



# Evaluation of children with lymphadenopathy

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## Abstract

**Aim:** To examine children who present with enlargement of lymph nodes in terms of demographic, clinical, serological and radiological aspects.

**Material and Methods:** Ninety-eight patients who presented with a complaint of enlargement of lymph nodes were examined in terms of demographic, clinical, serological and radiological aspects by screening file data retrospectively. The character of lymph nodes (reactive, malign) was evaluated according to the distribution, number, sizes and blood supply determined in ultrasonographic measurements. Fisher's Exact test and Mann-Whitney U Test were used in comparison of the groups. Kappa value was used in assessment of compatibility between the two groups.

**Results:** Cervical lymphadenomegaly was found most frequently in accordance with the complaint of swelling in the neck. Erythrocyte sedimentation rate, ultrasonography, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) IgM were not found to be statistically significantly different between the normal and abnormal physical examination groups (erythrocyte sedimentation rate;  $p=0.623$ , USG;  $p=0.753$ , EBV and CMV;  $p=1.00$ ). Cytomegalovirus and EBV IgM were not found to be statistically significantly different between the normal and abnormal ultrasonography groups (CMV;  $p=0.35$ , EBV;  $p=0.36$ ). There was no compatibility between physical examination and ultrasonography ( $=0.32$ ).

**Conclusion:** Lymphadenopathy is a common problem in the childhood and necessitates a careful physical examination and follow-up. Laboratory and imaging methods should be used when necessary. Although lymphadenopathy is mostly related with infections, care should be taken in terms of malignancy and malignancy should be eliminated. The important point is systemic evaluation and follow-up of the patient. It is important to note physical examination findings and clinical follow-up findings, because frequent ultrasonographic investigations may confuse physicians and families with high values of lymph node measurements despite normal physical examination. Therefore, using our fingertips with a good physical examination is still our most sensitive diagnostic tool instead of ultrasonography. (Türk Ped Arş 2014; 49: 30-5)

**Key words:** Epstein-Barr virus, infection, lymphadenopathy, ultrasonography, cytomegalovirus

## Introduction

Lymphadenopathy is abnormal size, number and stiffness of one of more lymph nodes. The term "lymphadenopathy" is used for all pathologic conditions of lymph nodes and the term "lymphadenomegaly" is used for enlarged lymph nodes. Lymphadenopathies are divided into two groups as local lymphadenopathy in which a single or multiple lymph nodes adjacent to each other are involved and extensive lymphadenopathy in which more than two lymph nodes which are not adjacent to each other are involved. In children, lymph nodes reach their largest size at about the age of 8-12 years and get smaller after adolescence. Although they lead to frequent presentation to pediatric oncology outpatient clinics with a prediagnosis of malignancy and to extensive concern in families, infections are in the first order in the etiology (1). It has been stated that the underlying cause is continuous antigenic stimulus caused by frequent childhood infections (2, 3). It is important to make the differential diagnosis between physiological lymph node enlargement (lymphadenomegaly) and malign lymph node. In our study, 98 children who presented with a complaint of enlarged lymph node to our pediatric oncology outpatient clinic were examined in terms of demographic data, lymph node involvement regions, infectious and viral markers and ultrasonographic (USG) findings.

## Material and Methods

Ninety-eight patients who presented to Ankara Gülhane Medical Academy (GATA), Department of Pediatrics, Pediatric Outpatient Clinic with a complaint of enlarged lymph nodes were included in the study by screening their file data retrospectively.

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In the patients who were included in the study, complete blood count, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), uric acid, viral markers (Epstein Barr virus (EBV) and cytomegalovirus (CMV) were investigated in addition to history and physical examination. The measurements were done using certain methods in Ankara GATA, Department of Biochemistry and Clinical Biochemistry and GATA, Department of Microbiology. In USG measurements of lymph nodes, the distribution, number and sizes of the lymph nodes and their structures according to blood supply (reactive, malign) were evaluated. Lymph node regions were divided into regions including anterior and posterior neck, preauricular, nape, supraclavicular, supramandibular, underside of the chin, axillary, epitrochlear, inguinal and popliteal regions. The number of the lymph nodes, long diameters and long diameter/short diameter ratios were evaluated and compared with the ultrasonographic measurements. In the children, a size of 2 cm in the neck, 1 cm in the axillary region and 1.5 cm in the inguinal region were considered normal and sizes above these values were considered lymphadenomegaly. The relation of lymphadenomegaly with viral markers was investigated. Oral antibiotic treatment was given in cases which were thought to be caused by infection as a result of physical examination and laboratory findings and these patients were called for follow-up visits at the end of treatment. The patients who had lymphadenomegaly for a long time, but who had no finding of infection were followed up without giving treatment and called for a follow-up visit one month later. The patients whose lymph nodes were found to be reduced in the follow-up visit or whose lymph nodes were not found to have enlarged further were not followed up any more.

#### Statistical analysis

Statistical Package for the Social Sciences (SPSS) statistical program was used in evaluation of the data. Fisher's Exact test and Mann-Whitney U test were used in comparison of the groups. A p value below 0.05 was considered statistically significant. Kappa ( $\kappa$ ) value was used in assessment of consistency between two groups.

#### Results

The mean age of 98 patients who were included in the study was  $6.1 \pm 3.1$  years (median: 6 years; range 2.4 months-14 years). 29 patients were female (30%) and 69 patients were male (70%). The male/female ratio was found to be 2.38.

The complaint at presentation was swelling in the neck in 86 patients (88%), swelling in the axilla in 8 patients (8%), swell-

ing in the anterior and posterior part of the ear in 2 patients (2%), swelling in the nape in one patient (1%) and swelling in the groins in one patient (1%). In addition, abdominal and chest pain accompanied in two patients. Sore throat was present in 26 (26%) of our patients.

86% of the patients presented when the family recognized a swelling, 12% presented when no reduction in the size of the lymph node occurred after antibiotic usage and 2% presented when lymphadenomegaly was found on physical examination. On physical examination, lymphadenomegaly was found in the anterior part of the neck with a rate of 62%, in the submandibular region with a rate of 18%, in the axillary region with a rate of 8%, in the posterior part of the neck with a rate of 6%, below the chin with a rate of 2%, in the preauricular region with a rate of 1%, in the nape with a rate of 1% and in the inguinal region with a rate of 1% (Table 1). In addition, splenomegaly was found in one patient (1%). Lymphadenomegaly smaller than 2 cm was palpated in the neck region in 26 of our patients (27%) and lymphadenomegaly larger than 1 cm was palpated in the axillary region in 3 of our patients (3%). The lymph nodes in the other regions did not have a pathological size.

The positivity for Epstein-Barr virus IgM (n=25) was found with a rate of 64% in the group in whom normal lymph node size was found on physical examination (n=16) and with a rate of 36% in the group in whom enlarged lymph nodes were found (n=9). There was no significant difference between the two groups (p=1.00) (Table 2). The positivity for cytomegalovirus IgM (n=17)

**Table 1. Distribution of cases with lymphadenopathy by regions**

Regions	n	%
Anterior neck	61	62
Posterior neck	5	6
Preauricular region	1	1
Retroauricular region	1	1
Nape	1	1
Submandibular	18	18
Below the chin	2	2
Axillary	8	8
Inguinal	1	1
Total	98	100

**Table 2. The relation between size on physical examination and EBV**

		Physical examination				p
		Normal		Large		
EBV IgM		n	%	n	%	
(n:25)	Positive 16	64	9	36		1.00

EBV: Epstein-Barr Virus; IgM: immunoglobulin M

was found with a rate of 70.5% in the group with normal physical examination (n=12) and with a rate of 29.5% in the group with pathological physical examination (n=5) 29.5%. There was no difference between the two groups (p=1.00) (Table 3).

The mean erythrocyte sedimentation rate was found to be 15±9 in the group with normal physical examination and 29±28 in the group with enlarged lymph nodes. The median erythrocyte sedimentation rate was found to be 15mm/h in the group with normal physical examination and 16 mm/h in the group with pathological physical examination.

The median erythrocyte sedimentation rate was found to be 15mm/h in the group with normal physical examination and 16 mm/h in the group with pathological physical examination (p=0.623) There was no significant difference between the two groups. (Table 4).

When 19 patients in the group with a pathological physical examination were evaluated ultrasonographically, 6 patient (31.6% 9 were in the normal group on USG and 13 patients were in the pathological group on USG (68.4%) and there was no significant difference between the two groups (p=0.753). There was no consistency between physical examination and ultrasonographic measurements ( $\kappa=0.32$ ) (Table 5). Epstein-Barr virus IgM was positive with a rate of 88.9% (n=8) in the group with normal ultrasonographic findings and with a rate of 100% (n=16) in the group with pathological USG findings. There was no difference between the two groups (p=0.36) (Table 6).

Cytomegalovirus IgM was positive with a rate of 50% (n=4) in the group with normal ultrasonographic findings and with a rate of 76.5% (n=13) in the group with pathological USG findings. There was no difference between the two groups (p=0.35) (Table 7).

Epstein-Barr virus positivity was found in 25 patients (25%) and CMV positivity was found in 17 patients (17%). The mean lactate dehydrogenase value was found to be 665 U/L. LDH was above 700 U/L in 8 patients. In three of our patients, the hemoglobin

value was below 10.5 g/dL. The highest erythrocyte sedimentation rate was found to be 110 mm/h. The mean white blood cell count was found to be  $9.28 \times 10^3/\mu\text{L}$ . The white blood cell count was above 20 000/mm<sup>3</sup> in two patients. The mean platelet count was found to be  $240 \times 10^3/\mu\text{L}$ . The highest platelet count was found to be  $506 \times 10^3/\mu\text{L}$ . The uric acid value was found to be 12.1 mg/dL in one patient and the mean uric acid value was found to be 5.8 mg/dL (Table 8).

## Discussion

Palpable lymph nodes are usually observed between the ages of 3 and 5 years (4). Palpable lymph nodes may be found in the neck with a rate higher than 90% especially in children aged between 4 and 8 years (5). In another study, this rate was reported to be 38-45% in school aged healthy children (6). Although lymphadenomegaly is observed frequently especially in the childhood, it leads to concern in families and physicians because of the possibility of a malign disease. Assessment by a specialist was required in 10% of 2556 patients with unexplained lymphadenopathy and biopsy was performed in 82 (3.2%) patients. Malignancy was found in 29 of all patients (1.1%) (7). 86% of our patients presented when the family recognized a swelling, 12% presented when no reduction in the size of the lymph node occurred after antibiotic usage and 2% presented when lymphadenomegaly was found on physical examination. Our patients were generally healthy and a sudden swelling without any complaint or a swelling found on regular physical examination without any complaint constituted the reasons of presentation in 88% of the patients.

In a study performed in our country in which the median age was seven years, approximately 80% of the patients were between the ages of 2 and 12 years, 5% of the patients were below the age of 2 years and 15% of the patients were above the age of 12 years. This is closely related with the fact that the period during which children are exposed to antigen stimulation with the highest rate is the play and school age period and physiological lymph node atrophy starts in adolescence (8). The mean age of our patients was 6.1 years and the median age was 6 years. 6.3% of the pa-

**Table 3. The relation between size on physical examination and CMV**

		Physical examination				p
		Normal		Large		
CMV IgM		n	%	n	%	
	Positive	12	70.5	5	29.5	1.00

CMV: cytomegalovirus; IgM: immunoglobulin M

**Table 4. The relation between size on physical examination and ultosonographic size**

		ESR (mm/sa)			p
		Median	Range	Mean±Standard Deviation	
Physical examination	Normal	15	1-45	15±9	0.623
Size	Large	16	3-110	29±28	

SD: standard deviation; ESR: erythrocyte sedimentation rate

**Table 5. The relation between size on physical examination and erythrocyte sedimentation rate**

Physical examination		USG		κ	p
		Normal	Large		
Size	Large	n	%	n	%
		6	31.6	13	68.4

κ: kappa; USG: ultrasonography

**Table 6. The relation between ultrasonographic size and EBV**

		USG				p
		Normal		Pathological		
EBV IgM	Positive	n	%	n	%	
		8	88.9	16	100	0.36

EBV: Epstein-Barr virus; IgM: immunoglobulin M; USG: ultrasonography

**Table 7. The relation between ultrasonographic size and CMV**

		USG				p
		Normal		Large		
CMV IgM	Positive	n	%	n	%	
		4	50	13	76.5	0.35

CMV: cytomegalovirus; IgM: immunoglobulin M; USG: ultrasonography

tients were below the age of 2 years, 89% were between the ages of 2 and 12 years and 4.8% were above the age of 12 years. Response to antigens is more rapid in children compared to adults.

Enlarged, palpable lymph nodes are usually related with reactive hyperplasia in the lymph node tissue in relation with regional inflammatory state (9). Lymphadenopathy occurs following lymphadenitis which occurs most commonly in relation with infections in the childhood (1). Although most of these lymphadenopathies develop as a result of viral infections in the childhood age group, careful assessment is important. Although infectious mononucleosis and CMV are important ethiological agents, upper respiratory viral infections are the most common cause in adenopathies. Sterptococci and staphylococci should be considered in regional adenopathies. Malignancy, autoimmune diseases and other infections including human immune deficiency virus are observed more rarely (10).

In our study, the majority of the cases were thought to be related with infection. Viral infection was considered in most of the cases and antibiotics were started in only 20%. Leukocytosis and increased erythrocyte sedimentation rate accompanied in these patients. White blood cell count was  $15 \times 10^3/\mu\text{L}$  in 5 patients and erythrocyte sedimentation rate was above 30 mm/h in 5 patients. These patients responded well to treatment. reactive thrombocytosis was present in two of these patients. However, we could find no difference in erythrocyte sedimentation rate between the groups with normal and abnormal lymphadenopathy. Lymphadenopathy in the neck and inguinal region is frequent especially after the age

of two in contrast to the first 6 months (2, 3). In our study, we found lymphadenopathies mostly in the neck region with a rate of 88%. We observed that there was generally a two fold increase in the dimensions of the lymph nodes on physical examination and ultrasonography and a three-fold increase in some patients, regional lymphadenopathy rather than extensive lymphadenopathy was present and organomegaly did generally not accompany. Epstein-Barr virus was positive in 25% of the cases. Enlarged lymph nodes were found in 36% of the positive cases and normal lymph nodes were found in 64%. Cytomegalovirus was positive in 17% of the cases. Enlarged lymph nodes were found in 30% of the positive cases and normal lymph nodes were found in 70%. Further investigations including abdominal ultrasonography and double way lung graphy were performed in 11% of the patients and were found to be normal except for splenomegaly in only one patient (1%).

In the study performed by Cairo et al. (11), a LDH level above 1000 IU/L was determined to be an independent prognostic factor in lymphomas. In other studies, LDH level as a prognostic criterion in lymphoma was reported to be 500 IU/L or lower or higher than two-fold of the normal (11-14). In our study, the mean LDH value was found to be 665 IU/L. LDH value was above 700 IU/L in 8 patients. Therefore, LDH level which can be affected by many factors should be evaluated carefully and subsequently an association with the clinical state should be made.

We found Epstein-Barr virus and CMV positivity in lymphadenopathies of the neck. Çavdar et al. (15) reported that 94.4% of 176 patients presented with lymphadenomegaly in the neck. Review of the history and the systems, history of recent infection, knowledge

**Table 8. Laboratory test results**

Variable	Unit	Mean±Standard Deviation	Range
EBV IgM	positive/negative	20.2±3.3	0.2-151
EBV IgG	positive/negative	45.6±6.8	0.9-279
CMV IgM	positive/negative	4.1±3.78	0.2-14
CMV IgG	positive/negative	1.73±1.3	1-438
LDH	IU/L	665±974	315-6390
Uric acid	mg/dL	5.8±3.2	2.3-12.1
ESR	mm/saat	15.4±14.1	1-110
WBC	10 <sup>3</sup> /μL	9.28±3.59	3-18.8
Hemoglobin	g/dL	12.2±1.48	5-14
Platelets	10 <sup>3</sup> /μL	240±10.50	57-506

Ig: immunoglobulin; WBC: white blood cells; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; CMV: cytomegalovirus; EBV: Epstein-Barr virus

of lymph node drainage sites, sexual activity in adolescents and history of drug usage may be helpful. While erythema, tenderness, increased temperature and fluctuance are in favour of lymphadenitis, hard, adherent, painless lymph nodes with rubber consistency which continue to enlarge and do not respond to treatment may be related with malignancy. We found Hodgkin lymphoma in one patient who had a lymph node with a size of 4x3 cm in the neck which did not respond to antibiotic treatment by biopsy.

Generally, USG is not as necessary as used in practice in the follow-up of lymphadenopathy. Follow-up with physical examination is more important. In our study, we did not find physical examination and ultrasonography to be compatible with each other. Since ultrasonography could not generally be performed immediately after physical examination and there were also patients who received treatment, we found the compatibility of ultrasonography with the initial physical examination to be 68,4% in our study. However, ultrasonography is generally compatible with instant physical examination and is valuable and helpful.

Lymph nodes reach the largest total lymph node mass at the age of about 8-12 years and start to get reduced with atrophy after adolescence. In young children, 2 cm in the neck, 1 cm in the axilla and 1.5 cm in the inguinal region are considered normal values and they do not require investigation. In a pediatric series including 457 individuals, lymph nodes larger than 3 cm were generally found to be related with malignancy (8). Epitrochlear and supraclavicular lymph nodes require further investigation, since they may be related with malignancy, even if they are smaller than 0.5 cm. In some studies, lymph nodes up to 0.3 cm in the supraclavicular region, 0.5 cm in the axilla, 1 cm in the neck and 1.5 cm in the inguinal region are generally not accepted to be pathological in the childhood (8, 9). Lymph nodes smaller than 2 cm were palpated in the neck in 26 of our patients (27%) and lymph nodes smaller than 1 cm were palpated in the axillary region in three of our patient (3%). EBV was positive in 21 (80%) of 26 patients with

an abnormal length measurement. Epstein-Barr virus was studied in 29 patients and 25 patients (86%) were found to be positive. Infection findings were present in 70% patients at presentation and 20% were treated with antibiotics.

Among patients in whom it is decided that enlarged lymph nodes are pathological after history and physical examination, the ones who are started to be followed up after etiological investigations are examined again in a short period like two weeks and follow-up or further investigation is decided according to the clinical status of lymph nodes. In our clinical practice, patients are reevaluated after 10-14 days following empirical antibiotic treatment as in some other centers. If the size is increased in this short time period, further investigations should be performed. If the size remains the same, the patient is further followed up for 2-3 weeks. If the lymph node is disappeared, the patient is no longer followed up. If the lymph node has started to get reduced, the patient may be followed up further for a while and then the follow-up is discontinued. If the lymph node has the same size or continues to get larger, further investigations should be performed (16). Our patients were followed up for a mean period of three months and the patients in whom lymph nodes did not get larger, in whom lymph nodes regressed after antibiotic treatment or in the follow-up and who had normal test results were no longer followed up. In one patient, a diagnosis of Hodgkin lymphoma was made by biopsy following further investigations. The other lymphadenopathies were evaluated to be reactive lymph nodes.

## Conclusion

Lymphadenopathy is a common problem in the childhood and necessitates careful physical examination and follow-up. Laboratory and imaging methods should be used when necessary. It is most commonly related with infections, but one should be careful about malignancies and malignancy should be eliminated. The important point is systemic evaluation and follow-up of the patient. It is important to record physical examination findings and clinical follow-up findings, because frequent USG investigations may lead to confusion in families and physicians with high values of lymph node measurements despite normal physical examination. Therefore, our most sensitive diagnostic tool is still our fingertips to be used on a careful physical examination rather than USG. Early diagnosis is always important in treatment.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Gülhane Military Medical Academy.

**Informed Consent:** Informed consent was not taken owing to retrospective patient's files analysis.

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