of tonsillar asymmetry was lymphoid hyperplasia followed by lymphoma and nonspecific benign changes. There was an association between the tonsillar asymmetry and tonsillar lymphoma with the likelihood ratio of 43.5 for children with tonsillar asymmetry and 8938.4 for children with asymmetry of tonsils and other signs of suspicion for malignancy.

Key words: Lymphoma; Child; Palatine Tonsil; Tonsillar Neoplasms.

LISTA DE ABREVIATURAS E SIGLAS

LNH – Linfoma não Hodgkin

TP- Tonsilas Palatinas

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1. INTRODUÇÃO GERAL

O linfoma é a terceira neoplasia maligna mais frequente da infância, representando cerca de 12% de todas neoplasias em indivíduos com menos de 15 anos, sendo menos frequente apenas que as leucemias e os tumores do sistema nervoso central (1).

Na população pediátrica, o linfoma é o tumor maligno mais frequente que acomete a região da cabeça e pescoço sendo o Linfoma não Hodgkin (LNH) o tipo mais comum (2). Segundo alguns estudos, este se apresenta usualmente como uma linfadenopatia cervical crônica (2 - 4). A apresentação extra-nodal ocorre em 4 a 20% dos pacientes com LNH de cabeça e pescoço (5, 6). As tonsilas palatinas (TP) são o local mais frequente de acometimento extra-nodal para o LNH (3).

Roh e colaboradores avaliaram 45 crianças com linfoma de cabeça e pescoço e em 15 % dos casos, o anel linfático de Waldeyer esteve envolvido (7). O LNH é responsável por cerca de 90% dos casos de linfoma que envolvem o anel de Waldeyer na população geral (8).

Quanto ao prognóstico dos pacientes com linfoma de TP, diversos autores encontraram associação entre o estadiamento inicial, de acordo com o sistema de estadiamento Ann Arbor, e a maior sobrevida livre de doença e sobrevida global (4,5,9,10). Gao e colaboradores observaram que o tamanho do linfoma tonsilar também tem relação direta com o prognóstico (11).

Considerando que o estadiamento é relacionado ao tempo de doença, entende-se que o diagnóstico e o tratamento precoce têm grande importância no prognóstico dos pacientes com linfoma de TP. Portanto o conhecimento das manifestações clínicas mais frequentes do linfoma em crianças e da relação que a assimetria tonsilar tem com o linfoma podem auxiliar os profissionais de saúde na condução de pacientes com suspeita de linfoma.

Ainda não é consenso se a presença de assimetria de TP tem associação com o linfoma de TP. Não são encontrados trabalhos com alto nível de evidência sobre as manifestações clínicas mais frequentes em crianças com o linfoma de TP na literatura mundial e não se conhece qual o subtipo mais frequente nesta localização.

2. OBJETIVOS

2.1 OBJETIVOS DO PRIMEIRO ARTIGO:

Objetivo geral:

Avaliar a prevalência das manifestações clínicas presentes no momento do diagnóstico de linfoma tonsilar em pacientes pediátricos.

Objetivos específicos:

Avaliar a prevalência das outras manifestações clínicas além da assimetria de TP presentes em crianças com linfoma tonsilar.

Avaliar a distribuição dos tipos de linfoma de TP na população estudada.

2.2 OBJETIVOS DO SEGUNDO ARTIGO:

Objetivo geral:

Avaliar a relação da assimetria de TP e linfoma em crianças por meio de revisões sistemáticas da literatura sobre linfoma de TP e assimetria de TP em crianças.

Objetivos específicos:

Avaliar os critérios utilizados na literatura para definir assimetria de TP.

Avaliar as causas descritas na literatura de assimetria de TP em crianças.

Avaliar a razão de verossimilhança da presença de assimetria de TP com a presença de linfoma em crianças.

Avaliar a razão de verossimilhança da presença de assimetria de TP e outros sinais sugestivos de malignidade com a presença de linfoma em crianças.

3. CAPÍTULO 1:

CLINICAL MANIFESTATIONS IN CHILDREN WITH TONSILLAR LYMPHOMA: A SYSTEMATIC REVIEW (12)

Clinical manifestations in children with tonsillar lymphoma: A systematic review

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Abstract

Background: The lymphoma is the most common childhood malignancy in the head and neck. Approximately 15% of head and neck lymphomas in children affect the Waldeyer's ring. Early diagnosis and treatment are of great importance in the prognosis of tonsillar lymphoma patients.

Objectives: To realize a systematic review of the literature on the clinical manifestations present at diagnosis of tonsillar lymphoma in pediatric patients.

Date Source: Articles in English, Spanish or Portuguese in the last 15 years about lymphoma in palatine tonsil in children from PubMed/Medline, LILACS, IBECs, Cochrane, SCIELO, BIREME and Scopus.

Study eligibility criteria: It was included articles and case reports that covered the pediatric age group, up to 18 years old and that contained information of the clinical manifestations of tonsillar lymphoma at diagnosis.

Results: We found 87 articles of which 18 were included; there were 66 cases of lymphoma of palatine tonsils. The most common clinical manifestations found in children with lymphoma in palatine tonsils were unilateral tonsillar enlargement (72.7%), alteration in appearance of the tonsil (45.4%) and cervical lymphadenopathy (30.3%). The presence of B symptoms occurred in only 16% of the patients. Burkitt was the most common type of lymphoma found.

Conclusion: The most common clinical manifestations of lymphoma in palatine tonsil are the tonsils asymmetry, alteration in the appearance of the mucous and cervical lymphadenopathy. A detailed description of cases of lymphoma in palatine tonsils and the use of criteria for classification of tonsillar asymmetry are important for future revisions.

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Keywords: Lymphoma; Children; Tonsillar neoplasm; Tonsil; Adolescent

Abbreviations: NHL, non-Hodgkin lymphoma; PT, palatine tonsils.

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1. Introduction

Lymphoma is the third most common childhood malignancy, accounting for about 12% of all cancers in people under 15 years old [1].

Among children lymphoma is the most frequent malignant tumor in the head and neck. The non-Hodgkin lymphoma (NHL) is the most common type [2] and its usual presentation is as chronic cervical lymphadenopathy [2–4]. The extra-nodal involvement is more common in NHL when compared to Hodgkin's lymphoma, and the palatine tonsils (PT) are the most frequent site of involvement for extra-nodal NHL [3]. Extra-nodal involvement in the head and neck occurs in 4–20% of patients with NHL [5,6].

Roh et al. evaluated 45 children with lymphoma of the head and neck and in 15% of these cases, the Waldeyer's ring was involved and all were diagnosed as NHL [7]. NHL is responsible for about 90% of lymphoma cases involving Waldeyer's ring [8].

As for the prognosis of patients with PT lymphomas, several authors found an association with a greater disease-free survival and overall survival and the initial stage, according to Ann Arbor Stage System [4,5,9,10]. Gao and collaborators found that the size of the tonsillar lymphoma also has direct relationship with the prognosis [11]. Whereas staging is related to duration of disease, the early diagnosis and treatment is of great importance for a better prognosis of patients with PT lymphoma.

Considering that doctors interpret a clinical sign as a clue to a disease, is critical to know what are the main clinical manifestations of tonsillar lymphoma in children, and their frequencies, to help doctors know what is important to pay attention for to identify suspected cases.

The aim of this study was a systematic review of the literature on the clinical manifestations of tonsillar lymphoma in pediatric patients to identify which are the clinical manifestation and their frequencies. No studies with a high level of evidence on this subject were found in worldwide literature.

2. Materials and methods

A systematic literature review was performed by searching databases at PubMed/Medline, LILACS, IBECs, Cochrane, SCIELO, BIREME and Scopus.

The research covered articles in English, Spanish and Portuguese, related to tonsillar lymphoma in children from January 1996 until June 2012.

The year of 1996 was chosen to simplify the search because there were only a few articles written before this year and most of them were not available on the Internet.

The MeSH terms and free text words used were “tonsillar lymphoma and children.” Only two authors were responsible for selecting all the articles that had been completely read. The inclusion of these articles was reviewed by the two authors.

Table 1

Articles included in the systematic review and the number of patients diagnosed with lymphoma in each study [12–29].

Author [12–29]	Country	Patients with lymphoma	Age: Median (years)
Tewfik et al. [12]	Canada	3	10
Berkowitz et al. [13]	Australia	7	5
García-Ortega et al. [14]	Spain	1	10
Broughton et al. [15]	USA	1	×
Smitheringale et al. [16]	England	5	2
Maitra et al. [17]	USA	1	7
Banthia et al. [18]	USA	1	14
Carvalho et al. [19]	Brazil	1	5
Williams et al. [20]	USA	1	2
Garavelo et al. [21]	Italy	2	7
Sayed et al. [22]	USA	29	7
Gheoghe et al. [23]	USA	1	10
van Lierop et al. [24]	South Africa	1	×
Dolev et al. [25]	Canada	6	9.5
Papouliakos et al. [26]	Greece	1	6
Zeglouli et al. [27]	Tunisia	1	5
Sturm-O'Brien et al. [28]	USA	2	×
Guimarães et al. [29]	Brazil	2	8
Total		66	7

×: children without specified age.

Articles and case reports were included covering the pediatric age group, considered up to 18 years old that contained information of the clinical manifestations of tonsillar lymphoma at diagnosis. Review articles without description of clinical cases, and those that did not clearly define the presence or absence of tonsillar lymphoma for each patient were excluded. Only the cases of lymphoma that were confirmed by histopathological examination were included. Considering that TP lymphoma in children is a rare condition, all case reports matching our criteria were included to increase the sample size and to avoid the loss of any potentially important information.

The evaluated data of the articles were: number of cases of PT lymphoma, gender, age, type of study, unilateral tonsillar enlargement, altered mucosa, fever, lymphadenopathy, weight loss, dysphagia, immunosuppression, previous radiotherapy, symptoms of snoring or apnea, type of lymphoma, also considered was the origin of the article, authors, year of publication, and other information considered relevant by the authors (local pain, voice alteration, treatment of acute bacterial tonsillitis without improvement and auricular fullness). During the evaluation of reported information in the articles clinical manifestations not mentioned were considered absent.

3. Results

There were 87 articles found after the research that were evaluated and completely read by the researchers, in which 18 (20.6%) met the inclusion criteria, all of them were transversal studies (Table 1).

Table 2

Prevalence of clinical characteristics of patients diagnosed with palatine tonsil lymphoma.

Sign/symptom	Cases	%
Unilateral tonsillar enlargement/Tonsillar asymmetry	48	72.7%
Color alteration/Visible lesion in PT	30	45.4%
Cervical lymphadenopathy	20	30.3%
Dysphagia	19	28.7%
Snore/apnea	16	24.2%
Recurrent tonsillitis	8	12.1%
Fever	7	10.6%
Weight loss	6	9%
Vocal alteration/difficulty to speak	6	9%
Local pain (tonsillar)	5	7.5%
Tonsillitis treatment without improvement	4	6.6%
Immunosuppression	4	6.6%
Auricular fullness	2	3%
Prior radiotherapy	1	1.6%
Total (n = 66)		

Table 3

Distribution of patients according to the type of lymphoma diagnosed.

Type of lymphoma	Number	%
Burkitt	33	50%
B-cell NHL	20	30%
T lymphoblastic	4	6%
Lymphocytic	1	1.6%
Histiocytic	1	1.6%
NK/T Cells	1	1.6%
Pecursor B-cell lymphoblastic	1	1.6%
Hodgkin	1	1.6%
Without identification ^a	4	6%
Total		

^a Even after immunophenotyping.

In the 18 included articles 66 cases of PT lymphoma were found. The data analyzed were considered for these 66 cases. The age ranged from one to 17 years with a mean of 7.4 years ($n = 62$). There was a predominance of male patients, 41 male patients and 21 female patients ($n = 62$) with a male/female ratio equal to 1.95. From the 66 cases of PT lymphoma in children, 45 (68.3%) were from North America and 80% of these children were from the U.S.A. and 20% from Canada. The second most represented continent was Europe with nine (13.7%) cases, followed by Australia with seven (10.5%), South America with three (4.5%), and Africa with two (3%) cases. The most frequent clinical findings in pediatric patients with a lymphoma diagnosis are shown in Table 2.

Burkitt's lymphoma was the most common type, followed by B-cell NHL (Table 3). The same nomenclature for description of types of lymphoma was maintained, respecting what was reported in the articles included.

4. Discussion

The most common clinical manifestations found were unilateral tonsillar enlargement or tonsillar asymmetry,

alteration of appearance of the PT (color alteration or visible lesion), cervical lymphadenopathy, dysphagia, and snoring or apnea. Other less frequent findings were fever, reoccurring tonsillitis, weight loss and voice alteration.

We believe that the frequency of the manifestations may be higher, because some case descriptions are not always properly detailed and some of these events may have been omitted, as described by Sayed et al. [22], who did not report fever in any of his sample cases. As most of the cases reported included in our review came from case series or case reports of patients who did not had previous known risk factors such as immunodeficiencies or HIV, in general the population of this review can be considered similar to the general population.

This was the largest review of PT lymphoma in children and the first systematic review that included case reports and appointed the most common symptoms in this disease, some of them were not previously considered as symptoms of PT lymphoma such as the dysphagia and snoring. This review also added new relevant data to literature, showing that Burkitt is the most prevalent subtype of PT lymphoma in children.

To achieve the objective of this study the method used, which was conducting a systematic review, was adequate. The studies analyzed were mostly case series, which is a study model that despite its limitations has information relevant to an initial approach to the topic.

This study suffers from the limitations inherent of the model studied, such as the impossibility of temporal association and the possibility of selection bias because case reports or case series were included. We only found this type of study, because so far to answer the question of our study there are only articles of the type series of cases, that have limitations to generalizability to the general population.

The low prevalence of systemic symptoms such as fever and weight loss can be partly explained by the predominance finding of NHL, since the systemic symptoms are more common in Hodgkin's lymphoma [2,4]. This data contrast with the data collected for the adult population, thus, emphasizing that the prevalence of clinical manifestations in patients with PT lymphoma varies according to age. In adults the most common manifestations are dysphagia or odynophagia present in 72% of cases and cervical lymphadenopathy in 60%. The presence of B symptoms (fever over 38 degrees, weight loss of more than 10% and night sweats) occurs in 14% of patients [9].

Regarding the gender distribution the results were similar to other studies of lymphoma in children. Lymphomas of the head and neck involve two male children for every one female, and manifest earlier in males [30,31].

It is important to point out that in 9 (13%) cases the most frequent manifestations (PT asymmetry, alteration in the appearance of the PT and presence of cervical lymphadenopathy) were absent.

Regarding tonsillar asymmetry, there was no standardization in the characterization of this change and most of the articles did not mention what were the criteria used. We

would like to point out the importance of using standardized classifications, such as the Brodsky classification, or a detailed description of the size and characteristics of the PT in published articles as essential for their reliable comparison [32,33].

PT lymphoma is in more than 90% of cases diagnosed in early stages (I or II) [9]. The presentation of lymphoma that affects the Waldeyer's ring usually occurs in early stages as compared to nodal NHL [34]. The prognosis of PT lymphomas in the early stages is worse than other extranodal lymphomas of the head and neck [35]. It also depends on the subtype, being in general, best for Hodgkin's lymphomas followed by Burkitt's lymphomas and lymphoblastic. Without proper treatment most of the lymphomas can cause death within a few days, weeks or months [4,36].

In our review the most common subtype was Burkitt's, which may be due to a higher frequency of this subtype of lymphoma in children. The Hodgkin's lymphoma occurred in only one case of our study. This was also observed in another study involving 87 cases of PT lymphoma [9]. This is in agreement with other studies that show that extranodal presentation of Hodgkin's lymphoma is rare [2–4,7,37].

In children, the most common NHL are the Burkitt type, lymphoblastic lymphomas and large cell lymphoma [36], but the prevalence of NHL subtypes varies with the geographic region. The lymphoma of B cells is more common in Europe and the United States while Burkitt's lymphoma has higher prevalence in the countries of Southern Europe and equatorial Africa [38,39]. In a study with 67 children with head and neck lymphomas in Papua New Guinea, 64% of the cases were Burkitt type [31].

In addition to the clinical manifestations, studies of images are also important for the management of patients with lymphoma. The PET/CT is a useful test for staging and evaluating response to treatment after six to eight weeks of chemotherapy completion. It also contributes in determining lymphomas prognosis, being superior to CT and to PET alone [40]. Its usefulness in primary PT lymphomas has also been described [41], however, the role of PET/CT as a diagnostic tool for suspected malignancy of PT is not yet well established [40]. Studies are needed to validate the possible indication of PET/CT for these cases. We believe that it may be a promising complementary exam to help in the indication for surgery in cases with low to moderate suspicion of lymphoma.

Ultrasound is widely used as the initial imaging technique in the assessment of head and neck masses in children, largely due to its ready availability and avoidance of ionizing radiation [42]. It may be a useful diagnostic tool when superficial cervical lymph nodes are present, the increase of intra-nodal vascularity may indicate malignancy and for these cases a fine needle aspiration or biopsy should be considered [43,44]. However ultrasound will only be helpful for children who present enlarged cervical lymphadenopathy, there are no study evaluating the role of endoral ultrasonography for tonsillar lymphoma diagnosis in children, although in adults

endoral ultrasonography is very efficient in exact tumor localization, is sensitive in recognition of satellite lesions and is better than transcutaneous in tonsillar tumors diagnosis [45].

Unilateral tonsillar enlargement most often is resultant of a benign process, such as the varying depth of the tonsillar fossa (most common cause), asymmetry in the anterior pillars. Color alteration or visible lesion in PT can also be present in chronic inflammation, chronic infection (tuberculosis, syphilis, actino-mycoses), granulomatous diseases (sarcoidosis), or benign tumors (papillomas) [46]. Cervical lymphadenopathy is most commonly caused by a local benign inflammatory process, and about 15% of biopsied cervical lymph nodes in children represent a malignancy [47]. Cervical lymphadenopathy can be caused by infections, mainly due to a viral upper respiratory tract infection, immunologic diseases, lipid storage diseases, endocrine diseases, and malignancies such as Hodgkin and non-Hodgkin Lymphoma [48].

Based on our findings of the clinical manifestations of tonsillar lymphoma, we propose that for children who present with many of the most frequent manifestations such as unilateral tonsillar enlargement, suspicious appearance of the PT and cervical lymphadenopathy and therefore have a high level of suspicion should undergo to surgery of tonsillectomy for diagnosis. Children who present only some of the manifestations and the suspicion is not high should have a close follow up and be submitted to complementary examinations such as ultrasound when cervical lymphonodes are present. PET/CT has a positive predictive value of 61% and a negative predictive value of 100% for NHL in children [49], it is an useful exam to exclude suspicious cases, nevertheless it is important to consider that the radiation may be harmful to the children, so it's benefits and risks should be pondered and discussed with the family. For cases with atypical manifestations we advise only a close clinical follow up and perform complementary examinations or surgery if the level of suspicion increases.

We also consider the time of onset of the clinical manifestations of great importance to determine the level of suspicion, so a new sign such as recent onset of snoring, dysphagia or vocal alteration should be investigated and when present be taken into account. The level of suspicion should be higher in immunosuppressed children who may present TP lymphoma without the most common clinical manifestations [16].

PT lymphoma is a relatively rare cancer, but clinical suspicion should be high, because the consequences of a delayed diagnosis can be devastating. Even though some manifestations of PT lymphoma can be found in children without lymphoma, doctors should be aware of the most common manifestation of PT lymphoma. The evaluation of the sensitivity and specificity of each clinical manifestation was not an objective of this review. The real role of tonsillar asymmetry and other common manifestations in children with lymphoma of PT is not clear; therefore we consider that future studies may help to clarify these issues.

5. Conclusion

The most common clinical manifestations found in children with PT lymphoma were unilateral tonsillar enlargement or tonsillar asymmetry, alteration of appearance of the PT, cervical lymphadenopathy, dysphagia, and snoring. The presence of B symptoms occurred in only 16% of the patients. Burkitt's was the most common type of lymphoma found, followed by B-cell NHL. A detailed description of the PT lymphoma cases and the use of criteria for the classification of tonsil asymmetry are important for future review.

Conflict of interest

Authors have no conflict of interest to be disclosed.

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4. CAPÍTULO 2:

ASSOCIATION BETWEEN UNILATERAL TONSILLAR ENLARGMENT AND LYMPHOMA IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS (13)

Association between unilateral tonsillar enlargement and lymphoma in children: A systematic review and meta-analysis

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Abstract

Lymphoma is the most common head and neck malignancy in children, and palatine tonsils asymmetry is the most frequent clinical manifestation of tonsillar lymphoma. However, several studies with children with tonsillar asymmetry found no case of lymphoma, showing that the relationship of tonsillar asymmetry with lymphoma is unclear. In this review, we aimed to identify the association between tonsillar asymmetry and tonsillar lymphoma in children by conducting systematic reviews of the literature on children with palatine tonsil lymphoma and tonsillar asymmetry. Articles comprising the paediatric age group (up to 18 years) with information concerning clinical manifestations of tonsillar lymphoma or the diagnosis of the tonsillar asymmetry were included. The main cause of asymmetry of palatine tonsils was lymphoid hyperplasia, followed by lymphoma and nonspecific benign changes. The asymmetry of tonsils was present in 73.2% of cases of lymphoma. There was an association between asymmetric palatine tonsils and lymphoma, with a likelihood ratio of 43.5 for children with asymmetry of palatine tonsils and 8938.4 for children with asymmetry of tonsils and other signs of suspicion for malignancy. We also provide recommendations on the management of suspicious cases of palatine tonsil lymphoma.

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Keywords: Lymphoma; Children; Tonsil; Tonsil asymmetry; Unilateral tonsillar enlargement

Abbreviations: PT, palatine tonsils; LR, likelihood ratio; CI, confidence interval.

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1. Introduction

Lymphoma is the third most common malignancy of childhood, accounting for approximately 12% of all cancers in individuals under 15 years of age [1].

In the paediatric population, lymphomas are the most frequent malignant tumours of the head and neck, and non-Hodgkin lymphoma is the most common type [2]. The extranodal involvement is more common in non-Hodgkin lymphoma when compared with Hodgkin lymphoma, and the palatine tonsils (PT) are the most frequent site of extranodal involvement in non-Hodgkin lymphomas [3].

Knowledge of the most frequent clinical manifestations of PT lymphoma is critical for detection and early diagnosis [4], allowing treatment during the initial stages and increased disease-free survival and overall survival [5–7]. The size of tonsillar lymphoma also has a direct relationship with prognosis [8].

In a study with 47 children with tonsillar asymmetry and 43 children with symmetric tonsils undergoing tonsillectomy, no difference in the PT volumes between groups was observed, with the apparent asymmetry resulting from the difference in the depth of the tonsillar fossa [9]. In another study of 13 children with asymmetric PT, there were no cases of lymphoma in these children and no difference in the PT sizes when compared to children without asymmetry [10].

Other studies with patients with apparent asymmetry of PT found no difference between the PT sizes in 39–52% of cases, and in most of the patients, the PT considered bigger was smaller than the contralateral [11–13]. Clinical asymmetry in these cases was attributed to variations in depth of the tonsillar fossa or to anterior tonsillar pillar asymmetry.

The asymmetry of PT is the most common clinical manifestation in children with PT lymphoma and is present in 72.7% of patients, followed by alteration of the appearance of PT and cervical lymphadenopathy [4]. The correlation of the apparent asymmetry of PT with the asymmetry of PT sizes after tonsillectomy is unclear, and the asymmetry is a common finding in healthy children, present in 1.7% of children aged 4–17 years [14], and therefore, the relationship between tonsillar asymmetry and PT lymphoma is not clear.

The relationship of tonsillar asymmetry with PT lymphoma in children remains controversial and there are no reviews with a high level of evidence on the subject in the literature. To establish this relationship, this article intends to calculate the likelihood ratio (LR) of the presence of PT asymmetry with the presence of PT lymphoma.

In diagnostics, the likelihood ratio of a test provides a way to estimate the pre- and post-test probabilities of having a disease. The LR is the ratio of the sensitivity divided by 1 minus the specificity of a test. It determines how many times the likelihood of a given test result increases in the presence of a positive test compared with the likelihood of a negative test. In this case, it will determine how many times the presence of asymmetric PT increases the chance of the presence of

PT lymphoma in children; currently, this relationship has not been established.

This study aimed to perform a systematic review of the literature on the presence of PT asymmetry at the time of diagnosis of PT lymphoma in paediatric patients and a systematic review on the presence of PT asymmetry in children regardless of its cause. Furthermore, we evaluated the relationship of PT asymmetry with PT lymphoma and determined the likelihood ratio of this indication of lymphoma.

2. Methods

The systematic reviews and meta-analysis followed the criteria defined by the PRISMA statement [15] and the current recommendations of the Cochrane Collaboration.

2.1. Study selection and search strategy

The following databases were systematically used by two authors (ACG, GMC): PubMed/MEDLINE, LILACS, Cochrane, Scopus and SCIELO. Two searches were performed on these databases. To detect cases of PT lymphoma in children, the first systematic review searched the following MeSH terms and free text words “tonsillar lymphoma and children”. To identify cases of tonsillar asymmetry, the second search was made by the following MeSH terms and free text words “unilateral tonsillar enlargement or tonsillar asymmetry and children”. The search was restricted to articles in English, Spanish and Portuguese languages related to PT lymphoma in children up to 18 years old, from January 1996 to December 2013.

Two authors were responsible for selecting all articles; all abstracts were read and from the information contained therein, if there was the possibility of cases of PT lymphoma or tonsil asymmetry in children, the articles were completely read. From the articles read, those that covered the considered paediatric age range and contained information of the clinical manifestations of PT lymphoma at diagnosis or cases of tonsillar asymmetry were included. The inclusion of articles was reviewed by both authors. Review articles without clinical cases and those that did not allow the definition of the presence or absence of PT lymphoma for each patient were excluded. Only cases of PT lymphoma confirmed by histopathology were considered.

The following data were assessed from the articles: number of cases of PT lymphoma, gender, age, tonsillar asymmetry, classification used to determine the tonsillar asymmetry, aetiology in other cases of tonsillar asymmetry, authors and year of publication. Reported information in articles was considered and clinical information of the patients not reported was considered absent.

The children in the study were classified according to the presence or absence of PT asymmetry, presence of PT lymphoma and also according to the presence of other suspicion factors for PT lymphoma. The considered suspicion factors

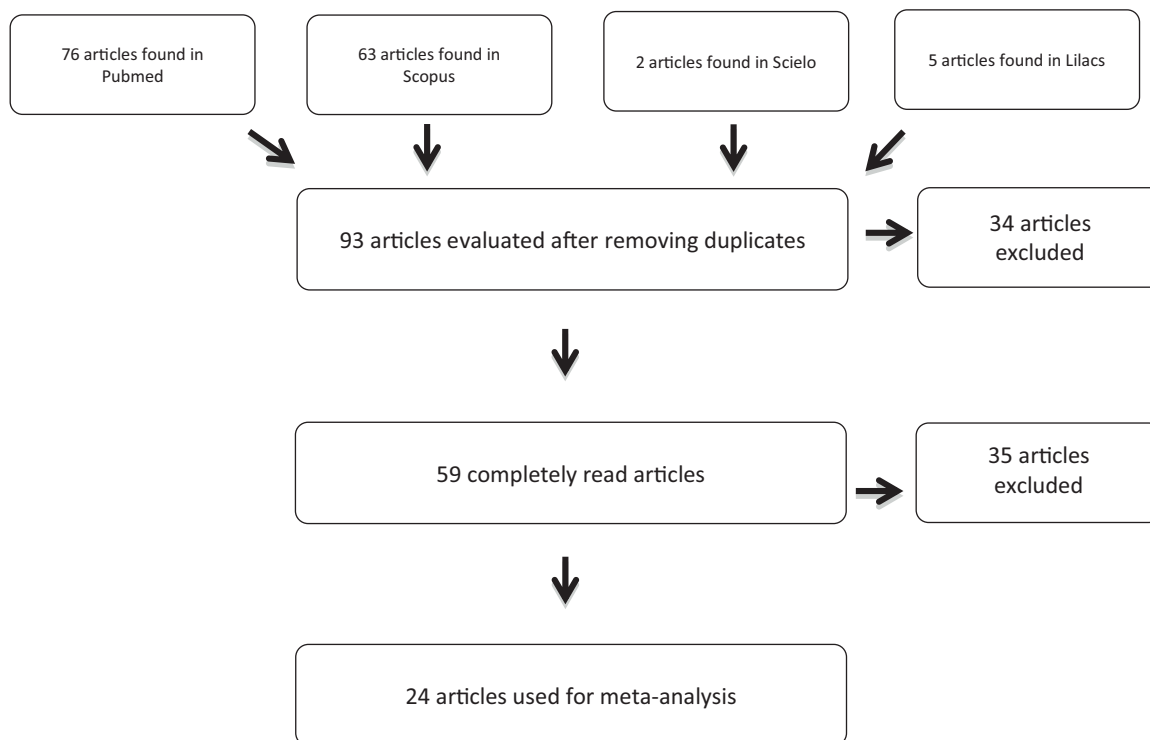


Fig. 1. Flowchart of articles included and excluded in the search of PT lymphoma.

for PT lymphoma were an alteration in the appearance of PT (colour alteration or visible lesion in PT), cervical lymphadenopathy larger than 3 cm, dysphagia, snoring, recurrent fever, weight loss greater than 10%, immunosuppression or prior radiotherapy.

The sensitivity of the PT asymmetry as a test for the diagnosis of PT lymphoma was calculated as the percentage of children with PT asymmetry among all those diagnosed with PT lymphoma. Since the prevalence of children without PT asymmetry and without lymphoma was lower than expected for the general population due to our search strategy, we also used the specificity of 1.7%, which is the prevalence of children with PT asymmetry without PT lymphoma [14].

We performed a meta-analysis of the data and calculated the likelihood ratio for the presence of PT asymmetry in the presence of PT lymphoma in children for the group of children with and the group without the presence of other factors of suspicion for lymphoma, with a confidence interval of 95%. The LR was calculated by dividing the sensitivity by (1 minus the specificity) for each study group.

The study was approved by the research ethics committee of the institution.

3. Results

One hundred and forty-six articles were found in the search for articles with PT lymphoma in children; 53 were

excluded for being duplicates. Of the 93 included studies, 30 were excluded because they did not contain clinical data, since these studies focused on pathology, immunology and gene expression. In addition, two others were excluded because they were literature reviews without cases, and two other articles were excluded because they were related to cerebellar tonsils. In total, 59 studies were read completely; 13 were excluded for not having detailed information of the cases; 11 were excluded because they did not allow differentiation of children from adult cases; seven articles were excluded for being cases of children without PT lymphoma or PT asymmetry; two articles were excluded as they were revisions without cases; one article was excluded for being an editorial; and one article was excluded for possessing the same sample of another included article. Finally, 24 articles remained for the meta-analysis (Fig. 1).

Sixty-two articles were found in the search for articles with tonsillar asymmetry or unilateral tonsillar enlargement in children; however, 30 articles were excluded for being duplicates, leaving 32. Five of the 32 included studies were excluded because they were related to cerebellar tonsils. Twenty-seven studies were completely read; seven were excluded because it was not possible to differentiate adult from children cases; four were excluded because they did not have histopathological results; two were excluded because they did not contain cases of tonsillar asymmetry; one was excluded due to cases being only in adults; and one was excluded because it had the same sample of another included

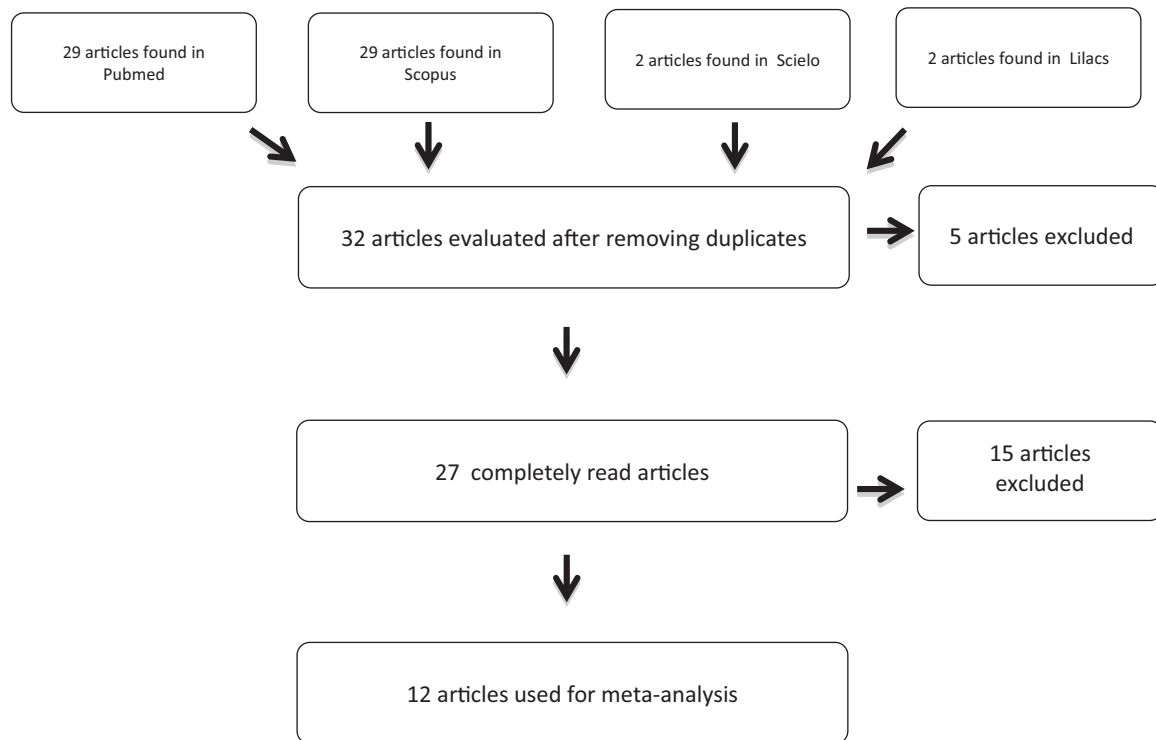


Fig. 2. Flowchart of articles included and excluded in the search of unilateral tonsillar enlargement in children.

article. Finally, 12 articles remained for the meta-analysis (Fig. 2).

Twenty-nine articles were selected after excluding duplicates in the search for PT asymmetry and PT lymphoma (Table 1) [9,10,12,13,16–40].

The age of children with PT lymphoma was described in 69 of 71 cases, ranging from 1 to 17 years, with a mean of 7.7 years.

Among the 71 children with PT lymphoma, 52 had PT asymmetry, 46 of them with other suspicious factors of malignancy, and in six children, PT asymmetry was the only clinical manifestation of lymphoma. Concerning the 19 children with lymphoma and without PT asymmetry, 16 had other suspicious clinical manifestations of neoplasia, and three had no suspicion for malignancy with an unexpected diagnosis after histopathological examination. A table with all the children included in the study shows the distribution of children with PT asymmetry alone or associated with other clinical manifestations of malignancy (Tables 2 and 3).

From the 27 articles of children containing asymmetric PT, no classification was used to define the PT asymmetry in 22 articles, and the asymmetry was just described as being that one of the PT was greater than the other or that PT asymmetry was present. In four articles, the classification of Brodsky [41] was used to assess the size of each PT and to determine the presence of asymmetry, while in one article the classification of Friedman [42] was

used to evaluate the size of PT and the presence of PT asymmetry.

From the 284 children with PT asymmetry, the cause of the asymmetry was due to lymphoid hyperplasia in 94 children, lymphoma in 52, chronic tonsillitis in 51, intratonsillar abscess in nine, actinomycosis in five, acute tonsillitis in five, atypical lymphoid proliferation in one, Proteus syndrome in one, and due to unspecified benign findings in 66 children.

PT asymmetry was present in 52 of 71 patients with PT lymphoma, which results in a sensitivity of 73% to this clinical sign. The asymmetry was absent in 225 of 457 patients without PT lymphoma, resulting in a specificity of 50.7%, and thus the likelihood ratio for PT asymmetry was 1.44 (CI: 1.22–1.70).

As the prevalence of PT asymmetry in children without PT lymphoma was very high in our study (50.7%) due to the search strategy of the articles that focused on patients with PT lymphoma or PT asymmetry, when considering the prevalence of children with asymmetric PT of 1.7% (Table 4), the LR for PT asymmetry is 43.55 (CI: 29.73–63.79).

To evaluate the association of other suspicious signs of malignancy in children with PT lymphoma for children with PT asymmetry, we arranged the children with PT asymmetry according to the presence of other signs of malignancy (Table 5) and found a LR of 205.2 (CI: 28.96–1454). Therefore, when considering children with PT asymmetry and other signs of malignancy, the LR for PT lymphoma is 8938.43 (CI: 860.98–92 750.66).

Table 1

Articles included in the systematic review and the number of patients with lymphoma and PT asymmetry in each study [9,10,12,13,16–40].

Authors	Patients with lymphoma	Patients with asymmetry
Amit et al. [16]	1	1
Ballin et al. [17]	0	39
Banthia et al. [18]	1	1
Berkowitz et al. [12]	7	53
Booth et al. [19]	3	1
Broughton et al. [20]	1	0
Cianci et al. [21]	1	1
Dolev et al. [22]	6	6
Garavelo et al. [23]	2	1
García-Ortega et al. [24]	1	1
Gheorghe et al. [25]	1	0
Guimarães et al. [26]	2	2
Kraus et al. [27]	0	1
Harley et al. [9]	0	47
Meirelles et al. [28]	2	2
Oluwasanmi et al. [29]	0	19
Papouliakos et al. [30]	1	1
Pelier et al. [31]	1	1
Prim Espada et al. [32]	1	9
Sahni et al. [33]	0	1
Sayed et al. [34]	29	19
Smitheringale [35]	5	3
Spinou et al. [13]	0	47
Tewfik et al. [36]	3	3
Ulualp et al. [37]	0	9
van Lierop et al. [10]	1	13
Williams et al. [38]	1	1
Yadav et al. [39]	0	1
Zeglaoui et al. [40]	1	1
Total	71	284

Table 2

Distribution of the children according to the presence of PT asymmetry and PT lymphoma.

	With PT lymphoma	Without PT lymphoma	Total
With PT asymmetry	52	232	284
Without PT asymmetry	19	225	244
Total	71	457	529

4. Discussion

Considering the prevalence of PT asymmetry in the children of 1.7%, the likelihood ratio found for PT asymmetry was 43.55, which represents a significant increase in the suspicion of PT lymphoma, but when the asymmetry

Table 4

Distribution of patients according to the presence of asymmetric PT and PT lymphoma, considering data from a previous study for the patients with PT asymmetry patients without PT lymphoma [14].

	With PT lymphoma	Without PT lymphoma	Total
With PT asymmetry	52	30	82
Without PT asymmetry	19	1754	1773
Total	71	1784	1855

Table 5

Distribution of patients with PT asymmetry according to the presence of other suspicious signs of malignancy.

	With PT lymphoma	Without PT lymphoma	Total
With other signs of malignancy	46	1	47
Without other signs of malignancy	6	231	237
Total	52	232	284

is associated with other signs of malignancy, the LR is 8938.43, *i.e.*, much higher and thus increasing the suspicion for PT lymphoma.

The use of LR to evaluate the performance of diagnostic tests is recommended and is considered a convenient way to express the results of systematic reviews and meta-analyses of diagnostic studies [43].

This was the first systematic review and meta-analysis that evaluated the relationship between the presence of PT asymmetry and PT lymphoma in children. Because PT lymphoma is a relatively rare condition, there are no controlled or cohort studies that examine the role of clinical manifestations for the diagnosis of lymphoma in children. We chose to include in this review case series and case reports of isolated cases, in order to increase the total number of cases and to include possible cases of PT lymphoma without tonsillar asymmetry or lymphoma cases without any clinical manifestation.

This study suffers from the inherent limitations of the model studied, and does not allow any temporal association and has the possibility of a selection bias. The methodology designed to find articles with cases of PT lymphoma or PT asymmetry in children was adequate, though the number of children without PT asymmetry and without lymphoma found in these studies was relatively low, with a prevalence of asymmetric PT of 50% in the children without lymphoma,

Table 3

Distribution of the children according to the presence of PT asymmetry, PT lymphoma and the presence of other suspicious clinical manifestations of lymphoma.

	With other suspicious clinical manifestations		Without other suspicious clinical manifestations	
	With PT lymphoma	Without PT lymphoma	With PT lymphoma	Without PT lymphoma
With PT asymmetry	46	1	6	231
Without PT asymmetry	16	12	3	213
Total	62	13	9	444

which is not expected for the general population. For this reason, aiming to circumvent this bias, we chose to perform the calculation of the LR using the prevalence of asymmetric PT in healthy children (without PT lymphoma) of 1.7%, which was described in the previous study [14].

Interestingly, few studies have used any classification to define the presence of tonsillar asymmetry: only five articles used a classification, representing 18.5% of the articles with cases of asymmetry of PT. The Brodsky classification was most often used.

Most cases of PT asymmetry in children were due to benign causes, and the most frequent histopathological finding was lymphoid hyperplasia. In 211 (74.2%) cases, the cause of asymmetry was nonspecific benign disorders, such as chronic tonsillitis or lymphoid hyperplasia. Other less-common causes of benign findings were intratonsillar abscess, actinomycosis and a case of Proteus syndrome. The lymphoma was the cause of PT asymmetry in 18.3% of 284 children with asymmetry of PT. We believe that this prevalence of lymphoma in this population is high and can be influenced by the inherent selection bias in the study design, since the cases of children with serious illnesses as a cause of PT asymmetry tend to be more reported in the literature than cases of children with asymmetry of PT caused by benign disorders such as chronic tonsillitis.

Several studies that evaluated the presence of PT lymphoma in children with PT asymmetry found no cases of lymphoma in this group [9,12,13,17,29,32]. Probably, no cases of lymphoma were present in these studies because lymphoma is a rare cause of isolated PT asymmetry, and none of these studies had a sample large enough to have a case of PT lymphoma. However, when we look at the children with PT lymphoma in this study, out of 71 cases of PT lymphoma, PT asymmetry was present in 52 cases (73.2%), as observed in a previous study that showed that tonsillar asymmetry is the main clinical manifestation of children with PT lymphoma [4]. In 46 (88%) of these 52 cases, the asymmetry was associated with other signs of malignancy, and in six (8.4%) of the 71 cases of PT lymphoma, PT asymmetry was the only reported clinical manifestation.

Further, three cases of lymphoma were incidentally found after tonsillectomies, without any previous suspicion for lymphoma [19,23]. Randall et al. evaluated the need for routine histopathological examination after tonsillectomy with or without adenoidectomy in children and in adults, and concluded that the incidence of incidental malignancy is rare, and histopathological examination should only be performed in the presence of suspicion for malignancy [44].

Based on our findings, we conclude that despite the chance of PT lymphoma in children with PT asymmetry being low, there is an association between PT asymmetry and lymphoma. Seeking an early diagnosis of PT lymphoma in children, we recommend that all children with asymmetry of PT should be properly examined and other clinical manifestations of suspicion for PT lymphoma should be sought,

since the presence of any of them increases the risk for lymphoma by 205 times. If the child presents with isolated asymmetric PT, a clinical follow-up is important to observe the appearance of any other sign of suspicion, and PT asymmetry should be monitored, noting whether it remains the same or if there is progression of asymmetry. In the case of onset of other signs of malignancy or progression of asymmetry, tonsillectomy is recommended for histopathological evaluation. If the child remains with asymmetric PT without any modification of the initial clinical status, we recommend only a less-frequent clinical follow-up, since this asymmetry may only be apparent or can be attributed to benign causes.

We also recommend that the PT of children with isolated PT asymmetry or unilateral tonsillar enlargement, who for various reasons are undergoing tonsillectomy, are sent for histopathological evaluation, since the chance of lymphoma in this population is higher than for the general population.

We believe that the existing and used classifications to assess PT asymmetry in studies are not accurate. The use of well-defined criteria for the characterisation of PT asymmetry and the development of a new specific classification for the asymmetry may help clarify the relationship of clinical PT asymmetry and the presence of PT lymphoma.

5. Conclusion

PT asymmetry was present in 73.2% of cases of PT lymphoma in children. There was an association between the presence of PT asymmetry in children and the presence of PT lymphoma with a LR of 43.5 for the PT asymmetry and 8938.4 for the PT asymmetry with other signs of malignancy. Compared to the normal paediatric population, the probability of the presence of PT lymphoma increases 43.5 times when PT asymmetry is present and 8938.4 times when other signs of malignancy are also present. The most frequent cause of PT asymmetry was lymphoid hyperplasia.

Conflict of interest

The authors have no conflict of interest to be disclosed.

Reviewers

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5. DISCUSSÃO GERAL

No primeiro artigo, intitulado “CLINICAL MANIFESTATIONS IN CHILDREN WITH TONSILLAR LYMPHOMA: A SYSTEMATIC REVIEW” foi realizada uma revisão sistemática da literatura mundial que buscou artigos com casos de linfoma de TP em crianças. Nesta revisão após a seleção inicial e aplicação dos critérios de inclusão 18 artigos foram incluídos, que continham 66 casos de linfoma de TP. Todas as manifestações clínicas relevantes para o diagnóstico presentes e descritas nos casos de linfoma, além do tipo de linfoma e local de origem do artigo foram consideradas e tabeladas.

A manifestação clínica encontrada mais frequente foi a assimetria tonsilar presente em 72,7% dos casos, seguida pela alteração na coloração ou presença de algum tipo de lesão na TP presente em 45,4% e linfonodomegalia cervical presente em 30,4% dos casos. Outras manifestações encontradas foram disfagia, ronco ou apneia, tonsilite recorrente, febre, perda de peso, alteração na voz, dor na TP, tratamento para tonsilite prévio sem melhora, imunossupressão, plenitude auricular e radioterapia prévia.

A frequência real das manifestações clínicas do linfoma de TP provavelmente deve ser superior do que a que encontramos, por se tratar de um estudo de revisão, em que em alguns casos algumas das manifestações presentes podem não ter sido relatadas pelos autores.

Quanto ao tipo dos linfomas de TP, o de Burkitt foi o mais prevalente presente em 50% dos casos seguido pelo LNH de células B em 30% e pelo linfoma linfoblástico de células T em 6% dos casos.

Houve um predomínio de pacientes do sexo masculino em relação ao sexo feminino com uma relação de 1,95 entre os gêneros, razão semelhante a encontrada em outros estudos de tumores de cabeça e pescoço e linfoma em crianças (14,15).

Apesar de a assimetria de TP ser a manifestação clínica mais frequente encontrada nas crianças com linfoma de TP, o primeiro artigo não avaliou a relação entre esta manifestação clínica e o linfoma, uma vez que as informações coletadas vieram apenas de artigos com casos de linfoma de TP. Com o objetivo de estudar e entender melhor esta relação escrevemos o segundo artigo intitulado “ASSOCIATION BETWEEN UNILATERAL TONSILLAR ENLARGMENT AND LYMPHOMA IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS”.

Neste segundo artigo, na introdução pode-se notar que a relação da assimetria de TP com o linfoma tonsilar é indefinida pelos artigos prévios, assim como a própria assimetria de TP, que em muitos casos a assimetria clinicamente aparente não foi confirmada após aferição detalhada. Em um estudo comparando crianças com assimetria de TP e crianças sem assimetria de TP que foram submetidas à tonsilectomia não foi observada diferença de volume entre os grupos, sendo a assimetria atribuída à diferença de profundidade da fossa tonsilar (16). Em outros estudos a assimetria clínica também não resultou em assimetria de tamanho aferida após a cirurgia e em nenhum destes estudos envolvendo

crianças com assimetria de TP sem outros sinais de suspeição de malignidade foram encontrados casos de linfoma de TP (17-20).

O segundo artigo desta tese avaliou a relação existente entre a assimetria de TP com o linfoma de TP em crianças por meio do estabelecimento da razão de verossimilhança. A razão de verossimilhança indica quantas vezes a chance de um diagnóstico aumenta quando um fator pesquisado está presente, neste caso ela determina quantas vezes a presença da assimetria de TP aumenta a chance da possibilidade do linfoma de TP em uma criança. A razão de verossimilhança é calculada pela sensibilidade de um teste dividida por 1 menos a especificidade deste teste ($\text{Razão de verossimilhança} = \text{Sensibilidade} / 1 - \text{especificidade}$).

As revisões sistemáticas e meta-análise realizadas no segundo artigo seguiram as orientações e critérios do grupo PRISMA assim como as recomendações da Cochrane, que sugerem etapas que devem ser seguidas para a realização de uma revisão sistemática de maneira adequada e correta (21).

Para este segundo artigo o período de busca foi estendido de janeiro de 1996 até dezembro de 2013 e além da revisão sistemática para a identificação de casos de linfoma de TP em crianças foi realizada uma revisão sistemática para identificar casos de assimetria de TP em crianças independentemente da causa da assimetria. Após o levantamento e seleção dos casos as crianças também foram classificadas quanto à presença de outros sinais de suspeição de malignidade com o objetivo de determinar o quanto a presença de outros sinais de suspeição de malignidade aumenta a chance do linfoma em crianças com assimetria de TP.

Nas revisões sistemáticas do segundo artigo, 29 artigos foram utilizados para a meta-análise, dos quais 27 artigos continham casos com assimetria de TP, em 22 destes artigos a assimetria foi definida sem nenhum critério específico, sendo apenas descrita nos artigos. Em apenas quatro artigos foi utilizada a classificação de Brodsky (22) para definir a assimetria e em um artigo a classificação de Friedman foi utilizada (23). Consideramos que as classificações existentes não são adequadas e são pouco difundidas entre os médicos, o que torna difícil a caracterização precisa da assimetria das TP. Uma nova classificação que utilize critérios bem definidos pode ser útil para futuros estudos que avaliem a relação da assimetria de TP com outras patologias, como o linfoma.

A razão de verossimilhança da assimetria de TP para a presença de linfoma de TP foi de 43,55, o que representa um significativo aumento da chance de linfoma na comparação com crianças sem assimetria de TP. Para as crianças com assimetria de TP calculamos a razão de verossimilhança da presença dos outros sinais de suspeição de malignidade, que foram encontrados no primeiro artigo, a fim de avaliarmos o quanto eles são importantes para a suspeição do linfoma, a razão de verossimilhança foi de 205,2, o que representa uma chance 205,2 vezes maior de linfoma quando as crianças com assimetria de TP também apresentam outros sinais de malignidade.

A partir dos dados obtidos, verifica-se que existe uma associação estatisticamente significativa entre a assimetria de TP e o linfoma tonsilar em crianças e que a chance de linfoma aumenta muito quando outros sinais de malignidade também estão presentes, comprovando a existência desta

associação que não estava clara na literatura. Recomendamos, portanto que todas as crianças com assimetria de TP sejam cuidadosamente examinadas e que os outros sinais de malignidade sejam buscados. Na presença da assimetria isolada consideramos que a criança deve ser acompanhada clinicamente para observar se ocorrerá mudança no padrão da assimetria ou o aparecimento de outros sinais de suspeição para malignidade, caso presentes deverá ser indicada a tonsilectomia para avaliação histopatológica das tonsilas.

Como a assimetria isolada que se mantém estável sem outros sinais de malignidade é quase sempre atribuída a etiologias benignas não recomendamos a tonsilectomia de rotina para estes casos, entretanto se por motivos diversos crianças com assimetria de TP tenham indicação de tonsilectomia, consideramos importante a avaliação histopatológica devido ao risco aumentado de linfoma para estas crianças.

6. CONCLUSÃO GERAL

A assimetria de TP é a manifestação clínica mais frequente de linfoma de TP em crianças sendo seguida pela presença de alteração na aparência da TP e linfonodomegalia cervical. Existe associação entre a assimetria de TP e linfoma em crianças sendo a razão de verossimilhança de 43,5 para a assimetria e 8938,4 quando outros sinais de suspeição para malignidade também estão presentes.

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8. ANEXOS

8.1. Aprovação no Comitê de ética em pesquisa FCM/UNICAMP



FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

<http://www.fcm.unicamp.br/fcm/pesquisa/comite-de-etica-em-pesquisa>

Ofício CEP 189/2013
Em 21/02/2013

Ilmo. Sr.
Alexandre Caixeta Guimarães
Pesquisador Responsável

Ref. : Dispensa de apresentação de projeto de pesquisa para avaliação do sistema CEP-
CONEP.

Prezado Senhor,

Informamos que o projeto de pesquisa “AVALIAÇÃO DA RELAÇÃO DA ASSIMETRIA DE TONSILAS PALATINAS E LINFOMA TONSILAR EM CRIANÇAS”, sob responsabilidade do pesquisador Alexandre Caixeta Guimarães, trata-se de uma pesquisa de revisão não sistemática da literatura mundial (chamados de “metanálise”), com isso tal projeto não necessita de apreciação e/ou aprovação do Comitê de Ética em Pesquisa com Seres Humanos, conforme descrito na Resolução CNS 196/96 item II.2 e item VII.

Sendo o que se apresenta para o momento, subscrevemo-nos.

Atenciosamente,

Prof. Dr. Carlos Eduardo Steiner
COORDENADOR DO COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

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