Generalised lymphadenopathy

What is generalised lymphadenopathy?

Generalised lymphadenopathy can be defined as enlargement of more than two non-contiguous lymph node groups. Lymph nodes have a considerable capacity to increase in size. Their size depends on the individual's age, their location and any immune activity in which they may be involved.

Most generalised lymphadenopathy is due to benign self-limited disease, such as viral or bacterial infection but it can be caused by a wide range of conditions - see 'Differential diagnosis', below.

General lymphadenopathy epidemiology[1]

In primary care unexplained lymphadenopathy has an annual incidence of 0.6%.

Fewer than 1 in 100 of these cases have a malignant aetiology, but this increases as the age of the patient increases. 4% of patients aged 40 years or older who present with unexplained lymphadenopathy are found to have an underlying cancer, but for those younger than 40 years this falls to 0.4%.

General lymphadenopathy symptoms (presentation)

History

A history should include the duration of the lymphadenopathy, whether any other household members are acutely ill and whether there are any accompanying symptoms.

Persistent fever, night sweats, general malaise or weight loss may be pointers to significant disease. Supraclavicular and infraclavicular lymph nodes are always suspicious of an underlying malignancy, particularly in those aged over 40 years.[1]

Bearing in mind the extensive list of differential diagnoses, it is important to keep the patient under review if spontaneous recovery does not occur. Presenting symptoms of more indolent diseases (eg, tuberculosis, malignancy) may occur some time after the development of the initial lymphadenopathy.

A sexual history and history of intravenous drug use should also be elicited.

Examination

Most children have palpable lymph nodes, the relative size of which could qualify for lymphadenopathy in an adult. These are most prominent in the anterior cervical, inguinal and axillary regions and continue to increase in size until the age of 8-12, after which atrophy occurs.

Measure body temperature to exclude pyrexia and check for any local sources of infection, including the scalp, skin, ears, nose, pharynx and chest. Perform a systematic examination to exclude signs of obvious malignancy and especially the abdomen to exclude hepatomegaly or splenomegaly.

- Bilateral anterior cervical lymph nodes up to 2 cm in diameter often are found in older healthy children or in those experiencing or recently recovering from an upper respiratory tract infection.
- Axillary nodes up to 1 cm, neck nodes up to 2cm and inguinal nodes up to 1.5 cm in diameter are also usually normal. [2]
- Supraclavicular nodes of any size at any age warrant further investigation, as they can be associated with malignancy in the chest and abdomen. Epitrochlear nodes (just above the elbow crease) can signify Hodgkin's disease.[1]
- Erythema, warmth, tenderness and fluctuance of a node suggest lymphadenitis of infective origin.
- Nodes that are firm, non-tender and matted together increase the possibility of malignancy.

What causes general lymphadenopathy? (Aetiology)

Generalised lymphadenopathy may be caused by a wide range of conditions, as follows:

Viral

- Common upper respiratory infections.
- Infectious mononucleosis, cytomegalovirus (CMV).
- Rubella, varicella, measles.
- HIV.
- Hepatitis A and hepatitis B.
- Roseola infantum - human herpesvirus type 6 (HHV-6).
- Dengue.
- Adenovirus.

Bacterial

- Septicaemia.
- Typhoid fever.
- TB.
- Syphilis.
- Plague.
- Lyme disease.
- Tularaemia.
- Brucellosis.

Protozoal

- Toxoplasmosis, leishmaniasis, American trypanosomiasis (also known as Chagas' disease).
- African trypanosomiasis (sleeping sickness).

Fungal

- Coccidioidomycosis.

Autoimmune disorders and hypersensitivity states

- Juvenile idiopathic arthritis.
- Systemic lupus erythematosus (SLE).
- Drug reactions (eg, phenytoin, allopurinol, primidone).
- Serum sickness.

Storage diseases

- Gaucher's disease.
- Niemann-Pick disease.

Neoplastic and proliferative disorders

- Acute leukaemias.
- Lymphomas (Hodgkin's, non-Hodgkin's).
- Neuroblastoma.
- Histiocytoses.

Investigations

In the vast majority of cases, once the history and physical examination are completed, the clinician will be able to determine that the condition is self-limiting and requires no further investigation. However, in the event of a worrying history or suspicious findings, the following investigations may be indicated.

Initial investigations

These will be governed by the history and examination and likely cause of lymphadenopathy. Investigations may not be required in cases of obvious cause and quick resolution with or without treatment.

- Investigation of patients with unexplained lymphadenopathy should include FBC, blood film and ESR, plasma viscosity or CRP (according to local policy).
- LFTs to look for liver metastases from a malignancy.
- Renal function, as reduced renal function may limit/affect the dose of any chosen therapy.
- Swabs from any site of infection for culture and sensitivities.

Further investigations

Further investigations will depend on the individual presentation but may include:

- Viral titres - eg, Epstein-Barr virus, HIV, hepatitis.
- Investigations for tuberculosis, syphilis serology, toxoplasma screen.
- Blood cultures.
- Autoantibody screen: SLE, rheumatoid arthritis.
- CXR: sarcoidosis, TB, primary or secondary malignancy.
- Ultrasonography may be helpful in evaluating the extent of lymph node involvement in patients with lymphadenopathy and may be more sensitive than CT scanning in some instances.
- Ultrasound, CT scan and/or MRI scan to look for nodal distribution and staging of any malignancy.
- Fine-needle aspiration.
- Newer imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) and magnetic resonance lymphography are increasingly being used in the diagnosis and monitoring of lymphomas and other conditions involving generalised lymphadenopathies.

Biopsy is regarded as the diagnostic method of choice. It allows an assessment of the architecture of the lymph node as well as histological, immunohistochemical, cytogenetic and molecular investigations.[3]

Differential diagnosis

- Subcutaneous lesions - eg, lipoma, abscess.
- Hernia.
- Skin lesions - eg, sebaceous cyst.
- Neck (see the separate Neck Lumps and Bumps article): thyroid tumours, branchial cleft cysts, cystic hygromas, salivary glands, thyroglossal duct cysts (usually in midline).

General lymphadenopathy treatment and management

The most important aspect of management is the recognition and exclusion of serious disease, which can often mimic trivial self-limiting conditions in the early stages. Patients and parents should be advised to seek further advice if lymph node enlargement does not resolve, new enlargements develop, old symptoms persist or new ones appear.

The following additional features of lymphadenopathy are suspicious should trigger further investigation and/or referral: [4] [5]

- Persistence for six weeks or more.
- Lymph nodes increasing in size.
- Lymph nodes greater than 2 cm in size.
- Widespread nature.
- Associated splenomegaly, night sweats or weight loss.

Treatment depends on the causative agent and may include the following:

- Expectant management - eg, viral infections, most cases of cat-scratch disease.
- Antimicrobial therapy - in the case of bacterial infection, the most likely culprits include *Staphylococcus* spp. and *Streptococcus* spp.; therefore, a beta-lactamase-resistant antibiotic is chosen. In patients with TB, follow local guidelines.
- Chemotherapy.

- Radiotherapy.
- Surgical care - apart from the diagnostic procedures outlined above, lymphadenitis may require aspiration or incision and drainage of large suppurative nodes to relieve discomfort, as well as obtaining aspirate for culture.
- Depending on the suspected underlying condition, referral to a paediatric infectious disease specialist, a surgeon, a haematologist or an oncologist may be required.

Complications

Complications depend to a large extent on the underlying aetiology. Two complications which may develop independently of the individual pathology are:

- Superior vena cava obstruction - insidious compression of the superior vena cava from mediastinal lymphadenopathy, presenting with cough, wheezing and respiratory tract obstruction.
- Abdominal lymphadenopathy presenting with abdominal or back pain, urinary frequency and constipation. Intussusception can lead to intestinal obstruction and can be life-threatening.

Prognosis

This depends almost entirely on the underlying aetiology. Malignancies such as lymphoma, leukaemia and neuroblastoma carry a poor prognosis. Non-malignant conditions with significant mortality and morbidity include HIV, juvenile rheumatoid arthritis and SLE. The onset of complications such as abdominal lymphadenopathy or superior vena cava syndrome can alter the prognosis independently of the primary disease process.

Further reading

- Assessment of lymphadenopathy; BMJ Best Practice, December 2012
- Neck lump; NICE CKS, October 2020 (UK access only)

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