Löfgren's syndrome

What is Löfgren's syndrome?

Löfgren's syndrome (LS) was first described in 1952 by Swedish Professor of Medicine Sven Löfgren. It is a clinically distinct phenotype of sarcoidosis, involving:[1]

- Hilar lymphadenopathy.
- Erythema nodosum.
- Joint symptoms.
- Fever.

Patients with Löfgren's syndrome generally have a good prognosis, are unlikely to develop chronic disease (sarcoidosis is considered chronic when symptoms last for more than three years) and most patients with Löfgren's can expect a self-limiting illness and spontaneous remission.[2] [3]

As with other forms of sarcoidosis, aetiology is unknown - the interaction of an unidentified environmental trigger and a genetically susceptible host is likely. 'A case-control etiologic study of sarcoidosis' (ACCESS) - a large US-based case-control study - failed to find any single environmental or occupational causative factor.[4] [5]

What differentiates individuals who develop Löfgren's syndrome from other forms of sarcoidosis is also unclear: the effects of different polymorphisms in the CR2 gene on chromosome 3 are being investigated, one particular haplotype of which appears to be associated with an increased risk of Löfgren's syndrome.[6] [7]

How common is Löfgren's syndrome? (Epidemiology)[8]

- LS occurs mostly in European Caucasians, especially in Sweden and in the Netherlands where LS patients constitute roughly a third of all sarcoidosis cases.
- It is less common in the UK and in the US, where only 0.9 and 0.7% of sarcoidosis patients present with LS, respectively. It is extremely rare in Asia.
- It usually occurs between the age of 25 to 40, with a second peak around the age of 40 to 60 and is more frequent in women (70%).

Risk factors

- Strong female predominance.
- Young to middle-age (mean age of onset - 35 years).
- There is a strong association with human leukocyte antigen (HLA)-DRB1 alleles. The association with HLA-DRB1*03 is particularly striking and is a very strong marker for a good prognosis.[9] [10]
- Seasonality - presentation is more common in spring months (northern hemisphere).[11]

Symptoms of Löfgren's syndrome (presentation)[8]

Patients typically experience an acute onset of the disease, usually with fever and characteristic symptoms consisting in bilateral hilar lymphadenopathy (cough and/or dyspnoea), erythema nodosum and/or bilateral ankle arthritis or periarticular inflammation. Other symptoms may include uveitis, parotitis, facial palsy, skin (except lupus pernio), liver or spleen involvement.

The different manifestations of LS differ according to sex: erythema nodosum is found predominantly in women while arthropathy/arthritis is more common in men.

Differential diagnosis

Löfgren's syndrome needs to be distinguished from other causes of:

- Erythema nodosum - eg, infection (*Streptococcus* spp., tuberculosis (TB), mycoplasma); drugs, inflammatory bowel disease, non-Hodgkin's lymphoma, Behçet's disease.
- Hilar lymphadenopathy - lymphoma, tuberculosis and lung cancer need to be excluded, particularly where lymphadenopathy is not symmetrical.
- Arthritis.
- Pyrexia of unknown origin.
- Cellulitis.

Diagnosing Löfgren's syndrome (investigations) [8]

Investigations indicating active sarcoidosis include: [1]

- CXR (abnormalities include mediastinal lymphadenopathy or pulmonary infiltration).
- Gallium-67 scan may be used when CXR is normal; shows increased hilar or paratracheal uptake).
- Lung function tests (decreased forced vital capacity).
- Serum calcium level (may be elevated).
- Serum angiotensin-converting enzyme (may be increased).
- Lymph node biopsy.

> Always remember to perform CXR in those presenting with periarticular ankle signs.

The ankle arthritis may best be demonstrated by MRI scan. MRI of the joints or ultrasonography typically shows periarticular inflammation with subcutaneous and soft tissue oedema accompanied by small amounts of joint and tenosynovial fluid without evidence of synovial thickening or synovitis.

The diagnosis of sarcoidosis is not standardised but is based on three major criteria: a compatible clinical and/or radiological presentation, the histological evidence of non-necrotising granulomatous inflammation in one or more tissues and the exclusion of alternative causes of granulomatous disease. Certain clinical features are considered to be highly specific of the disease (eg, Löfgren's syndrome, lupus pernio, Heerfordt's syndrome) and do not require histological confirmation.

Management of Löfgren's syndrome[1] [12]

- Once Löfgren's syndrome can be confidently diagnosed, the patient can be reassured that the condition is benign and normally self-limiting.
- Routine biopsy is not required to confirm the diagnosis unless there are atypical features.
- Management is supportive - eg, non-steroidal anti-inflammatory drugs for arthralgia.
- Prednisolone may be required for more severe cases.
- Follow-up should continue until any hilar lymphadenopathy has resolved.

Prognosis

LS patients herald a benign and self-remitting disease, which is especially true for individuals carrying the HLA-DRB1*03 allele. Chronic trend of more than 2 years occurs in 8-22% of LS patients and is associated with older age and the need for treatment.[8]

Further reading

- Sven Halvar Löfgren; whonamedit.com

- Brown F, Modi P, Tanner LS; Lofgren Syndrome. StatPearls, Aug 2022.
- Franzen DP, Brutsche M, Nilsson J, et al; Sarcoidosis - a multisystem disease. Swiss Med Wkly. 2022 Jan 14;152:w30049. doi: 10.4414/smw.2022.w30049. eCollection 2022 Jan 3.

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