

## DIFFERENT LYMPHSCINTIGRAPHIC PATTERNS IN PATIENTS WITH LYMPHEDEMA DISTICHIASIS

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### ABSTRACT

*Mutation of the transcription factor FOXC2 gene has been identified as the cause of lymphedema-distichiasis syndrome (LD). Subjects with LD usually present with lower extremity lymphedema and distichiasis – an additional row of eyelashes. Typically, lymphoscintigrams of patients with LD show good transport of the radiotracer from the feet to the inguinal lymph nodes accompanied by reflux of tracer to the skin of the lower extremities (“dermal backflow”). We have examined two patients with LD syndrome and were able to demonstrate two different distinct lymphoscintigraphic patterns: lymphatic hyperplasia with reflux and obstructive.*

**Keywords:** FOXC2, lymphedema, distichiasis, lymphoscintigraphy

Familial lymphedema covers a group of genetic disorders with several phenotypic subgroups. Familial lymphedema may present an autosomal dominant or recessive pattern of inheritance with varying degrees of penetrance. The most common forms are thought to be Nonne-Milroy disease with dominantly inherited primary congenital lymphedema and non-syndromic Meige disease, which is primarily of pubertal or later onset also described with dominant type of inheritance (1). Genetic mutations of the

VEGFR-3 receptor gene were described in several families with Milroy’s disease, however, the genetic background of Meige disease is not yet understood.

Transcription factor FOXC2 mutation is responsible for lymphedema with distichiasis (LD). This human genetic disease is associated with haploinsufficiency of FOXC2 and is mainly a result of nonsense mutations, insertions or deletions that produce frame-shifts (2-5). FOXC2 is located on the long arm of chromosome 16 (6).

Lymphedema-distichiasis syndrome is considered rare, usually is associated with lymphatic hyperplasia, and affected individuals typically exhibit distichiasis (the additional row of eyelashes). The association of distichiasis with lymphedema of the lower limbs was probably first described in 1899 (6). Additional features of FOXC2 mutations may include cardiac defects, cleft palate, extra-dural cysts, and venous abnormalities (7,8).

Patients with LD usually present signs of lymphedema of the lower extremities during late childhood or even later. Dagenais et al. found that FOXC2 is expressed in lymphatic primordial, jugular lymph sacs, lymphatic collectors and capillaries as well as in other tissues associated with abnormalities in LD syndrome but the pathways and mechanisms by which FOXC2 acts, remain unknown (1). The cause of the lymphatic malfunction in the presence of normal or increased numbers

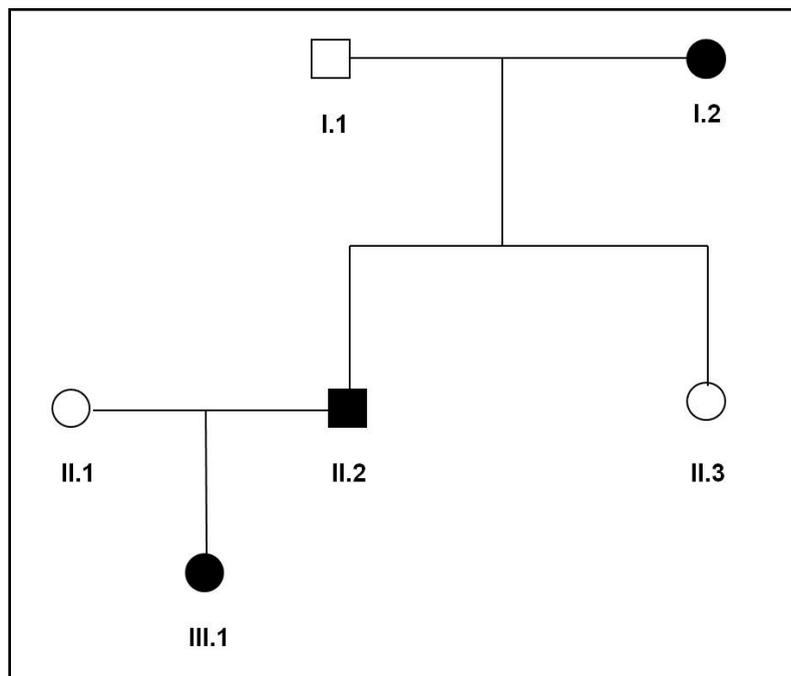


Fig. 1. Pedigree of the family "A" with lymphedema distichiasis.

of lymph vessels characteristic for patients with LD is not clear. Poor function of lymphatic vessels may be the result of a proximal abnormality or obstruction (6,9), or mutations in FOXC2 may affect the development of lymphatic vessels and veins and affect the formation and function of the valves (10,11). Other results indicate that an abnormal interaction between lymphatic endothelial cells and pericytes, along with valve defects, underlie the pathogenesis of LD (12).

Distichiasis is a congenital anomaly in which accessory eyelashes occur along the posterior border of the lid margins in the position of the Meibomian gland orifices. The accessory eyelashes may be represented by a few cilia or (less commonly) an additional regular, well formed row. Ophthalmologic complications of distichiasis include photophobia, corneal irritation, corneal ulceration and partial ectropion of the lateral third of the eyelashes (13,14). Occasionally, distichiasis is asymptomatic because the lashes curl away from cornea or because of the corneal

hypoesthesia (15). The distichiasis can be managed in a number of different ways including: epilation (plucking), cryotherapy, electrolysis, lid splitting operations and laser treatment. Most of these measures give only temporary relief (6).

#### CASE REPORT

We describe two families with symptoms of the Lymphedema Distichiasis Syndrome.

The first family (family "A"; Fig.1): a 3 year-old Caucasian girl (III.1) who was previously treated for recurrent corneal irritation because of the accessory eyelashes presented to our Ophthalmology Clinic for further treatment. She had no signs of lymphedema. Her mother (II.1) has slightly elevated serum bilirubin level and mild thrombocytopenia but no vascular problems.

Her father (II.2) – a Caucasian 30 years old man, has been suffering from distichiasis since about 15 years of age. Both he and his daughter have had multiple epilations

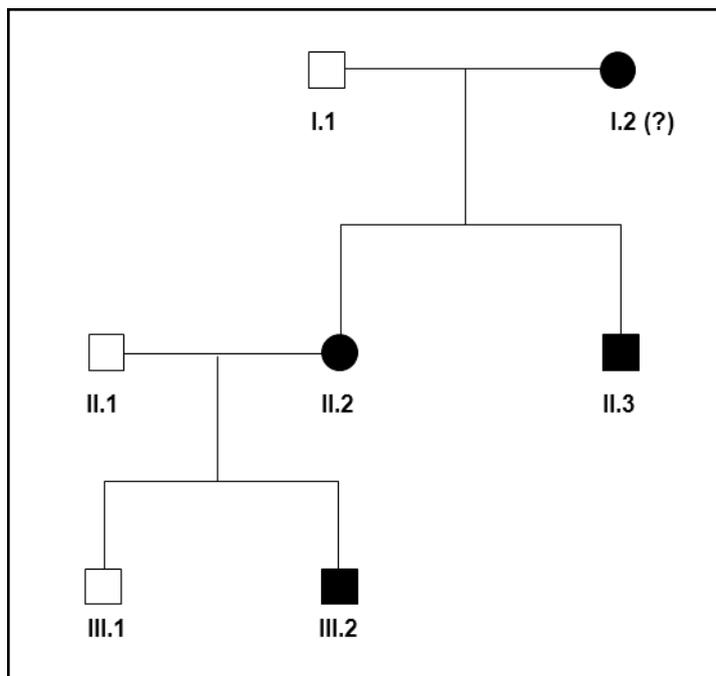


Fig. 2. Pedigree of the family "B" with lymphedema distichiasis.

without persistent success. He was diagnosed with primary lymphedema when he was about 11 years old. He was treated with complex decongestive therapy and currently uses grade 2 compression knee-high stockings and antibiotics for recurrent skin infections. He is also under treatment for hypertension. On physical examination, foot and calf edema was observed with positive Stemmer's signs and varicose veins on both legs.

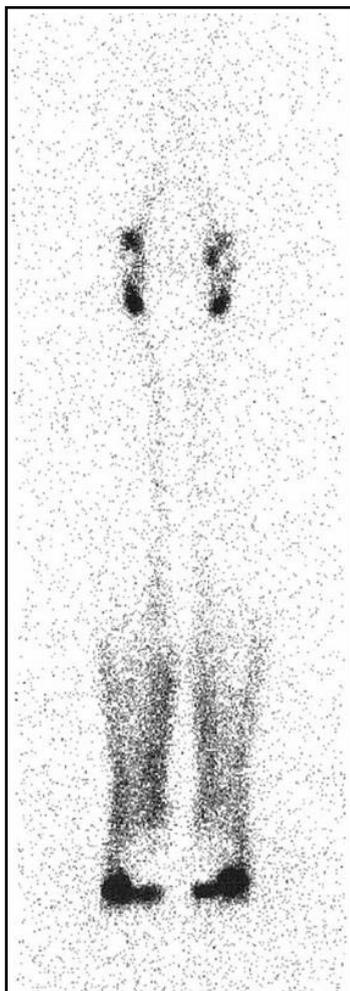
His family history is notable with the same ophthalmic problem and bilateral leg lymphedema in his mother (I.2) since she was 12 years old. She has used only compression knee-high stockings and has removed accessory eyelashes by herself. She is a 53 year old Caucasian woman with no other disease. His father (I.1) is a 53 year old Caucasian man with no chronic medical problems. His sister (II.3) is a 26 year old Caucasian woman with no chronic medical problems.

In the second family (family "B"; Fig. 2): a 16 month old Caucasian boy (III.2) presented to Ophthalmology Clinic due to

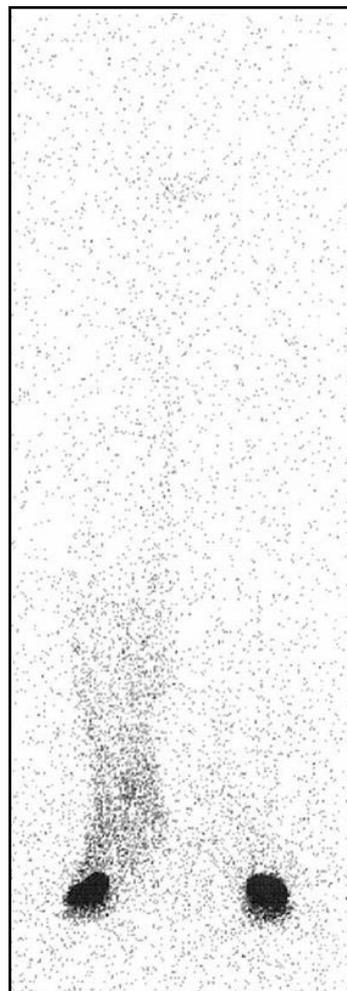
recurrent corneal irritation. The problem was diagnosed as distichiasis and resolved by epilation with local anesthesia. There was no other medical problem including no leg edema.

His mother (II.2), a 29 year old Caucasian woman, was diagnosed many years ago with distichiasis during routine ophthalmic consultation, however she has no corneal abrasion. Problems have been resolved by epilations from time to time. She has bilateral leg lymphedema, diagnosed at age 16, primarily misdiagnosed as venous insufficiency. She is using grade 2 compression knee-high stockings. She has no other medical problems (such as varicose veins).

Her mother (I.2.) is a 56 year old Caucasian woman with no leg swelling, who suffered from distichiasis since childhood (she removes them by herself). She lives in a small village and did not agree to a physical examinations. Her father (I.1) is a 57 year old healthy Caucasian man. Her brother (II.3) is 33 years old with both problems: lymphedema since age 16 and distichiasis since childhood.



*Fig. 3. Bilateral lower extremity lymphoscintigram – patient II.2 from family B.*



*Fig. 4. Bilateral lower extremity lymphoscintigram – patient II.2 from family A.*

He is treated using compression knee-high stockings and epilations for distichiasis.

The boy's father (II.1) suffered from hypertension but has no other medical problems.

His older brother (III.1) is 5 years old with no signs of distichiasis and/or swelling.

Lower extremity lymphoscintigraphy was performed in patient II.2 from family A and in patient II.2 from family B. In one of the patients (II.2 B), the lymphoscintigraphic pattern was consistent lymphatic valvular insufficiency (severe, bilateral “dermal

backflow” with visible lymphatic trunks and proximal lymph nodes) (*Fig. 3*), however, in the other patient (II.2 A), lymphoscintigraphy was typical for peripheral lymphatic obstruction with “dermal backflow” and no visualized lymph nodes (*Fig. 4*).

A mutation in FOXC2 was confirmed for this patient (II.2A) with atypical lymphatic changes.

#### **SUMMARY AND CONCLUSIONS**

The clinical diagnosis of lymphedema is

not always straightforward except in advanced cases with classical skin changes, and confirmatory investigation should include lymphoscintigraphy. Lymphoscintigrams of patients with LD typically reveal good transport of the tracer from the feet to the inguinal and iliac lymph nodes and reflux of tracer into the skin lower leg (“dermal backflow”) (6,9), whereas patients with obstructive type of lymphedema show slow or lack of the isotope transport and little or no visualization of regional lymph nodes and “dermal backflow” related to lymphatic reflux (6).

Distinctly different lymphoscintigraphic patterns in our two patients revealed two different types of lymphatic system defects present in families with distichiasis lymphedema syndrome. Two possible types of lymphatic system abnormalities (lymphatic hyperplasia and hypoplasia) may be present in subjects with distichiasis-lymphedema syndrome, and this observation may agree with the recent discovery of a novel FOXC2 mutation (16).

We believe that this is the first lymphoscintigraphic documentation of different types of lymphatic abnormalities in patients with LD syndrome.

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