Research Article / Araştırma Makalesi

Evaluation of Clinical and Etiological Characteristics of Cases with Pediatric Lymphadenopathy

Pediatrik Lenfadenopati Olgularının Klinik Ve Etiyolojik Özelliklerinin Değerlendirilmesi

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Abstract: Lymphadenopathies are among the common causes of frequent hospital admissions in childhood.Lymphadenopathy (LAP) may be most frequently seen during the follow-up of infectious diseases, but some chronic, malignant, and autoimmune diseases may also be encountered in the etiology of lymphadenopathy.In this study we aimed to investigate the clinical, epidemiologic, and etiological characteristics of pediatric patients presenting with lymphadenopathy.A total of 380 pediatric patients with lymphadenopathy who were followed up in the Eskisehir Osmangazi University Pediatric Infectious Diseases Clinic between January 2015 and January 2023 were included in the study.The mean age of the patients was 84 months and 65% of the patients were male.According to etiologic characteristics; 359(94%) cases had infectious and 21(6) cases had non-infectious LAP.Most frequently nonspecific lymphadenitis (68%), Epstein-Barr Virus (12.8%), cytomegalovirus (3.6%), suppurative lymphadenitis (1.9%) and tuberculous lymphadenitis (1.8%) were observed in cases with LAP. Cases with non-infectious LAP had rheumatologic diseases (n:11), hemato-oncologic malignancies (n: 6), and congenital cysts (n:4). When infectious and non-infectious LAP cases were compared, involved lymph nodes were larger (p:0.04) in the non-infectious group.In the non-infectious group,lymph nodes were relatively harder and conglomerated(p:0.03, p:0.04).Computed tomography scan was more frequently performed in the non-infectious group(p:0.01).Although lymphadenopathy in childhood is mostly due to infectious causes, rheumatologic diseases, hemato-oncologic malignancies, and congenital cysts should be kept in mind, especially in prolonged, treatment-refractory cases. Detailed history and physical examination are the first and the most important steps in the differential diagnosis of cases presenting with lymphadenopathy to prevent the application of unnecessary tests and investigations
Keywords: lymphadenopathy, child, etiology

Özet: Lenfadenopatiler çocukluk çağında, sık hastaneye başvuru sebeplerindendir. Lenfadenopati daha çok enfeksiyon hastalıklarının izleminde olabileceği gibi bazı kronik hastalıklar, malign hastalıklar, otoimmün hastalıklar da lenfadenopati etiyolojisinde karşımıza çıkabilmektedir. Bu çalışmada lenfadenopati ile başvuran çocuk olguların, klnik, epidemiyolojik ve etiyolojik özelliklerinin araştırılması amaçlanmıştır. Çalışmaya, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Hastanesinde Ocak 2015- Ocak 2023 tarihleri arasında, Çocuk Enfeksiyon Hastalıkları Kliniğinde, lenfadenopati sebebiyle takip edilen 380 çocuk olgu dahil edildi. Olguların %35 ine medikal tedavi uygulanırken, 22 olguda ise cerrahi tedavi uygulandı. Etiyolojik özelliklerine göre; 359 (%94) ünde enfeksiyöz, 21 (6) inde non enfeksiyöz LAP mevcuttu. Enfeksiyöz etkenlerden en sık sırasyla, non-spesifik lenfadenit (%68), Epstein Barr Virüs (%12.8), Sitomegalivirus (%3.6), süpüratif lenfadenit (1.9) ve tüberküloz lenfadenitdi (%1.8). Non enfeksiyöz LAP olguların, 11 inde romatolojik hastalıklar, 6 sında hemato-onkolojik malignite, 4 olguda ise konjenital kist mevcuttu. Enfeksiyöz ve non enfeksiyoz LAP olguları karşılstırıldığında, non-enfeksiyoz LAP grubunda LAP boyutu daha büyükdü (p:0.04). Non-enfeksiyon grupda, daha çok sert ve konglemerasyon karakterde LAP mevcuttu (p:0.03, p: 0.04). Bilgisayarlı tomografi çekimi, non enfeksiyoz grupda dah sıkdı (p: 0.01). Çocukluk çağında lenfadenopatiler çoğunlukla enfeksiyoz sebeplere bağlı olsada, özellikle uzamış, tedaviye yanıtsız olgularda, romatolojik hastalıklar, hemato-onkolojik maligniteler ve konjenital kistlerde akılda tutulmalıdır. Gereksiz tetkiklerin önlenmesi açısından, ayrıntılı öykü ve fizik muayene, lenfadenopati ile başvuran olguların ayrıcı tanısında ilk ve en önemli basamağı oluşturmaktadır.
Anahtar Kelimeler: çocuk, lenfadenopati, etyoloji

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1. Introduction

Lymphadenopathies are among the common causes of hospital admissions in childhood. The term "lymphadenopathy" is used to refer to lymph nodes that are larger than their normal sizes, whereas "lymphadenitis" refers to lymphadenopathies related to infectious processes (1). The incidence of lymphadenopathy in childhood has been reported to be 45-57% in many studies (2). While lymphadenopathy may be mostly observed in the follow-up of infectious diseases, some chronic diseases, malignancies, and autoimmune diseases may also be encountered in the etiology of lymphadenopathy (3). Lymphadenitis in childhood develops as a result of viral, bacterial, parasitic, or mycobacterial infections. Viruses typically cause diffuse lymphadenopathy and lesions of viral lymphadenitis tend to be bilateral, multiple, and smaller in size compared to bacterial lymphadenitis (4). Acute and chronic bacterial infections affect lymph nodes. The majority of acute bacterial infections are caused by staphylococci and beta-hemolytic group A streptococci. *Francisella tularensis*, *Pasteurella spp*, *Haemophilus influenza* type B and *Propionibacteria spp, Fusobacteria spp*, and *peptostreptococci* are rarely detected bacterial agents causing cervical lymphadenopathy. Chronic bacterial infections of the lymph nodes are mostly caused by non-tuberculous mycobacteria, and other common infectious agents including *Bartonella hanselea, Mycobacterium tuberculosis*, and Brucella (5).

Rheumatologic, autoimmune, hemato-oncologic, metabolic, lymphoprolative diseases, drugs, and congenital cysts are the most common causes of non-infectious lymphadenopathies (5,6). Although hemato-oncologic malignancies are among the rarest causes of childhood lymphadenopathies, they are the most feared, suspected, and investigated etiologic factors. Leukemia and lymphoma are the most common causes of lymphadenopathy in childhood malignancies. Leukemia represents approximately 30% of all malignancies and 75% of leukemias are acute lymphoblastic leukemia (ALL). Lymphomas constitute 11% of childhood malignancies, including non-Hodgkin lymphoma (6%) and Hodgkin lymphoma (5%) (7). Lymphadenopathies of the head and neck are frequently observed in Hodgkin lymphoma and these lymphadenopathies are usually painless, non-tender, elastic in consistency, non-adherent to the surrounding tissue, and located in the cervical and supraclavicular regions. Systemic symptoms including fever, night sweats, and weight loss are observed in one-third of the cases (8). Congenital masses are painless and benign, and usually present from birth. Thyroglossal duct, branchial, dermoid, and thymic cysts, cystic hygroma, ectopic thyroid, hemangioma, teratoma, lipoma, and fibroma are benign masses seen in the neck region in children (9). In this study, we aimed to retrospectively evaluate the epidemiologic characteristics, etiologies, and clinical and laboratory findings of patients aged 0-18 years who were followed up and treated for lymphadenopathy.

2. Materials and Methods

A total of 380 pediatric patients with acute/chronic lymphadenopathy who were followed up in the Osmangazi University School of Medicine Pediatric Infectious Diseases Clinic between January 2015 and January 2023 were included in the study. Clinical and epidemiologic characteristics, laboratory and radiologic findings, and treatments they received were evaluated retrospectively. Complete blood counts, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels were recorded. Additional studies (serologic tests for Epstein-Barr virus (EBV), cytomegalovirus, Brucella, *Mycobacterium tuberculosis*, ultrasonography, and computed tomography) were also performed according to clinical indications. Excisional biopsy was performed in cases of suspected malignancy.

Firstly, cases with pathologically enlarged lymph nodes detected during physical examination were included in the study. Physical examination findings were reconfirmed by ultrasonography in almost all cases. Swelling of lymph nodes secondary to bacterial, viral, or fungal infections,

autoimmune disease, and malignancy were defined as lymphadenopathy. Lymphadenopathy was defined as a lymph node larger than 1 cm in the axillary and cervical region, 1.5 cm in the inguinal region, 0.5 cm in the epitrochlear region, and any size in the supraclavicular and popliteal region. Enlarged lymph node size accompanied by pain, redness, and increased temperature was described as lymphadenitis. Enlargement of the lymph node secondary to infection in the lymph drainage area was considered reactive lymphadenopathy. Lymphadenopathies occurring secondary to viral and bacterial infection, such as acute tonsillitis and acute pharyngitis, were also evaluated as reactive lymphadenopathy. Lymphadenopathies due to group A streptococci were also included in this group. Lymph nodes were classified according to anatomical site, size (<1 cm, 1-2 cm, 2-3 cm, >3 cm), number of sites involved (localized/one anatomical site or generalized/ 2 or more non-contiguous lymph node sites) and duration of lymphadenopathy (< 2, 2-4 and >4 weeks). Cases were classified as infectious and non-infectious LAP according to clinical, laboratory, and histopathologic findings. The non-infectious group included hemato-oncologic malignancies, rheumatologic diseases, and congenital cysts. This study was approved by the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (2023/201). Our study aims to determine the clinical, epidemiological, and etiological characteristics of pediatric cases followed up in our center due to lymphadenopathy.

Statistical analysis was performed using the SPSS statistical package (version 18 for Windows). Data were expressed as mean ± standard deviation (SD) or median (interquartile range) for continuous variables or percentages for categorical variables. Comparison of groups was performed using chi-square or Fisher's exact test. A paired sample t-test was performed for the values of $p< 0.05$ to determine the significant difference between repeated measures. Differences and correlations were considered significant at $p< 0.05$.

3. Results

The mean age of the patients included in the study was 84 months and 65% of them were male. The most common presenting symptoms and signs were neck swelling (81%), malaise (29%), fever (23%) and anorexia (14%). The most common anatomical locations were cervical (80.5%), submandibular (9.5%), and axillary (5.2%) regions. LAP size was 1-2 cm in 74.8% and 2-3 cm in 16.1% of the cases. Multiple LAPs were present in 97.1% and single LAPs in 2.9% of the cases. LAPs were soft in 98.8%, mobile in 97.9%, and painless in 96% of the cases. Hepatomegaly was present in 15 and splenomegaly in 12 cases. Ultrasonography was performed in 98% and computed tomography in 5% of the cases. Medical treatment was applied in 35% and surgical treatment in 22 cases (Table 1).

According to etiologic characteristics; 359 (94%) patients had infectious and 21 (6%) had non-infectious LAP. Most frequently nonspecific lymphadenitis (68%), Epstein-Barr Virus infection (infectious mononucleosis:12.8%), cytomegalovirus infections (3.6%), suppurative lymphadenitis (1.9%), and tuberculous lymphadenitis (1.8%) were observed in cases with LAP. Group A streptococcus was identified in the throat swab cultures of 7 cases presenting with lymphadenopathy. Among the non-infectious LAP cases, rheumatologic diseases were present in 11, hemato-oncologic malignancies in 6, and congenital cysts in 4 cases (Table 2). Excisional biopsy was performed in 27 of all cases for both diagnosis and treatment. A total of 27 cases underwent diagnostic biopsies, while granulomatous lymphadenitis was revealed in 16, lymphoma in 4, Langerhans cell histiocytosis in 1, congenital cysts in 4 and recurrent lymphadenopathy in 2 cases (Table 3). When infectious and non-infectious LAP cases were compared, affected lymph nodes were larger in the non-infectious LAP group (p:0.04). In the non-infectious group, the affected lymph nodes were relatively harder and conglomerated (p:0.03, p:0.04). Computed tomography scan was more frequently performed in the non-infectious group (p: 0.01) (Table 4).

Table 1. Clinical and Epidemiologic Characteristics of the Cases

	n:380 (%)
Age(month)	84 (3-204)
Gender	
Male	250 (65)
Female	130 (35)
Symptoms-Signs	
Swelling in the neck	309 (81)
Malaise	109 (29)
Fever	89 (23)
Loss of appetite	52 (14)
Weight loss	19 (5)
Rash	9 (3)
Anatomical Location	
Cervical	306 (80.5)
Submandibular	36 (9.5)
Axillary	20 (5.2)
Inguinal	13 (3.5)
Supraclavicular	5 (1.3)
Size	
< 1 cm	25 (6.6)
1-2 cm	284 (74.8)
2-3 cm	61 (16.1)
>3cm	10 (2.6)
Number	
Single	11 (2.9)
Multiple	369 (97.1)
Hard	5 (1.2)
Soft	375 (98.8)
Mobility	
Mobile	372 (97.9)
Fixed	8 (2.1)
Painful	15 (4)
Painless	365 (96)
Hepatomegaly	15 (4)
Splenomegaly	12 (3)
Laboratory parameters	
Leukocytes (mm^3)	9900 (2500-38.000)
Lymphocytes (mm^3)	4700 (800-35.000)
Neutrophils (mm^3)	4000 (600-17.800)
Platelets (mm^3)	303000 (380-325.000)
C-reactive protein (mg/dl)	68 (0.1-203)
Sedimentation (hours)	16 (3-97)
[1]LDH	801 (125 -1350)
Uric Acid	3.9 (1.3-5.8)
Radiological Imaging	
Ultrasonography	370 (98)
Computed tomography	18 (5)
Biopsied cases	27 (7.1)
Treatment	
Antibiotherapy	136 (35)
Surgery + Medical Treatment	22 (5.7)
Duration of Treatment	
< 1 week	14 (3.7)
1-2 weeks	104 (27.4)
>3 weeks	30 (7.9)

[1] *LDH: Lactic dehydrogenase*

Table 2. Etiologic Characteristics of the Cases **n:380 (%)**

Infectious Lymphadenopathy	359 (94)
Nonspecific Lymphadenopathy	261 (68)
Epstein-Barr Virus	49 (12.8)
Cytomegalovirus	14 (3.6)
Suppurative Lymphadenitis	7 (1.8)
Tuberculous Lymphadenitis	7 (1.8)
Mumps	6 (1.6)
Deep Neck Infection	4 (1)
Cat Scratch disease	3 (0.8)
Toxoplasmosis	2 (0.5)
Tularemia	2 (0.3)
Brucellosis	2 (0.5)
Parvovirus infection	1 (0.3)
Syphilis	1 (0.3)
Rheumatologic diseases	
[1]PFAPA syndrome	11 (2.8)
Kawasaki Disease	4 (1)
[2]FMF	2 (0.5)
Sarcoidosis	2 (0.5)
[3]JIA	1 (0.3)
Hyper immunoglobulin-D Syndrome	1 (0.3)
Malignancies	6 (1.5)
Lymphoma	4 (1)
Follicular Lymphoma	1 (0.3)
Classical Hodgkin Lymphoma	1 (0.3)
Mix-Cellular Hodgkin Lymphoma	1 (0.3)
Nodular sclerosing Hodgkin Lymphoma	1 (0.3)
Leukemia	1 (0.3)
[4]Pre-B ALL	1 (0.3)
Langerhans Cell Histiocytosis	1 (0.3)
Congenital Cysts	4 (1)
Branchial Cleft Cyst	2 (0.5)
Thyroglossal Cyst	2 (0.5)

[1] ***PFAPA syndrome(disease:*** *Periodic fever, Aphthous stomatitis, Pharyngitis and Adenitis*
[2] ***FMF:*** *Familial Mediterranean Fever* [3] ***JIA:*** *Juvenile Idiopathic Arthritis* [4] ***Pre-B ALL*** *precursor B-cell Acute Lymphoblastic Leukemia*

Table 3. Characteristics of Biopsied Cases	**n:27 (%)**
Granulomatous Lymphadenitis	**16 (59)**
Tuberculous Lymphadenitis	**7 (26)**
Cat Scratch disease	**3 (11)**
Tularemia	**2 (7.4)**
Brucellosis	**2 (7.4)**
Syphilis	**1 (3.6)**
Sarcoidosis	**1 (3.6)**
Malignancies	**5 (18.4)**
Follicular Lymphoma	**1 (3.6)**
Classic Hodgkin Lymphoma	**1 (3.6)**
Mix-Cellular Hodgkin Lymphoma	**1 (3.6)**
Nodular sclerosing Hodgkin Lymphoma	**1 (3.6)**
Langerhans Cell Histiocytosis	**1 (3.6)**
Congenital Cysts	**4 (15.2)**
Branchial Cleft Cyst	**2 (7.4)**
Triglossal Cyst	**2 (7.4)**
Reactive Lymphadenitis	**2 (7.4)**

Table 4. Comparisons between Cases of Infectious and Non-infectious Lymphadenopathy

	Infectious n:359 (%)	Non-infectious n:21 (%)	P-value
Age	84 (3-204)	88 (24-180)	0.6
Gender			0.2
Male	237 (66)	12 (57)	
Female	122 (33)	9 (43)	
Symptoms-Signs			
Malaise	100 (27)	9 (42)	0.1
Fever	79 (22)	8 (38)	0.02
Loss of appetite	47 (13)	5 (23)	0.3
Weight loss	18 (5)	1 (4.8)	0.7
Rash	7 (1.9)	2 (7.5)	0.08
Anatomical Location			
Cervical	282 (81)	16 (80)	
Submandibular	34 (9)	2 (10)	
Axillary	19 (5.4)	1 (5)	0.7
Inguinal	13 (3.7)	0 (0)	
Supraclavicular	4 (1.1)	1 (5)	
Size			
< 1 cm	25 (7)	0 (0)	
1-2 cm	269 (75)	14 (67)	0.04
2-3 cm	55 (15.5)	6 (28)	
>3cm	9 (2.5)	1 (5)	
Number			
Single	9 (2.5)	2 (9.5)	
Multiple	349 (97.5)	19 (91)	0.1
Hard	2 (0.6)	1 (5)	
Soft	356 (99.4)	20 (95)	0.03
Mobility			
Mobile	52 (98.3)	20 (95.2)	0.3
Fixed	6 (1.7)	1 (4.8)	
Painful	15 (4.2)	0 (0)	0.4
Painless	343 (95.8)	21 (100)	
Conglomeration	8 (2.2)	2 (9.5)	0.04
Hepatomegaly	13 (3.6)	1 (5)	0.6
Splenomegaly	11 (3.1)	1 (5)	0.5
Radiological Imaging			
Ultrasonography	349 (98)	21 (100)	0.01
Computed tomography	14 (4)	4 (20)	

4. Discussion

In our study in which the clinical and etiologic features of pediatric cases with lymphadenopathy were examined, the most common indications for hospital admissions were neck swelling, fever, and malaise. Similarly, in their studies, Kumar et al. and Ahuja et al. reported swelling in the neck and fever as the most common presenting symptoms and signs in patients presenting with lymphadenopathy (10,11). Oğuz et al. and Soldes et al. reported that fever was more common in patients with infectious lymphadenopathy, while weight loss and night sweating were more frequently seen in patients with malignancies (12,13). In our study, weight loss was seen at similar rates in the infectious and non-infectious groups. This fact may be explained by the presence of chronic infectious diseases such as tuberculosis in the infectious group of our study. Another reason is that in our study, the non-infectious lymphadenopathy group comprised not only hemato-oncologic malignancies but also more benign cases such as rheumatologic diseases and congenital cysts.

In our study, cases with multiple lymphadenopathies were more frequently seen and the most commonly cervical and submandibular lymph nodes were involved. Many studies cited in the literature have reported that cases with localized, single lymphadenopathies are more frequently

observed than those with diffuse and multiple lymphadenopathies (10,14). Contrary to the literature, the greater number of cases with multiple lymphadenopathies in our study may be explained by the higher rates of cases with nonspecific lymphadenitis, and lymphadenitis secondary to viral infections caused by Ebstein-Barr virus, and cytomegalovirus. Most commonly lymphadenopathies were localized in the cervical and submandibular regions, as reported in many studies in the literature (15-20). However, contrary to the literature, there was no significant difference in anatomical location of affected lymph nodes between infectious and non-infectious lymphadenopathy groups (12,13).

In our study, cases with lymph nodes smaller than 2 cm were more commonly observed and lymph nodes were larger in the non-infectious lymphadenopathy group compared to the infectious lymphadenopathy group. Similarly, many studies in the literature have reported that cases with relatively smaller lymph nodes are mostly seen in infectious lymphadenopathies, while larger lymph nodes are present in non-infectious lymphadenopathies as in malignancies (12,16,20).

In our study, in the non-infectious lymphadenopathy group, the affected lymph nodes were more frequently harder and conglomerated compared to the group with infectious lymphadenopathy. However, there was no significant difference between the two groups regarding mobile and fixed, painful and, and painless lymph nodes. Many studies in the literature have reported that hard, immobile, painless, and conglomerated lymph nodes were more commonly seen in patients with non-infectious lymphadenopathy such as in cases with malignancy, while mobile, soft, and painful lymph nodes were more common in patients with infectious lymphadenopathy (12,13,21). In our study, contrary to the literature, there was no significant difference between the two groups in terms of the presence of mobile or painful lymph nodes, which we attributed to the fact that the non-infectious group included not only cases with malignancy but also cases with lymphadenopathy due to congenital cysts and rheumatologic diseases.

In our study, the most common etiologic factors in the infectious lymphadenopathy group were nonspecific lymphadenopathies where causative factors could not be determined, Ebstein-Barr virus, cytomegalovirus, tuberculosis, suppurative lymphadenitis, toxoplasma, and brucella. In the non-infectious group, rheumatologic diseases such as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis and Kawasaki syndromes, hemato-oncologic malignancies such as lymphoma and ALL (Acute Lymphoblastic Leukemia) were the most commonly seen etiologies. Similarly, Kumar et al. and Öksüz et al. reported that the most common infectious agents were EBV, CMV, and TBC (tuberculous lymphadenitis) (10,20,22). In our study, unlike the literature, the number of cases with tuberculous lymphadenopathy was higher in the infectious group. This may be explained by the recent increase in the prevalence of tuberculosis in the community. In the non-infectious group, rheumatologic diseases were more common than malignancies. We attributed this to the fact that patients with a preliminary diagnosis of malignancy were first referred to the outpatient clinics of pediatric hematology and then outpatient clinics of pediatric infection because our center is a tertiary care hospital. In our study, tuberculosis, granulomatous lymphadenitis secondary to cat scratch disease, malignancies such as lymphoma and Langerhans cell histiocytosis, congenital cysts such as thyroglossal cyst and branchial cleft cyst were the most common diagnoses in biopsied cases, while reactive lymphadenitis was found in only 2 cases. Many studies cited in the literature reported very different biopsy results. While benign pathologic findings such as reactive lymphadenitis were found more frequently in some studies, malignant pathologies such as Hodgkin and non-Hodgkin lymphoma were detected more often in some studies (12,20,23,24). In our study, the fact that a smaller number of recurrent cases of lymphadenitis were revealed as a result of biopsy compared to the literature was attributed to our use of more selective indications such as refractoriness to treatment and the presence of a chronic disease process when deciding to perform biopsy.

The main limitation of our study is that it was a single-center retrospective study. The fact that our center was a tertiary care hospital and only cases admitted to the pediatric infection clinic were included in the study led to heterogeneity in our study groups.

In conclusion, although lymphadenopathies in childhood are mostly due to infectious causes, rheumatologic diseases, hemato-oncologic malignancies, and congenital cysts should be kept in mind, especially in prolonged, treatment-refractory cases. Detailed history and physical examination are the first and the most important step in the differential diagnosis of cases presenting with lymphadenopathy to prevent resorting to unnecessary tests, and investigations.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 27, Date: 26.07.2022

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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