J Mol Pathophysiol 2013; 2:5-10 *ISSN:2146-832X*

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Journal of Molecular Pathophysiology

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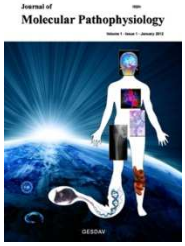

Mini Review

Paediatric Lymphadenopathy – A clinicopathological review

Purushotham Krishnappa[1], Sowmya Ramakrishnappa[2], John Paul Evangel Judson[3]

[1]Department of Pathology, International Medical University, Kuala Lumpur, Malaysia.
[2]Department of Anatomy, Malaysian Allied Health Sciences Academy, Kuala Lumpur, Malaysia.
[3]Department of Anatomy, International Medical University, Kuala Lumpur, Malaysia.

Received: January 30, 2013

Accepted: February 25, 2013

Published Online:

DOI: 10.5455/jmp.20130225103511

Corresponding Author:
Dr Purushotham Krishnappa,
International medical university, malaysia
purushk78@gmail.com

Keywords: Lymph nodes, Malignancy, Infections, Investigations.

Abstract
Lymph node enlargement is one among the common physical findings seen in the clinics. It can be a normal age related physiological change, may also hint chronic infections and serious conditions like malignancy. Although the underlying etiology often is simple self-limited infection, more serious underlying etiologies must be recognized quickly and treated appropriately. Serious infections and malignancies are important considerations, which should not be missed. Therefore, an understanding of the differential diagnosis is critical in directing an appropriate and timely evaluation. An organized step-by-step approach is essential to avoid an inappropriately rapid or over aggressive attempt at diagnosis or missing a serious disease process. The differential diagnosis of lymphadenopathy is broad. A thorough medical history and meticulous clinical examination is important in narrowing this differential.

BACKGROUND

The lymphatic system comprises of ducts and nodes spread throughout the body. They circulate the lymph back into the veins [1]. Lymph nodes are nodular aggregates of lymphoid tissues located along lymphatic channels throughout the body [2]. They are major sites where foreign substances and infectious agents interact with the cells of the immune system. The predominant cells in lymph nodes are lymphocytes, which produce immune responses to the antigens and macrophages which digest the debris and act as the "scavenger" cells of the body [3]. There are over 500 lymph nodes gathered in a variety of groupings throughout the body [4]. These nodes represent an integral part of both the immunologic and reticuloendothelial systems [2, 4]. Lymph nodes are identified by their area of drainage (Fig 1).

The lymph nodes become swollen/enlarged and very often hint at a wide variety of underlying diseases including infections, malignancies, autoimmune disorders and miscellaneous conditions. It is of highest importance to efficiently differentiate the patients with lymphadenopathy and serious illness from the self-limited disease. The history and physical examination are particularly important in determining the differential diagnosis and ultimately the timing, workup and treatment of lymphadenopathy.

Definition

Lymphadenopathy is enlargement of the lymph nodes beyond the normal state for that particular region of the body and age of the patient. Practically this is any node >1.0 cm in greatest diameter, but certain nodes should be considered enlarged at different sizes (i.e. epitrochlear nodes > 0.5 cm, inguinal nodes > 1.5 cm, submandibular nodes > 1.5 cm) [5-7]. Lymphadenopathy can be localized or generalized.

Etiology

Generalized lymphadenopathy

Generalized lymphadenopathy is defined as enlargement of >2 non-contiguous lymph node regions. It is often secondary to the generalized infection and associated with systemic diseases [2, 8]. The etiology of generalized lymphadenopathy varies with the age of the patient as indicated in the Table 1 below.

Etiology of regional lymphadenopathy

Regional lymphadenopathy is defined as the enlargement of lymph nodes within contiguous anatomic regions [9]. Figure 2 and 3 shows patients of cervical and axillary lymphadenopathy respectively. Regional lymphadenopathy is often secondary to infection within the involved node and/or its drainage area. Viral and bacterial infections are the most common causes of adenopathy, especially in association with common viral URIs and bacterial pharyngitis. Localized lymphadenitis is most frequently attributed to staphylococci and beta-hemolytic streptococci infection [10]. Firm, fixed nodes should raise the question of malignancy irrespective of the presence or absence of systemic symptoms and signs [11].

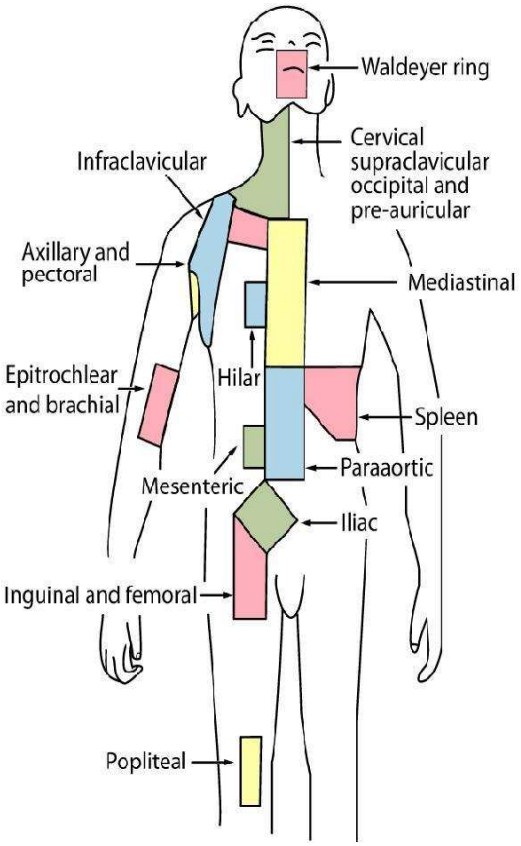

Fig 1. Lymphnodes by region

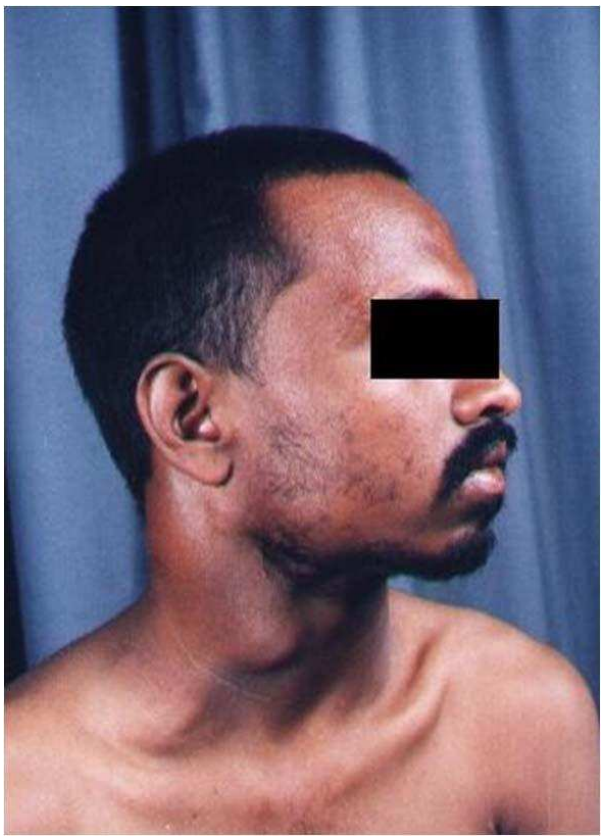

Fig 2. Patient with cervical nodes

Fig 3. Patient with Axillary Nodes

Table 1. Etiology of generalized lymphadenopathy in significance to age

	Infant	Child	Adolescent	Adult
Common causes	Syphilis	Viral infections	Viral infections	Viral infections
	Toxoplasmosis	EBV	EBV	EBV
	CMV	CMV	CMV	CMV
	HIV	HIV	HIV	HIV
		Toxoplasmosis	Toxoplasmosis	Tuberculosis
		Bacterial infections	Syphilis	Bacterial infections
Rare causes	Chagas disease	Serum sickness	Serum sickness	Sarcoidosis
	Congenital tuberculosis	SLE, JRA	SLE, JRA	Leukemia/lymphoma
	Reticuloendotheliosis	Leukemia/lymphoma	Leukemia/lymphoma	Metastasis
	Lymphoproliferative disease	Tuberculosis	Tuberculosis	Amyloidosis
	Metabolic storage disease	Measles	Histoplasmosis	Rheumatoid arthritis
	Histiocytic disorders	Sarcoidosis	Sarcoidosis	Dermatomyosistis
		Fungal infection	Fungal infection	
		Langerhan cell histiocytosis	Drug reactions	
		Drug reactions	Castleman disease	

Table 2. Etiology of regional lymphadenopathy according to the site of node

Cervical
- Oropharyngeal infections
- Scalp infections
- Mycobacterial lymphadenitis
- Viral infection
- Cat scratch disease
- Toxoplasmosis
- Kawasaki disease
- Thyroid disease
- Kikuchi disease
- Sinus histiocytosis
- Autoimmune lymphoproliferative disease

Supra clavicular
- Infection or Malignancy in the mediastinum
- Metastatic malignancy from the abdomen
- Lymphoma
- Tuberculosis

Anterior auricular
- Conjunctivitis
- Other eye infection
- Oculoplandular tularemia
- Facial cellulitis

Axillary
- Cat scratch disease
- Arm or chest wall infection
- Malignancy of chest wall
- Leukemia/lymphoma
- Brucellosis

Inguinal
- Urinary tract infection
- Venereal disease
- Other perineal infections
- Hilar tuberculosis
- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Leukemia/lymphoma
- Hodgkin's disease
- Metastatic malignancy
- Sarcoidosis
- Castleman disease

Posterior auricular
- Otitis media
- Viral infection

Para-aortic
- Aortitis
- Lower Gastro intestinal tract cancers
- Testicular cancers
- Hodgkin's disease

Mediastinal
- Sarcoidosis
- Tuberculosis
- Lymphoma
- Silicosis
- Malignancies (primary/secondary)

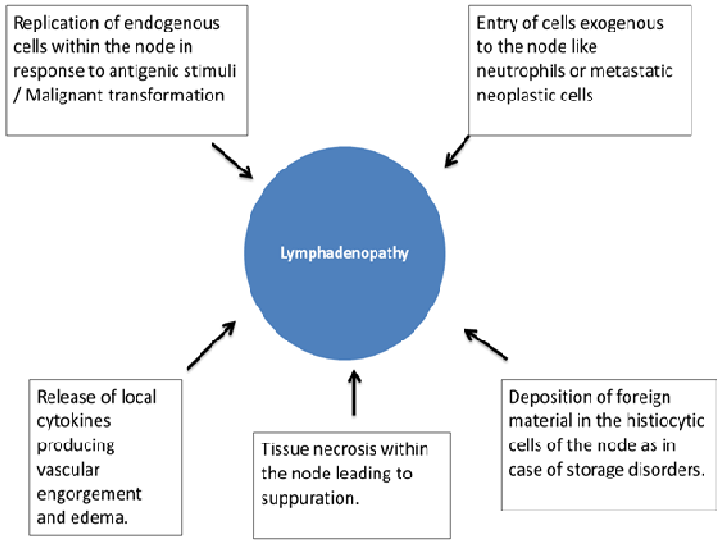

Fig 4. Pathogenesis/Mechanism of lymph node enlargement. Pathogenic organisms reach lymph nodes directly by lymphatic flow from the inoculation site or by lymphatic spread from the inoculation site or by lymphatic spread from adjacent nodes. If initial involvement of regional nodes does not contain the infection adequately the organisms can reach non-contiguous nodes by hematogenous spread [12].

Approach to a case of lymphadenopathy requires the four important steps

1. History
2. Physical examination
3. Investigations
4. Treatment

History

With organized approach and combination of careful history taking & skillful physical examination, the majority of cases with lymphadenopathy will yield a specific etiology and treatable cause leaving only a minor fraction of cases posing diagnostic dilemma [4,5].

A few important points in history taking that can contribute towards diagnosis are:

- Age of the patient
- Location of the enlarged nodes
- Duration of lymphadenopathy
- Recent history of illness
- Symptoms of sore throat, dysphagia or odynophagia, drooling, dental caries
- History of symptoms or signs of skin lesions or inflammation
- History of recent immunization
- Ongoing use of medications/ drug history
- Exposures to cats, pets, wild animals, and/or raw/undercooked meat
- Travel history
- Similar complaints in other family members.

Physical examination

The findings on physical examination which will be helpful in making the diagnosis are:

- Cervical and axillary nodes less than 10 mm and inguinal nodes less than 15mm are considered normal during childhood.
- Mobile, discrete, non-tender nodes – often suggests "benign" presentation.
- Tenderness, erythema, and warmth of overlying skin – may suggest acutely infected nodes.
- Fluctuance of the node or mass – may suggest abscess formation.
- Firm and non-tender, fixed to underlying tissue or overlying skin – may suggest malignancy.
- Evidence of throat redness and tonsillar exudates
- Evidence of skin lesion or inflammation in an area which may be drained by lymph nodes.
- Evidence of lymph node enlargement in other regions consistent with generalized lymphadenopathy.
- Evidence of hepatic and/or splenic enlargement
- Evidence of pallor, petechiae, jaundice or bruising

Management

Findings in the history, physical examination that suggests a specific or uncommon diagnosis should direct the performance of additional or more specific laboratory tests. If the history and/or physical examination suggest a localized bacterial adenitis culture from the possible primary focus is to be done coupled with a course of antibiotics (which include staphylococcal and streptococcal coverage) may be prescribed [9]. A lymph node that is fluctuant, suggestive of acute bacterial lymphadenitis may be managed by fine needle aspiration for diagnostic material for culture that may direct antimicrobial therapy. When the history and physical examinations are not suggestive of a malignant or systemic condition, observation only with a follow-up may be the most reasonable course. If the lymphadenopathy persists, or the presentation is more worrisome, the initial diagnostic work-up should include a complete blood count with differential, erythrocyte sedimentation rate, placement of a PPD tuberculin skin test and a chest radiograph to evaluate for mediastinal adenopathy or pulmonary disease. Serological tests for syphilis, HIV, EBV, CMV infection; Brucella infection, toxoplasmosis, tularemia are done in suspected cases. If leukemia is suspected a bone marrow examination is done to confirm the diagnosis [9, 13].

Radiological investigations like ultrasound, CT scan will provide accurate information about the numbers, location, content and nature of lymph nodes. In the abdomen, it is able to put mesenteric, mesocolic and retroperitoneal lymph nodes, which cannot be evaluated by physical examination [14].

A lack of response to antibiotic therapy or, a dominant node that persist for six weeks without identification of an infectious etiology warrants biopsy to confirm he diagnosis and to exclude malignancy. When neither fine needle aspiration, serologic studies, skin tests, nor therapeutic trail of antimicrobial therapy are sufficient to confirm the cause of the infection or, to exclude a more serious cause and, when there is no decrease in the size of the node within 4-8 weeks of follow-up, an excision biopsy should be considered. Children with supraclavicular lymphadenopathy and children with persistent fever or weight loss with no specific diagnosis should undergo early biopsy [13].

Most cases of lymphadenitis are due to benign, self-limiting causes, which require very little diagnostic study and no specific therapy [14]. Patients with several nodes that are only slightly enlarged and minimally tender, in association with few inflammatory signs, and serology is negative suggesting non specific etiology require only observation, following a wait and watch policy. Some authors recommend the initial empirical use of antibiotics during early follow-up period [6, 10]. Most such lymph nodes usually regress within 2-3 weeks. And most of the infectious causes are viral diseases, for which there is no specific treatment. When one or more lymph nodes continue to enlarge or does not regress even after 4-6 weeks, such patients need further diagnostic evaluation. The role of surgery depends on the etiology of the Lymph node enlargement. Though it is not the first line of management, it is recommended in cases refractory to medical management and cosmetic reasons. Treatment for noninfectious lymph node disorders depends on the identified cause of lymphadenopathy [16].

CONCLUSION

Lymphadenopathy is a common clinical finding. In spite of the fact that a wide arena of diagnosis is possible, only a minor proportion of cases are associated with significant pathology. Although a wide range of diagnostics tests are available to aid towards diagnosis, a good clinical examination and history will lead close to diagnosis, thus preventing the patient unnecessary investigations and sparing the patient of much physical and emotional trauma.

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