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Evaluation of Head and Neck Lymphadenopathies in Childhood

Çocukluk Döneminde Baş ve Boyun Lenfadenopatilerinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of this study was to evaluate the sociodemographic properties, clinical, laboratory, and radiological findings, and diagnosis of patients with head and neck lymphadenopathy (LAP) who applied to the Department of Pediatric Oncology of Medical Faculty of Gazi University.

Material and Methods: Cases who applied to the Gazi University Faculty of Medicine, Department of Pediatric Oncology between January 2009 and December 2019 due to head and neck LAP were evaluated. The sociodemographic properties and clinical, laboratory, and radiologic findings of the patients were retrospectively assessed by scanning their records.

Results: Seven hundred patients with head and neck LAP between the ages of 0-18 were included in this study. Four hundred seventy nine (68.4%) of the cases were males and 221 (316%) were females. The mean age of the patients was 7.08±4.25 years. Localized LAP was present in 509 (72.7%) cases and generalized LAP were present 191 (27.3%) cases. Of 700 cases, benign causes were detected in 581 (83.1%) cases, malignant causes were detected in 54 (7.7%) cases, and LAP-like masses were detected in 65 (9.2%) cases. Lymph node diameter over 3 cm, accompanying fever and weight loss, supraclavicular region involvement, fixed, firm, and rubbery lymph nodes, leukocytosis, elevation of C-reactive protein, erythrocyte sedimentation rate, and uric acid levels, accompanying hepatomegaly, weakness, itching, and hearing loss were significant malignancies. The most frequent cause in the benign group was upper respiratory tract infections. The most frequent cause in the malignant group was Hodgkin's lymphoma. Biopsy was performed from 125 of the cases for diagnosis. Malign causes were detected in 54 (43.2%) patients and benign causes were detected in the remaining 71 (56.8%).

Conclusion: Head and neck LAP is a frequently encountered finding in childhood. Benign causes are the more frequently detected causes in its etiology. However, malignant causes are detected less frequently; therefore, early diagnosis is important in the prognosis of the patient.

Keywords: Childhood, head and neck, etiology, lymphadenopathy

ÖZ

Amaç: Bu çalışmanın amacı Gazi Üniversitesi Tıp Fakültesi Pediatrik Onkoloji Anabilim Dalı'na başvuran baş boyun lenfadenopatisi (LAP) hastalarının sosyodemografik özelliklerini, klinik, laboratuvar ve radyolojik bulgularını ve tanılarını değerlendirmektir.

Yöntemler: Ocak 2009 ile Aralık 2019 tarihleri arasında Gazi Üniversitesi Tıp Fakültesi Çocuk Onkolojisi Anabilim Dalı'na baş boyun LAP nedeniyle başvuran olgular değerlendirildi. Hastaların sosyodemografik özellikleri ile klinik, laboratuvar ve radyolojik bulguları, kayıtları taranarak geriye dönük olarak değerlendirildi.

Bulgular: Çalışmaya 0-18 yaş arası 700 baş boyun LAP'li hasta dahil edildi. Olguların 479'u (%68,4) erkek, 221'i (%31,6) kadındı. Hastaların yaş ortalaması 7,08±4,25 yıldı. Lokalize LAP 509 (%72,7) olguda, jeneralize LAP ise 191 (%27,3) olguda mevcuttu. Yedi yüz olgunun 581'inde (%83,1) benign nedenler, 54'ünde (%7,7) malign nedenler, 65'inde (%9,2) LAP benzeri kitleler tespit edildi. Lenf bezi çapının 3 cm'den büyük olması, ateş ve kilo kaybının eşlik etmesi, supraklaviküler bölge tutulumu, sabit, sert ve lastiksi lenf düğümleri, lökositoz, C-reaktif protein yüksekliği, eritrosit sedimentasyon hızı ve ürik asit düzeyleri, hepatomegali, halsizlik, kaşıntının eşlik etmesi ve işitme kaybı önemli malignitelerdi. Benign grupta en sık neden üst solunum yolu enfeksiyonlarıydı. Malign grupta en sık görülen neden Hodgkin lenfomasıdır. Olguların 125'inden tanı amaçlı biyopsi yapıldı. Hastaların 54'ünde (%43,2) malign nedenler, geri kalan 71'inde (%56,8) benign nedenler tespit edildi.

Sonuç: Baş-boyun LAP'yi çocukluk çağında sık karşılaşılan bir bulgudur. Etiyolojisinde en sık saptanan nedenler benign nedenlerdir. Ancak malign nedenler daha az sıklıkla tespit edilir; bu nedenle erken tanı hastanın prognozu açısından önemlidir.

Anahtar Sözcükler: Çocukluk çağı, baş ve boyun, etiyoloji, lenfadenopati

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INTRODUCTION

Head and neck lymphadenopathic are a common finding of physical examination in childhood. Lymphadenopathy (LAP) is the enlargement of lymph nodes, which is a component of the immune system, for various reasons. Benign causes are the more frequently detected causes in the etiology of LAP. Although malignant causes are detected less frequently, early diagnosis is important in the prognosis of the patient (1,2). In general, for a lymph node to be considered outside the normal limits, its largest diameter must be greater than 10 mm; however, it is considered pathological if this diameter is more than 5 mm in the epitrochlear region and more than 15 mm in the inguinal region. Lymph nodes of any size in the supraclavicular region are always considered pathological. The causes of lymph node enlargement can be summarized as follows (3,4):

- Increase in lymphocytes, plasma cells, monocytes, and histiocytes in the lymph node due to antigenic stimulation (reactive hyperplasia),

- Infiltration of the lymph node by infectious agents and inflammatory cells during infections (lymphadenitis),

- Infiltration of lymph nodes by metabolite- laden macrophages in storage diseases such as Gaucher's disease and Nieman Pick's disease,

- Infiltration of the lymph node by primary or metastatic neoplastic cells.

Localized LAP is defined as the presence of LAP in a single lymph node region, whereas the presence of LAP in two or more lymph node regions that are not adjacent to each other is defined as generalized. Lymphadenopathies with a duration of less than four weeks are considered as acute LAP, and lymphadenopathic persisting for 4 weeks are considered as chronic LAP (2,3).

Careful physical examination and supportive tests such as laboratory, imaging, and biopsy are important in the diagnosis of LAP. The patient's age, infections, tooth decay, vaccinations, comorbid diseases, drug use, tuberculosis contact, animal contact, insect bites, and travel history should be questioned in the history (5,6). The duration, number, size, and characteristics (hard, soft, mobile, fixed, etc.) of LAP should be recorded in detail during physical examination. It is essential to perform a complete systemic examination for each patient. The tests are decided on the basis of the history and physical examination. Complete blood count, peripheral smear, C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), lactic dehydrogenase (LDH), uric acid, and liver and kidney function tests can be planned. If infection is suspected, throat culture, PPD, and viral serological tests [Epstein-Barr virüsü (EBV), cytomegalovirus, human immunodeficiency virus, toxoplasma, and rubella] can be performed. Chest radiography is helpful in determining the presence of mediastinal LAP or in detecting pulmonary diseases such as tuberculosis (6,7).

Ultrasonography (USG), a non-invasive imaging method, is not necessary for every patient. USG can be a guide for biopsy and drainage or in the differential diagnosis of abscesses, infected cysts, cystic hygromas, and hemangiomas (3,4). If there are suspicious findings in the history, physical examination, laboratory and/or imaging, and lymph node biopsy, which is an invasive advanced examination method, can be performed. The biopsy should be performed excisionally from the largest and fixed lymph node that can be palpated, and the lymph node should be removed with its capsule intact. When pathological findings are observed in the complete blood count, bone marrow aspiration and biopsy should be performed before lymph node biopsy (8,9).

In this study, we aimed to evaluate the sociodemographic, clinical, laboratory, and radiological findings and diagnoses of patients with head and neck LAP at the Gazi University Faculty of Medicine, Department of Pediatric Oncology, and compare them with similar studies in our country and other countries.

MATERIALS AND METHODS

We planned to retrospectively evaluate children presenting with head and neck LAP with sociodemographic, clinical, and laboratory findings. This study was approved by Gazi University Ethics Committee (approval number: 07, date: 14.07.2020).

In this study, 700 patients aged 0-18 years who applied to Gazi University Faculty of Medicine, Department of Pediatric Oncology between 01.01.2009 and 31.12.2019 due to head and neck lymphadenopathic were retrospectively evaluated. The data of the cases were obtained by examining the patient files. Sociodemographic data, symptoms, physical examination findings, and laboratory and imaging findings were recorded in the case report form.

Age, gender, duration of symptoms, presence of infection in the history, localization of LAP, palpation findings in physical examination, complete blood count and peripheral smear, biochemical parameters (LDH, uric acid), CRP, ESR, viral serology, culture results, chest X-ray, USG, and lymph node biopsy results were recorded.

Statistical Analysis

Quantitative data were represented by mean ± standard deviation. Percentages described qualitative data, and the comparison of these data was performed using the chi-square test. Fisher's exact test was used in the analysis of nominal variables when the distribution could not be matched to the chi-square test. The Mann-Whitney U test was used in the analysis of continuous variables. All analyses were performed using SPSS 22.0 software and $p<0.05$ was considered statistically significant.

RESULTS

In this study, 700 patients aged 0-18 years who applied to the Gazi University Faculty of Medicine, Department of Pediatric Oncology due to head and neck lymphadenopathic were retrospectively evaluated. The distribution of 700 patients with head and neck LAP by age and sex is shown in Table 1.

When evaluated according to the duration of LAP, the symptoms were acute in 40.3% (n=282) and chronic in 59.7% (n=418) of the cases. Localized LAP was detected in 72.7% (n=509) and generalized

Table 1. Distribution of patients by age and sex

		Patients, (n=700)
Gender	Male	479 (68.4%)
	Female	221 (31.6%)
Age, year $\bar{X}$ ± SD (min.-max.)		7.08±4.25 years (5 days-17.5 years)

SD: Standard deviation, min: Minimum, max: Maximum.

LAP in 27.3% (n=191) of the cases. There was a history of infection in 441 patients. Upper respiratory tract infection was found in 74.8% (n=330) of 441 patients with a history of infection, and EBV infection was the second most common infection. According to the serological test results, EBV VCA immunglobulin M positivity was detected in 148 (21%) patients.

The mean lymph node size of the patients was 2.29±1.66 cm (0.5-17 cm) in this study. While the lymph node size was between 1 and 3 cm in approximately 80% of the cases, the lymph node size was 3 cm or more in 14% (n=98) of the cases. The rate of malignancy was found to be higher in cases with a lymph node size of 3 cm ($p<0.001$). Supraclavicular area involvement was significantly higher in malignant cases ($p<0.05$).

Additional systemic findings were detected in 18.3% (n=128) of 700 cases. Splenomegaly was observed in 41 patients, and other frequently observed additional findings were hepatomegaly, dental caries, and cardiac murmur. In our study, the symptoms of hearing loss in 4 patients with nasopharyngeal carcinoma and 2 patients with nasopharyngeal Burkitt lymphoma were reported.

When complete blood count and biochemical parameters were evaluated, leukocytosis (n=138), leukopenia (n=7), elevated CRP (n=149), elevated ESR (n=124), elevated LDH (n= 285), and increased uric acid levels (n=32) were detected in the patients in our study. Leukocyte, CRP, ESR, and uric acid levels were found to be higher in malignant cases than in benign cases ($p<0.05$) (Table 2).

In this study, chest X-ray was performed in 689 patients, and cervical USG was performed in 644 patients as the imaging method. According to the imaging features of the lymph nodes of 644 patients who underwent cervical USG, USG results were reported as possible benign reactive LAP in 542 (77.4%) and possible malignant LAP in 102 (14.6%) patients in our study. The radiological findings are shown in Table 3. According to the biopsy results, 54 patients were diagnosed with malignant pathology.

Lymph node biopsy was performed in 125 patients, benign histology was found in 71, and malignant causes were found in 54. Biopsy was required in 71 of 581 patients who were evaluated as having benign LAP in our study. Reactive hyperplasic lymph nodes were the most common benign cause, and the most common malignant pathology was classical Hodgkin lymphoma. The distribution of malignant cases according to biopsy results is given in Table 4.

Non-lymphadenopathic masses were found in 9.3% (n=65) of 700 cases. Branchial cleft cyst was the most common non-LAP mass in our study. The distribution of 700 patients included in the study according to their diagnoses is given in Table 5.

DISCUSSION

Head and neck lymphadenopathic are a common finding of physical examination in childhood. Although malignant causes are less common, early diagnosis is important. A detailed history, complete systemic physical examination, and laboratory and imaging methods are necessary to determine the etiology (7,10).

In this study, approximately 65% of 700 cases had a history of infection in the last 1 month. We found the most common upper respiratory tract infection (47.1%) and the second most common EBV infection in our study. When evaluated according to serological test results, EBV VCA IgM positivity was observed in 21.1% (n=148) of our patients. In the literature, Bozlak et al. (11) had a history of infection in 45.9% of the cases, and EBV infection was found in 27.1% of the patients. Aykaç et al. (12) upper respiratory tract infection in 52.1% of the cases and EBV infection in 20.5% of the cases. Our study is similar to the results of other centers in our country. Due to the high incidence of EBV infection, EBV infection should be considered by all physicians in the differential diagnosis of LAP.

Non-LAP masses were detected in 65 (9.3%) of the 700 patients included in our study, and 22 of them were branchial cleft cysts. In the literature, Riva et al. (13) found branchial cleft cysts in 21% of the cases in the study. We believe that congenital malformations should be considered in the differential diagnosis of cervical LAP, and appropriate imaging methods such as USG should be planned. Chest radiographs were taken in approximately 98% of the patients in our study. Because the patients who applied to the pediatric oncology department were included in the study, we believe that such a high rate of chest X-ray was taken to detect accompanying mediastinal

Table 2. Comparison of benign and malignant patients by biochemical parameters

		Benign lymphadenopathies, (n=581)		Malign lymphadenopathies, (n=54)		p
		n	(%)	n	(%)	
Leukocyte count	Low (<4,000/mm^3)	4	(0.7%)	3	(5.6%)	**0.014**
	Normal (4,000-11,000/mm^3)	457	(78.7%)	39	(72.2%)	
	High (≥11,000/mm^3)	120	(20.7%)	12	(22.2%)	
CRP	Normal (≤5 mg/L)	232	(40.0%)	10	(18.5%)	**0.001**
	High (>5 mg/L)	122	(21.0%)	22	(40.7%)	
ESR	Normal (≤20 mm/H)	200	(34.4%)	14	(25.9%)	**<0.001**
	High (>20 mm/H)	97	(16.7%)	24	(44.4%)	
LDH	Normal (140-280 U/L)	329	(56.6%)	30	(55.6%)	0.491
	High (≥280 U/L)	238	(41.0%)	24	(44.4%)	
Uric acid level	Normal (≤5.5 mg/dL)	542	(93.3%)	48	(88.9%)	**0.033**
	High (>5.5 mg/dL)	22	(3.8%)	6	(11.1%)	

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactic dehydrogenase.

Table 3. Distribution of patients by imaging results

	(n=700), frequency (%)	
Chest X-ray	**689**	**(98.5)**
None	11	(1.6)
Normal	671	(95.9)
Mediastinal enlargement	18	(2.6)
Cervical USG	**644**	**(92)**
Undone	56	(8.0)
Benign	542	(77.4)
Malign	102	(14.6)

USG: Ultrasonograpy.

Table 4. Distribution of patients with malignant biopsy results

Malignant biopsy results	(n=54), frequency (%)	
Hodgkin lymphoma	**35**	**(64.8)**
Classical Hodgkin lymphoma (mixed cellular type)	14	(25.9)
Classical Hodgkin lymphoma (nodular sclerosing type)	13	(24.1)
Classical Hodgkin lymphoma (lymphocyte-rich type)	4	(7.3)
Unclassified Hodgkin lymphoma	3	(5.6)
Nodular lymphocyte-predominant Hodgkin lymphoma	1	(1.9)
Non-Hodgkin's lymphoma	**8**	**(14.8)**
T-lymphoblastic lymphoma	3	(5.5)
Burkitt lymphoma	2	(3.6)
Anaplastic large cell lymphoma	1	(1.9)
Pediatric follicular lymphoma	1	(1.9)
Peripheral T-cell lymphoma	1	(1.9)
Others	**11**	**(20.4)**
Nasopharyngeal carcinoma	4	(7.3)
Papillary thyroid carcinoma	4	(7.3)
Medullary thyroid carcinoma	1	(1.9)
Langerhans cell histiocytosis	1	(1.9)
Fibroblastoma	1	(1.9)

enlargement. Routine chest X-ray is unnecessary for every child with LAP, and all children should be protected from radiation exposure.

In our study, we observed that the lymph node diameter was 3 cm in 60% of the cases diagnosed with malignancy. The diameter of the lymph node was found to be higher in malignant cases than in benign cases, and the difference was statistically significant. Kumral et al. (14) it has been reported that the lymph node size was greater than 3 cm in 58.3% of the patients with malignancy. It may be recommended to consult the pediatric hematology and oncology departments in order not to miss the malignant causes in patients whose etiology could not be determined, lymph nodu size is larger than 3 cm, and there are no additional systemic findings.

Table 5. Distribution of patients by diagnosis

	(n=700), frequency (%)	
Benign lymphadenopathies	**581**	**(83.0)**
Infections	437	(62.4)
Non-specific reactive lymphadenopathy	144	(20.7)
Malign diseases	**54**	**(7.7)**
Hodgkin lymphoma	35	(5.0)
Non-Hodgkin lymphoma	8	(1.1)
Other malignancies	11	(1.6)
Non-lymphadenopathic masses	**65**	**(9.3)**
Branchial cleft cysts	22	(3.0)
Thyroid gland pathologies	17	(2.4)
Thyroglossal cyst	16	
Congenital vascular anomalies	5 (0.8)	(2.3)
Thymus gland anomalies	5 (0.8)	

When we evaluated the laboratory findings of our cases, leukocyte, CRP, ESR, and uric acid levels were found to be significantly higher in the malignant group than in the benign group. The majority of our patients with malignant diagnosis consisted of Hodgkin lymphoma. Because inflammatory markers such as ESR and CRP are also elevated in Hodgkin's disease, we can attribute the elevation in the malignant group to this. In our study, we had only 8 patients with a diagnosis of non-Hodgkin lymphoma who presented with cervical LAP. We may not have found the LDH increase to be statistically significant because of the small number of patients, the absence of high tumor burden, and the low stage of in our cases.

In our study, we found other accompanying findings such as splenomegaly in 5.9% of the cases and hepatomegaly in 4.9%. In the study by Yaris et al. (15), hepatomegaly was observed in 14.2% of the cases and splenomegaly was observed in 13.2% of the cases, and both findings were found to be significantly higher in the malignant group than in the benign group. It is essential to perform a complete systemic physical examination in patients with LAP. The symptoms of hearing loss in 4 patients with nasopharyngeal carcinoma and 2 patients with nasopharyngeal Burkitt lymphoma were reported in our study. It should be known that hearing loss is an important symptom in tumors located in the nasopharynx. Nasopharyngeal examination is important in sudden hearing loss accompanied by cervical LAP.

In our study, biopsy was performed in 125 patients (17.9%) for whom biopsy was indicated as a result of history, physical examination, laboratory, and/or imaging findings. Because of biopsy, malignancy was detected in 43.2% of our patients. Benign causes such as non-specific reactive lymph node hyperplasia in 9.3% and branchial cleft cyst in 3% of the patients were found in our study. Benign causes were observed less frequently because selected cases consulted to the pediatric oncology department were included in our study.

We detected the most common Hodgkin lymphoma (64.8%) and non-Hodgkin lymphoma was the second most common (14.8%) according to biopsy results. Unsal et al. (16) reported that malignancy

was found in 23.4% of 98 patients who underwent biopsy, and Hodgkin lymphoma was the most common and non-Hodgkin lymphoma was the second most common. Indolfi et al. (17) Have been reported to be malignant in 75% of 88 patients who underwent biopsy from 405 patients. Our biopsy results were consistent with those reported in the literature. Physicians should consider Hodgkin lymphoma in the differential diagnosis if there is a prolonged history, unresponsiveness to antibiotic therapy, and persistence of painless and rubbery cervical LAP on physical examination.

CONCLUSION

Although the cause is often a simple infection, LAP may be a finding in complicated diseases such as neoplastic diseases in children. Despite malignant causes being seen less frequently, early diagnosis is important in the prognosis of the patient. The existing findings of each patient should be evaluated very well, physical examination should be performed in detail, and the LAP should be closely followed up by the doctor until the disappearance of LAP in children.

Ethics

Ethics Committee Approval: This study was approved by Gazi University Ethics Committee (approval number: 07, date: 14.07.2020).

Informed Consent: Retrospective study.

Peer-Review: Externally peer-reviewed.

Authorship Contributions

Concept: E.S.Y., A.O., Ö.V., F.G.P., C.K., Design: E.S.Y., A.O., Ö.V., F.G.P., C.K., Data Collection or Processing: E.S.Y., A.O., Ö.V., F.G.P., C.K., Analysis or Interpretation: E.S.Y., A.O., Ö.V., F.G.P., C.K., Literature Search: E.S.Y., A.O., Ö.V., F.G.P., C.K., Writing: E.S.Y., A.O., Ö.V., F.G.P., C.K.

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