RESEARCH PERSPECTIVE

Genetics of Childhood Lymphedema-Angiodysplasia Syndromes
by: Mike Bernas, MS

This issue of Lymph Link focuses on imaging and I thank Dr. Armer for allowing me the opportunity to write the Perspectives column in her place.

Imaging is not yet a standardized component of the evaluation of patients with lymphedema. A large portion of the NLN members are physicians, therapists and patients who have no or limited access to imaging, so imaging is often thought of as unnecessary.

Historically, at the time of pioneering lymphedema treatments, no good and easy imaging existed. The idea still continues to be written and taught even today that lymphedema can be diagnosed and classified with only a good clinical evaluation. Imaging adds to our treatment of the lymphedema patient by giving the physician and patient the ability to “see” the lymphatic system (where blockages exist and how severe they are). Imaging helps us understand lymphatic alterations for diagnosis, prognosis, treatment, and in classification of this life-long condition. Perhaps classification will become one of the more valuable uses of imaging in the future. Dr. Lee and his colleague have recently published an article describing their experience with the classification of patients with lymphedema by combining both a clinical score and an imaging score. This first attempt may require some revision, but we are working towards a framework (including genetics) that will ultimately change the classification of patients with lymphedema from our current method of looking mostly at clinical presentation to a real understanding of the anatomy, physiology, and genetics.

Dr. Cheville has described the basics of imaging and more specifically lymphoscintigraphy (LAS) in the lead article of this issue. She introduced some of the issues and controversies concerning standardization of the technique. The lack of a standardized technique is widely talked about and sometimes I think the apparent lack of worldwide standardization is used as an escape for those who do not want to image or can’t image. At the recent International Congress of Lymphology (Salvador, Brazil Sept. 2005), Dr. Alain Pecking chaired the main session concerning Lymphangioscintigraphy and standardization. This session provided an understanding was formulated that the “standardization of the techniques is less important than standardization of the image.” What this means is that when the procedures are done well, in any facility and with any of a variety of differing techniques (an interested technician and knowledgeable physician can help), you can obtain an image that is clear, informative, valuable, and easily interpreted for the benefit of the patient.

I like Dr. Cheville’s unusual case study for many reasons. This case appeared straight forward as lymphedema of the arm, but LAS imaging of the arm failed to show a lymphatic abnormality. Obviously there was swelling and credit must be given to both Dr. Cheville and the sharp nuclear medicine physician who did not give up but went forward with an injection into the scalp looking for the cause of the supraclavicular swelling. In this case, one could look at it as a failure to see the alteration in the lymphatics of the arm (is this true?) or as a confirmation of the value of imaging to define the true lymphatic defect causing the physical problem and the value of combining different imaging modalities for use in selected patients.

Dr. Stewart’s case helps demonstrate the usefulness of imaging (LAS +MRI) for her patient and the management issues impacted due to imaging results. In this case, a better prognosis was obtained in that lakes and cisterns that may cause more severe leakage were not identified. Other reflux cases display lakes and cisterns and these focus the area for additional ablation techniques.

In this month’s question corner, Steve Norton answers two really great questions from patients concerning their imaging results. I understand Steve’s comments about the “haze” in images, however, any clinician with a basic level of understanding and a little practice can interpret these images with only a small amount of direction.

In his first question, no lymphatic vessels were seen in the patient’s image. I would like to echo Steve’s comments concerning obtaining a good, properly done image (we can’t be sure in this case) and his diagnosis by exclusion as being very important. He also notes correctly that LAS is a functional test and as such, if no fluid is moving, the lymphatic system would not be highlighted. This case brings up more fascinating questions as to how the tissue fluid is returning to the central circulation (movement through tissue planes, altered venous capillaries, reduced infiltrate, or combinations of these).
In our laboratory we are fortunate to work with several transgenic mouse models of human lymphedema including some which have the same mutations and physical appearance as in humans (lymphedema distichaisis and FOXC2) \(^2\). We also have the Ang-2 knockout mice \(^4\) (there are unconfirmed reports of patients having the same mutation) which do in fact exhibit complete lack of lymphatic vessels and nodes in their lower body (most live successfully to adults). Might this not indicate that humans may also have a similar condition and the answer to this question is that there truly are no lymphatics?

The second excellent question addresses the opposite situation when a "normal" image is obtained in a patient with swelling. Although we would disagree that this is a frequent finding in our experience with patients with lymphedema, the previous discussions on obtaining good images must be re-emphasized. Additionally, we must consider that patients with swelling may also have a "normal" LAS image if their swelling is the result of other medical conditions (e.g. venous disease, Klippel-Trenaunay and related syndromes, lipedema, etc.) which are not lymphedema.

What will the future hold? This is still a young and evolving field. Bi-modal imaging of the lymphatic system (Dr. Pecking) utilizing a combination gamma camera/CT produces beautiful fine anatomical CT images with a corresponding functional LAS on the same image. Kobayashi and colleagues \(^5\) have described multiple dendrimer (artificially made compounds) agents for gadolinium enhanced lymphatic imaging using MRI which demonstrated clear anatomical and functional imaging of the mouse lymphatic system (including the thoracic duct) with the high spatial resolution of MRI. Another MRI based technique utilizes an antibody linked with magnetofluorescent particles \(^6\) to successfully in vivo (in a mouse) image endothelial vessels. These and other newer techniques may be transferred to patients in the future to allow us to more clearly and accurately define the lymphatic system including its anatomy, physiology, and function.

In summary, we are at an exciting point in lymphatic imaging and we can no longer say that clinical diagnosis is sufficient without imaging. A good image adds to the diagnosis, classification, prognosis, and treatments (including documentation of effects) of patients and future advances will rely more on imaging and we must continue to incorporate it into our current practice.

References:


