Value of Gray-Scale and Color Doppler Sonography in the Evaluation of Cervical Lymphadenopathy

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Abstract

Background: Cervical Lymphadenopathy is a relatively common finding in pediatric age group and is caused by a wide spectrum of diseases from transient infections to malignancies especially lymphomas.

Objectives: Evaluation of the reliability of gray scale and Doppler Sonography in differentiation of reactive from malignant enlarged cervical lymph nodes.

Materials and Methods: Thirty untreated patients with enlarged cervical lymph nodes of >3 weeks duration, were examined prospectively. All of these patients underwent clinical, laboratory and radiological evaluation including B-mode ultrasound and color Doppler sonography. Then LN biopsy was performed taking it as a gold standard.

Results: According to LN biopsy, seventeen of the studied patients (57%) had reactive lymphadenopathy, while 13 patients (47%) had malignant lymph nodes 11 with lymphoma and 2 metastatic from neuroblastoma. Mean age of patients with reactive lymph nodes was 5.47 ± 2.5 years, while mean age of malignant group was 8.76 ± 3 years. There was statistically significant difference in the malignant group as regards male sex, presence of weight loss, splenomegaly, generalized lymphadenopathy, compared to the reactive group. Also there was a statistically significant difference in the malignant group as regards hemoglobin level, ESR, LDH, and the presence of mediastinal lymphadenopathy. By Ultrasound, rounded shape, sharp borders, absent hilar echogenecity, peripheral and mixed vascularity, and an L/T cutoff value <1.97 were identified as being significantly higher in the malignant group. On the contrary, resistive index RI and pulsatility index PI had no significant difference between the malignant and reactive group. L/T ratio <1.97 and absence of hilar echogenecity had a sensitivity of 92.3% and 85% respectively, and a specificity of 76.5% and 94% respectively. The combination of grey scale and color Doppler had a sensitivity of 87%, a specificity of 92%, and an accuracy of (87%).

Conclusion: Combination of grey-scale and color Doppler ultrasonography is recommended for the differentiation between the malignant and benign lymphadenopathy in children.

Key Words: Lymphadenopathy – Ultrasound – Doppler.

Introduction

PEDIATRIC cervical lymphadenopathy is a challenging medical condition for the patient, the parent, and the physician. 38-45% of normal healthy children [1] and 90% of children aged 4-8 years old [2] will have cervical lymphadenopathy.

A pathologic or abnormal lymph node is commonly quoted to be >1 cm in size however in the pediatric population >2 cm is considered abnormal. Acute lymphadenopathy is 2 weeks duration, subacute is 2-6 weeks duration, and chronic is considered any lymphadenopathy that does not resolve by 6 weeks [3].

In 2005 Ahuja, et al. [4] described the use of ultrasound to differentiate reactive from malignant lymphadenopathy. Reactive lymphadenopathy had the following characteristics; size less than 1 cm, oval shape with short: Long axis ratio less than 0.5, normal hilar vascularity, and a low resistive index with high blood flow when using Doppler technology. Malignant lymphadenopathy had the characteristics of being greater than 1 cm, round with a short: Long axis ratio greater than 0.5, necrotic center, no echogenic hilus, a high resistive index with low blood flow, and the ability to identify extracapsular spread. Using these parameters they found a sensitivity of 95% and a specificity of 83% success rate of differentiating reactive from malignant lymph nodes.

Aim of study: Evaluation of the reliability of sonography, and especially duplex sonography, in differentiation of benign from malignant enlarged cervical lymph nodes, considering pathological diagnosis as gold standard.
Material and Methods

This was a prospective study which included 30 patients attending the outpatient clinic in Cairo University children hospital, presenting with enlarged cervical lymph nodes of more than 3 weeks duration. The duration of the study was 9 months. Patients having CL of less than 3 weeks duration having contraindication of LN biopsy (Bleeding disorders, cardio respiratory failure) were dropped (excluded from the study). The major criteria of selection of patients was Cervical lymphadenopathy with more than 3 weeks duration of all age and sex groups.

All patients were subjected to full clinical evaluation including present, past and family history of Tuberculosis, history of cat bite, Cervical lymph nodes evaluation including: Size, number, consistency, fixation and other groups of LN involved including supraclavicular and mediastinal LN, evidence of septic/infective foci in head and neck i.e. otitis media, tonsillitis, dental, sepsis, scalp lesions and other chronic dermatosis, presence of splenomegaly, ascites, jaundice, bleeding tendency, skin rash, chest signs for T.B., abdominal mass, wt loss, persistent fever, bone pains or other significant symptoms.

Patients underwent complete blood count, peripheral blood smear, ESR, bleeding time, clotting time. Patients were comprehensively examined by ultrasound for cervical lymphadenopathy using B-mode (ie, brightness mode) ultrasound and color Doppler sonography. Scanning was performed with the patient in the supine position, and with the neck hyperextended using a pad or pillow under the shoulders in order to provide optimum exposure of the neck. For the examinations, An Ultrasonix XP machine with a 10-14MHz multi-frequency linear array transducer was employed for gray scale and color Doppler evaluations of the nodes. Gray-scale sonography was used for evaluation of the nodal size, shape, borders, the Solbiati index (ie, ratio of maximum transverse and longitudinal diameters; L/T-index,' and hilar echogenicity. Color Doppler sonography was used for assessment of the vascular patterns of the hilum, center and periphery of the node. Doppler waves were used to measure the mean arterial peak systolic and end diastolic velocities. In the evaluation of the vascular resistance (resistive index RI, pulsatility index PI) of lymph nodes, spectral Doppler is used and the more prominent vessels are usually selected for the measurement. Measurements are obtained from three consecutive waveforms and the smallest sample volume should be used.

After duplex sonographic examination, the patients underwent surgical intervention, and excisional biopsy of the lymph node. The results of histologic analysis of the excised lymph node specimen were compared with the sonographic findings. The analysis of the same lymph node by sonographic and histologic examination was assured by choosing the largest one in every patient.

The research deputy and ethics committee approved this study. An informed consent was obtained from the parents before the study.

Data were presented as Mean±SD. Statistical analysis was performed with SPSS for windows version 17.0 using Chi-square test and Independent-Samples t-test, whenever appropriate. A p-value less than 0.05 was considered statistically significant.

Receiver operator characteristic (ROC) curves were used to set the assessment point for L/T ratio, RI and PI and assess their sensitivity and specificity. Also the sensitivity, specificity, positive and negative predictive values and accuracy for L/T index, absence of hilar echogenicity, shape, borders, vascular distribution of the lymph node, and resistive RI and pulsatility PI index were also calculated.

Results

According to LN biopsy, seventeen of the studied patients (57%) had reactive lymphadenopathy, while 13 patients (47%) had malignant lymph nodes 11 with lymphoma and 2 metastatic from neuroblastoma. Mean age of patients with reactive lymph nodes was 5.47±2.5 years, while mean age of malignant group was 8.76±3.3 years. Table (1) shows that male sex, weight loss, generalized lymphadenopathy, splenomegaly, presence of mediastinal lymph nodes, less hemoglobin level, higher ESR and LDH levels were statistically significant risk factors associated with the malignant group. Table (2) shows that rounded shape, sharp borders, and absent hilar echogenicity on sonar, were also risk factors, being significantly more in the malignant group. Mixed vascularity was present in 9 out of 13 patients in the malignant group and in 2 patients only in the reactive group, while peripheral vascularity alone was present in 3 out of 13 in the malignant group the mean value of the largest diameter was 1.43±0.13cm in the reactive group compared to 1.69 in the malignant group with no significant difference. The mean value of L/T ratio in malignant group was 1.82±0.13 and 2.6±0.96 in non-malignant nodes (p<0.001).
Based on the ROC curve (Fig. 1), the cutoff point for L/T ratio was 1.97 with sensitivity of 92% and specificity of 76.5%. Also based on the ROC curve (Fig. 2) the cutoff value of 0.82 of the resistive index had a sensitivity of 61.5% and specificity of 70.6%, and the cutoff value of the pulsatility index of 1.23 had a sensitivity of 69.2% and a specificity of 64.7%. Table (3) shows that L/T ratio and absent hilar echogenecity had the sensitivities of 92.3%, 85% respectively. While the resistive index and the pulsatility index had a sensitivity of 61.5% and 69.2% respectively. Table (3) shows that L/T ratio and absent hilar echogenecity had specificities of 76.5% and 94% respectively. While the resistive index and the pulsatility index had a specificity of 70.6% and 64.7% respectively. Combined grey scale sonar and color Doppler had a sensitivity of 87%, a specificity of 92%, and an accuracy of 87%.

Figs. (3-5) show a lymphomatous LN, a metastatic LN from neuroblastoma, and a reactive LN respectively.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+Ve predictive value</th>
<th>–Ve predictive value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/T ratio</td>
<td>92.3%</td>
<td>76.5%</td>
<td>75%</td>
<td>93%</td>
<td>83%</td>
</tr>
<tr>
<td>Absent Hilar echogenecity</td>
<td>85%</td>
<td>94%</td>
<td>92%</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>Grey scale US</td>
<td>78%</td>
<td>99%</td>
<td>98%</td>
<td>83%</td>
<td>98%</td>
</tr>
<tr>
<td>Pulsatility index PI</td>
<td>69.2%</td>
<td>64.7%</td>
<td>60%</td>
<td>73.3%</td>
<td>66.6%</td>
</tr>
<tr>
<td>Resistive index RI</td>
<td>61.5%</td>
<td>70.6%</td>
<td>61.5%</td>
<td>70.6%</td>
<td>66.6%</td>
</tr>
<tr>
<td>Grey scale and color Doppler</td>
<td>87%</td>
<td>92%</td>
<td>83%</td>
<td>92%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Table (1): Clinical and laboratory data of reactive and malignant lymph nodes.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Reactive (No. %)</th>
<th>Malignant (No. %)</th>
<th>p value</th>
<th>Reactive (Mean ± SD)</th>
<th>Malignant (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.005</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>5.47±2.5</td>
<td>8.76±3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>10.3±0.84</td>
<td>9.6±0.6</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>8.05±2.7</td>
<td>8.7±2.5</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ptt</td>
<td>246.7±76.3</td>
<td>198.8±80</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>28.8±14.7</td>
<td>71.9±21.7</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>LDH</td>
<td>193.3±52.6</td>
<td>347.2±72.5</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value <0.05 was considered significant.

Table (2): Characteristics of the LN on gray scale US and color duplex US.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Reactive (No. %)</th>
<th>Malignant (No. %)</th>
<th>p value</th>
<th>Reactive (Mean ± SD)</th>
<th>Malignant (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rounded shape</td>
<td>6</td>
<td>10</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharp borders</td>
<td>2</td>
<td>3</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent Hilar echogenecity</td>
<td>5</td>
<td>2</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed (hilar and peripheral)</td>
<td>2</td>
<td>3</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascularity alone</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value <0.05 was considered significant.

Table (3): Value of Grey scale US and Color duplex US IN Differentiating malignant from reactive LN cutoff value of L/N 1.97, ri 0.82, pi 1.23.
Discussion

Palpable neck lymph nodes are common in children. This is because reactive hyperplasia of lymph nodes is strongly associated with inflammatory processes commonly seen in children. It has been reported that up to 90% of children aged 4-8 have palpable neck nodes [2]. Cervical lymphadenopathy is also a clinical manifestation of malignancy. Cervical lymph node metastases are often found in children with head and neck cancers, and neck nodes are also a common site of lymphomatous involvement [5-7]. Giuffrida D et al. [8] found sonography examination highly informative to differentiate whether the cause of CL is benign or malignant. He reported that an oval shape with central echogenic hilum indicate benign lesion where as roundness with absence of central echogenic hilum indicate malignant lesion. Size of lymph nodes was used previously as an indicator of malignancy [9]. Different cut-off points of nodal size (maximal short axis axial diameter) to differentiate malignant from benign nodes have been reported previously (5, 8 and 10mm) [10-12]. In our study, the mean value of the largest diameter of the lymph node was 1.43 ± 0.13cm in the reactive group compared to 1.69 in the malignant group with no significant difference. This is in concordance with Nemati et al [13] who found no significant difference between the size of reactive and malignant lymph nodes. Size cannot be used as an absolute criterion, as inflammatory nodes can be as large as malignant nodes, whilst malignancy can be found in small nodes. It has been reported also that lymph nodes in the upper neck, including those in the submandibular and subdigastric region, tend to be larger than those in the lower neck [14-
We found that rounded shape of the lymph nodes was significantly more in the malignant group. This is in agreement with Reede et al. [18] who reported that benign reactive nodes tend to maintain their normal oval shape, whereas malignant nodes usually have a more rounded configuration. L/T ratio was a significant risk factor for malignancy in our study. The cutoff point for L/T ratio was 1.97 with sensitivity of 92% and specificity of 76.5%. This is in concordance with the cutoff point of 2 reported by Asai et al. [19] and Krishna et al. [20] who reported also high sensitivity and specificity with this cutoff point. There was a significant relation in our study between the presence of sharp borders and the nodes being malignant. This is in agreement with Shozushima et al [21] who noted that Malignant nodes (including metastases and lymphoma) tend to have sharp borders, whereas benign nodes usually have unsharp borders [21]. Absent hilar echogenicity was present in 85% of the malignant nodes and in only 6% of the reactive nodes. This is in agreement with Rubaltelli et al. [22] and Vassallo et al. [23] who noted that 84 to 92% of benign nodes have an echogenic hilus. However, Vassallo et al. [23] have also reported that 51.5% of metastatic nodes have an echogenic hilus. Although the echogenic hilus is a manifestation of the normal anatomy of lymph nodes, it is also possible to see it in early nodal malignancy, because the medullary lymphatic sinuses have not been sufficiently disrupted to eradicate it [24]. Ahuja et al. and Ying et al. [25-27] found that metastatic (69-95%), and lymphomatous (72-73%) nodes tended to have an absent hilus, whereas normal nodes usually had an echogenic hilus (75-100%).

Na D.G et al. [28] described the role of colour doppler sonography in differential diagnosis of CL, depending upon the vascular pattern. Normal and reactive lymph nodes tend to show hiliar vascularity or appear apparently avascular. However, metastatic nodes tend to have peripheral or mixed (presence of both peripheral and hilar) vascularity [29-35] and mixed vascularity is also common in lymphomatous nodes [28,35,36]. In our patients with malignancy, 69% of the patients had mixed (hilar and peripheral vascularity) while 23% of the patients had peripheral vascularity. This may be explained by the fact that 11 out of 13 of our malignant cases were lymphoma, and it has been reported that unlike metastatic nodes, peripheral vascularity alone is less common in lymphoma [28,29,32 36]. Some authors regard pulsatility and resistive indices, as useful for the differentiation between benign and malignant lymph nodes [37-41] whereas others do not agree with these findings. [42,43] It has been reported that the RI and PI of reactive lymph nodes is lower than that of metastatic lymph nodes [28,32,36,44,45]. Steinkamp et al. [36] suggested that the optimal cut-off for RI and PI in distinguishing reactive and metastatic nodes were 0.8 and 1.6, with a sensitivity of 80 and 94%, respectively, and a specificity of 94 and 97%, respectively. However, in our study, the optimal cut-off values for RI and PI of 0.82 and 1.23 had sensitivities of 61.5% and 69.2% respectively, and had specificities of 70.6% and 64.7% respectively, with no significant difference in RI and PI between reactive and malignant nodes. This is in agreement with Adibelli et al. [47] who found that there was no significant difference in RI and PI between benign and malignant nodes.

In our study the sensitivity and specificity of grey scale sonography was 78% and 99% respectively. This is in concordance with Asai et al. [19] who reported a sensitivity of 98.0% and a specificity of 76.5% and Ahuja et al. [47] who noted that Gray-scale sonography has a sensitivity of 95% and a specificity of 83% in differentiating malignant and reactive nodes. In our study, combined grey scale US and CDUS had high specificity but low sensitivity, similar to those reported by Nemati et al. [13]. In our study, there was improvement in accuracy by addition of color Doppler to grey scale ultrasonography, but that there was no significant difference in RI and PI between malignant and reactive nodes. This is in agreement with Nemati et al. [13] who found no significant difference in RI and PI between malignant and reactive nodes, but contrary to Ahuja and Ying [48] who indicated high sensitivity and specificity of color Doppler Ultrasonography in distinguishing malignant from reactive nodes.

From this study, we conclude that US especially Grey Scale Ultrasonography had a high sensitivity, specificity and accuracy in differentiating malignant from reactive lymph nodes, and is recommended to be in the initial workup of persistant lymphadenopathy, but biopsy may still be necessary for confirmation, if the ultrasound findings are equivocal.

References


