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).

Epidemiology

- An annual incidence of 0.6-0.7% has been estimated for the general population.\(^1\)
- Unexplained lymphadenopathies are not common (less than 1% of the general population). 75% of all lymphadenopathies are localised and often caused by a specific pathology in the area of drainage.\(^2\)
- 25% of lymphadenopathies are generalised and are often a sign of a significant underlying disease. A diagnosis of lymphoma, malignancy, HIV infection or tuberculosis should not be missed.\(^2\)
- In the UK, HIV and tuberculosis (TB) remain conditions of continuing concern in patients presenting with generalised lymphadenopathy.\(^3, 4\)

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.\(^2\)

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, TB, malignancy) may occur some time after the development of the initial lymphadenopathy.

In adolescents, a sexual history and history of intravenous drug use should be elicited.

Examination
Most children have palpable lymph nodes whose relative size 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 and inguinal nodes up to 1.5 cm in diameter are also usually normal. A 1.5 cm inguinal or a 2 cm anterior cervical node, for example, would be considered normal in a child aged 7 years but would warrant further investigation in an infant aged 2 months.
- 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.
- 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.

Causes
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 fever
- Adenovirus

**Bacterial**

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

**Protozoal**

- Toxoplasmosis, leishmaniasis, Chagas' disease
- African trypanosomiasis (sleeping sickness)

**Fungal**

- For example, 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: liver infiltration.
- Infection swabs from primary infection site 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 TB, 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.
- CT scan/MRI scan: eg, nodal distribution, staging of lymphoma.
- 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.

Excisional 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.

Differential diagnosis

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

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.

Any of the following additional features of lymphadenopathy should trigger further investigation and/or referral:

- 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.[8]
- **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 & references

3. HIV and STIs; Health Protection Agency (archived content)
5. Referral for suspected cancer; NICE Clinical Guideline (2005)

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