Lymphoedema — primary or secondary, how does one tell?

Glen Brice, Fiona Connell

A recent editorial in *Lymphatic Research and Biology* suggests that many cases of apparent secondary lymphoedema may, in fact, have an underlying primary cause, even though the primary event cannot yet be identified (Rockson, 2008). A primary disease is usually defined as one arising spontaneously and not associated with, or caused by, a previous disease or injury, while secondary disease is one that follows and results from an earlier disease, injury, or event.

If one were to use the above definitions it should be easy to delineate primary lymphoedema from secondary. If the medical history does not reveal an injury, previous surgery or infection, then the condition would be primary. If there was a precipitating factor, it would be secondary. Simple!

How then to explain the finding that breast cancer-related arm lymphoedema affects only a proportion of women who undergo similar operations, and sometimes develops months or years later. Evidence has been published to show that there may be lymphatic abnormalities in the contralateral, non-operated side in those who develop post-surgical oedema (Pain et al, 2004). This suggests an underlying inherent 'weakness' in the lymph system which is exposed by the surgical trauma. In other words, a primary weakness only unmasked by a secondary event. At present in clinical practice, if there is no obvious precipitating factor, we regard lymphoedema as a primary disease and postulate that there is a congenitally determined, but unidentified cause.

Glen Brice is Genetics Counsellor and Fiona Connell is Clinical Research Fellow in Lymphoedema at South West Thames Regional Genetics Service, St George's University of London

At a molecular level many diseases are considered to be genetic or primary conditions. If an individual develops a disease while their neighbour does not, is this due to the unique combination of small detrimental changes in genes which they have inherited, while those who do not develop signs of the disease are similarly spared by a combination of 'protective' genes? Increasingly, medical journals report new disease-causing mutations, or single nucleotide polymorphism (SNP) studies purporting to be able to define a sub-group in the population more likely to develop a particular disease (Song et al, 2008; Khatri et al, 2008).

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SNPs are small variants within the genetic material of unknown significance. Some studies suggest that a particular combination of SNPs may increase the risk of developing certain diseases. Specific SNP studies have not been published for those suffering from lymphoedema. To date, three genes have been described which cause inherited lymphoedema. Vascular endothelial growth factor-3 (VEGFR-3) for Milroy disease (congenital onset, dominantly inherited lower limb oedema), FOXC2 for lymphoedema distichiasis syndrome and SOX18 for the rare condition lymphoedema-hypotrichosis-telangiectasia syndrome (Ferrell et al, 1998; Fang et al, 2000; Irrthum et al, 2003). Together, these three genes account for only a small percentage of apparent familial lymphoedema and a tiny proportion of lymphoedema in general.

Our studies and those of other groups have amassed numerous families with clear evidence for a familial trait, but in the vast majority no single causative gene can be identified. Is this due to the effects of a number of genes working together to produce the phenotype? The increasing use of SNP analysis to reliably identify those with the greatest risk of developing disease may help to uncover novel mechanisms for the development of, and protection from, lymphoedema.

We now know of numerous genes involved in the development and maintenance of the lymphatic system, and perhaps specific combinations of SNPs in these genes are the explanation for some cases of lymphoedema. In addition to genes specific to the lymphatic system, there are many genes involved in the development of other parts of the vascular system which could influence whether or not an individual develops lymphoedema and the extent to which they are affected.

Without gene-specific treatments, the issue of primary or secondary causation is probably, in most situations, of academic interest only. The vast majority of lymphoedema is treated by physical means — compression hosiery and massage. The underlying genetic fault will have little relevance to these forms of treatment. If, in the future, gene-specific treatments become available, the need to determine the underlying molecular cause will become paramount.

In secondary and acquired lymphoedema, where the precipitating defect is usually restricted to a relatively local area, it may not be necessary to know if there is an underlying genetic defect. The use of local, lymphatic-specific growth factors may be sufficient to create collateral pathways, bypassing the damaged areas. This approach has been used in animal models of lymphoedema with some success (Tammela et al, 2007; Saito et al, 2006).

Only by continuing to study individuals and families with lymphoedema, perhaps with genome wide screening technology, will we better be able to understand what is clearly a complex and dynamic system. JL

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Papers presented during the 3rd National Seminar on Evidence-based and Integrated Medicine for Lymphatic Filariasis, other Chronic Dermatoses and HIV/AIDS on February 5–7, 2008 in Kasaragod, South India are available to download from: www.journaloflymphoedema.com

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Papers include:

- Global strategy for LF with India 2008 and the international development of the Lymphoedema Framework, *Christine Moffatt*
- Morbidity control of lymphatic filariasis by patient empowerment through creation of patient support peer group cooperatives using self-care ayurveda and yoga treatments, *KS Bose KS, SR Narahari, GM Aggithaya, K Vivekananda, J Neethu, KS Prasanna*
- The impact of lymphoedema on patient's lives (a review of the quality of life literature), *P Morgan*
- Empowering disabled people due to filariasis: lymphatic filariasis project at Satyabadi, Puri district, Orissa (India), *GB Acharya*
- Effect of health education in reduction of filarial morbidity in patients, *MK Showkath Ali, K Regu, R Rajendran MK Mohanan, Girish Babu*
- An instrument to assess health-related quality of life due to lymphatic filariasis for assessing the impact of morbidity management under filariasis elimination programme, *K Krishnamoorthy, A Krishna Kumari, KT Harichandrakumar, LK Das*
- Determination of disability weight for different clinical manifestations of lymphatic filariasis, *A Krishna Kumari, KT Harichandrakumar, LK Das, K Krishnamoorthy*
- Perception of treatment providers on the health status of patients with different clinical manifestations of lymphatic filariasis, *KT Harichandrakumar, A Krishna Kumari, LK Das, K Krishnamoorthy*
- Management of AIDS through Swastha Vritta: an Ayurvedic perspective, *Dr Galib, BJ Patgiri, PK Prajapati*

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