A Pictorial Essay on Ultrasonography of Lymphadenopathies in Children

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Received: November 29 2022; Accepted: January 15 2023

Abstract

The purpose of this review is to become familiar with ultrasound (US) characteristics of normal and pathological lymph nodes and with diagnostic imaging approach to lymphadenopaties. Lymphadenopathy is a common finding in the paediatric population. Due to the many pathologies that can present in a similar fashion, imaging is a valuable method used in diagnostic process. Ultrasound is the modality of choice for lymph node detection in children, with a high safety profile as it does not use radiation. In this review the US appearance and characteristics of normal lymph nodes, and of some more common lymphadenopathies, are presented. Special attention is paid to distinguishing between benign and malignant lymph nodes on the basis of US characteristics. All findings must always be correlated with clinical and laboratory findings, and frequently followed by fine-needle aspiration or excisional biopsy as some US morphologies of benign and malignant nodes may overlap. However, the criteria that raise suspicion for malignancy are round shape, predominantly hypoechoic echogenicity, heterogenous echotexture, absent or displaced hilum, irregular outlines, necrosis, multiple confluent lymph nodes, the presence of microcalcifications, and peripheral or mixed flow pattern on colour Doppler imaging. **Conclusion** – US is the first line imaging method in palpable masses in children, first to confirm the presence of lymph nodes, and second to better delineate the lymph node's characteristics, which guides further diagnostic decisions and treatment.

Key Words: Ultrasound • Lymph Nodes • Lymphadenopathies • Children.

Introduction

Palpable lymph nodes are a common reason for paediatric visits, and a regular reason for performing ultrasound (US) examinations of children (1, 2). Most cases prove to be benign in origin and sometimes there is no pathology involved at all, as previous studies have shown that palpable lymph nodes are also common in healthy children (3, 4).

In the workup of palpable lymph nodes clinicians form a differential diagnosis by relying on the patients' history and physical examination. Valuable information that should be gathered during the workup includes: the onset and duration of the mass, changes in size, and the presence of fever, pain, or any other symptoms of infection. Physical examination findings of palpable mobile, elastic and soft nodes suggest reactive adenopathy, while firm and nonmobile lymph nodes are usually associated with potential malignant causes (3–5). Sometimes clinicians are sufficiently confident in determining the aetiology of enlarged lymph nodes on the basis of the information gathered, and additional workup is not needed. However, if the lymphadenopathy fails to resolve itself either spontaneously or with antibiotic therapy after 4 to 6 weeks, additional symptoms appear, or when there is a suspicion of malignancy, further diagnostic tools are necessary, imaging being one of them (4). Normal lymph nodes are small, bean-shaped structures that are part of the body's immune system. Most commonly, palpable lymph nodes can be found in the neck region, inguinal region (groin) and axillary region. Lymph nodes are also found in the chest and abdomen, but they are usually not palpable. The US characteristics of lymph nodes are the same, regardless of location. There are no lymph nodes in the central nervous system (2).

Lymph nodes in children grow in size for approximately the first 6 years and then slowly undergo involution that coincides with puberty (2). The size of a normal lymph node correlates with its location. Most nodes larger than 10 mm, measured along the short axis, are considered enlarged, the only exception being jugulodigastric nodes which can measure up to 15 mm and are still considered normal (1, 3, 6). Obviously, lymph node size is only one parameter, and for final diagnosis all US parameters must be taken into account.

US is the first-choice imaging method for palpable lymph nodes in children. It is a widely available, portable, cost-effective imaging modality, with a high safety profile, as it is radiation- and sedationfree. It provides quick, real-time characterization of the mass, with excellent contrast and spatial resolution, and it can be used for guidance during interventional procedures, such as tissue sampling and biopsy or drainage. The main technical limitation of US is if the mass cannot be imaged appropriately. This may be because the mass is too deep or too large to be displayed in its entirety, or it is too hyperechoic (3). Other limitations of US include operator dependent variability and artefacts due to a noncooperative patient.

The main role of US is to clarify whether the palpable mass is a lymph node or not. Yaris et al. showed that approximately every fifth case considered to be lymphadenopathy turns out to be something else (7). Palpable masses can sometimes simulate lymph nodes even though they originate from other tissues (8). The most commonly encountered masses include: lipomas, abscesses, thyroglossal duct cysts, branchial cysts, dermoid cysts, thyroid nodules, vascular malformations, pilomatrixomas and others (3, 9). In this pictorial essay, the US characteristics of normal superficial lymph nodes, as well as different lymphadenopathies, are described. US techniques can be applied to any region of the body where superficial lymph nodes are found (such as the axillae, groin area, neck region etc.), as well as to nonpalpable lymph nodes.

The purpose of this review is to become familiar with US characteristics of different lymphadenopaties, to be able to recognize the suspected malignant lymph nodes, and to be aware of US limitations. The current position of new US techniques, such as contrast-enhanced ultrasound (CEUS) and US elastography, is discussed. A practical diagnostic imaging approach to lymphadenopathies is suggested.

Ultrasound Techniques

First, we have to create a comfortable environment for the child and parents during the US examination, and gain their cooperation (10). When performing US of a palpable mass, a high-frequency linear probe (mostly 10-15 MHz, newer probes 18-22 MHz) is used. Grey-scale US is used, as it provides high-resolution images of superficial structures. Characterizing the mass with grey-scale US requires its visualization in at least two planes, but preferably three - sagittal, transverse and antero-posterior. The Doppler technique is an important additional tool in evaluating lymph node vascularization. Usually colour or power Doppler is good enough to detect the pattern of lymph node vascularization. With a cooperative child, a pulsed Doppler can offer additional information by obtaining the resistance index (RI) values and the shape of the spectral Doppler curve.

New US technologies, such as intravenous CEUS (11, 12) and US elastography (13, 14), represent a new potential approach to evaluation of pathological lymph nodes. CEUS involves the administration of intravenous contrast agent containing microbubbles of inert gas that start oscillating when they are hit by the US beam, which affects ultrasound backscatter and increases vascular contrast, allowing for better assessment of vascularity and contrast retention in lesions (11, 15). There is no evidence that CEUS has any great potential in differentiation between benign and malignant lymphadenopathies, but it is proving to be a clinically valuable method for detecting complications in children with suppurative lymphadenopathy (11). The basic principle of US elastography is that pathological processes alter the elastic properties of the involved tissue, which influence US wave propagation reflected in a change of the velocity of the shear waves (13, 14). Studies on adults showed that US elastography might be useful for differentiating between benign and malignant lymph nodes, as it appears that most inflammatory processes do not change the elastographic architecture of lymph nodes (16). Current guidelines as yet do not recommend its use in everyday clinical practice (12, 17).

US guided fine needle or sometimes core needle biopsy is performed in cases of unexplained lymphadenopathy (3, 9). US guidance allows precise sampling.

Ultrasound Characteristics of Normal Lymph Nodes and Lymphadenopathies

US characterisation of lymph nodes can prove sufficient for diagnosis, in correlation with the clinical picture and laboratory findings, or it can help with determining the next best step in the patient's workup. The US characterisation criteria describing the lymph node are presented in Table 1. They include a description of the lymph node's location, its size and shape, as well as morphology and the echostructure of the lymph node and the surrounding soft tissue. The patterns of lymph node vascularisation are well known and described, but there are no clear, commonly accepted cut-off values for RI. Usually, RI values regarded as normal are around 0.6. Hyperaemia due to inflammation and higher diastolic flow caused by vessel dilatation result in lower RI (usually around 0.5), while hypercellularity in malignant lymphadenopathies (around 0.7 or higher) results in higher RI (18–20). Caution is needed when interpreting RI due to the overlap between the groups.

Normal Lymph Nodes

Normal lymph nodes are seen on US as homogenous, well-defined, oval or bean-shaped structures, usually with a short to long axis ratio (S/L ratio) of around 0.5 (Fig. 1) (3, 19, 21–23). The cortex is hypoechoic relative to muscle, with a central echoic fatty hilum, which is usually continuous with the surrounding connective tissue of the node. With colour or power Doppler, a single vessel can be found that is barely perceptible, with RI around 0.6, or even unseen (1, 3, 4, 19, 24). Normal nodes usually have central vascular flow on

Table 1. Lymph Node Characterisation Criteria
Characteristics
Location: anatomical region
Size parameters - at least 2 planes (transversal and longitudinal), preferably 3
Shape: short axis to long axis ratio (S/L ratio) - Oval (S/L ratio around 0.5) - Rounded (S/L ratio around 1.0) - Irregular asymmetric shape
 Morphology and echostructure: – LN hilum: presence/absence, position – LN cortex: echogenicity, thickness (uniform/nonuniform), architecture: homogenous, non-homogenous, presence of localized structural changes
Border or margins of LN: well-defined, thickened irregular, blurred
 Vascularization of LN with colour and pulse Doppler Flow: absent/present Vessel location: central, peripheral, mixed (central and peripheral) Resistance index
Surrounding tissues: normal/abnormal



Fig 1. A normal lymph node under the left strenocleidomastoid muscle (middle internal jugular region of the neck). Conventional ultrasound shows a well-defined, oval lymph node with hypoechoic cortex (arrow) and central hyperechoic linear hilum (arrowhead). The lymph node is smaller than 1 cm, S value is 4 mm, L 10 mm and the S/L ratio is less than 0.5. Perinodal tissue is well preserved.

colour Doppler, or may appear avascular due to the small size of the node (3, 21, 22). Each lymph node is surrounded by a fibrous capsule. Perinodal tissues are well-defined and clearly distinguishable (3).

Reactive Lymphadenitis

Reactive lymphadenitis can be caused by all types of pathogens, however, viral infection is the most frequent cause of lymphadenitis in childhood. Upper respiratory tract infections are the most common cause of acute bilateral lymph node enlargement (5, 10, 25). The nodes are usually soft and mobile, without erythema, and may be accompanied by tonsillar or adenoidal hypertrophy (1, 26]. Diffuse lymph node enlargement in adolescents, especially if accompanied by hepatosplenomegaly, is most commonly caused by Epstein-Barr virus or Citomegalovirus (1, 26). These two viral pathogens can also cause chronic lymphadenopathy, that persists for 6 weeks or longer (5, 25, 26). On US, reactive lymph nodes appear enlarged, but they generally maintain an S/L ratio ≤ 0.5 , with their normal structure and composition, a hypoechoic cortex, and well-defined borders (Fig. 2) (3, 4, 10). Doppler US usually shows hyperaemia, with a more prominent hilar vessel or a branched pattern of vascularity and lower RI values, around 0.5 to 0.6 (1, 3, 19). In cases of reactive lymphadenitis, a watch-and-wait approach is recommended, as spontaneous resolution is the most common



Fig. 2. A reactive lymph node. a) Conventional ultrasound of a reactive lymph node due to tonsillitis and cervical lymphadenitis in a 2-year-old boy shows an enlarged (S: 18 mm, L: 40 mm), well-defined, oval lymph node, with normal structure and maintained S/L ratio (18/40 = 0.45) on the lateral border of the middle internal jugular (III) region, on the right side of the neck. b) Colour Doppler US of another reactive lymph node in the same region shows the central hilar vessel and central vessel net distribution.

outcome. Additional imaging is not required (1, 26). If liver and spleen involvement is suspected, abdominal US should be performed (25).

Bacterial Lymphadenopathies

Bacterial lymphadenopathies can be divided into acute and chronic infections. Most acute cases are caused by staphylococci and beta haemolytic serogroup A streptococci, followed by anaerobic bacteria from dental caries. The most common causes of subacute and chronic infections are nontuberculous mycobacteria (NTM), bartonella and tuberculosis bacteria (25, 27).

Acute bacterial lymphadenitis is most commonly seen at ages from 1 to 4 years old, most commonly affecting the cervical lymph nodes, and originates from the oropharyngeal space (3, 4, 27). In an uncomplicated infection, the nodes tend to be enlarged unilaterally, tender or even painful, and warm, with localised erythema (1, 4, 27). On US, uncomplicated bacterial lymphadenitis appears as unilaterally enlarged lymph nodes with an S/L ratio >0.5 and preserved homogenous, hypoechoic cortex and hyperechoic fatty hilum, that may progress into a confluent nodal mass. Doppler US shows hyperaemia with low RI. Signs of perinodal inflammation may be present, with hyperechogenic fat swelling (Fig. 3) (1, 3, 28). If not treated, the infection may progress to suppuration and abscess formation. Uncomplicated bacterial lymphadenitis can be managed with antibiotics, and does not need further imaging workup (3, 26, 27).

On US, complicated suppurative adenopathy will show the reduction or even loss of the hyperechoic fatty hilum, and anechoic regions of necrosis with or without septations and foci of air, and decreased vascularity on colour Doppler (1, 3, 4). Surrounding perinodal tissues usually demonstrate reactive oedema (1, 3). In cases of abscess formation, a heterogenous hypoechoic or anechoic mass with thickened and irregular walls and increased



Fig. 3. Acute bacterial lymphadenitis in a 1-year-old girl. US shows a heterogeneous, mostly hypoechoic, enlarged, rounded lymph node (arrow) in the left submandibular region, with poor differentiation between the cortex and hilum. There is also hyperechoic fat stranding characteristic for perinodal inflammation (star).

peripheral vascularity can be seen (Fig. 3) (3). If the abscess cannot be properly evaluated with grey-scale and Doppler, due to the poorly defined borders of the mass, or if there is uncertainty as to whether the formation is solid and hypoechoic or indeed cystic in nature, CEUS may be performed to better define and delineate the size and shape of the abscess cavity before a decision on treatment and whether the abscess will require drainage (Fig. 4). In most severe cases the adjacent vasculature can become compromised with inflammation of the vessels, spasms or even septic thrombophlebitis (Lemierre syndrome) (1, 3, 4). In complicated cases, follow up US may be appropriate to evaluate the response to treatment.

Cat-scratch disease is one of the most common causes of chronical lymphadenopathy, caused by the bacteria Bartonella henselae. The typical presentation involves erythema at the site of the scratch and regional lymphadenopathy, with or without general malaise three weeks after the scratch (5, 25, 26). When cat-scratch disease is suspected, inquiring about the presence of pets or any animal scratches in the child's history plays an important role. Axillary, epitrochlear and cervical lymph nodes are most often affected (1, 4). US findings can be



Fig. 4. Suppurative cervical lymphadenitis in a 1-year-old girl on contrast-enhanced ultrasound of the lymph node with dual display. The conventional US image on the right side of the image shows an enlarged lymph node with heterogeneous structure and poorly defined borders. The contrast-enhanced image on the left side of the image clearly demarcates the irregular shape of the abscess cavity (nonenhanced part of the lymph node - stat) and hyperenhanced surrounding tissue.

variable and nonspecific. Nodes can be enlarged, oval or lobulated, heterogenous, or homogenous, usually hypoechoic with a preserved hyperechoic hilum. Nodes can have either sharp or poorly demarcated borders, depending on the perinodal inflammation. Doppler US usually shows central hyperaemia with enlargement of the hilar vessel and its branches (Fig. 5). The appearance of the affected node can progress to anechoic due to necrosis (1, 4, 29, 30). Surrounding tissue can appear normal or slightly hyperechoic (1, 30). Often, images of large and well-perfused lymph nodes help to lead to the question about whether the child was scratched by a cat. The disease is usually self-limiting and does not require additional imaging.

Atypical mycobacterial infections which cause granulomatous inflammation, are most commonly caused by Mycobacterium avium complex (4, 5).

Affected children are usually less than 5 years old, presenting with unilateral enlarged axillar or neck mass that persists for more than 3 weeks, but otherwise show no symptoms of systemic illness. After 2 to 3 weeks, the skin becomes thin with violet discoloration. In cases where necrosis of the affected lymph node occurs, spontaneous fistulisation may develop (Fig. 6) (5, 25, 26).

Usually US shows an enlarged, round or lobulated lymph node, that is often hypoechoic and heterogeneous in composition, containing central necrosis (1, 4, 31). The nodal margins may be distinct or blurred with a hyperechoic perinodal halo, depending on the inflammatory infiltration of adjacent fatty tissue (1, 31). The affected lymph node may be surrounded by smaller reactive nodes. In cases with spontaneous fistulisation, a connecting tract between the node and the skin can be seen. In



Fig. 5. Cat-scratch disease in a 17-year-old boy. a) US shows a cluster of considerably hypoechoic, enlarged, ovoid shaped axillary lymph nodes, with relatively thin hyperechoic surrounding soft tissue (fat stranding). b) In comparison to normal lymph node vascularisation there is increased hilar vascularity of an oval, hypoechoic lymph node (S: 12 mm, L: 21 mm, S/L ratio is 0.57) in the elbow region on Doppler US. No necrosis of lymph nodes was identified.



Fig. 6. Development of a draining sinus tract in a 4-yearold boy with an atypical mycobacterial infection. a) The grey scale US image shows an enlarged, ovoid, hypoechoic lymph node with a particularly hypoechoic round area (star), representing necrosis. There is also spontaneous fistulation (arrow) with fluid collection located in the subcutaneous fat tissue (arrowheads), b) Doppler US of the same lymph node shows diminished vascularisation of necrotic area.

later stages intranodal calcification may occur and is identifiable on US as strong echoes within the hypoechogenic lymph node (1, 31).

Nontuberculous mycobacterial lymphadenopathy usually presents with chronic enlargement that can be treated simply by observation in mild cases as it can resolve spontaneously. However, complete surgical excision of the affected lymph node is the most effective curative option (32). In cases of conservative treatment follow up US can be performed for monitoring the progression or regression of the disease.

Malignant Lymphadenopathies

Most common lymphadenopathies associated with malignancies in children younger than 6 years old are due to neuroblastoma and leukaemia, followed by rhabdomyosarcoma and non-Hodgkin's lymphoma. After 6 years of age, lymph nodes are most often affected due to Hodgkin's lymphoma, non-Hodgkin's lymphoma, and rhabdomyosarcoma (33). In cases of lymphoma and leukaemia, cervical lymphadenopathy is a common initial finding (3, 25). If supraclavicular, lower cervical or posterior cervical lymph nodes are enlarged, malignancy should always be considered (26, 33). In addition, if lymph nodes are rapidly increasing in size, are bigger than 2 cm on palpation, nontender and fixed, they are much more likely to be malignant (5, 26).

On US, malignant lymph nodes tend to have a rounder shape, with S/L ratio around 1.0 (Fig. 7) (3, 23, 34). Sometimes asymmetrical cortical thickening can be seen due to focal tumour infiltration in metastatic lymph nodes (35). Usually, malignant lymph nodes are markedly hypoechoic and homogenous in composition (1, 10, 24, 35). Lymphomatous lymph nodes can sometimes demonstrate internal reticulation, giving them a micronodular appearance (1, 3). In cases of rapid tumour growth, when it outgrows its blood supply, spots of necrosis can appear, either as anechoic cystic necrosis or echogenic coagulation necrosis (Fig. 8) (24, 35). A special case is metastatic papillary thyroid carcinoma, known for its psammoma bodies which result in the hyperechoic appearance of the lymph node on US (1, 24).



Fig. 7. Non-Hodgkin lymphoma in a 3-year-old boy who presented with painless lymphadenopathy in the lower internal jugular and supraclavicular region on the right side of the neck. a) Conventional US shows many enlarged, rounded, hypoechoic lymph nodes with sharp margins and displaced hyperechoic or absent hilum, all US characteristics that give rise to suspicion of malignant lymph nodes. In contrast to reactive lymphadenitis, there is also no perinodal soft tissue oedema. b) Doppler US demonstrates peripheral vascularization of the lymph nodes.



Fig. 8. Burkitt lymphoma with central necrosis in a 5-yearold boy. The conventional US image of contrast-enhanced ultrasound on the right side of the dual image shows the irregularly shaped and enlarged lymph node with poorly defined margins (arrowheads) and a central anechoic area suspected to be necrosis (star) which is much better demonstrated on the contrast-enhanced part of the image (left), as the nonenhanced area.

Malignant lymph nodes can have well-defined borders, believed to be due to the increased cellularity of the affected lymph node, causing an increase in the acoustic impedance difference between the node and surrounding tissues (1, 34-36). However, irregular or blurred borders are also common and should not exclude malignancy, as they can indicate the extracapsular spread of the tumour, particularly in metastatic lymph nodes (Fig. 9) (24, 35, 36). Multiple confluent lymph nodes may be seen, but this is also common in bacterial infections (1, 3, 34). A common feature of malignant lymph nodes is an absent, or present but displaced, hyperechoic hilum, although in the early stages of the disease the hilum might still be lying centrally (1, 10, 35). Furthermore, the absence of the hilum can also be seen in tuberculous nodes or even in benign cases, therefore, as with any other characteristic, the presence or absence of an echogenic hilum should not be the sole criterion in determining the malignancy of a lymph node, and hilar vascularity should always be evaluated with Doppler US (21, 35, 37). Malignant lymph nodes can demonstrate peripheral or mixed vascularity, where we can see both hilar and peripheral vascularization and a higher RI compared to inflammatory lymph nodes (around 0.7 or higher). This is ascribed to vessel compression due to the effect of the mass (1, 10, 36, 38). While peripheral vascularization is highly suspicious for malignancy, the use of RI values has limited use in clinical settings due to the lack of



Fig. 9. Nodal metastasis in an 11-year-old girl with a neuroblastoma. On conventional US, a hypoechoic lymph node with structural distortion and unsharp, blurred borders was found on her right thigh.

standardized cut-off values for distinguishing between malignant and benign changes (21, 24).

Biopsy (fine-needle or core) or surgical excision is needed to confirm the diagnosis and further imaging (abdominal US with chest X-ray and crosssectional imaging – CT or MRI) should be performed to evaluate the extent of the disease (3, 26).

Discussion

Different causes of lymphadenopathy can present with a similar clinical picture, therefore radiological examination can be very useful in forming differential diagnosis. Complete lymph node characterisation in correlation with clinical findings can show the highly suggestive appearance of the lymph node, that can be diagnostically decisive. Due to its high safety profile, US examination can be repeated several times and is therefore a very useful tool for evaluating response to treatment, or as a follow up in watch-and-wait cases. There are currently no specific guidelines for radiological follow up of lymphadenopathies. The basic management algorithm in children with lymphadenopathy used in our institution, based on the US characteristics of lymph nodes, is presented in Fig. 10.

The main issue in US examination of lymphadenopathies is how to differentiate between benign and malignant lymphadenopathy. US does not have high specificity in distinguishing between benign and malignant nodes using any one criterion described in this article, finding all or some of the features that would indicate a higher chance of malignancy, such as round shape with predominantly hypoechoic echogenicity, heterogenous echotexture, irregular borders and an absent or displaced hilum, multiple confluent lymph nodes, necrosis, peripheral or mixed vascular flow pattern, and high RI, should raise alarm (9, 21). However, the role of RI and its usefulness in clinical practice remains controversial. One issue often raised is that the optimal cut-off value for distinguishing between benign and malignant nodes is not universal and varies from study to study. Most of these studies were conducted on adults, which raises the



Fig. 10. Follow up imaging based on the ultrasound characteristics of lymph nodes. LN=Lymph node; US=Ultrasound; FNAB=Fine needle aspiration biopsy; CEUS=Contrast-enhanced ultrasound.

question whether the same applies in the paediatric population.

Another issue with children is that it is often much harder to perform adequate colour Doppler, let alone gain an accurate RI reading, as children do not like to be still for any amount of time, and especially in an unknown environment such as during an examination at the doctor's office. Consequently, the operator should be well versed in dealing with the paediatric population, and further steps should be taken to elicit cooperation from children. If the child is old enough to understand, the examination should be explained to them. If the patient is too young, distraction techniques can be used, such as a pacifier, toys, music, video players, etc. In all cases, a parent should be present for further reduction of stressors. Newer US imaging methods currently appear to be of limited value. While US elastography shows promise in differentiating between benign and malignant lymph nodes, further studies must be done before it can be used in clinical practice. CEUS is less promising in accurate differentiation between benign and malignant lymph nodes, but it shows high potential in evaluating suppurative lymphadenitis, with its capability to better differentiate the necrotic parts of lymph nodes, and abscess and fistula canal delineation.

Conclusion

US is the first line imaging method in palpable masses in children, first to confirm the presence of lymph nodes, and second to better delineate the lymph node's characteristics, which guides further diagnostic decisions and treatment. The US lymph node characteristics are similar regardless of lymph node location. US plays an important role in the differential diagnosis of evaluated masses, and it directs further management. It is also used as a follow up method for objective assessment of response to treatment. CEUS of the lymph node can be a valuable method in differential diagnosis and evaluation of a lymph node abscess. More studies are needed to determine the clinical value of US lymph node elastography in children.

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

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