Pediatric Cervical Lymphadenopathy

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INTRODUCTION

Cervical lymphadenopathy is common in the pediatric population, with estimates of 38% to 45% of otherwise healthy children having palpable lymphadenopathy.1 Park2 reported that 90% of children between the ages of 4 and 8 years have lymphadenopathy. In the head and neck, most providers consider nodes greater than 1 cm enlarged, except for anterior deep cervical (jugulodigastric) nodes, which may reach 1.5 cm before they are considered enlarged.3,4 Most cases represent benign lymphadenopathy and are self-limited.5,6 The differential diagnosis for cervical lymphadenopathy in children is broad, and a thorough history and physical examination are important in identifying the correct diagnosis. Infection is the most common cause of pediatric cervical lymphadenopathy and is the emphasis of the current discussion. The management of pediatric cervical lymphadenopathy is also discussed, including when imaging and biopsy should be considered.

KEYWORDS

• Cervical lymphadenopathy • Pediatric • Neck mass • Differential diagnosis • Infectious

KEY POINTS

• The differential diagnosis for cervical lymphadenopathy in a pediatric patient is broad, but the most common cause is infectious.
• Thorough history and physical examination are essential to identify the correct diagnosis.
• Ultrasound is the initial imaging modality of choice for most pediatric patients who require further evaluation of cervical lymphadenopathy.
• Fine-needle aspiration biopsy (FNAB) may be used as the initial biopsy method in selected pediatric patients with cervical lymphadenopathy, possibly obviating the need for open biopsy in some cases.
• Clinical judgment should guide the clinician to open biopsy in the setting of negative FNAB and suspected malignancy.
ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The neck is often considered in several anatomic subsites (Fig. 1), including the submental, submandibular, anterior cervical, posterior cervical, supraclavicular, and parotid (preauricular) sites. Anterior cervical nodes are located anterior to the posterior border of the sternocleidomastoid muscle (ie, in the anterior triangle of the neck) and are often divided into upper, middle, and lower groups. They may further be divided into superficial and deep nodes relative to their location along the external or internal jugular veins, respectively.\(^7\) Posterior cervical nodes are posterior to the posterior border of the sternocleidomastoid muscle (ie, in the posterior triangle of the neck). This basic subsite classification of cervical lymph nodes established by Hajek and colleagues\(^8\) has been reported to be the most reproducible classification scheme on neck ultrasound, which is an important imaging study in the pediatric population. Mastoid (postauricular) and suboccipital locations may also be included as anatomic subsites of cervical lymph nodes.\(^7\)

CLINICAL PRESENTATION AND PHYSICAL EXAMINATION

A thorough history and physical examination are paramount in accurately diagnosing cervical lymphadenopathy in pediatric patients. Important historical questions should be asked to help narrow the differential diagnosis. The onset and duration of the neck mass, changes in mass size or character, recent illnesses, fever, anorexia, weight loss, night sweats, fatigue, recent travel, animal exposure, treatment (such as antibiotics), and response to treatment should all be addressed. During physical examination, mass locations (including laterality), size, mobility, tenderness, and characteristics on palpation (soft, rubbery, fluctuant, firm, warm), and overlying skin changes should be noted.\(^6,7,8\)

Key historical information and physical examination findings may indicate a benign versus malignant origin. Benign reactive lymphadenopathy with infectious origin may

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**Fig. 1.** Cervical lymph node subsites in the pediatric patient. (A) Submental; (B) submandibular; (C) upper, (D) middle, (E) lower anterior cervical; (F) posterior cervical; (G) supraclavicular; (H) parotid. (Courtesy of Dawn Rosenberg Davis, Yazoo City, MS.)
be suggested by an associated illness (viral or bacterial), such as an upper respiratory infection, pharyngitis, tonsillitis, or otitis media. Viral-associated cervical lymphadenopathy is often soft, small, bilateral, mobile, nontender, and without overlying skin changes, although this general rule may not be true with some of the more subacute and chronic viral infections, such as Epstein-Barr virus (EBV) and cytomegalovirus.6,7

Bacterial-associated cervical lymphadenopathy is usually of acute onset and unilateral. Bacterial lymphadenitis develops more commonly in submandibular (50%–60%) or upper cervical (25%–30%) regions compared with other cervical lymph node subsites.7 Up to 25% of patients with acute bacterial lymphadenitis will demonstrate fluctuance on physical examination, and this is especially true with Staphylococcus aureus lymphadenitis.

Concerning findings that may suggest malignancy include nodes that are rapidly enlarging, firm, nontender, and fixed to the skin or underlying structures. Also, generalized lymphadenopathy, supraclavicular nodes regardless of size, lower cervical nodes, increased patient age (>8 years), lymph nodes greater than 2 to 3 cm, and hepatosplenomegaly are associated with increased risk of malignancy.1,10,11 Associated systemic symptoms, such as weight loss, night sweats, unexplained fever, or fatigue, should initiate further workup for possible malignancy or chronic inflammatory conditions.12,13 Lymphadenopathy present for greater than 6 months is much less likely to be malignant.13

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a pediatric patient with cervical lymphadenopathy is broad and should include benign and malignant causes (Box 1). In a study of 126 children initially diagnosed with lymphadenopathy, Yaris and colleagues10 reported that 22.2% actually had another disease process, such as a congenital neck mass; 76.6% of the patients had lymphadenopathy associated with benign disease; and 23.4% had malignancy. The current discussion focuses on the most common etiologies of pediatric cervical lymphadenopathy, which are infectious in nature (Box 2). These are divided into acute, subacute, and chronic causes. Cases in the subacute and chronic categories are often a greater challenge to diagnose and manage.5,9

Acute lymphadenopathy is defined as lymphadenopathy that is present for fewer than 3 weeks.3 Causes of acute cervical lymphadenopathy include bacterial and viral infections, and overall these are the most common causes of cervical lymphadenopathy in children. In cases of cervical lymphadenitis, thorough history and physical examination are usually sufficient for diagnosis, preventing the need for unnecessary biopsy.11,14 Among these acute causes, viral upper respiratory tract infection is the most common cause of pediatric cervical lymphadenopathy.15 This lymphadenopathy is self-limited and will improve with resolution of the inciting viral illness.

Acute bacterial lymphadenitis is most commonly caused by S aureus in the neonate and in children up to age 4 years. Group B streptococcus infection should also be considered in the neonatal age group. In children aged 1 to 4 years, Group A β-hemolytic streptococcus infections become more prevalent, though S aureus is still the most common isolate in this age group. Anaerobic infections should be considered in older children and adolescents, especially in the setting of poor dentition or periodontal disease.6,7 Treatment should include antibiotic therapy targeted at the suspected pathogens, with a solo agent (such as clindamycin) usually sufficient for adequate empiric coverage for S aureus and Streptococcus pyogenes. Local resistance patterns of methicillin resistant S aureus should be examined when making this antibiotic selection. Other oral antibiotic options include amoxicillin/clavulanate,
trimethoprim/sulfamethoxazole, cephalosporins, or macrolides. Intravenous anti-
biotic options include clindamycin alone, clindamycin and ceftriaxone, and vanco-
mycin among others. When abscess formation is clinically suspected or noted on 
examination or imaging, incision and drainage is indicated for complete treatment 
in addition to antibiotic therapy. Cultures from the abscess contents should be ob-
tained for targeted antibiotic therapy.16

Subacute lymphadenopathy is defined as 
lymphadenopathy present for 2 to 6 weeks, whereas chronic lymphadenopathy per-
sists for greater than 6 weeks. Possible infectious causes of subacute and chronic 
cervical lymphadenopathy include cat-scratch disease (*Bartonella henselae*), myco-
bacterial infections (tuberculosis vs atypical mycobacterium), EBV, toxoplasmosis, 
cytomegalovirus, and HIV.5,17

Cat-scratch disease is a granulomatous infection caused by *B henselae*. It is usually 
transmitted by a cat scratch or bite in the skin of a child. Lymphadenopathy may 
develop weeks after exposure and persist for months before resolving. Fewer than 
half of infected patients demonstrate systemic symptoms. Serologic testing (*B hense-
lae* titers) can confirm the diagnosis of cat scratch disease, and excisional biopsy is

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**Box 1**

**Differential diagnosis of pediatric cervical lymphadenopathy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>Congenital</td>
<td>Branchial cleft cyst, Thyroglossal duct cyst,</td>
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<tr>
<td></td>
<td>Dermoid cyst</td>
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<tr>
<td></td>
<td>Vascular malformation (eg, lymphatic malformation, venous malformation, arteriovenous malformation)</td>
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<tr>
<td></td>
<td>Vascular tumor (eg, hemangioma)</td>
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<td></td>
<td>Sternocleidomastoid tumor</td>
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<tr>
<td>Malignancy</td>
<td>Lymphoma (eg, Hodgkin/Non-Hodgkin)</td>
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<tr>
<td></td>
<td>Leukemia</td>
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<td></td>
<td>Thyroid cancer</td>
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<td>Rhabdomyosarcoma</td>
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<td>Nasopharyngeal carcinoma</td>
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<td>Parotid tumor</td>
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<td></td>
<td>Neuroblastoma</td>
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<td></td>
<td>Metastatic disease</td>
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<tr>
<td>Other</td>
<td>Kawasaki disease</td>
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<tr>
<td></td>
<td>Sarcoïdosis</td>
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<tr>
<td></td>
<td>Drug-induced (eg, phenytoin, isoniazid, pyrimethamine)</td>
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<tr>
<td></td>
<td>Vaccination-induced (eg, after diphtheria, tetanus, pertussis vaccine)</td>
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rarely indicated. Most patients will have spontaneous resolution of symptoms without medical or surgical treatment; however, antibiotics may hasten resolution of lymphadenopathy.\(^9,15\) First-line treatment is once-daily azithromycin for 5 days, but other antibiotic options include clarithromycin, rifampin, ciprofloxacin, and sulfamethoxazole/trimethoprim. Surgical management is indicated only when there is a need for confirmation of diagnosis, or when the lymph node is complicated by an enlarging violaceous skin mass or chronic draining sinus, or to improve cosmesis.\(^18,19\) Surgical management has a high probability of success in these situations.

Atypical mycobacterial infection (most commonly *Mycobacterium avium-intracellulare* and *M. scrofulaceum*) typically presents with gradual onset, chronic cervical lymphadenitis in young children and should be suspected if lymphadenopathy persists despite routine antibiotic therapy. Upper anterior cervical and submandibular nodes are most commonly affected; however, preauricular and parotid nodes may also be involved. The affected nodes may become enlarged, indurated, or tender, and, in late stages of infection, often develop overlying violaceous skin discoloration and fragility (Fig. 2). Approximately half of patients develop fluctuance in the involved node, and approximately 10% will develop a spontaneous draining tract if not adequately treated.\(^20\) Purified protein derivative (PPD) tuberculin skin testing may be performed but is usually negative or only weakly positive. Definitive diagnosis is made on histology showing noncaseating granulomatous inflammation, acid-fast

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**Box 2**  
**Infectious causes of pediatric cervical lymphadenopathy**

- **Viral causes**
  - Upper respiratory tract infection (eg, rhinovirus, adenovirus, influenza virus)
  - Epstein-Barr virus
  - Cytomegalovirus
  - HIV
  - Herpes simplex virus
  - Measles
  - Mumps
  - Rubella

- **Bacterial causes**
  - Streptococcal infection
  - Staphylococcal infection
  - Anaerobic bacterial infection
  - Mycobacterial infection
  - Cat-scratch disease

- **Other**
  - Toxoplasmosis
  - Histoplasmosis

bacilli, or positive cultures of the mycobacterial species from the lymph node material. Treatment ideally involves complete surgical excision of the affected node; however, curettage may be considered if there is high risk of facial nerve injury with complete excision. Postoperative antibiotic therapy should be considered to treat residual disease and usually involves combination drug therapy, such as azithromycin and rifampin.7,9 Infectious disease consultation may be considered for medical management of these patients.

*M tuberculosis* cervical lymphadenitis, or scrofula, is uncommon, but may occur in individuals in the urban setting with prior exposure to tuberculosis. Cervical lymphadenitis may arise from paratracheal node extension or from direct spread of an apical lung lesion into supraclavicular nodes. It is difficult to clinically distinguish atypical mycobacterial infection from *M tuberculosis* infection based on symptoms alone. However, 28% to 71% of individuals with *M tuberculosis* lymphadenitis will have abnormal chest radiograph findings. Purified protein derivative skin test positivity is also highly suggestive of *M tuberculosis* infection.7 Treatment includes infectious disease consultation and prolonged administration of systemic antibiotics.

Infectious mononucleosis is associated with primary EBV infection and involves pharyngitis, fever, and acute cervical lymphadenopathy, often posterior cervical in location. Fatigue is a commonly associated symptom, but patients may also demonstrate a skin rash, palatal petechiae, palpebral edema, or splenomegaly. Diagnosis is confirmed with positive results of a heterophile antibody test (Monospot). In children younger than 12 years, elevated antibodies against the viral capsid antigen is diagnostic, because approximately 25% to 50% of children in this age group demonstrate a false-negative Monospot test.21,22 Treatment is supportive care.

Toxoplasmosis is a parasitic infection caused by *Toxoplasma gondii*, a protozoan that may infect humans because of its possible presence in cat feces or raw pork meat. This disease may present in a variety of ways depending on the immune status of the person infected. Except for those with congenital toxoplasmosis, which is not discussed in this article, most immunocompetent children who are exposed to *T gondii* are asymptomatic. Cervical or occipital lymphadenopathy is the most typical clinical manifestation. The associated lymphadenopathy is usually discrete, nontender, and nonsuppurative, and resolves by 4 to 6 weeks after onset. Diagnosis may be performed using multiple direct or indirect methods, with indirect detection of serum antibodies to *T gondii* the most commonly used method in immunocompetent individuals.23
Cytomegalovirus infection causes an illness similar to that seen with EBV infection. Cervical lymphadenopathy is a prominent feature, with posterior cervical nodes being the most commonly enlarged, similar to EBV. Compared with EBV, cytomegalovirus causes more frequent hepatosplenomegaly, rash, and upper airway obstruction. Pharyngitis and sore throat are comparatively more common in EBV. Cytomegalovirus infection is diagnosed through serologic assay.7

HIV may present in a multitude of ways. One possible presentation is with chronic cervical lymphadenopathy. When the cause of chronic cervical lymphadenopathy is unknown or when HIV infection is suspected, serologic testing for the presence of HIV should be performed.9

**DIAGNOSTIC MODALITIES**

Thorough history and physical examination are key to identifying the correct diagnosis. However, when indicated, laboratory tests and imaging may be helpful in this process. Yaris and colleagues10 reported that 61.2% of diagnoses in their pediatric study population were obtained through history and physical examination and laboratory testing alone. The remaining 38.8% of diagnoses were obtained after biopsy.

Laboratory tests that a provider should consider (when clinically indicated) are complete blood cell count with differential, erythrocyte sedimentation rate (ESR), rapid strep test, and lactate dehydrogenase (LDH). Yaris and colleagues10 also reported that in their cohort of patients the only laboratory test result that was significantly associated with malignancy was for elevated levels of LDH. Other laboratory tests are available and should be performed when specific infectious causes are suspected. Serologic testing is available for *Bartonella*, EBV, cytomegalovirus, toxoplasmosis, and HIV. In addition, if tuberculosis is suspected, intradermal skin testing is performed using PPD antigen.5,10,14

Most children presenting with cervical lymphadenopathy will not require imaging for accurate diagnosis. However, when the diagnosis is still unclear despite a thorough history and physical examination and other diagnostic workup, imaging may be helpful. In addition, if a concerning condition is suspected, imaging may provide further characterization of the mass or assist in surgical planning if indicated. In children, ultrasound is the recommended initial imaging modality for cervical lymphadenopathy. Ultrasound has multiple benefits in that it avoids radiation exposure, usually has no need for sedation or general anesthesia, is rapidly obtained and interpreted, and is usually less costly than some other forms of neck imaging (eg, computerized tomography or magnetic resonance imaging [MRI]).3,5,12,14,24

High-resolution and color Doppler ultrasound can help differentiate between benign reactive nodes, infected or inflamed nodes, and those suspicious for malignancy.1 An oval shape with minimal hilar vascularity and echogenic fatty hilum characterizes benign or reactive lymph nodes. Infected or inflamed lymph nodes may have increased vascularity, central necrosis, and inflammation of adjacent soft tissues. An absent or eccentric hilum, aggregation of nodes into a mass, irregular borders, cystic necrosis, irregular capsular blood flow pattern, and displacement of hilar vascularity are all concerning findings on ultrasound that may indicate malignancy.1,12,25,26

Computerized tomography or MRI should be considered when further anatomic characterization of lymphadenopathy is required for diagnosis or surgical planning. Chest radiography should be considered in the setting of suspected malignancy. Yaris and colleagues10 reported a significant association between enlarged mediastinal lymph nodes and malignancy in their patient population.
FINE-NEEDLE ASPIRATION BIOPSY

Fine-needle aspiration biopsy (FNAB) may be helpful in the diagnosis of select patients with persistent cervical lymphadenopathy. Benign reactive lymphoid hyperplasia is the most common finding on FNAB, which is consistent with results from open biopsy. Anne and colleagues\textsuperscript{27} and Handa and colleagues\textsuperscript{28} supported FNAB as a minimally invasive and reliable diagnostic method with no complications in the pediatric study population. van de Schoot and colleagues\textsuperscript{29} showed FNAB results of 86% sensitivity and 96% specificity in 39 pediatric patients with lymphadenopathy. Most (61%) patients in their study required only FNAB for diagnosis, obviating the need for further surgical intervention.

Fine-needle aspiration biopsy has several limitations in the pediatric population. For high-yield specimens and accurate interpretation of results, an experienced pediatric cytopathologist is necessary and may not be available at all institutions. Sedation or general anesthesia is often required to perform FNAB in young children. The possibility exists for more diagnostic inaccuracy with FNAB when compared with open biopsy, with some studies reporting up to 20% of FNAB samples as nondiagnostic.\textsuperscript{9} In the setting of negative FNAB and suspected malignancy, open biopsy should be considered for definitive diagnosis, and clinical judgment should be used in these cases.\textsuperscript{5,27}

INDICATIONS FOR OPEN BIOPSY

Despite the potential benefits of FNAB, open biopsy remains the gold standard for histologic diagnosis of cervical lymphadenopathy in the pediatric population.\textsuperscript{1} When open biopsy is indicated, the largest node should be completely excised, with the capsule intact to preserve tissue architecture.\textsuperscript{9,16}

In general, treatment depends on the underlying cause, allowing for directed therapy. Most cervical lymphadenopathy in the pediatric population is benign and self-limited. Therefore, clinical observation is appropriate in most of these patients. Some cases require biopsy for definitive diagnosis. Currently, no formal published guidelines indicate when pediatric cervical lymphadenopathy should be biopsied. However, multiple parameters can be used to help guide the provider in this decision-making process (Box 3).\textsuperscript{5,6,14} In the general population seen by primary care providers, biopsy is required in a small minority of cases (3.2%), of which only 1.1% had malignancy in some reports.\textsuperscript{30} In other reports, biopsy results of

<table>
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<th>Box 3</th>
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<tr>
<td>Parameters indicating possible need for biopsy of cervical lymphadenopathy</td>
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<tr>
<td>• Suspicion of malignancy.</td>
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<tr>
<td>• Lymphadenopathy of unknown cause that persists for greater than 4 to 6 weeks, despite a trial of antibiotics.</td>
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<tr>
<td>• Lymphadenopathy increasing in size over 2 weeks.</td>
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<td>• Lymphadenopathy greater than 2.0 cm.</td>
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<tr>
<td>• Supraclavicular lymphadenopathy.</td>
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<tr>
<td>• Abnormal chest radiograph.</td>
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<tr>
<td>• Systemic signs/symptoms suggesting malignancy: weight loss, hepatosplenomegaly, fever, and arthralgia.</td>
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Data from Refs.\textsuperscript{5,6,14}
approximately 15% of cervical lymph nodes in children show malignancy.\textsuperscript{10,31} These numbers increase significantly in the patient population seen in referral centers and pediatric oncology-hematology departments, where 28% to 38% of cases require biopsy, of which 23% to 30% are malignant.\textsuperscript{10,32,33} When lymphadenopathy is persistent for greater than 4 to 6 weeks or increases in size despite appropriate treatment, biopsy should be considered. Biopsy should also be obtained if malignancy is suspected.\textsuperscript{10,16} A multidisciplinary approach before a biopsy is performed may be beneficial in patients whose diagnosis is unclear, because some studies have shown decreased need for biopsy performance due to better diagnosis with multispecialty physician assessment.\textsuperscript{34}

SUMMARY

Cervical lymphadenopathy is common in the pediatric population. A thorough history and physical examination are critical for accurately diagnosing this condition. The pediatric population has an increased incidence of infectious processes as the cause of lymphadenopathy compared with adults, but neoplasms should also be considered. Judicious use of imaging studies, namely ultrasound, can provide valuable information for accurate diagnosis. Surgical intervention is rarely indicated for evaluation, but when biopsy is necessary, FNAB may provide accurate diagnostic material, possibly obviating the need for open biopsy in some patients. If malignancy is suspected, open biopsy should be performed.

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REFERENCES
