Diagnostic Approach to Lymphadenopathy in children

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Abstract

Although the finding of lymphadenopathy sometimes raises fears about serious illness, in patients seen in primary care settings, it is usually a result of benign infectious causes.

In most cases, a careful history and physical examination will identify a readily diagnosable cause of the lymphadenopathy, such as upper respiratory tract infection, pharyngitis, periodontal disease, conjunctivitis, lymphadenitis, tinea, insect bites, recent immunization, cat-scratch disease or dermatitis, and no further assessment is necessary.

Localized adenopathy should prompt a search for an adjacent precipitating lesion and an examination of other nodal areas to rule out generalized lymphadenopathy.

In general, lymph nodes greater than 1 cm in diameter are considered to be abnormal.

Supraclavicular nodes are the most worrisome for malignancy.

A three- to four-week period of observation is prudent in patients with localized nodes and a benign clinical picture.

Generalized adenopathy should always prompt further clinical investigation.

When a node biopsy is indicated, excisional biopsy of the most abnormal node will best enable the pathologist to determine a diagnosis.

Definition: Lymphadenopathy is defined as an abnormality in the size and/or character of a lymph node. In general nodes greater than 1 cm in diameter are considered to be enlarged (for inguinal nodes, >15 mm; for epitrochlear nodes, >5 mm) [1-3].

Enlarged lymph nodes are one of the most common complaints of childhood on admission to physician and pediatrician. It is also a common finding on routine examination of children who are brought to the doctor for other reasons [1-3].

There are various classifications of lymphadenopathy, but a simple and clinically useful system is to classify lymphadenopathy as “generalized” if lymph nodes are enlarged in two or more noncontiguous areas or “localized” if only one area is involved. Distinguishing between localized and generalized lymphadenopathy is important in formulating a differential diagnosis [4-5].

Any palpable supraclavicular, popliteal, or iliac lymph node is considered abnormal.

Lymph nodes drain contiguous areas: [2]
- Cervical nodes drain head and neck area.
- Submental and submandibular drain Buccal mucosa, cheek and nose
- Axillary nodes drain arm, thorax, and breast.
- Epitrochlear nodes drain forearm and hand.
- Inguinal nodes drain leg and groin.
- Supraclavicular nodes drain Right-sided thorax and Left-sided abdomen

A systematic approach to the evaluation and management of lymphadenopathy [6]

Our approach to the evaluation of peripheral lymphadenopathy in children occurs in stages over approximately four weeks [6].

●"Early" excisional biopsy refers to biopsy when the child is initially seen at a referral center. Early excisional biopsy is indicated for children with worrisome features (see worrisome features below)

It also may be indicated for suspected nontuberculous mycobacterial (NTM) infection (eg, young child with unilateral, non-tender, cervicofacial lymphadenitis with violaceous, thin overlying skin)

Worrisome features — In children with peripheral lymphadenopathy, worrisome clinical features include [7-8]

- Systemic symptoms (fever >1 week, night sweats, weight loss [>10 percent of body weight])
- Supraclavicular (lower cervical) nodes
- Generalized lymphadenopathy
- Fixed, non-tender nodes in the absence of other symptoms
- Lymph nodes >2 cm (0.8 inches) in diameter that have increased in size from baseline or have not responded to two weeks of antibiotic therapy
- Abnormal chest radiograph, particularly mediastinal mass or hilar adenopathy
- Abnormal CBC and differential (e.g. lymphoblasts, cytopenias in more than one cell line)
- Lack of infectious symptoms in the ear, nose, and throat regions
- Persistently elevated ESR/CRP or rising ESR/CRP despite antibiotic therapy

For those without worrisome features:

• The first stage is to evaluate and treat conditions that appear obvious based upon the history and examination (e.g. throat culture for group A streptococcal pharyngitis, heterophile antibodies or specific titers for Epstein-Barr virus or cytomegalovirus mononucleosis, serology for Bartonella henselae for cat scratch disease, medical or surgical therapy for NTM).

• If the cause remains uncertain after the initial evaluation, the second stage is to evaluate and/or treat common causes of generalized or localized lymphadenopathy (according to site) or to provide a two-week trial of antibiotic therapy or a two- to three-week period of observation.

• If the cause remains uncertain after the second stage evaluation and treatment and the adenopathy has not decreased in size, less common causes and causes that require specific treatment (e.g. tuberculosis) are evaluated.

• If after four weeks of observation and/or empiric therapy, the diagnosis remains uncertain and the lymph node has not regressed in size, biopsy may be warranted.

The evaluation may include blood tests (complete blood count [CBC], erythrocyte sedimentation rate/C-reactive protein [ESR/CRP], serology), cultures, imaging, a trial of antimicrobial therapy, and/or lymph node biopsy. The sequence varies depending upon associated symptoms, whether the lymphadenopathy is generalized or localized, and the site of localized lymphadenopathy.

This stepwise approach may avoid unnecessary biopsies. In many patients, the adenopathy will resolve or the cause will become obvious during the evaluation period, with or without therapy [7]. Even with "can't miss" diagnoses, such as leukemia, lymphoma, or tuberculosis, the four-week period of evaluation is unlikely to affect treatment success.

Several studies have correlated clinical features and biopsy results to predict the risk of malignancy or other treatable etiology in children with peripheral lymphadenopathy [9-10].

In a prospective study of biopsy results in 45 children <18 years (mean age 7.8 years) with non-fluctuant peripheral lymphadenopathy, the risk of malignancy increased with increasing age, size of node, number of sites of adenopathy, supraclavicular nodes, fixed nodes, and abnormal radiographs [8]. Factors that were not helpful for discriminating between benign and malignant causes were fever; cough; splenomegaly; skin erythema, discoloration, or induration; tender nodes; or leukocytosis. In a similar study in 123 patients (9 to 25 years of age), the risk of malignancy or granulomatous disease was increased in patients with lymph node size >2 cm (0.8 inches); abnormal chest radiograph; lack of ear, nose, and throat symptoms; and presence of systemic symptoms (e.g. night sweats, weight loss, hemoglobin ≤10 g/dL) [11].

Diagnosis

A thorough history and examination is essential when assessing a child with lymphadenopathy .Because infections are the most common cause of acute or chronic lymphadenopathy, it is important to focus on the presence of, or recent exposure to infection [12].

History [2-13]

Age —some infections have a predilection for specific age groups

• **Characteristics of the lymphadenopathy:**
– Site?
– Duration (days or weeks)?
– Overlying skin changes, for example, discolouration, induration?
– Painful or fluctuant?
– Other nodes involved; generalised or local?

• **Recent infections:**
– History of recent URTI preceding cervical lymphadenopathy ?
– Gum or tooth infection; mouth ulcers?
– Respiratory symptoms: cough, shortness of breath, orthopnoea?
– Skin infections: cellulitis or impetigo?
– Sexually transmitted
• **Constitutional or associated symptoms** (e.g., Fatigue? fever, weight loss, or night sweats, Bleeding or easy bruising)
• **Exposures:** Cat exposure (cat scratch disease), uncooked meat (Toxoplasmosis), tick bite (Lyme disease)
• **Medications** (e.g. Phenytoin or Isoniazid)
• **Travel** to or residence in an endemic area should raise suspicion for Tuberculosis, Lyme disease
• **Signs and symptoms**
– Localized lymphadenopathy: Involves enlarged nodes in any 1 region
– Generalized lymphadenopathy: Involves ≥2 noncontiguous regions secondary to a systemic process, such as EBV infection.
– Supraclavicular nodes seen with malignancy: Right-sided supraclavicular node is associated with mediastinal malignancy; left-sided node suggests abdominal malignancy.

Physical Exam (14)

Complete physical exam is imperative to look for signs of systemic disease such as skin, oropharyngeal, or ocular findings;
hepatosplenomegaly.
The child's weight should also be checked to be sure there has been no weight loss.
If localized lymphadenopathy is suspected, examine the area that the lymph node drains for pathology.
For example, an arm papule may be associated with axillary lymphadenopathy in cat scratch disease.
Cervical, axillary, and inguinal nodes, as well as liver and spleen, must be palpated to help determine if signs of systemic disease or infection are present.

Characterize nodes. Be sure to note:
– Location: Be as exact as possible (see above).
– Size: Specify dimensions.
– Consistency: Soft, firm, solid, cystic, fluctuant,rubbery. Firm, rubbery nodes may be associated with lymphomas, while soft nodes are generally palpated with reactive lymphadenopathy.
– Fixation: Normally freely mobile; infection or malignancy may cause adherence to surrounding tissues or nodes.
– Tenderness: Suggests inflammation

Careful assessment of the size of the enlarged nodes is important as bigger nodes are associated with higher likelihood of more serious pathology, and accurate measurement allows for meaningful comparison over time. In a study of 123 children and young adults undergoing a biopsy for peripheral lymphadenopathy, lymph nodes greater than 2 cm in diameter increased the chance of a diagnosis of either significant infection, sarcoidosis or malignancy [11].

Conversely, a palpable lymph node measuring less than 1 cm is probably normal (17).

The site of the enlarged nodes is also significant. Lymph nodes palpated in the supraclavicular region often reflect mediastinal disease and should prompt the request of a chest X-ray (CXR). In a study of 75 children undergoing a biopsy for lymphadenopathy, all patients with supraclavicular lymphadenopathy were found to have significant pathology [15].

Diagnostic evaluation (14, 15)

Consider the following tests if ≥1 nodes are persistently enlarged, have increased in size, have changed in consistency or mobility, or if systemic symptoms are present:

CBC: Consider with generalized lymphadenopathy, or if malignancy is in differential diagnosis.
Purified protein derivative (PPD) testing: Consider with persistently enlarged node (2– 4 weeks) or travel to areas where tuberculosis is endemic.
ESR or CRP: Increased with infection or inflammation
Throat culture: If concern for group A β–hemolytic streptococcal (GAS) pharyngitis
EBV/Cytomegalovirus (CMV) titers: Consider with persistent generalized adenopathy.
Bartonella henselae titers: Consider with persistently enlarged unilateral node and/or history of cat exposure.
Toxoplasma gondii titers: Consider with generalized lymphadenopathy and exposure to undercooked or raw meat.
HIV testing: Consider with persistent generalized lymphadenopathy and failure to thrive.
Lactate dehydrogenase (LDH), uric acid, and liver enzymes: Consider if history and physical exam raise concern for malignancy.
Rapid plasma reagin (RPR): Consider with rash and generalized lymphadenopathy or other signs of syphilis.
Antinuclear antibody (ANA): If persistent generalized lymphadenopathy and other signs of systemic disease, to rule out systemic lupus erythematosus (SLE)

Imaging

Chest radiograph: Helpful with supraclavicular nodes, systemic symptoms, or if positive PPD
US: May help differentiate cystic from solid masses
CT: May help delineate anatomy or extent of the lesion

Differential Diagnosis of Lymphadenopathy in the Pediatric Patient [16]
Infections
Bacterial Localized: Staphylococcus aureus, group A Streptococcus (e.g. pharyngitis), anaerobes (periodontal disease), cat-scratch disease, tularemia, bubonic plague, diphtheria, chancroid Generalized: Brucellosis, leptospirosis, lymphogranuloma venereum, typhoid fever **Viral** Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus, hepatitis B, mumps, measles, rubella, dengue fever **Mycobacterial** Tuberculosis, atypical mycobacteria **Fungal** Coccidiomycosis, cryptococcosis, histoplasmosis **Protozoal** Toxoplasmosis, leishmaniasis **Spirochetal** Lyme disease, syphilis
Malignancy
Leukemia, lymphoma, metastasis from solid tumor
Immunologic
chronic granulomatous disease, dermatomyositis, drug reaction, rheumatoid arthritis, , serum sickness, systemic lupus erythematosus, autoimmune lymphoproliferative disease, Langerhans cell histiocytosis
Endocrine
Addison disease, hypothyroidism
Miscellaneous
Amyloidosis, Castleman disease, Churg-Strauss syndrome, inflammatory pseudotumor, Kawasaki disease, Kikuchi disease,

Diagnostic procedures/Other

Biopsy should be considered if:
– Nodes are persistently enlarged, especially if accompanied by signs of systemic disease such as hepatosplenomegaly, weight loss, and exanthema.
– Nodes are fixed to underlying skin.
– Ulceration is present.
– Node is supraclavicular, nontender, or increasing in size or firmness.
Fine-needle aspiration: Cost-effective, but sometimes nondiagnostic; may result in fistulous tract
Open biopsy: Often diagnostic, but requires general anesthesia

Treatment (18)

Acute lymphadenitis should be treated with antibiotics directed against Streptococcus and Staphylococcus:

Cephalexin 50 mg/kg/d in 4 divided doses OR
Cefadroxil 30 mg/kg/d in 2 divided doses OR
Dicloxacillin 50–100 mg/kg/d in 4 divided doses.
Max 4 g/d.
Consider using clindamycin 20–30 mg/kg/d in 4 divided doses OR trimethoprim-sulfamethoxazole (TMP–SMX) 8–10 mg/kg/d PO/IV in 2 divided doses in areas with a high prevalence of methicillin resistant Staphylococcus aureus (MRSA)
Penicillin-allergic patients: Erythromycin 50 mg/kg/d in 4 divided doses

First Line
Empiric treatment with antibiotics: 1st- or 2nd generation cephalosporin to cover group AS treptococcus and S. aureus if meticulous history and physical exam are not revealing.

Consider empiric treatment with clindamycin or trimethoprim sulfamethoxazole if there is a high incidence of MRSA in the community

Second Line
Consider broader antibiotic coverage for B. henselae and atypical mycobacterium: Azithromycin 10 mg/kg dose on day 1, followed by 5 mg/kg divided once for 4 more days.

Summary

Palpable lymph nodes are common in children and may be a normal finding or a sign of serious disease. Because parents frequently are concerned about lymphadenopathy, the role of the primary care practitioner is to provide reassurance when appropriate and carry out a systematic evaluation when warranted. The history and physical examination frequently can elucidate the cause of the lymphadenopathy.

Infectious diseases are the most common underlying cause, and antibiotics frequently are indicated if there is lymphadenitis. Generalized lymphadenopathy is less common than localized lymphadenopathy and occurs in the setting of systemic disease. Worrisome features of lymphadenopathy that should lead to additional evaluation and possible biopsy include supraclavicular location; size greater than 2 cm in a cervical lymph node; a hard, firm, or matted consistency of an enlarged lymph node; lack of associated infectious symptoms; lack of improvement over a 4-week period; and accompanying constitutional symptoms. CBC, ESR, and chest radiographs are an inexpensive, useful screening test that can aid the clinician in determining whether a biopsy should be performed.

References

1. Nield LS, Kamat D. Lympadenopathy in children: when and how to evaluate. Clin Pediatr. 2004;43:25-33.
2. M. William Schwartz, .The 5-Minute Pediatric Consult Sixth Edition, Lymphadenopathy. 2012 ; 514 -515.
3. Leung AKC, Robson LM. Childhood cervical lymphadenopathy. J Pediatr Health Care. 2004;18:3-7)
4. Allhiser JN, McKnight TA, Shank JC. Lymphadenopathy in a family practice. J Fam Pract. 1981;12:27–32.
5. Williamson HA Jr. Lymphadenopathy in a family practice: a descriptive study of 249 cases. J Fam Pract. 1985;20:449–58.
6. Kenneth L McClain, Peripheral lymphadenopathy in children: Evaluation and diagnostic approach: Up to date. 2020.
7. Oguz A, Karadeniz C, Temel EA, et al. Evaluation of peripheral lymphadenopathy in children. Pediatr Hematol Oncol 2006; 23:549.
8. Ling RE, Capsomidis A, Patel SR. Urgent suspected cancer referrals for childhood lymphadenopathy. Arch Dis Child 2015; 100:1098.
9. Soldes OS, Younger JG, Hirschl RB. Predictors of malignancy in childhood peripheral lymphadenopathy. J Pediatr Surg 1999; 34:1447.
10. Niedzielska G, Kotowski M, Niedzielski A, et al. Cervical lymphadenopathy in children--incidence and diagnostic management. Int J Pediatr Otorhinolaryngol 2007; 71:51.
11.Slap GB, Brooks JS, Schwartz JS. When to perform biopsies of enlarged peripheral lymph nodes in young patients. JAMA 1984; 252:1321.
12. Nield LS, Kamat D. Lymphadenopathy in children: when and how to evaluate. Clin Pediatr 2004;43:25–33.)
13. Malley R. Lymphadenopathy. In: Textbook of Pediatric Emergency Medicine, 5th ed, Fleisher GR, Ludwig S, Henretig FM (Eds), Lippincott Williams and Wilkins, Philadelphia 2006. p.421.)
14. Friedmann AM. Evaluation and management of lymphadenopathy in children. Pediatr Rev. 2008;29(2):53–60
15. Lake AM, Oski FA. Peripheral lymphadenopathy in childhood. Ten-year experience with excisional biopsy. Am J Dis Child 1978;132:357–9.
16. Alison M. Friedmann, Evaluation and Management of Lymphadenopathy in Children Pediatrics in Review 2008;29;53
17. Gosche JR, Vick L. Acute, subacute, and chronic cervical lymphadenitis in children. Semin Pediatr Surg 2006;15:99–106].
18. Nield LS, Kamat D. Lymphadenopathy in children: When and how to evaluate. Clin Pediatr.2004;43:25–33