An Update on Primary Lymphoedema and the Diagnostic Algorithm

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Primary lymphoedema occurs as a result of a genetic predisposition causing the lymphatic system to fail to develop normally, or to be maintained adequately, causing abnormal drainage of lymph which results in swelling of the affected region. Primary lymphoedema may occur as an inherited condition, or less commonly as part of a complex syndromic disorder (Connell, Brice et al 2010). A patient with primary lymphoedema may only have problems with swelling, but some forms of primary lymphoedema occur in association with other health problems e.g. congenital heart disease, systemic/internal lymphatic abnormalities (fluid around the heart or lung), or very rarely haematological malignancy (leukaemia).

Primary lymphoedema is not one disease, but the presenting feature of several distinct clinical entities. Historically, primary lymphoedema was categorised into three groups depending on the patient's age at onset of swelling: lymphoedema congenita (presenting at birth), praecox (pubertal onset) or tarda (onset after 35 years of age). Mutations in several genes are known to cause primary lymphoedema. Some, but not all, of these genes have been shown to play a role in lymphangiogenesis (the process of developing and maintaining a healthy lymphatic system). The discovery of these gene mistakes has changed our diagnostic approach in the clinic, which is now based on clinical phenotyping (the process of associating a patient's lymphoedema with other health problems) and genotyping (DNA tests looking for the underlying causal gene mistake) in addition to age of onset of swelling.

Our experience and research has led us to realise that primary lymphoedema can be broadly divided into five different categories. Causal gene mistakes have been identified for a number of disease subtypes within the five categories. We have developed a colour-coded diagnostic pathway that describes specific primary lymphoedema phenotypes and guides the clinician on gene tests that may be available for their patient (Connell, Gordon et al 2013).

The diagnostic pathway helps the clinician to offer appropriate genetic testing (assuming the underlying gene mistake is known), and screen and treat for associated health problems. Patients and families benefit hugely from receiving a formal genetic diagnosis of their primary lymphoedema as it allows the clinician to confidently predict the clinical prognosis and offer screening for family members. In addition, use of this pathway has facilitated our discovery of new causative genes, as we analyse and compare the DNA of patients with similar patterns of lymphoedema and other health problems. We are hopeful that this ongoing research will aid the development of improved treatment options.

References:

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