DISTICHIASIS AND LYMPHEDEMA
A HEREDITARY SYNDROME WITH POSSIBLE MULTIPLE DEFECTS
A REPORT OF A FAMILY

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DISTICHIASIS, THE PRESENCE OF an extra row of lashes at the site of the meibomian gland openings, is a rare and dominantly inherited condition. It may be an isolated abnormality or may occur with a variety of other defects (Table 1).

Hereditary lymphedema (Nonne-Milroy-Meige Syndrome) is also a rare condition affecting the lower extremities, with onset of the swelling varying from the time of birth to early adulthood. Various vascular, neurological, and occasionally ocular abnormalities have been reported in patients with this disorder.[1]

The specific association between distichiasis and hereditary lymphedema was first reported by Campbell,[2] who also noted the occurrence of strabismus in the same pedigree (Figure 1). A more extensive study by Falls and Kertesz[3] included pterygium colli and partial ectropion of the lower lid, along with the abnormal lashes and lymphedema, in a hereditary syndrome. In addition to the association of multiple conditions seen in their primary family (Figure 2), these authors also reported a sporadic case of distichiasis and lymphedema alone. More recently Robinow, Johnson, and Verhagen,[4] in a summary of three additional families have characterized Lymphedema-Distichiasis as a hereditary syndrome of multiple congenital defects. The families reviewed showed vertebral anomalies and spinal extradural cysts in addition to the two principal features of the syndrome. In addition, some of the affected members had other disorders in which the relationship to the hereditary condition was not clear (Table 1).

The six patients reported here represent three generations of one family (Figure 3). All four adults showed both distichiasis and lymph-

TABLE 1. OTHER ANOMALIES ASSOCIATED WITH LYMPHEDEMA, DISTICHIASIS, AND THE DISTICHIASIS–LYMPHEDEMA SYNDROME

Lymphedema	Ref. No.	Distichiasis	Ref. No.	Distichiasis-Lymphedema	Ref. No.
Turner's syndrome	8	Congenital ectropion	16	Webbed neck	8
Vascular anomalies		Mandibulofacial dysostosis	12	Partial ectropion	8
Urinary anomalies	14	Ptosis	10	Vertebral anomalies	4
Strabismus	10	Strabismus	3	Spinal extradural cysts	4
Ptosis	1	Syndactyly	10	Bronchial asthma	4
Spina Bifida	1	High myopia			
Mental deficiency	1	Dental anomalies	2		
Epilepsy	1	Mental deficiency	16		
		Epicanthus	5		

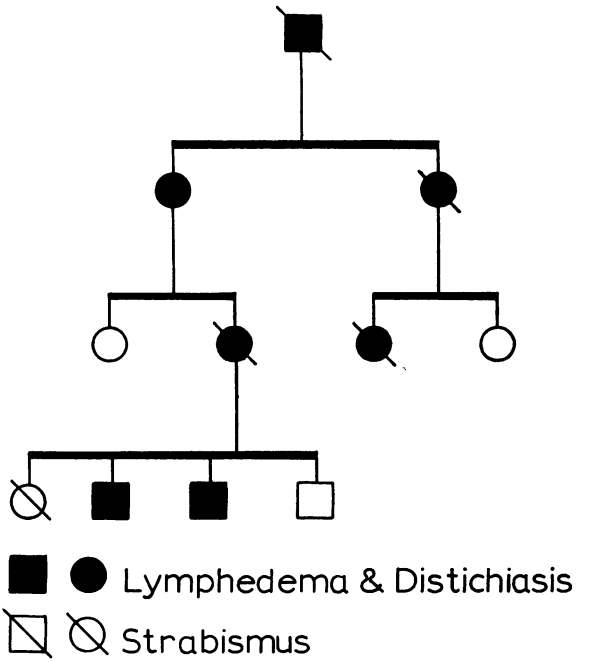

FIGURE 1

A family with Distichiasis and Lymphedema also associated with Strabismus (redrawn from Campbell).

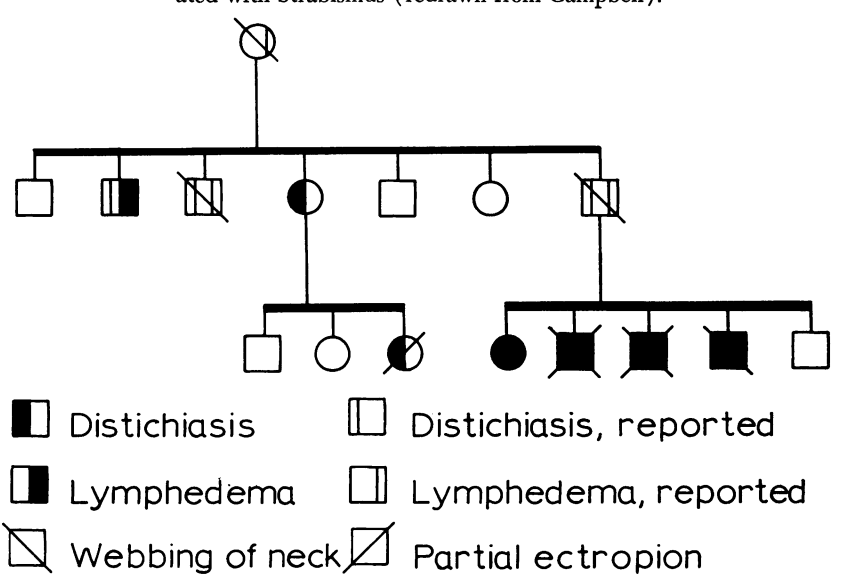

FIGURE 2

A family with Distichiasis and Lymphedema also associated with Pterygium Colli and partial Ectropion (redrawn from Falls and Kertesz).

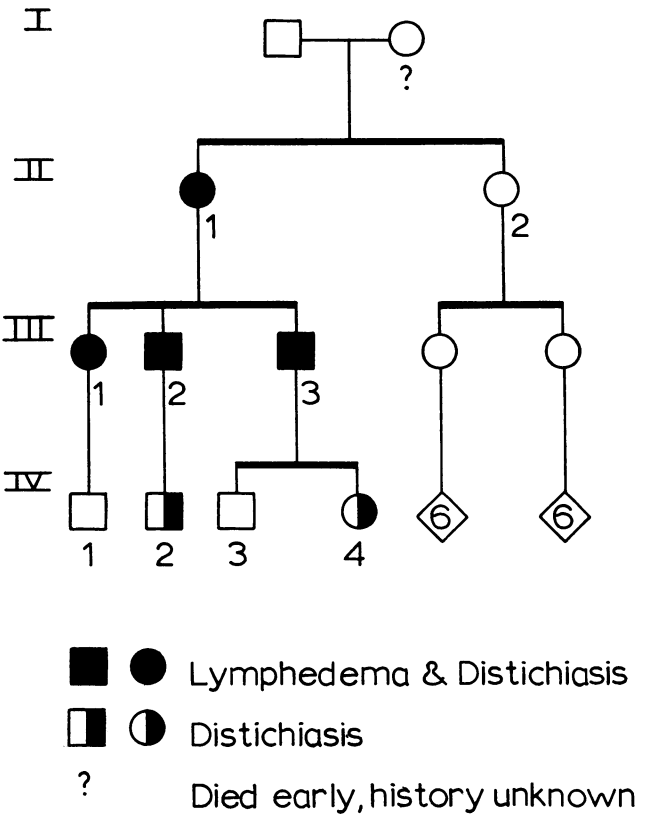

FIGURE 3
A previously unreported family with Distichiasis and Lymphedema (Hoover and Kelley family).

edema of the legs. The two younger patients did not exhibit clinical swelling of the extremities but did show distichiasis of all four lids. There was some coincidence between the presence of distichiasis and astigmatism of three diopters or more in this family.

CASE 1

This eight-year-old negro male (IV_2, Figures 4–7) was referred as part of a general examination relating to his poor performance in school. He complained only of occasional episodes of photophobia.

He was small for his age, in the tenth percentile of both height and weight, while head circumference was at a third percentile (48-cm). An appearance of mandibular hypoplasia was attributed to premaxillary overbite and per-

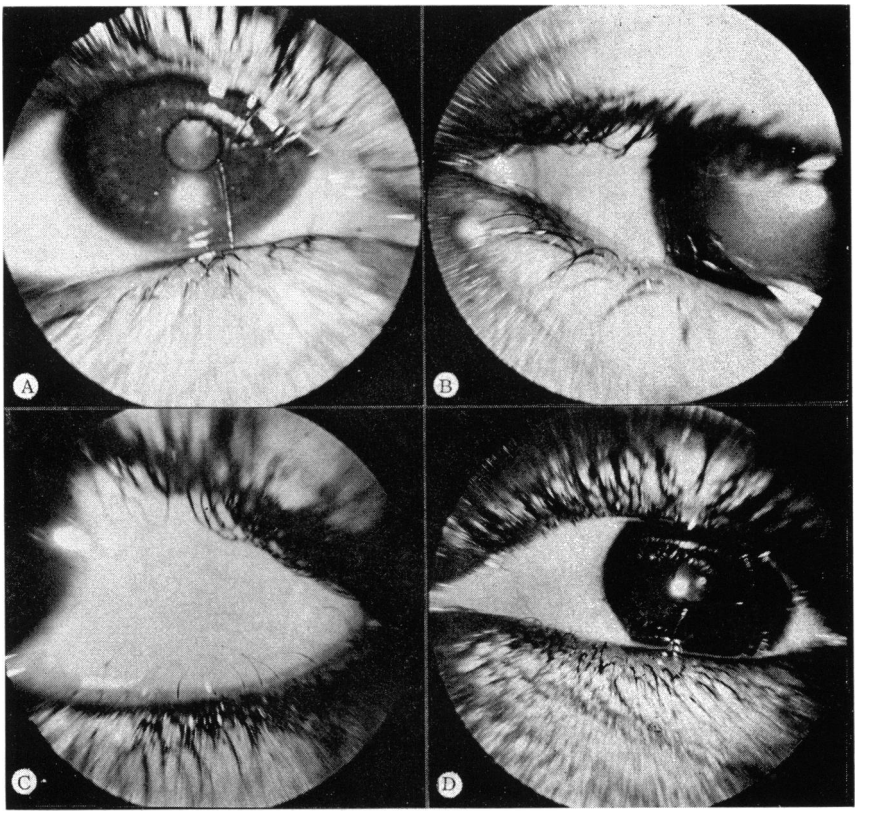

FIGURE 4

Distichiasis of all four lids was seen in all cases. A, II (1) single large pigmented cilia right eye. B, complete row of cilia on the left. C, cilia at the meibomian gland openings case III (1). D, cilia touching cornea case IV (2).

sistent thumb sucking and no other evidence of mandibulo-facial dysostosis was found.

The ocular exam showed a mild hyperopia with an astigmatism of +3 diopters at 90 degrees in each eye. The vision was 20/25 in each eye. All lids were involved with distichiasis. Ten to twelve fine hairs occupied the usual site of the meibomian glands along each lower lid, extending upward and backward to contact the globe. Only two or three hairs were seen on the upper lid; these were longer but less centrally located and did not reach the cornea. There was very slight but definite superficial staining of the cornea on the initial examination. Bilateral epicanthus was noted but no other lid abnormality was detected.

Because of the episodes of photophobia and the corneal staining, the abnormal hairs were removed with electrolysis of the follicles under the operating microscope.[5]

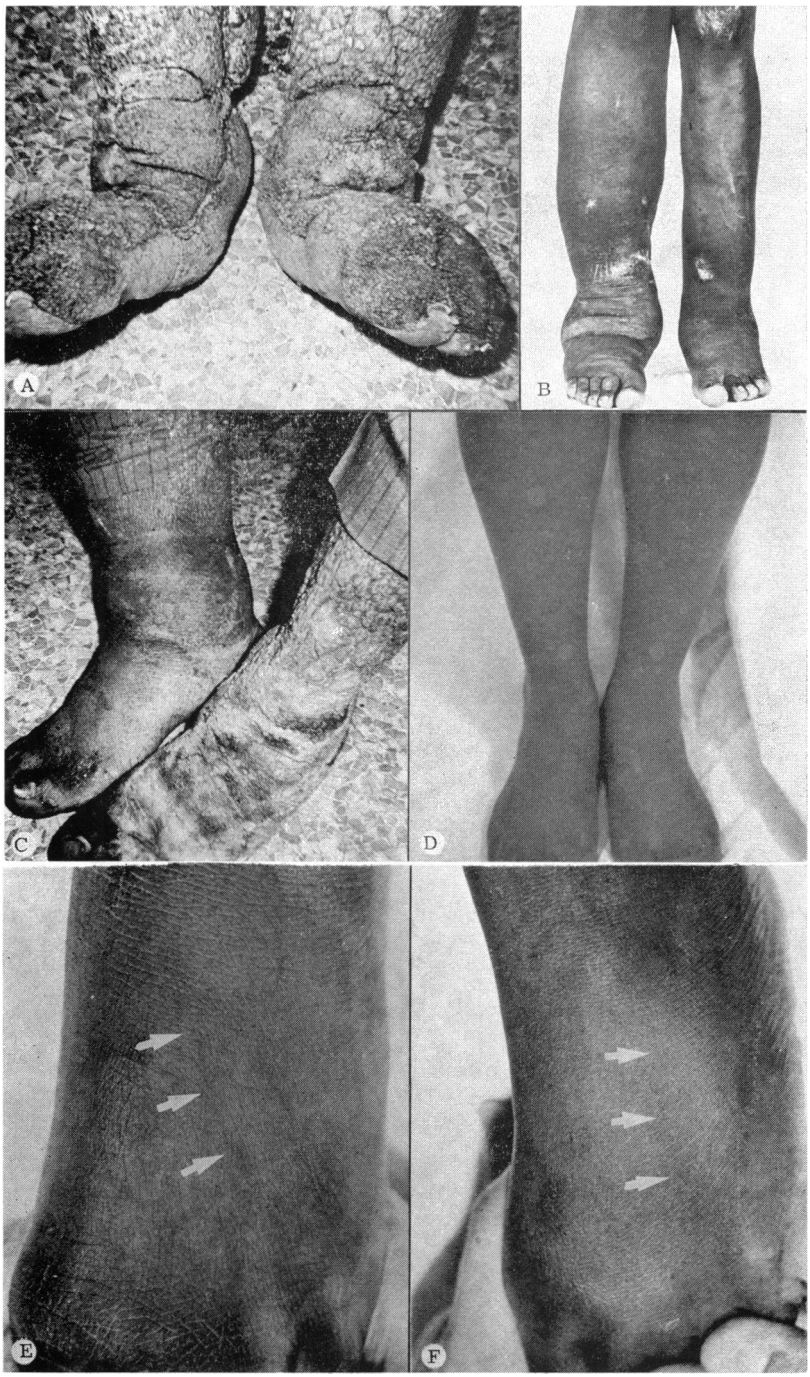

FIGURE 5

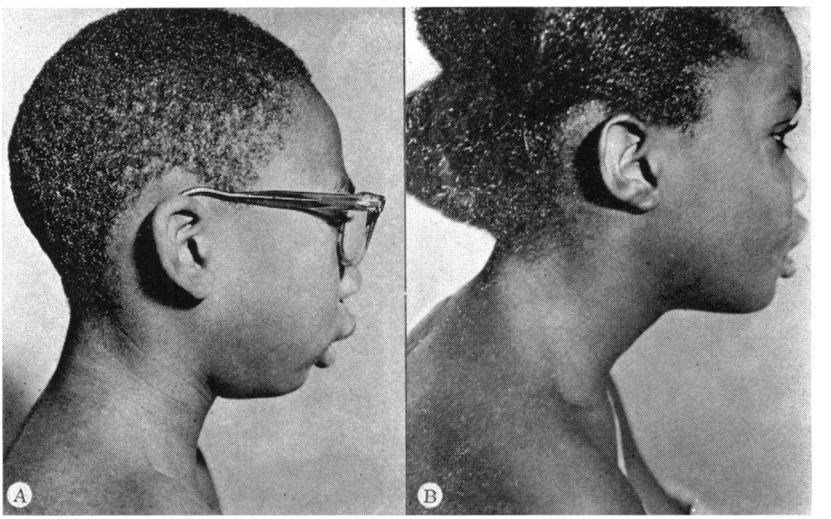

FIGURE 6
No clear evidence of webbing of the neck.

When the familial occurrence of lymphedema became evident, an alph-azurine blue dye test was performed in an attempt to outline the lymphatics of the lower extremities. The dye spread rapidly from the sites of injection at the interdigital spaces and appeared soon after in the urine. Both popliteal and inguinal nodes could be palpated. These results ruled out complete aplasia of the lymph system. Other anomalies of the lymphatics may be present but the consulting radiologist reported the injection of the more irritating radio-opaque dye to be hazardous in the presence of impaired drainage and a complete lymphangiogram was not performed.

Examination one year following the removal of the lashes found a complete row of abnormal hairs again present along the lower lids. However, he was asymptomatic and doing better in school. No further surgical therapy was undertaken.

CASE 2

The 52-year-old paternal grandmother of the propositus (II_1, Figures 4–7) had been seen three years earlier for intermittent blurring of vision, tearing, and irritation. Abnormal hairs were noted on all lids and a diagnosis of acquired inflammatory trichiasis was made. Bilateral corneal staining was

FIGURE 5
Lymphedema in all adults but not in children. A, case II (1). B, Case III (2). C, Case III (3). D, Case III (1) controlled on conservative therapy. E, Case IV (2) after injection of dye, no edema, dye has spread along foot (arrows). F, Case IV (4) after injection of dye, no edema, dye has spread along foot (arrows).

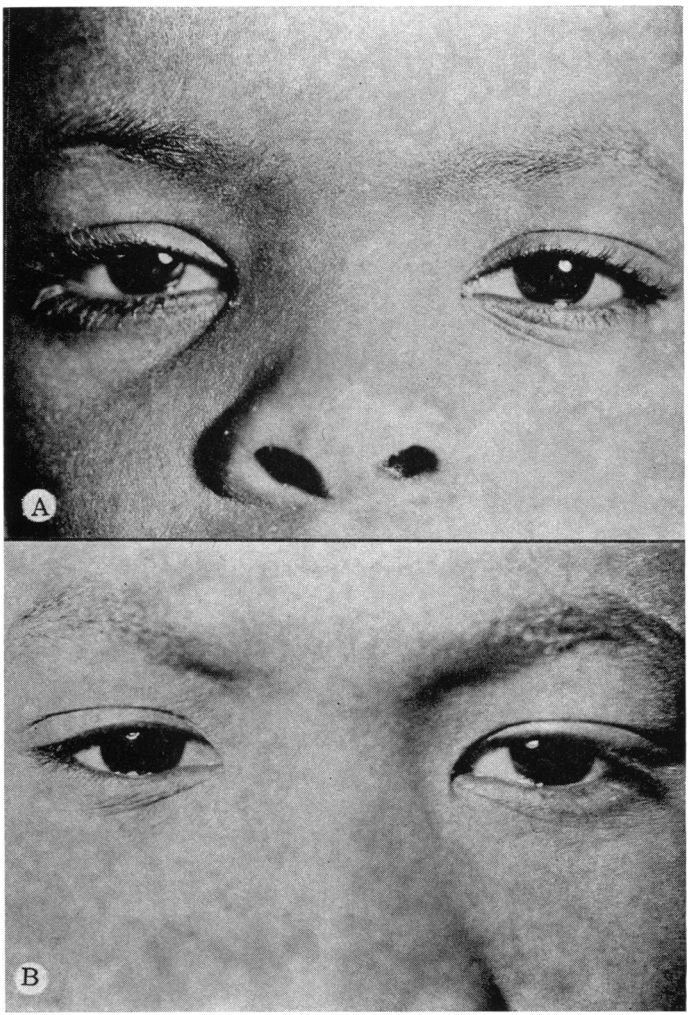

FIGURE 7
No clear evidence of ectropion.

found on the initial visit. In August, 1967, all the extra lashes were removed with electrolysis to the follicles. Ocular examination in March, 1970, showed a vision of 20/30 + 2 in each eye, with correction of − 2.00 + 3.75 × 170 OD and − 4.25 + 4.00 × 60 OS. A total of thirty lashes was seen exiting from follicles located at the usual site of the meibomian glands. These were heavier and more obvious than those in her grandson but the eyes were white and quiet. Only slight superficial punctate staining was detectable. The remainder

of the eye examination was unremarkable. She was asymptomatic and did not desire any further therapy for the abnormal lashes.

Her medical history included diuretic therapy for mild hypertension and swelling of the lower extremities. Examination of the legs revealed lymphedema of an extreme degree (Figure 5A). This swelling had progressed gradually since the age of ten with no relation to trauma or infection. All surgical procedures had been rejected and the only form of therapy, aside from intermittent diuretics, was elastic stockings. She had no complaints related to the lymphedema and led an active life.

CASE 3

This 24-year-old negro male (III_2, Figures 4–7) refused a complete examination. The following is a summary of his surgical record and an incomplete examination in his home.

In 1960 while working in construction, a ladder struck his left ankle causing an ulcer which failed to respond to local therapy. During multiple accident room visits, mild varicosities were noted. Tests for sickle cell hemoglobin and syphilis were negative. He was next seen in March, 1968, when swelling was noted in both legs, the right being more severe than the left. A succession of operations were performed to excise the swollen tissue and cover the involved area with split thickness skin grafts (Kondoleon procedures). The surgical specimens showed low-grade inflammation, scarring, and lymphangiectasis consistent with long standing edema. Two years later he still experienced some trouble with weightbearing on the right foot and there was some deformity of the right foot position due to scarring.

A limited examination of the eyes showed seven or eight fine, lightly pigmented lashes at the posterior border of each lower lid and three abnormal lashes on each upper lid at the usual site of the meibomian glands. He was asymptomatic and refused further examination and any form of therapy.

CASE 4

This 26-year-old male (III_3, Figures 4–7) also refused a complete ocular examination in the clinic and was seen in the home. He gave a history of swelling of the lower legs since the age of nine, with no associated trauma or ulcers. A review of his records showed that pitting edema of the lower legs and lichenification of the skin had been noted on admission for appendectomy in 1965. According to the patient, a surgical procedure had been performed on the legs in the past, presumably of the Kondoleon type similar to his brother's operation. He made sporadic emergency room visits for treatment of bronchial asthma. At the time of the field visit he was relatively asymptomatic both in regards to his legs and any ocular problems.

A brief ocular examination showed no abnormalities other than the distichiasis, which affected all four lids. The hairs were of the fine, lightly pigmented type. No corneal changes could be seen with the handlight and loupes.

CASE 5

This 25-year-old female (III_1, Figures 4–7) gave a history of mild intermittent swelling of the lower legs, which was much worse during her one pregnancy. She was treated with diuretics at that time. She was essentially asymptomatic at the time of examination with no complaints of ocular irritation, tearing, or photophobia.

Ocular examination showed an uncorrected vision of 20/20 in each eye with no significant astigmatism. A complete row of twenty fine lashes was found at the posterior margin of the lower lids on both sides, four widely spaced abnormal lashes on the right upper lid, and two larger more heavily pigmented lashes on the left upper lid. There was very fine superficial punctate staining of the lower cornea on the right.

CASE 6

This eight-year-old female (IV_4, Figures 4–7) had been followed at irregular intervals since the age of one month. The earliest records reveal that the delivery was complicated by premature rupture of the membranes and that the mother was febrile at the time of delivery. She was treated for "iron deficiency" anemia during the first year of life. An inability to talk was clearly evident by the age of four. An examination for hearing and speech defects showed no physical or biochemical cause for the learning problem. Psychological testing found her IQ in the "trainable retarded" range (below 55).

She gave no positive responses to questioning about ocular symptoms but the mother stated that she would occasionally rub the eyes and act as if there was some irritation. The vision could not be tested other than noting the ability to follow the light with each eye. Retinoscopy after cycloplegia showed a $0.0 + 3.50 \times 90$ astigmatism in each eye.

Distichiasis affected all four lids but there were fewer lashes than in the preceding patients; two on each lid of the right eye and three on each lid of the left eye. There was no corneal staining.

The lower extremities appeared normal except for some thickening and hyperpigmentation of the skin in the area of some superficial scars. An alph-azurine blue dye study was performed. It showed rapid spreading of the injected dye, clearly outlining the lymphatics of both feet and the lower legs. As in the first patient, absence of lymphatics was ruled out but other anomalies such as hypoplasia or ectasia could not be eliminated.

In addition to the above affected members of the family, five unaffected direct descendants were examined along with the two unaffected spouses.

CASE 7

This 60-year-old female (II-2) was examined in her home after refusing a complete examination. She was found to have no ocular abnormalities and no evidence of lymphedema.

CASE 8 AND CASE 9

The two daughters (III-4, 5) of patient number seven showed no evidence of distichiasis or lymphedema. By history, their twelve children are said to be in good health up to the present time.

CASE 10

This six-year-old cousin (IV-1) of the propositus had 20/20 vision with a retinoscopy of − 0.50 sphere in each eye. There was no evidence of abnormal lashes or other ocular anomalies.

CASE 11

This seven-year-old male (IV-3) showed no ocular or systemic abnormalities. His vision was 20/20 in each eye with a retinoscopy of 0.0 + 1.00 × 115 OD and 0.0 + 0.75 × 95 OS.

CASE 12

This 28-year-old mother (III-2a) of the propositus was essentially normal with a correction of − .75 + .75 × 90 giving vision of 20/20 in each eye.

CASE 13

This 24-year-old mother (III-3a) of patient number six was also essentially normal with an uncorrected vision of 20/20 in each eye and a retinoscopy of + 0.50 in each eye.

COMMENT

The association between lymphedema and distichiasis appears to be firmly established. It was the most common single association in all reported pedigrees and was the only finding in the isolated case reported by Falls and Kertesz. As noted by these authors, the two entities as separate conditions are extremely uncommon. Our own review of hospital records, covering a period during which there were more than 300,000 ophthalmological outpatient visits, unearthed no other examples of distichiasis. The diagnosis of familial lymphedema was indexed only eighteen times in the same period.

The true incidence of lymphedema with distichiasis is not clear. The lymphedema is the more dramatic condition and had been diagnosed and treated prior to our investigation in all of the adult patients. Despite repeated general and ocular examinations, the distichiasis was not diagnosed in any of the adults until specifically sought for in our study. Patient number two had been diagnosed and treated at the clinic as having acquired or inflammatory trichiasis until the familial nature of the disorder became clear. In one of the early reports of hereditary

lymphedema,[6] the initial contact was related to persistent and unexplained blepharitis. This may have been related to eyelid or eyelash anomalies but there was no further mention of this in the report. It will require a careful examination of many patients with hereditary lymphedema before the true extent of the association can be determined.

The association of other anomalies with the above two entities is another area of some uncertainty. Our family did not show clear evidence of pterygium colli or partial ectropion as noted by Falls and Kertesz; nor was there any ptosis, strabismus, spine or facial abnormalities as reported by other authors. There was epicanthus but only in the children. Variation in this regard is not unexpected. Even in the family reported by Falls, only two of the ten affected members had all four features of their syndrome. Some variation in the number of positive findings may be related to age. Thus the lymphedema in all cases associated with distichiasis had been of the Meige type (onset near puberty). Perhaps the expression of the gene varies from one family to another. Three affected members of our family had an astigmatism of three diopters or more. This was not found in the unaffected relatives. This may be due to chronic low grade irritation or may, more possibly, be related to the underlying genetic mechanism. The association with mental retardation may be fortuitous, although it has been noted by other authors.[7] The association with spinal abnormalities has been found in three families and deserves emphasis as a potential cause of subtle neurological complaints. The importance of other associations requires further delineation.

Falls and Kertesz reviewed a number of the possible genetic mechanisms which might account for the simultaneous occurrence of distichiasis and lymphedema. A single autosomal dominant gene determining both conditions seemed to be the most likely explanation. We tried to determine if this gene was linked to (on the same chromosome as) any of the genetic markers currently being used in attempts to map the chromosomes. These included over twenty blood group, cell type, and protein characteristics. With eight of the ten immediate family analyzed, no linkage pattern could be found.

The treatment of distichiasis has been discussed by Fox, who found, as in our cases one and two, that epilation with electrolysis had only temporary effects.[8] He suggested an operation to remove a strip of the posterior lid margin including the abnormal follicles. This more radical form of therapy has been deferred since our patients have had only occasional symptoms and no evidence of corneal scarring. A conservative approach to the lymphedema is also advised since many adults lead an active life despite gross edema; however, chronic infections or other indications may dictate surgical intervention.

SUMMARY

A family of six members representing three generations is presented; the four adults affected by both distichiasis and hereditary lymphedema, the two children affected by distichiasis of all four lids but no evidence, as yet, of lymphatic abnormality. Other associated conditions reported by previous authors (pterygium colli, partial ectropion, and spinal abnormalities) were not seen in these patients. A rare autosomal dominant gene is assumed to determine both conditions. Linkage between this gene and the available genetic markers could not be established.

ADDENDUM

Since this paper was prepared, a second family has presented to our clinic. We have had a chance to examine the eyes of the mother and eight children. The 40-year-old mother and nine-year-old daughter sought help because their eyes were itching and burning.

The mother had distichiasis of all four lids without staining of the corneas, a small angle strabismus (10–15 prism diopters of esotropia), epicanthus, partial ectropion of the lower lids, pterygium colli, and spinal abnormalities on x-ray. She had good vision without glasses and no neurological complaints. Further studies have not been performed. The roentgenograms were read: "... The right pedicle of T8 appears small in comparison to other similar structures and in the lateral projection from T8 inferiorly to T12, the sagittal diameter of the spinal canal appears to be enlarged ..." No myelograms or further studies have been performed.

The nine-year-old daughter had distichiasis of all four lids without corneal staining, partial ectropion of the outer aspect of her lower lids, good vision without correction, epicanthus, pterygium colli, and mild lymphedema of the lower limbs. The spinal roentgenograms were read: "... The interpedicular distances of L1 through L5 are uniformly enlarged over the standards for this age by at least 3-mm. The sagittal diameter of the spinal canal at this level appears normal ... ."

An eight-year-old son, who had no complaints and was said to be normal, had distichiasis of all four lids without corneal staining. He did not have pterygium colli, no ectropion of the lower lids, and no lymphedema. Spinal films have not been taken.

A six-year-old asymptomatic daughter was said to be normal but had distichiasis of all four lids. There was questionable pterygium colli and questionable partial ectropion of the lower lids. There was no lymphedema. No spinal films have been obtained.

No spinal films or further studies have been performed on any other

members of the family. Five other siblings have none of the observable characteristics we have associated with this syndrome. Because of their very recent visit, the examinations are as yet incomplete.

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DISCUSSION

DR FALLS. I would like to discuss this paper in three aspects – (1) awareness, (2) textbook picture, and (3) treatment.

We see what we are aware of and we see what we are looking for.

Second, textbook picture. The point has been brought out ably by the authors that there is a great variation in expressivity of this gene, and I would like to state that you won't see a complete textbook picture in one individual. This is extremely rare. You have to look for the subtle variations of these genetically ascertained diseases so that when you see one or two of them you begin to look for others, or at other members of the family to make a complete compilation of the diseases' spectrum. In my family I was not aware of any vague neurological complaints; we will review my family again for this interesting possibility of extradural cyst.

Treatment: Be conservative. At first I attempted to get rid of the lashes, and they came back in, really coarse cilia. They are very uncomfortable. The original cilia are usually a soft type of cilia and don't give too much trouble. Leave them alone.

Lastly, I would like to re-emphasize the point that whenever you have an hereditary disorder, look at other members of the family. You can tell these individuals that this is a dominantly inherited trait, and their children have one chance in two of being affected.