A RARE CASE OF LYMPHOEDEMA-DISTICHIASIS

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Lymphoedema-distichiasis is a rare autosomal-dominant condition characterised by a second row of eye lashes (distichiasis) and pubertal onset of lower limb lymphoedema. It was first described in 1964 by Falls and Kertesz, but it took almost 40 years for the gene that causes the condition to be located on chromosome 16 (Fang et al, 2000). The prevalence of lymphoedema-distichiasis syndrome is not known; however, one person in 6000 will develop primary lymphoedema (Dale, 1985).

Aetiology and presentation

The identified gene, named FOXC2, controls the function of other genes and is active during the development of the foetus. This effect possibly explains the other congenital abnormalities such as varicose veins, cleft palate, droopy eyelid, vertebral abnormalities and heart defects which can be associated with lymphoedema-distichiasis. FOXC2 was found to be abnormal in families affected by lymphoedema-distichiasis, however, many mutations have been seen (Bell et al, 2001). In the short term, the discovery of a mutation allows family members to be screened for their risk of developing the condition. Genetic counsellors can also use this information to offer advice on passing the condition on to subsequent generations.

The distichiasis arises from the meibomian glands (there are approximately 50 of these sebaceous glands on the rim of the upper eyelids and 25 on the lower eyelids), which develop abnormally as hair follicles. These can vary from a full set to the odd extra lash. They are normally soft and pale, but often cause irritation of the cornea. Distichiasis can easily be overlooked as the extra lashes are difficult to see, the best way to identify it being by slit-lamp examination.

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In lymphoedema-distichiasis the lymphatics appear to function normally prior to puberty and before the development of swelling. When the swelling becomes apparent and over time, lymphoscintigraphy would almost certainly show features consistent with lymphatic reflux. In line with the heterogeneity of the condition, onset of oedema has been seen at birth and during the early years and well on into adulthood (Brice et al, 2002; Erickson et al, 2001; Finegold et al, 2001). Interestingly, there is an earlier onset age in males (Brice et al, 2002). FOXC2 gene appears to cause hyperplasia of the collecting lymphatics of the leg, and the swelling is usually below the knee (Dale, 1987). However, there have been reported cases where the swelling extends into the thighs, and it is generally bilateral and asymmetrical. Cellulitis is common and, again, males are more likely to experience this (Brice et al, 2002).

There is often clinical evidence of venous disease and the onset of varicose veins in children are a frequent finding. Mellor et al (2007) found that patients with FOXC2 mutations have abnormal veins and venous duplex ultrasound shows venous incompetence with backflow.

Case study

Patient X is a 48-year-old woman whose swelling started at the age of 14/15 in the right ankle and spread up to the knee. This was quickly followed by swelling in the left leg, which started in the foot and ankle but soon spread up into the entire lower leg. Initially the swelling was made worse by long periods of standing but did reduce over night, however, this is no longer the case. The swelling is now constant, but does not extend past the knees or affect the trunk in any way. It is of note that the swelling was much worse during her two pregnancies, as is often the case with primary lymphoedema.

She has suffered from cellulitis on approximately four occasions, two of which required hospitalisation for IV antibiotics. Her previous lymphoedema treatment included diuretics, which she took for approximately 10 years from the age of 16.

On examination (September 2007), oedema was present throughout the toes, feet and lower legs, no sensory changes were detected and there were no complaints of pain related to the swelling. The skin was intact, although the patient did experience lymphorrhoea on occasions. The tissues were thickened and pitting

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and a negative Stemmer's sign was noted. A full Doppler assessment showed a slightly reduced ankle brachial pressure index (ABPI) and minor varicose veins and telangiectasia were noted to both legs. There was a slight bluish discoloration in keeping with underlying venous disease. She gave a family history of her maternal grandmother, mother, brother and son, all suffering from the same swelling and shape below the knee and generalised discoloration to the feet.

Psychologically, the patient stated that although she had known of the lymphoedema clinic's existence since 2004, she had never been able to attend, as she felt too self-conscious about the appearance of her legs, particularly the 'staining' throughout the right lower leg from several episodes of cellulitis.

She was diagnosed with unspecified primary lymphoedema praecox and prescribed a treatment plan of skin care, exercise and strong compression hosiery. Referral to a specialist centre for assessment and diagnostic investigation was arranged to determine the possible genetic type of primary lymphoedema due to the very clear, strong family history and the patient's concerns that her daughter may go on to develop the condition, as her son was already showing signs. While waiting to see the specialist centre, she developed a further episode of cellulitis and the patient's GP was informed of the consensus document on the management of cellulitis in lymphoedema available online at: www.thebls.com.

Follow up was arranged for October 2007 when the patient would be accompanied by her son. On measurement of the patient's legs, the limb volume had reduced, the shape had improved, subcutaneous tissues were softer and pitting and the skin was in good condition. The telangiectasia and varicose veins were unchanged. An assessment of her son confirmed that he too had below-knee swelling, although this was mild, the subcutaneous tissues were thickened and pitting, the shape was unaffected and the skin was satisfactory. He gave a lymphoedema history of the swelling being present since he was a toddler, but that it had never restricted his activities. He complained of frequent pins and needles throughout both feet and toes, even when standing or at rest, and there was discoloration to both feet. A varicose vein was noted to the medial aspect of the right lower leg. A referral to a vascular surgeon was requested from the GP for further investigation.

Referral to the specialist centre offered this family a chance to have a confirmed diagnosis of lymphoedema-distichiasis, genetic screening and potential genetic counselling.

The patient and her son were seen by the specialist centre in November 2007 who confirmed a diagnosis of lymphoedema-distichiasis for both of them. Neither was aware of their distichiasis which could only be seen under a bright light using a magnifying lens. The only other possible phenotypic feature in the patient was a flat uvula. The patient was tested for FOXC2 mutation and if this is positive she could go on to have both her children tested to see if they are affected. Blood was also taken for lymphocyte subsets to investigate the patient's immune status, which is particularly necessary for those who get cellulitis, as in this patient's case. It was felt that there was no point in undertaking lymphoscintigraphy or venous duplex ultrasound, as they will almost certainly both be abnormal and show features consistent with lymph and venous reflux. To prevent further attacks of cellulitis, the patient was commenced on penicillin V 250mg twice a day for two years, only to be stopped prior to this if the antibiotic disagreed with the patient or was ineffective.

In February 2008 she was seen again at the lymphoedema clinic with her son, the swelling had maintained, no further attacks of cellulitis were reported and she was continuing well. However, since the appointment at the specialist centre, the 17-year-old son has experienced severe irritation from the extra eyelashes in the upper lid which has required hospital treatment to remove them, and there has been some mild abrasion to the cornea. Both patients will continue with self-management techniques of skin care, exercise, strong compression hosiery, alongside regular monitoring.

Discussion

Referral to the specialist centre offered this family a chance to have a confirmed diagnosis of lymphoedema-distichiasis, genetic screening and potential genetic counselling. It highlights the importance of family history on assessment and also that extending care to more than one family member can be extremely beneficial. Although at the present time this has not changed the patient's treatment plan, there is potential for the development of new treatments using knowledge of the underlying cause.

There have recently been advances in the understanding of genetics and lymphangiogenesis in lymphology, but there is still a long way to go. Promising lymphoedema treatment results have been achieved using viral gene-transfer vectors that encode lymphangiogenic growth factors but, as yet, only in preclinical models (Alitalo et al, 2005). The details of this work are expanded in a review by Schoppmann et al (2005), who reports a recent study using identified lymphatic growth factors and their ligands to restore lymphatic flow across incision wounds. It would be revolutionary if future developments led to the ability to grow new lymphatics, or, indeed, restore function to existing ones, but even the possibility of the introduction of skin flaps being transplanted into lymphoedematous areas to restore lymphatic function and reduce oedema would be incredible.

Conclusion

Although distichiasis is easily missed, it is worth familiarising yourself with the appearance of the extra lashes when a patient with lymphoedema-distichiasis is presented to you. This may help in the identification of future patients.

Lymphoedema-distichiasis presents as pubertal onset lymphoedema and these patients will often have marked venous disease and therefore they could be misdiagnosed, which will almost certainly lead to less than optimum treatment options.

The recent advances in the identification of molecular markers and growth factors in lymphangiogenesis are extremely exciting. There will undoubtedly be many future developments but, at present, it is important to remember the patient's feelings. These technological advances may raise hope but the actuality may be many years away. JL

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Key points

- Lymphoedema-distichiasis is a rare autosomal-dominant condition characterised by a second row of eye lashes (distichiasis) and pubertal onset of lower limb lymphoedema.
- The identified gene, named FOXC2, controls the function of other genes and is active during the development of the foetus. This effect possibly explains the other congenital abnormalities such as varicose veins, cleft palate, droopy eyelid, vertebral abnormalities and heart defects which can be associated with lymphoedema-distichiasis.
- Referral to the specialist centre offered this family a chance to have a confirmed diagnosis of lymphoedema-distichiasis, genetic screening and potential genetic counselling.
- The recent advances in the identification of molecular markers and growth factors in lymphangiogenesis are extremely exciting.