PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Approach to Lymphadenopathy.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Approach to Lymphadenopathy

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Objectives

1. Define lymphadenopathy
2. Illustrate common pediatric presentations of lymphadenopathy
3. Describe an approach to narrow the differential according to presenting signs and symptoms
4. Discuss initial investigations to narrow or confirm your diagnosis
5. Outline differential diagnoses for common causes of both generalized and localized lymphadenopathy in the pediatric patient

Introduction

Hi everyone, my name is Anna Whalen-Browne, and I am a medical student at the University of Alberta. This podcast has been developed in collaboration with Dr. Melanie Lewis who works as a pediatrician at the Stollery Children's Hospital here in Edmonton.

Ultimately, the goal of this podcast is to work through clinical presentations of lymphadenopathy in pediatric patients. Initially, we will describe an overall approach to evaluate lymphadenopathy in children, and then we will describe a system to narrow the differential according to presenting signs and symptoms. Next, we will discuss initial investigations to narrow or confirm the suspected diagnosis, and finally we will go over a broad differential diagnosis for both generalized and localized lymphadenopathy in a pediatric patient.

Attention to lymph nodes is important to almost all medical specialties in both adult and pediatric medicine. Not only can lymph node characteristics help us decipher possible underlying pathologies, but changes in these glands can also tip us off that there may be more worrisome sinister disease going on. On the other hand, it is important to note, particularly when assessing the pediatric population, that up to half of otherwise healthy children may have palpable lymph nodes on examination (2). Therefore, in this podcast, we will discuss what lymph node characteristics elicited on history and physical examination should make us more or less worried.

Let's begin our discussion with a case. You are a clerk working in a community pediatrics clinic, and as you head out for lunch your preceptor asks you to get started on patients after lunch as he will be a few minutes late. Conveniently, when you check the EMR, you see that both patients are in because of "enlarged lymph nodes". "Great!" you think to yourself, this should be simple! But little do you know…

What is your approach to this presentation? What questions will you ask on history and what signs will you look for on physical examination to try to determine what is going on?

Before we get started on developing an approach to evaluating these patients, let's begin by discussing the definition of lymphadenopathy. Medical literature defines lymphadenopathy as an abnormal number, size, or consistency of lymph nodes (1). With this definition encompassing a large variety of clinical presentations, it is necessary to have an approach to narrowing one's differential diagnosis. These are the clues that we must gather through history taking and physical examination.

History

A good way to open the encounter is to determine what brought the patient into the clinic today specifically. Was the lymphadenopathy just noticed? Were there recent changes in the quality of the nodes? Were there other changes in the child's health or new symptoms that are worrying the child or parent? These questions can offer you clues into the possible etiology of lymphadenopathy, and can also help you get an idea of the severity and acuity of the presentation.

Next, we want to learn more details about the patient and their presenting complaint. To this end, we must first gather information on the lymphadenopathy. Specifically, it is important to determine the number, location, onset, duration, quality, growth/evolution/fluctuations, pain or tenderness of the nodes as well as changes to the overlying skin. Secondly, it is equally important to gather a thorough history of the patient's health status otherwise. This includes demographics such as the patient's age, known medical conditions, and recent or concurrent illnesses including upper respiratory tract infections, infections of the gums, mouth, or teeth, respiratory symptoms such as cough and shortness of breath, skin infections, and sexually transmitted infections if the patient is sexually active. In order to get a full picture of what could be contributing to the lymphadenopathy, it is also important to do a comprehensive review of symptoms. Ask about fatigue, unintentional weight loss, night sweats, fever, bleeding or bruising, joint/bone pain or swelling, and rash. Finally, as with any clinical presentation, it is important to review all other aspects of the patient's history such as recent travel history, exposure to animals including pets, possible exposure to tuberculosis, recent immunizations, current or recent medications, and past medical, surgical, and family history including solid or hematologic malignancies.

Physical Examination

Next, it is crucial to perform a thorough physical examination of the child. Start with general appearance. Note whether the patient appears well or ill, and assess vital signs. Ensure to always also check growth parameters in pediatric patients including height, weight, and head circumference in infants. Examine for lymphadenopathy all areas with regional lymph nodes including the neck, axilla, epi-trochlear area, and groin. Record the location and number of regions, size, fixation, tenderness, and consistency of lymphadenopathy, as well as changes to overlying skin including swelling, erythema or induration. Examine the head and neck for scalp infection, conjunctivitis, dental caries, mouth ulcers, pharyngitis, tonsillitis, rhinitis, or other. Thoroughly examine the child's skin for rashes, infection, petechiae, purpura, or eccymoses. Finally, perform a cardiovascular exam, a pulmonary exam listening and percussing for areas of consolidation, an abdominal examination specifically looking for any palpable masses or hepatosplenomegaly, and a joint exam looking for any arthritis.

Classification Systems

Now that we have covered the overall skeleton of history taking and physical examination of a patient with lymphadenopathy, let's now discuss a system to narrow your differential according to presenting signs and symptoms. We will then apply this system to our two patients.

Let's begin with a deeper look into qualifiers specific to the lymph nodes. Through both history and physical examination, you first must work to determine whether the lymphadenopathy is localized, meaning confined to one region of the body, or generalized, meaning there are detectable lymph nodes in 2 or more regions of the body (3). With this information, it is possible to narrow your differential significantly, and further rank your patient's differential within one of these two broad categories.

Next, it is important to establish a timeline of the lymphadenopathy in order to further classify the presentation as acute, subacute, or chronic. We define acute lymphadenopathy as a presentation fewer that two weeks in duration, while subacute describes presentations between 2-6 weeks in duration, and chronic lymphadenopathy being greater than 6 weeks in duration (2). This division, again, can significantly help narrow your differential diagnosis for a specific presentation of lymphadenopathy, and can help in the interpretation of the rest of the findings on history or physical examination.

The final major classifier when dealing with a presentation of lymphadenopathy is the presence of associated signs and symptoms, specifically fever and splenomegaly. Based on the categories above which classify the lymphadenopathy as either localized or generalized, acute or subacute or chronic, and with the absence or presence of either fever or splenomegaly, it is possible to follow a particular path in terms of further questions and investigations in order to ultimately lead us to a specific diagnosis or etiology.

However, although the three aforementioned classification systems can be of significant help in guiding us down a particular path towards a cause of this presentation, it is important to remember that many of the additional clues that can help in deciphering each clinical presentation of lymphadenopathy must still be gained by a thorough history and physical examination.

Now that we have discussed an overall approach to assessing lymphadenopathy in children and described a system to narrow the differential according to presenting signs and symptoms, we will now discuss initial investigations to narrow or confirm the suspected diagnosis.

Investigations

Determining which investigations will be most high yield for pediatric patients presenting with lymphadenopathy can be challenging, and must be done with heavy reliance on one's clinical reasoning. Lymph node characteristics that may deter us from pursuing aggressive investigations include lymph nodes being few in number, localized, less than 1 cm in size, acute in onset, mobile, tender to palpation, and unassociated with changes to overlying skin, or associated with infectious symptoms such as rhinorrhea, otalgia, and cough. The Centor Criteria can help us determine whether patients presenting with sore throat and lymphadenopathy require further investigation for *Strep. pharyngitis* infection, or even empiric antibiotic treatment pending culture confirmation(4). If many low risk features of lymphadenopathy are present, the most important step is to ensure proper patient follow-up to evaluate for changes, progression, or persistence of lymphadenopathy as well as onset of new symptoms.

If high-risk features dominate in a presentation of pediatric lymphadenopathy, one should consider more aggressive investigations sooner in the course of disease. Such worrisome symptoms include lymphadenopathy that is generalized, subacute or chronic, fixed, non-tender to palpation, associated with changes in the overlying skin, or with certain additional symptoms such as fever, weight loss, night sweats, joint or bone pain, or splenomegaly.

Such investigations include a complete blood count with differential (CBC-diff), peripheral blood smear, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and liver function tests (LFTs). Depending on the clinical history and examination, it may also be appropriate to perform culture and sensitivity for bacterial causes such as *Streptococcal* pharyngitis, or serologic investigations for other infections such as Epstein-Barr virus (EBV) which causes infectious mononucleosis, and *Borrelia burgdorferi* which causes Lyme disease. Testing may also be warranted for *Mycobacterium* species, which can include either a tuberculin skin test or interferon blood test. Chest radiography may also be included to evaluate for mediastinal lymph nodes or pulmonary disease, a step that is particularly important in any child presenting with lymphadenopathy and respiratory symptoms.

Based on exposure history and specific signs and symptoms, testing for rare infectious causes of lymphadenopathy may also be warranted in certain cases. This could include investigations for *Bartonella henselae* which causes cat-scratch disease, toxoplasmosis, cytomegalovirus (CMV), brucellosis, syphilis, human immunodeficiency virus (HIV), tularemia, histoplasmosis, or coccidiomycosis.

Ultrasonography including Doppler may also be performed in cases of lymphadenopathy in which there is one specific worrisome node or group of nodes. This can be used to assess whether the palpable mass is of soft-tissue origin, an abscess that would require incision and drainage, or from inflammatory or malignant causes. Ultimately, an excision biopsy may be required to definitively rule out a neoplastic cause in a child positive for high-risk features on early investigations, or with otherwise inconclusive investigations but worrisome clinical features.

Suddenly the clock strikes 1pm and it's time to try out your new approach to lymphadenopathy on your two first patients of the afternoon. Let's give it a try.

Case 1

Your first patient is a 16-year-old male named Saman. He is presenting today with a three-week history of an enlarged lymph node in the left side of his lower neck. He is coming in today because he read on the Internet that it could be a sign of cancer. While he hasn't been sick recently, he does describe being increasingly fatigable over the past month, ever since starting his new part time job as a dishwasher on evenings and weekends. He has no medical conditions apart from exercise-induced asthma that is well controlled on Ventolin. He is not taking any other medications and his immunizations are up to date. He is allergic to cats, and dogs, and has not travelled recently. He isn't sure if he's had any fevers lately, but sometimes does sweat at night. He's lost about 8 pounds since the beginning of the school year, he thinks, but attributes this to his new position on the rugby team. He is not sexually active.

On physical exam, you notice that he is pale but appears otherwise well. His temperature today in clinic is 38.5 degrees Celsius but his vital are otherwise normal. You do not notice any jaundice or purpura but you do note some ecchymoses on the shins bilaterally. You don't appreciate any signs of infection on examination of the head and neck, either in the eyes, ears, or mouth. Respiratory and cardiovascular exams are unremarkable. You are able to appreciate a 2.5cm firm, non-mobile lymph node in the left supraclavicular area that is not painful to palpation. A thorough examination also reveals scattered smaller but similar lymph nodes in the epi-trochlear and inguinal areas. You are also able to palpate the spleen.

Feeling worried from what you read of these lymphadenopathy characteristics over lunchtime, you excuse yourself to find your preceptor to discuss your findings. You both agree that this patient's presentation has multiple worrisome features, and requires immediate investigation. Saman's lymphadenopathy is generalized in location, subacute in duration, and is associated with fever and splenomegaly. You order a STAT CBC with

differential, peripheral blood smear, ESR, CRP, and LFTs. You also order serology for EBV, and a chest X-ray to assess for hilar lymphadenopathy.

When the results return a few hours later, your fears are confirmed. The CBC-diff, inflammatory markers, and LFTs indicate systemic disease and the peripheral blood smear and CBC differential is positive for blasts, which is highly suggestive of hematologic malignancy. The chest X-ray shows mediastinal lymphadenopathy, and serology for EBV is negative. Although the pediatric oncology team is immediately involved at this point, you later learn that an excision biopsy of the cervical lymph node allowed histological confirmation of Non-Hodgkin Lymphoma, and that treatment was immediately commenced.

Case 2

All the while, while waiting for Saman's initial bloodwork to come back, you saw your other patient who was presenting with lymphadenopathy, a 5-year-old female named Heidi. She is presenting today with what her fathers describe as an enlarged lymph node in the left neck that was noticed two days ago. Her fathers are bringing her in today as overnight she developed a fever, and has been complaining of a sore throat. Her father denies the presence of a cough, but does mention that she has been more irritable over the past few days and has been preferring soft foods such as yogurt and oatmeal. She is previously healthy, and is not on any medications apart from children's acetaminophen when she woke up this morning. She does not have any known allergies and her immunizations are up to date. She has not travelled recently. Her fathers recorded her temperature overnight as an axillary temperature of 39.1 degrees Celsius, but she has not had any night sweats otherwise or recent weight loss.

Heidi's temperature today in clinic is 38.4 degrees Celsius but her vitals are otherwise within normal limits. She is tracking well on her growth curve. She appears well today in clinic, and you do not notice any jaundice, purpura, petechiae, or ecchymoses. Examination of the oropharynx reveals bilaterally erythematous tonsils, but there is no visible exudate. Tympanic membranes are unremarkable. There is a single 1cm palpable lymph node in the left anterior cervical chain that is rubbery, mobile, and tender to palpation. The respiratory, cardiovascular, and gastrointestinal examinations are unremarkable, and a thorough examination for lymphadenopathy does not reveal any further palpable lymph nodes. There is no splenomegaly.

Based on the history and physical examination gathered, you feel that this clinical picture fits one of infectious pharyngitis causing acute lymphadenitis. You are reassured by the fact that the lymphadenopathy is localized, acute in onset, and associated with infectious symptoms of pharyngitis. Remembering the Centor Criteria to assess the probability of *Streptococcal* pharyngitis, you calculate her risk as 51-53%, and follow the recommendation to perform a rapid strep antigen test or culture. The rapid antigen test comes back positive, and after discussion with your preceptor, you decide to treat with penicillin and arrange for proper follow up with Heidi and her dads.

Differential Diagnosis

Now that we have worked through two distinctive patient cases using our new approach to lymphadenopathy, let's discuss differential diagnoses for both generalized and localized lymphadenopathy in the pediatric patient.

Let's review the defining features of these two categories. Remember that generalized lymphadenopathy requires the presence of palpable lymph nodes in more than one region of the body, as was uncovered through physical examination of our first patient Saman. These regions may include the neck, axilla, epi-trochlear area, groin, or other area with regionalized nodes.

Let's now run through a differential diagnosis of generalized lymphadenopathy in children. Infectious etiologies comprise a number of viruses, fungi, bacteria, and parasites. Common viruses include Epstein-Barr virus and cytomegalovirus, both of which are often accompanied by splenomegaly and fever, herpes simplex virus, varicella zoster virus, Rubeola, and Rubella, all of which also have recognizable dermatologic signs, as well as Adenovirus, Hepatitis B virus, and human immunodeficiency virus. Fungal causes include coccidiomycosis, blastomycosis, and histoplasmosis, all of which would most likely have signs and symptoms of pneumonia as well as a persuasive travel history. Bacterial causes include Group A streptococcal disease which may also be characterized by a rash followed by desquamation, as well as Brucellosis, Tularemia, Leptospirosis, Syphilis, and Lyme disease, all of which often have fever, myalgias or headaches, as well as specific exposure histories. Finally, parasitic causes of generalized lymphadenopathy in pediatric patients include toxoplasmosis which may be otherwise asymptomatic, Leishmaniansis, and malaria, all of which may have pertinent exposure histories.

There are also many non-infectious causes of generalized lymphadenopathy in children, including neoplastic, immunologic, metabolic, iatrogenic, and other causes. Neoplastic causes can be either primary such as Hodgkin or Non-Hodgkin lymphoma, as was the diagnosis in our first case, or metastatic such as acute lymphocytic or myelogenous leukemia, neuroblastoma, or rhabdomyosarcoma. As you may expect, many of these neoplastic causes may also present with generalized systemic symptoms including fever and splenomegaly. Immunologic causes include vasculitis syndromes, serum sickness, autoimmune hemolytic anemia, and chronic granulomatous disease (5). Less common metabolic etiologies include Gaucher disease and Niemann-Pick disease. Common medications that can cause generalized lymphadenopathy include phenytoin, phenobarbital, carbamazepine, isoniazid, aspirin, barbituates, penicillin, tetracycline, iodides, sulfonamides, allopurinol, and phenylbutazone. Finally, there are a number of other conditions that don't fit into the categories above, including sarcoidosis, hemophagocytic lymphohistiocytosis, Castleman disease, Langerhans cell histiocytosis, Kikychi-Fujimoto disease, Rosai-Dorfman disease, hyperthyroidism, papular acrodermatitis, and progressive transformation of germinal centers (5).

Let's now works through a differential diagnosis of localized lymphadenopathy in pediatric patients. Remember that localized implies the presence of palpable nodes in one single region of the body, as was the case for Heidi, our second patient. Common lymph node groups affected included occipital, auricular, submental, submaxillary, cervical, supraclavicular, axillary, epi-trochlear, inguinal, and popliteal nodes. Naturally, we can divide our differential diagnosis based on the common causes of localized lymphadenopathy in each of these regions. Occipital lymphadenopathy is most commonly caused by scalp infections, insect bites, seborrhea, as well as roseola, and less commonly rubella and acute lymphoblastic leukemia. Posterior auricular lymphadenopathy can be caused by rubella and roseola, while anterior auricular lymphadenopathy causes include ocular infection, cat scratch disease, tularemia and listeriosis. Lymphadenopathy localized to the submental and submaxillary areas can be due to infection of the tongue, gums, buccal mucosa, or dental infections. Cervical lymphadenopathy can be caused by infections of the upper respiratory tract, pharynx, oral cavity, bacterial adenitis, tuberculosis, Epstein-Barr virus, cytomegalovirus, cat scratch disease, non-tuberculous mycobacterium, toxoplasmosis, and other more rare diseases. Lymphadenopathy localized to the supraclavicular nodes is most often of neoplastic origin, whether it be primary or metastatic. Common causes of axillary lymphadenopathy in children include cat-scratch disease, and infection or laceration to the skin of the arms. Epi-trochlear lymph nodes may be involved in patients with viral diseases, sarcoidosis, or hand infections. Inguinal lymphadenopathy is commonly caused by genital herpes, syphilis, gonococcal infection, or lymphoma. Finally, popliteal lymphadenopathy is most often caused by local infection (6).

Although the differential diagnoses outlined include many of the common causes of generalized and localized lymphadenopathy in children, these lists are not all-inclusive and it is important to consider additional causes, based on the history gathered and physical examination performed.

Take Home Points

As we conclude this podcast, I would like to mention a few take-home points about the approach to lymphadenopathy:

1. Palpable lymph nodes are common and do not always indicate pathology.
2. Features on history and physical examination that make us more worried about sinister disease include lymph nodes that are:
    - Generalized
    - Chronic (or subacute)
    - Associated with systemic signs and symptoms such as fever, splenomegaly, night sweats, weight loss, abnormal bleeding or bruising, joint or bone pain, and rash
3. Always gather a thorough history (in addition to history specific to the lymphadenopathy) including past medical history, recent or current illnesses, medications, allergies, immunizations, family history, travel history, sick contacts, and social history.

4. Always perform a thorough physical examination (in addition to physical examination for lymphadenopathy) including examination for signs of infection, rashes or changes to the skin, arthritis or bone pain, and hepatosplenomegaly.
5. Investigations should be tailored based on findings on history and physical examination, and may include but are not limited to:
    - CBC with differential
    - Peripheral blood smear
    - Inflammatory markers (ESR, CRP)
    - Liver function tests
    - Bacterial rapid antigen test or culture and sensitivity
    - Serology (may include EBV, *Borrelia burgdorferi*, and other more rare causes of infectious lymphadenopathy)
    - Tuberculin skin test or interferon blood test for *Mycobacterium* species
    - Chest radiography
    - Ultrasonography (with or without Doppler)
    - Biopsy
6. The differential diagnoses for generalized and localized lymphadenopathy in children are extensive, and various potential causes must be considered and ruled in or out through history, physical examination, and proper investigations.
7. Treatment of lymphadenopathy is not discussed in this podcast, but should be determined based on the cause.

Thank you for listening!

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