

## Original Article

# Lymph node biopsy in children: Indications and etiology

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## ABSTRACT

**Background:** Peripheral lymphadenopathy manifests in a variety of benign and malignant conditions and is often challenging to distinguish pathologic from non-pathologic etiology based on clinical presentation alone. Therefore, lymph node biopsy is often required as an essential part of management. This study aimed to determine the causes of peripheral lymphadenopathy in children needing excision biopsy in our setting and establish a correlation with clinical features and laboratory findings.

**Methods:** A retrospective review of medical records of children aged 0-14 years undergoing lymph node biopsy at our institution, between January 2015 and June 2018, was conducted. Demographic, microbiological, and histopathological findings were reviewed.

**Results:** A total of 69 patients underwent lymph node biopsy, the majority of whom were male (n=40, 58%), with a mean age of 7.9 years. The histopathological findings confirmed lymphoma (n=27), tuberculosis (n=24), benign reactive changes (n=14), and Langerhan Cell Histiocytosis (n=4). Cervical lymph nodes were most frequently involved (n=64). Associated symptoms included fever (n= 27), weight loss (n=2) and cough (n=7). Only one patient developed a postoperative complication (wound infection). A clinical diagnosis of tuberculosis (TB) had been presumed in 19 patients, but only 2 (11%) were confirmed to have TB, whereas 10 were found to have histopathological findings of lymphoma.

**Conclusion:** Excisional biopsy is useful in the management of children with lymphadenopathy, allowing treatment to be initiated based on a histopathological diagnosis.

**Keywords:** Peripheral lymphadenopathy, Lymph node biopsy, Etiology

## INTRODUCTION

Lymphadenopathy is common in the pediatric age group; as many as 90% of children between ages 4-8 years manifesting enlarged lymph nodes at some point, however, the incidence of unexplained and significant lymphadenopathy is less than 1%. [1,2] Based on the duration of symptoms, lymphadenopathy can be termed as either acute (<3 weeks) or chronic (>6 weeks). Lymphadenopathy can also be classified based on etiology: either benign or malignant.

Fortunately, in the majority of children, this is a benign and transient pathology, usually secondary to minor infective etiologies. [2] However, in a small group where serious infectious or malignant conditions are the cause of lymphadenopathy, it is important to distinguish

between possible causes to initiate management accordingly.

The biggest challenge faced by a physician is to distinguish pathologic from non-pathologic etiology and it is often difficult to ascertain the cause based on clinical presentation alone. It is this group of children that may benefit from a lymph node biopsy to reach a definitive diagnosis. [1,2] Tissue sampling is frequently required for diagnosis. Fine needle aspiration may be unrepresentative in up to 75% of patients where malignancy is suspected. [3] It is also difficult to perform aspiration in children, who often do not tolerate the procedure without general anesthesia.

This study aimed to determine the causes of peripheral lymphadenopathy in children needing excision biopsy in

our setting and to establish a correlation with clinical features and laboratory findings.

## METHODS

A retrospective review of records of all children up to age 14 years undergoing peripheral lymph node biopsy at the Indus Hospital, Karachi, from January 2015 to July 2018 was conducted. Information on age, gender, symptoms and their duration, site of lymphadenopathy, histopathological and microbiological findings were recorded. Data were entered and analyzed using SPSS version 21. In all patients, a lymph node biopsy was performed when a significantly enlarged lymph node persisted or increased in size, did not respond to conservative treatment, and/or when there was a clinical suspicion of tuberculosis (TB) or lymphoma. All patients either went through a tuberculosis screening process, were reviewed by an infectious disease specialist before referral for biopsy or were referred by the pediatric oncology team. The screening process involved evaluation for exposure to TB, symptoms and its duration, ESR levels, and a standard x-ray chest, as well as oncological workup where clinically indicated. Conservative management included observation or treatment with first-line antibiotics. All lymph node biopsies were performed under general anesthesia (GA).

Institutional Review Board (IRB) approval was sought before the start of the study. An IRB exemption was granted.

## RESULTS

A total of sixty-nine children underwent peripheral lymph node biopsy at our hospital during the study period. This included 40 males and 29 females (M: F = 1.3:1). The mean age at the time of the procedure was 7.9 years ( $\pm 3.54$ ). The most common site of lymphadenopathy was cervical (n=64, 92.8%), followed by inguinal and axillary nodes in a minority of patients (Table 1). A small number of patients (n=3) had lymphadenopathy involving more than one site. A specific histopathological diagnosis was made in 55 patients (79%) whereas the remaining biopsy specimens showed reactive changes. The commonest diagnosis was lymphoma, followed by tuberculosis with a small minority demonstrating Langerhan cell histiocytosis (LCH) (Table 1). In the 27 patients diagnosed to have lymphoma, Hodgkin's lymphoma was the most common subtype, present in 19 patients, with mixed cellularity type, (n=9), nodular sclerosis (n=8) and lymphocytic predominance (n=2) diagnosed based on the WHO histological classification. Of the eight children with non-Hodgkin's lymphoma, histological subtypes included TCLL (n=5), BLL (n=2), and PTCL (n=1).

Table 1: Demographics and symptoms based on histopathological diagnosis

	<b>Lymphoma</b>	<b>TB</b>	<b>Reactive</b>	<b>LCH</b>	<b>Total</b>		<b>P-value</b>
	<b>N=27</b>	<b>N=24</b>	<b>N=14</b>	<b>N=4</b>	<b>N=69</b>	<b>%</b>	
Age – mean, SD	7.6 $\pm$ 3.2	9.1 $\pm$ 3.8	6.4 $\pm$ 3.0	7.5 $\pm$ 4.8	7.9 $\pm$ 3.5	-	0.13 <sup>†</sup>
<b>Gender</b>							
Male	23	6	9	2	40	58.0	<0.001*
Female	4	18	5	2	29	42.0	
<b>Associated symptoms</b>							
Fever	12	10	2	3	27	39.1	
Cough	3	3	1	1	8	11.5	
Weight loss	2	0	0	0	2	2.9	
<b>Location</b>							
Cervical	26	21	13	4	64	92.8	0.65*
Inguinal	1	2	0	0	3	4.3	
Axillary	0	1	1	0	2	2.9	
<b>Symptom duration in months (Mean, <math>\pm</math> SD)</b>	6.7 $\pm$ 4.0	3.4 $\pm$ 2.7	4.6 $\pm$ 4.1	5.5 $\pm$ 3.9	5.05 $\pm$ 3.8	-	0.015 <sup>†</sup>

\*Fisher's exact test; <sup>†</sup> One Way ANOVA

An associated complaint of fever was noted in 27 (39.1%) patients, followed by cough in 8 (11.5%) children. Weight loss was reported by 2 patients (Table 1). The mean duration of symptoms was 5 months ( $\pm 3.8$ ) for all patients; the duration was significantly

longer in the lymphoma group 6.7 months ( $\pm 4.0$ ) as compared to others (p-value 0.015). When stratified based on diagnosis, lymphoma was predominantly seen in males (n=23, 85.2%), while females were primarily affected by tuberculosis (n=18, 75%) with a

significant p-value (<0.001). However, there was no significant difference in the mean ages, stratified based on the diagnosis (p-value 0.13).

A contact-history for TB was elicited in 8 out of 24 patients (33%). AFB smear and culture were performed in 17 children, of whom only 2 were reported as positive; the specimen was sent for GeneXpert testing in 16 patients, of whom 9 were reported to be positive. It is important to note that 19 patients had been clinically diagnosed to have TB and started on ATT for a mean duration of 3 months (range 1-9 months) before presentation in the surgical service; they were referred for biopsy due to persistence of symptoms despite treatment. On histopathology, 10 were found to have lymphoma, 7 had reactive lymphadenitis and only 2 were confirmed to be tuberculosis in etiology, of which one was diagnosed to have multi-drug resistant TB.

All biopsies were performed as daycare procedures. The postoperative course was reviewed for all patients, and only a minor complication of superficial surgical site infection was reported in one patient.

## DISCUSSION

Lymphadenopathy is generally a self-limiting condition of benign infective etiology. However, if the lymph nodes do not regress in size, persist for a longer duration, do not respond to first-line antibiotics or involve 2 or more non-contiguous areas, this could be indicative of a more serious etiology requiring a detailed workup. It is therefore essential to take a detailed history, conduct a thorough physical examination, including checking for lymphadenopathy at all possible sites in all children; if indicated, laboratory and radiological tests should be requested.[4] However, in many instances the diagnosis cannot be reliably ascertained even with all these efforts. In such instances, an excisional biopsy is required to establish a definite diagnosis.[5] Additionally, when a malignant etiology is suspected, as in cases of lymphoma, it is essential to document the histopathological subtype to initiate appropriate management. Similarly, when children with suspected tuberculosis lymphadenopathy do not respond to first-line ATT, a lymph node biopsy may be warranted to confirm the diagnosis and to rule out drug-resistant TB.

Since our facility is a national referral center for pediatric oncology and pediatric TB, these diagnoses contribute to a disproportionately large percentage in our study population; a similar finding has been reported from other oncological referral centers where malignancy formed a major percentage of cases.[6,7] In contrast, authors from general pediatric facilities report reactive hyperplasia in larger percentages of their patients [8,9], similar results seen in a local study

assessing lymph node biopsies in the general pediatric population.[10]

The indications for lymph node biopsy are not clearly defined [11] and hence are often based on the assessment of individual clinicians. In our hospital, general pediatricians, pediatric oncologists, or pediatric infectious diseases specialists initially see all children with lymphadenopathy. We have a dedicated pediatric TB clinic, which refers to children with a specific request for lymph node biopsy. As a result, we are rarely required to initiate workup for children with enlarged nodes; instead, a pre-selected group of children is seen in our outpatient clinics. This selection bias is reflected in our study findings, where only 20% of children were found to have reactive nodes, with the remaining diagnosed to have lymphoma, tuberculosis, or LCH.

The lymphoid growth stage peaks between 5 to 10 years of age, and therefore symptomatic lymphadenopathy is most commonly seen during this age group.[12] This also corresponds to the greater exposure in this age group to other children in school and play settings, with increased frequency of upper respiratory tract and ear infections.[13] Our study was consistent with this pattern, with an overall mean age of 8 years. Although children with tuberculosis had an older mean age at presentation, while those with reactive hyperplasia presented at a younger age, this difference was not found to be statistically significant. This indicates that age alone cannot reliably predict the need for lymph node biopsy.

The cervical group of nodes was most frequently biopsied in our series, accounting for 64 (92%) cases. Similar findings have been reported by others [8,12] since this area drains the commonest portal of entry of microorganisms. This is also the most conspicuous site and therefore more likely to be noticed by parents and physicians.

This is a retrospective study with a skewed patient population. This is reflected in the diagnostic break-up reported in our series. However, this highlights the importance of carefully screening children with lymphadenopathy, especially if high-risk criteria are present on history and examination.

## CONCLUSION

Lymphoma was the most common cause of lymphadenopathy in our series followed by TB. Excisional biopsy has the advantage of a confirmed histopathological diagnosis to guide treatment. Biopsy should be done if there is an increase in the size of the lymph node or if the lymph node persists after 4 to 6 weeks of treatment.

**Consent to Publication:** No clinical photograph is used in this manuscript.

**Authors Contribution:** Author(s) declared to fulfill authorship criteria as devised by ICMJE and approved the final version. Authorship declaration form, submitted by the author(s), is available with the editorial office.

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