Original Article

DOI: 10.4274/haseki.galenos.2021.6871
Med Bull Haseki 2021;59:145-151

Evaluation of Cervical Lymphadenopathy in Children: Is Epstein-Barr Virus Infection Predictable?

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Abstract

Aim: The aim of this study was to evaluate the paediatric patients with cervical lymphadenopathy (LAP) and to compare the clinical and laboratory features between Epstein-Barr virus (EBV) infections and the other aetiologies.

Methods: We conducted a retrospective, single-center study of paediatric patients with cervical LAP from a tertiary care hospital in Turkey between October 2017 and March 2020. The medical records including demographic information, clinical features and laboratory results were collected from paediatric patients with cervical LAP. Patients were divided into two groups according to whether the aetiology of LAP was EBV infection or the others. Clinical and laboratory findings were compared between the two groups.

Results: A total of 175 patients included in the study. Nonspecific lymphadenitis was the most common diagnosis occurring at a rate of 54.3%. EBV infection was responsible for 17.1% of all causes. The presence of fever, white blood cell (WBC) and lymphocyte count were significantly higher and LAP size was significantly larger in patients with cervical LAP caused by EBV infection.

Conclusion: Fever, elevated WBC and lymphocyte count may be predictors for EBV infection in children with cervical LAP. In patients who had these features, serological tests for EBV could make a significant contribution to reach an accurate diagnosis without wasting time.

Keywords: Cervical LAP, children, EBV infection

Introduction

Cervical lymphadenopathy (LAP) is commonly defined as cervical lymph nodes measuring more than 1 cm in diameter is a common finding on physical examination in children and creates parental anxiety. The prevalence rate is about 38% to 45% of otherwise healthy children (1,2). There are too many conditions in the differential diagnosis of cervical LAP. Although the most common causes are bacterial and viral infectious diseases resulting in reactive hyperplasia, malignancies, congenital abnormalities and autoimmune diseases can also be the reason (3,4). One of the primary infectious causes of cervical LAP is Epstein-Barr virus (EBV) infection usually appears in early childhood in developing countries like our country (5). More serious disorders such as malignancy should be excluded rapidly in order to avoid unnecessary investigations and to relieve the parent. The aim of this study was to investigate the demographic, clinical and laboratory characteristics, treatment, and outcomes in children with cervical LAP and to compare the clinical and laboratory features between EBV infections and the other aetiologies.

Methods

Study Design and Data Collection

This study was conducted with the approval of the Marmara University Clinical Research Ethics Committee of our hospital (date: January 3rd 2020 and decision no: 09.2020.6).

A retrospective single-center study was conducted of paediatric patients with cervical LAP at outpatient clinic and ward of paediatric infectious diseases of tertiary care hospital in Turkey. The medical records were collected from paediatric patients with cervical LAP in our hospital, between October 2017 and March 2020. The following demographic information, clinical features, laboratory results and management data were collected

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Received: 01.01.2021 **Accepted:** 04.02.2021

retrospectively: age, gender, LAP size and location, duration of symptoms and antibiotic therapy, previous use of antibiotic therapy, duration of hospital stay, surgical drainage, ultrasonography, computed tomography, magnetic resonance imaging, complete blood count, C-reactive protein, lactate dehydrogenase (LDH), uric acid level, liver function tests, excisional biopsy and final diagnosis.

Definitions

Enlarged >10 millimeters lymph nodes in the cervical region were accepted as cervical LAP.

The diagnosis of primary EBV infection was confirmed in the presence of IgM antibodies to EBV viral capsid antigen.

Statistical Analysis

Data were entered into Microsoft Office Excel 2010 (Microsoft, Redmond, WA, USA). The statistical analysis was performed using SPSS version 22.0 (IBM, SPSS). Normally distributed data were assessed using means and the Student's t-test. The significance of the nonparametric data was assessed using the Mann-Whitney U test. The statistical significance of the dichotomous outcomes was determined using the chi-square test, Fisher's Exact test, the Fisher-Freeman-Halton test, and Yates's continuity correction. A multivariate logistic regression analysis was performed. A p-value of <0.05 was considered statistically significant.

Results

A total of 175 children with cervical LAP were examined in our hospital between October 2017 and March 2020. Among the 175 patients, 133 (76%) had received antibiotics before admission. Surgical drainage was who performed in 40 patients (22.8%). At least one pathogen was identified in 32 of 40 (80%) patients performed surgical drainage. *Staphylococcus aureus* was the most common organism isolated in 10 (31.2%) patients, followed by *Streptococcus viridans* in 8 patients (25%) and *Streptococcus pyogenes* in four patients (12,5%). Lymph node excisional biopsy was performed in 27 (15.4%) patients. The results of biopsies were as follows: 16 patients (59.2%) of reactive lymphadenitis, 7 patients of necrotizing granulomatous lymphadenitis, three patients of Hodgkin's lymphoma and one patient of nasopharyngeal carcinoma. The most common cause of cervical LAP was nonspecific lymphadenitis in 95 (54.3%) patients. In 30 patients (17.1%), a diagnosis of EBV infection was performed.

The mean white blood cell (WBC) count at the time of admission was 12014.29±5759.29 (range, 2500-38200) /mm^3. The most LAP localization was the right cervical region in 63 (36%) patients and 53 (30.3%) patients had cervical LAP bilaterally. The patient characteristics are summarised in Table 1.

Patients were divided into two groups; patients with cervical LAP caused by EBV infection (Group 1; n=30), and patients with cervical LAP caused by the other aetiologies (Group 2; n=145). Clinical and laboratory findings were compared between the two groups. The male/female ratio was similar between the two groups. Duration of symptoms, antibiotic therapy and hospital stay of the patients were significantly shorter in Group 1 ($p<0.05$).

The prevalence of fever, tonsillopharyngitis and hepato/splenomegaly was found significantly higher in Group 1. Patients with EBV infection had a lower percentage of hospitalization and antibiotic use ($p<0.05$). According to the univariate analysis, the following laboratory values were significantly higher in Group 1: lymphocyte, granulocyte, WBC count, alanine aminotransferase, aspartate aminotransferase and LDH ($p<0.05$). Mean lymph node size was 4.32±0.84 cm in Group 1 and 2.87±0.49 cm in Group 2. Lymph node size in Group 1 was significantly larger than Group 2 ($p<0.05$) (Tables 2, 3).

In the multivariate analysis, we detected that WBC, lymphocyte count and prevalence of fever were significantly higher [odds ratio (OR)=1.000; 95% confidence interval (CI): 0.999-1.000, OR=1.001; 95% CI: 1.000-1.002, OR=51,591; 95% CI: 2.225-1169,919, respectively], and lymph node size was significantly larger (OR=30,562; 95% CI: 4.346-214,925) in Group 1 (Table 4).

Discussion

Cervical LAP is one of the most common problems in children. It creates anxiety in parents with diverse aetiologies including malignancy (6). EBV infection is also in the differential diagnosis (7). In this study, we tried to investigate pediatric cervical LAP characteristics and detect the difference of cervical LAP caused by EBV from the other aetiologies.

In this study, we detected that among the 175 patients, 108 (61.7%) were male. Similar to our study, previous studies report that cervical LAP is more likely to be seen in boys (8,9). The spectrum of clinical manifestations and findings can vary according to aetiology. A retrospective study by Aykac et al. (4) conducted on children reported that the most frequent symptoms and findings were fever (45.3%), tonsillopharyngitis (53%) and hepatomegaly (10.3%). In another study conducted on Sudanese children with cervical LAP, Bilal et al. (10) reported that the most common clinical examination findings were fever (71.3%), cough (57%), weight loss (55%) and sore throat (46.2%). One of the important reasons for cervical LAP is dental caries resulting in odontogenic infections. Our

Table 1. The demographic and clinical characteristics of the patients			
		Min-Max	**Mean ± SD (median)**
Age (years)		0.2-18	6.56±4.48
Duration of symptoms $_{(median)}$		2-120	12.42±13.11 (10)
Duration of antibiotic therapy (day) $_{(median)}$		0-28	10.36±7.45 (10)
Duration of hospitalisation $_{(median)}$		0-29	5.11±7.07 (0)
LAP size (cm)		2-6	3.12±0.78 (3)
		n	**%**
Gender	Female	67	38.3
	Male	108	61.7
Clinical symptoms and findings	Fever	55	31.4
	Tonsillopharyngitis	27	15.4
	Limited neck mobility	20	11.4
	Tooth decay	25	14.3
	Odynophagia	5	2.9
	Hepato/splenomegaly	12	6.9
Prior antibiotic treatment	No	42	24
	Yes	133	76
Final diagnosis	Pharyngotonsillar infections	10	5.7
	Odontogenic infections	24	13.7
	Non-specific lymphadenitis	95	54.3
	Epstein-Barr virus infection	30	17.1
	Tularemia	3	1.7
	Cat-scratch disease	2	1.1
	Tuberculous lymphadenitis	7	4
	Nasopharyngeal carcinoma	1	0,6
	Hodgkin lymphoma	3	1.7
Hospital unit	Outpatient	94	53.7
	Inpatient	81	46.3
Excisional biopsy	No	148	84.6
	Yes	27	15.4
Antibiotic treatment	No	50	28.6
	Ampicillin-sulbactam	47	26.9
	Ampicillin-sulbactam + clindamycin	24	13.7
	Others	54	30.9
C-reactive protein, mg/dL	Negative (<3 mg/dL)	82	46.9
	Positive (>3 mg/dL)	93	53.1
Imaging modalities	Ultrasound imaging	113	64.6
	Computed tomography	4	2.3
	USG + CT	37	21.1
	USG + Magnetic resonance imaging	15	8.6
	USG + CT + MRI	6	3.4
LAP localization	Right	63	36
	Left	59	33.7
	Bilateral	53	30.3

LAP: Lymphadenopathy, USG: Ultrasound imaging, CT: Computed tomography, MRI: Magnetic resonance imaging, Min-Max: Minimum-maximum, SD: Standard deviation

results about the reason for cervical LAP are similar to previous studies.

Several studies confirmed that clinical symptoms and findings lasting more than four weeks may indicate increased risk for malignancy (8,11,12). In accordance with previous studies, we detected that the mean duration of symptoms was 12.42±13.11 and only four patients were diagnosed with malignancy. These results suggest that patients with persistent cervical LAP and chronic symptoms may present malignancy and further evaluation may be required for these patients.

Cervical LAP frequently represents a transient response of lymphatic tissue to a benign local or generalized infection, but it can also rarely be caused by other more significant pathology such as malignancy. The most common cause of cervical LAP in children is reactive hyperplasia secondary to known or unknown infectious agents (12). A systematic review of 2687 cervical LAP in paediatric patients showed that the most common cause was nonspecific benign etiology occurring at a rate of 67.8% (13). In another study, Indolfi et al. (14). reported that among 392 paediatric patients with head and neck LAP, 220 patients (56.1%) had a history of infection and 101 patients (24.9%) nonspesific reactive lymphadenitis. Similarly, we found that nonspecific lymphadenitis was the most common cause of cervical LAP.

Bacterial infections resulting in cervical LAP range from aerobic and anaerobic to mycobacterial infections. The most commonly reported microorganisms isolated from suppurative cervical LAP are *Staphylococcus aureus*, followed by group A streptococcus (*Streptococcus pyogenes*) and anaerobic bacteria (12,15). Indolfi et al. (14) reported that the most frequently isolated pathogen was S. pyogenes in 31 patients (22.9%), followed by *S. aureus* in 10 patients (7.4%). In accordance with the previous reports, the most commonly isolated pathogen in our study was *S. aureus. S. viridans* was the second most common microorganism. Compared with other studies, we detected a higher incidence of *S. viridans*. The reason for this can be explained by the high number of patients with dental caries.

Table 2. Comparison of patient characteristics of the two groups by univariate analysis

		EBV lymphadenitis (Group 1)	Other aetiologies (Group 2)	p
		Mean ± SD (median)	Mean ± SD (median)	
Age (years)		5.77±4	6.73±4.57	[1]0.286
Duration of symptoms (median)		7.23±5.2 (6)	13.5±13.98 (10)	[2]0.002*
Duration of antibiotic therapy (day) (median)		1.33±3.46 (0)	12.23±6.64 (14)	[2]0,000*
Duration of hospitalization (median)		1.27±2.49 (0)	5.91±7.44 (2)	[2]0.001*
		n (%)	n (%)	
Gender	Female	7 (23.3%)	60 (41.4%)	[3]0.100
	Male	23 (76.7%)	85 (58.6%)	-
Clinical symptoms and findings	Fever	23 (76.7%)	32 (22.1%)	[3]0.000*
	Tonsillopharyngitis	17 (56.7%)	10 (6.9%)	[4]0.000*
	Limited neck mobility	5 (16.7%)	15 (10.3%)	[4]0.241
	Tooth decay	0 (0%)	25 (17.2%)	[4]0.006*
	Odynophagia	1 (3.3%)	4 (2.8%)	[4]0.614
	Hepato/splenomegaly	12 (40%)	0 (0%)	[4]0.000*
Prior antibiotic treatment	No	15 (50%)	27 (18.6%)	[3]0.001*
	Yes	15 (50%)	118 (81.4%)	-
Surgical drainage	No	29 (100%)	105 (72.4%)	[3]0.003*
	Yes	0 (0%)	40 (27.6%)	-
Positive culture	No	14 (100%)	61 (65.6%)	[4]0.005*
	Yes	0 (0%)	32 (34.4%)	-
Hospital unit	Outpatient	23 (76.7%)	71 (49%)	[3]0.010*
	Inpatient	7 (23.3%)	74 (51%)	-
Excisional biopsy	No	30 (100%)	118 (81.9%)	[4]0.005*
	Yes	0 (0%)	27 (18.1%)	-

[1]Student t-test, [2]Mann-Whitney U Test, [3]Yates's continuity correction, [4]Fisher's Exact Test, EBV: Epstein-Barr virus

Table 3. Comparison of patient characteristics and laboratory findings of the two groups by univariate analysis				
		EBV lymphadenitis (Group 1)	Other aetiologies (Group 2)	p
		Mean ± SD	Mean ± SD	
White blood cells/mm^3		14546.67±6702.07 (12800)	11490.34±5424.14 (10400)	[1]0.009*
Hemoglobin, g/dL		11.91±1.48 (11.7)	11.64±1.38 (11.6)	[1]0.595
Alanine aminotransferase, IU/L		117.67±125.68 (67.5)	23.4±32.93 (15)	[1]0.000*
Aspartate aminotransferase, IU/L		112.63±112.56 (73)	35.66±32.39 (29)	[1]0.000*
Uric acid mg/dL		3.64±1.06 (3.5)	3.37±1.05 (3.2)	[1]0.180
Lymphocytes/mm^3		8593.33±4083.35 (8500)	3693.79±1723.58 (3400)	[1]0.000*
Granulocytes before treatment/mm^3		4036.67±2725.04 (3300)	6428.28±4902.21 (5300)	[1]0.001*
Granulocytes after treatment /mm^3		3166.67±1577.94 (3050)	3736.57±2116.47 (3400)	[1]0.115
Lactate dehydrogenase, IU/L		408.8±200.2 (352.5)	270.51±101.09 (259)	[1]0.000*
LAP size (cm)		4.32±0.84 (4.5)	2.87±0.49 (3)	[1]0.000*
		n (%)	n (%)	
Antibiotic treatment	No	27 (90%)	23 (15.9%)	[2]0.000*
	Ampicillin-sulbactam	1 (3.3%)	46 (31.7%)	-
	Ampicillin-sulbactam+ Clindamycin	0 (0%)	24 (16.6%)	-
	Others	2 (6.7%)	52 (35.9%)	-
C-reactive protein, mg/dL	Negative (<3 mg/dL)	15 (50%)	67 (46.2%)	[3]0,859
	Positive (>3 mg/dL)	15 (50%)	78 (53.8%)	-
Imaging modalities	Ultrasound imaging	27 (90%)	86 (59.3%)	[4]0.033*
	Computed tomography	0 (0%)	4 (2.8%)	-
	USG + CT	3 (10%)	34 (23.4%)	-
	USG + MRI	0 (0%)	15 (10.3%)	-
	USG + CT + MRI	0 (0%)	6 (4.1%)	-
LAP localization	Right	6 (20%)	57 (39.3%)	[2]0.000*
	Left	4 (13.3%)	55 (37.9%)	-
	Bilateral	20 (66.7%)	33 (22.8%)	-

[1]Mann-Whitney U Test, [2]Chi-square test, [3]Yates's continuity correction, [4]Fisher Freeman Halton Test, LAP: Lymphadenopathy, USG: Ultrasound imaging, CT: Computed tomography, MRI: Magnetic resonance imaging, SD: Standard deviation, EBV: Epstein-Barr virus

Table 4. Multivariate logistic regression analyses of predictor for EBV lymphadenitis			
	OR	95% CI	p
White blood cells	1.000	0.999-1.000	0.034*
Lymphocytes	1.001	1.000-1.002	0.001*
LAP size	30.562	4.346-214.925	0.001*
Fever	51.591	2.225-1169.919	0.013*
Constant	0.000	-	0.000*

EBV: Epstein-Barr virus, OR: Odds ratio, CI: Confidence interval, LAP: Lymphadenopathy

Many viruses, including EBV, may cause a self-limited and uncomplicated cervical LAP in children. In large cohort studies with paediatric patients, rate of cervical LAP caused by EBV was reported as 15% Abdel-Aziz et al. (7), 8.8%, % by Deosthali et al. (13) and 32.7% by Sarsu et al. (16) In addition, Bozlak et al. (9) and Indolfi et al. (14) demonstrated that EBV was responsible for 27% and 29.6 of infectious causes of cervical LAP, respectively. A cross-sectional study by Bilal JA conducted on 82 children with cervical LAP reported that EBV infection was diagnosed in 13 (15.9%) patients (17). These different rates can be caused by different study designs, including different geographic regions and age groups. In our study, EBV infection was serologically diagnosed in 30 (17.1%) patients with cervical LAP.

Determining diagnostic pathway for patients with cervical LAP is difficult because of broad differential diagnoses. The differential diagnosis of cervical LAP includes many viral infectious diseases such as EBV infection. Some symptoms and findings may guide the differential diagnosis. A recent history of upper respiratory tract infection, dental caries and fluctuation suggest a reactive process (18,19). Weight loss, lymph nodes more than 2.5 cm in size being hard and fixed to the underlying tissue, multiple sites of LAP have been

associated with a higher risk of malignancy (20-23). We think that determining clinical and laboratory predictors of EBV may be helpful to differential diagnosis and prevent unnecessary investigations and medical procedures. In this study, we found that WBC, lymphocyte count, liver enzymes, prevalence of fever, tonsillopharyngitis and hepato/splenomegaly were significantly higher and LAP size was significantly larger in children with cervical LAP caused by EBV than the other aetiologies. These results are similar to previous studies conducted on children with cervical LAP (7,17,24-27). When patients have these symptoms or findings, a serologic assay for EBV may be warranted to help with the diagnostic evaluation on the first step.

Study Limitations

The important limitations of this study were its retrospective, single-center design and relatively small sample size.

Conclusion

Our study determined that there were independent association between fever, elevated WBC, lymphocyte count, lymph node size and cervical LAP caused by EBV infection. The presence of these features may be warning sign for EBV and serological tests for EBV specific IgM and IgG antibodies can take place in the first step for differential diagnosis in these patients.

Authorship Contributions

Concept: N.Y., E.K., Design: N.Y., E.K., Data Collection or Processing: N.Y., Analysis or Interpretation: N.Y., E.K., Literature Search: N.Y., Writing: N.Y., E.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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