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SHORT ARTICLE

Primary lymphedema and genetic implications

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Abstract

Primary lymphedema can be familial (in which more than one member of the same family has a lymphedema phenotype), syndromic (in which lymphedema is one symptom of a complex clinical syndrome) or sporadic (in which an isolated family member has lymphedema). All types of lymphedema are determined by genetic alteration of one or more genes. Not all the genes involved are known.

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Primary lymphedema is determined by a genetic disorder with variable penetrance that depends on the kind of mutation and the gene affected. By definition, it can therefore be associated with clinical events, which are genotype-positive for gene mutation. The observation of lymphedema in different generations of certain families has led to the development of genetic tests. Much has yet to be discovered about the anatomical and functional bases of the disease.

Primary lymphedema consists of accumulation of fluid composed mainly of proteins (>5 mg/dl). Manifestations are swelling and a variable increase in tissue thickness, related to protein-induced fibrosis (stimulation of fibroblasts to produce collagen fibers).

Lymphedema is a chronic disease that often causes functional impairment, with variable psychological repercussions (Fig. 1).

For progressive and complete local growth of the lymphatic system, it is essential that the cell membrane receptors involved in the process of lymphatic replication respond to the stimulus of growth factors circulating in the extracellular environment. The receptors must recognize these factors and transmit information to the cell nucleus and organelles, so that cell replication and cell migration to their anatomical destination can resume.

Certain especially hereditary mutations are associated with membrane receptor dysfunction, in which receptors do not recognize growth factors as activators of replication and migration. The lymphatic system does not develop completely in a specific anatomical area: the lymph node reference station remains incomplete or fails to develop. This results in a reduced capacity to transport lymph, which manifests earlier (at birth or in subsequent decades) and more intensely (especially as regards functional implications, i.e. development and progression of edema) with greater genetic defects.

Lymphedema can be familial, involving several members of the same family; sporadic, affecting only one member of a family; or syndromic, which means that it is only one aspect of a syndrome. Clear relationships have been demonstrated between certain genetic mutations and primary lymphedema. Further studies have also shown a specific hereditary pattern in certain secondary forms (Fig. 2) (1, 2).

It is important to study genetic mutations for an understanding of the incidence, penetrance and prevalence of the disease.

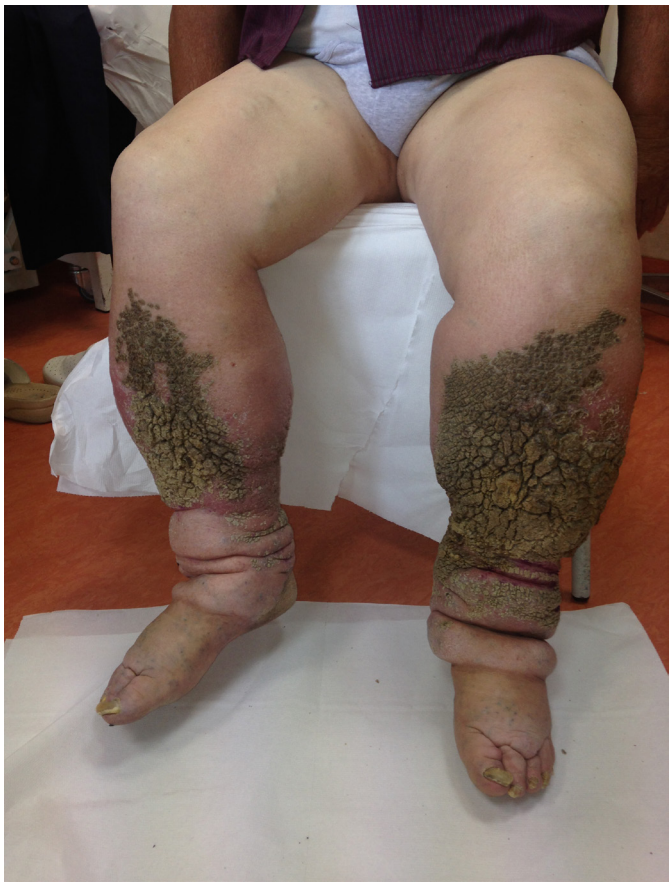

Figure 1. Primary lymphedema with complications.

With regard to the VEGFR3 gene (also called *FLT4*), approximately 40 different mutations have been documented. Pathological mutations have been located in the two (intracellular) tyrosine kinase domains, whose coding sequence is between exons 16 and 27. The VEGFR3 gene is important for lymphangiogenesis and structural maintenance of lymphatic endothelium: it is activated by binding to growth factors VEGF-C and VEGF-D (3, 4).

The FOXC2 gene performs key function in angiogenesis, lymphangiogenesis and vascular remodelling. It is also implicated in the development of metastases and rapid progression of certain tumors, especially breast cancer. FOXC2 mutations can also be associated with speech disorders.

Selection of patients for genetic testing for mutations in the two major genes implicated in primary lymphedema (VEGFR3 and FOXC2) is based on: presence of lymphedema (diagnosed clinically and/or by lymphoscintigraphy), medical history, onset before 50 years of age, specific clinical signs, and family history.

After informed consent (5, 6), genetic testing consists in investigating all the genes currently known to be responsible for lymphedema: *CCBE1* (OMIM:612753), *CELSR1* (OMIM:604523), *FAT4* (OMIM:612411), *FLT4/VEGFR3* (OMIM:136352), *FOXC2* (OMIM:602402), *GATA2* (OMIM:137295), *GJC2* (OMIM:608803), *HGF* (OMIM:142409), *KIF11* (OMIM:148760), *SOX18* (OMIM:601618), *VEGFC* (OMIM:601528).

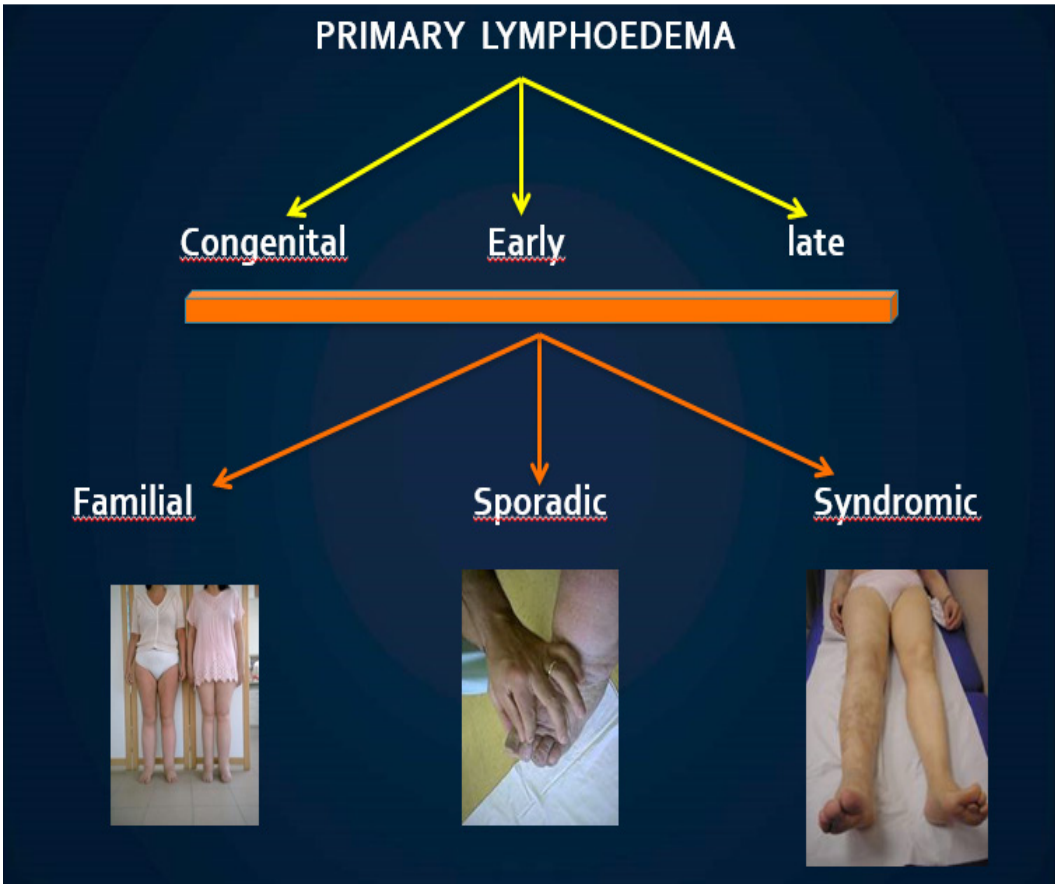

Figure 2. Different kinds of primary lymphedema.

In patients with a family history of lymphedema, additional research is performed directly on the known genes. Family members (ancestors, collaterals and descendants) found positive in the first phase are then investigated. For those with positive genotype without the corresponding phenotype, lymphoscintigraphy is necessary to detect subclinical alterations in lymph transport.

More information can now be obtained with new tools, including next generation sequencing, which enables the simultaneous study of many genes found altered in familial and sporadic forms and now considered potential causes of primary lymphedema (7, 8, 9).

For sporadic forms, genetic study must be performed after lymphoscintigraphy and the somatic test is only useful if the germinal test is negative (thus excluding *de novo* mutations).

The aim of genetic testing is to identify and possibly "correct" the lymph system growth defect by specific recombinant protein synthesis that restores the biological network with its circulating growth factors and cell membrane receptors.

Today we know that inheritance of primary lymphedema can also be modulated by clinical expressivity (as confirmed by positive lymphoscintigraphy in subclinical cases). For sporadic cases, this suggests genetic complexity that may be related to an influence of environmental factors on protein transcription, determining the manifestation of phenotypic lymphedema (10).

Other modified genes, to be yet discovered, could have a role in the development of primary lymphedema. The association between these new mutations and lymphedema status requires further study, especially in other members of affected families.

Combined clinical and genetic assessment allows clinicians to determine the best way to manage patients and their relatives. It can also provide key information about transmission risk, including prenatal diagnosis, and how to organize specific follow-up, such as monitoring of blood abnormalities in individuals with GATA2 mutations. It is also useful for enrolling patients in clinical trials of specific new drugs (like VEGF inhibitors), certifying legal disability and rationalizing the time and costs of genetic testing and research (11).

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