CORNEAL DYSTROPHY ASSOCIATED WITH CONGENITAL ICHTHYOSIS AND ALLERGIC MANIFESTATIONS IN MALE MEMBERS OF A FAMILY*

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In the complete form of this familial syndrome males suffer from corneal dystrophy, congenital ichthyosis (ichthyosis simplex), and allergic manifestations such as asthma and hay fever. The complete syndrome was noted in two patients. Other male members had corneal dystrophy and allergy, corneal dystrophy and ichthyosis, ichthyosis alone, ichthyosis and allergy, or asthma (Fig. 1). Except for two debatable cases, transmission of the syndrome occurs through apparently unaffected females.

FIG. 1.—Pedigree chart of family group. The anomalous marking of IV. 1 represents the occurrence of a corneal “white ring”.

Corneal Dystrophy.—This manifests itself as small, highly refractile nodules in the corneal epithelium, in the superficial layers of the corneal stroma, and in the endothelium (Fig. 2, opposite). The superficial and endothelial nodules are circular and mostly equal in size. In some areas two or more dots are adjacent like a short string of crystalline beads. The nodules in the corneal stroma are similar in appearance but more variable in size. There is little interference with vision.

Occasionally these eyes experience sudden attacks of pain when they feel as if “full of red-hot sand”. There is severe photophobia and watering, and the pain is aggravated when the lids move across the cornea. One patient (III. 4) has trained himself to relieve the pain by drawing the lids away from the globe. The lids themselves are swollen and purple at the height of an attack. Attacks

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FIG. 2.—Typical slit-lamp appearances of the corneal dystrophy as seen in the proband (III. 4).

usually last 2 to 3 hours, but the period is inconstant, varying from a few minutes to an exceptionally severe attack recorded as lasting for 18 hours. Attacks commonly occur on opening the eyes in the morning. The story is reminiscent of that of a recurrent epithelial erosion of the cornea, but no breach in epithelial continuity has been actually observed. Patients know by experience that the acute symptoms will pass over, and by the time they have presented themselves for consultation the eyes shew a little conjunctival injection and the ordinary appearances of the dystrophy. There is photophobia during the later stages although epithelial breaches of continuity are not demonstrable. The attacks occur with varying degrees of severity but are roughly proportionate to the degree of corneal involvement. This varied considerably in four brothers examined (Fig. 3; III. 3, 4, 5, and 7). The instillation of a drop of lubricant such as paroleine at night proved an effective prophylactic measure.

FIG. 3.—Variations in extent and distribution of corneal dystrophy noted in III. 3, III. 4, III. 5, and III. 7.

The cornea of one female member (IV. 1) shewed a "white ring". Both eyes of this patient shewed remnants of pupillary membranes. No other abnormalities were noted in other females examined.

Skin Lesions.—Affected patients suffered from a moderately severe form of congenital ichthyosis (ichthyosis simplex). The trunk and limbs were most affected by the characteristic scales (Fig. 4, A and B). The skin of the patients' faces was comparatively lightly disfigured. In no case was there any tendency to ectropion, or any difficulty in closure of the eyes. The corneae were adequately protected from exposure, which played no part in producing the corneal lesions.

FIG. 4.—Legs of III. 4, shewing typical appearances of ichthyosis simplex.

All stated that they had suffered from their skin trouble from early years. One had been told that his skin was normal before the age of 2 years. The others "had always suffered from" their ichthyosis. All were able to lead normal lives if their scaly skins received regular attention. Life in the services had been a little embarrassing as their comrades often feared infection. Hot weather proved beneficial so that one patient (III. 3) was benefited by sunbathing, and another (III. 5) found that his skin shewed great improvement when he was stationed at Singapore.

Although many members of the family shewed allergic manifestations of one sort and another, this atopy did not seem to affect the skin. There was no history of the eczematous exacerbations from which many cases of ichthyosis simplex are liable to suffer.

Allergic Manifestations.—An interesting study was that of the allergic manifestations which appeared in several male members of the family. These consisted

in individual cases of "hay fever", or asthma or both. For instance, one man (III. 3) always developed "hay fever" when he put on one particular suit of clothes; in the past he had had occasional attacks of asthma. A second brother (III. 4) suffered from "hay fever". Case III. 7 always got asthma when the cocker spaniel belonging to III. 3 approached; on one occasion when he had a bad attack of asthma unexpectedly, he found that the dog had previously been in the house without his knowledge. It was interesting to find that III. 5 suffered from ichthyosis and corneal dystrophy but not asthma. However, his son IV. 3 developed severe asthma, though he avoided the ichthyosis and the corneal dystrophy.

Detailed Description of Individual Cases

All the known members of the family are identified by the serial pedigree numbers shewn in Fig. 1. Where individuals were not examined by the author the source of the information is noted. The family evidence has been cross-checked by several individuals as far as possible and the sources of such information are cited. With one or two exceptions the intelligence of the witnesses was of a high order, and their information can be considered accurate as far as it goes.

The more medically interesting members of the family group are marked with an asterisk.

FIRST GENERATION

I. 1 (husband of I. 2) died years ago but was personally known to III. 3 and 4; he is reputed to have been unaffected by the syndrome.

I. 2 (wife of case I. 1) now dead, was unaffected according to the evidence of III. 3 and 4.

*I. 3 (Neil), now dead, is reputed unaffected according to III. 3, 4, 5, and 7. He was the first husband of I. 4 whose place in the pedigree is of importance. By this marriage he was the father of two apparently unaffected daughters (II. 6 and 7). He was unrelated to I. 5 (Costello) the second husband of I. 4.

*I. 4, now dead, is reputed apparently unaffected on the evidence of III. 3 and 4. By her first husband (I. 3) she had two daughters (II. 6 and 7). Her daughter (II. 7) was the mother of the main group of patients considered. In her second marriage to I. 5 she had two sons: II. 8 with ichthyosis and asthma, and II. 9, with ichthyosis. She was thus plainly responsible for the transmission of the syndrome.

*I. 5 (Costello), now dead, was unaffected according to III. 4. He bore no relationship to I. 3. His marriage to I. 4 produced two affected sons (II. 8 and 9).

SECOND GENERATION

II. 1, now dead, was unaffected according to his children (III. 3, 4, 5, and 7). His marriage to II. 7 produced five children who were all abnormal (III. 3-7).

II. 2, female, now dead, was unaffected. She produced two unaffected sons (III. 1 and 2).

II. 3-5, three sons of I. 1 and 2, were all unaffected by the syndrome, and are now dead without issue. The evidence of III. 3, 4, 5, and 7 is conclusive.

II. 6, female, daughter of I. 3 and 4, is now dead but was well known to III. 3, 4, 5, and 7. She seems to have had a cataract in one eye. There were no signs of her being affected by the syndrome. Her husband was healthy and unrelated to the others and she had an unaffected son (III. 8).

*II. 7, now dead, was the wife of II. 1. She was apparently unaffected by the syndrome,

but all her children (III. 3-7) were abnormal. There is an odd history of her going blind for 14 days and then recovering. None of her children could give the exact cause of this attack; from their descriptions it was probably of functional origin.

*II. 8, now dead, the elder son of I. 4 and 5, was well known to III. 3 and 4. He suffered severely from ichthyosis and also from asthma, but his eyes were unaffected. He had two daughters (III. 9 and 10), who were unaffected as far as other members of the family knew.

*II. 9, now dead, younger son of I. 4 and 5, had severe ichthyosis according to III. 3 and 4, but his eyes were unaffected and there was no record of asthma or other allergic affection. He had three unaffected daughters (III. 11-13).

THIRD GENERATION

III. 1 and 2, sons of II. 2 by an unrelated husband, are unaffected. They have no children (Evidence of III. 3).

*III. 3, aged 50 years, son of II. 1 and 7, a highly intelligent toolroom machinist, has suffered all his life from congenital ichthyosis. He practises sunbathing so as to cause desquamation and has found that tea leaf poultices give relief by softening the skin. His corneae shew a moderate degree of dystrophy with nodules in the epithelium, superficial corneal stroma, and endothelium (Fig. 3). He has frequent attacks of pain and photophobia, the average attack lasting 3 to 4 hours and temporarily incapacitating him. He also gets attacks, of "hay fever" but not always from pollen. For instance, if he wears a particular suit an attack will ensue. He has in the past had attacks of asthma, but latterly these have become infrequent. He has two daughters (IV. 1 and 2). This patient and his daughters were examined by L. H. Savin.

*III. 4, proband, son of II. 1 and 7, has been examined on numerous occasions by the author. He is aged 47 years, an active and intelligent man, and the manager of a busy firm of timber merchants. He has had ichthyosis as long as he can remember, and gets frequent attacks of vasomotor rhinitis "like hay fever". Both corneae shew corneal dystrophy with epithelial, superficial stroma, and endothelial nodules (Figs 2 and 3). He has been having attacks of pain in his eyes since 1916. In a typical attack he woke up in distress at 3 a.m., and his wife reported that he had previously been "sniffing in his sleep". On opening his eyes he felt excruciating pain, "like red-hot sand in his eyes". This became even worse as his lids "ground across his eyeball". His eyelids felt as if "blistered underneath" and they were swollen and purple. The eyes poured with tears. He managed to ease the pain by pulling the lids away from the eyeball. The acute phase lasted 10 minutes and gradually passed off in 7 to 8 hours. Watering of the eyes continued longer so that he was unable to report for work for 18 hours. On slit-lamp examination 2 days after the attack there was no sign of any breach in the corneal epithelium though there was a mild conjunctival congestion. The corneal dystrophy appeared as usual. A slit-lamp examination has been made after several attacks with similar findings. His corrected vision in each eye is 6/5 and J.1.

*III. 5, also examined by the author, son of II. 1 and 7, office worker aged 44 years, has always had ichthyosis simplex, which was much improved when he was in Singapore. The corneae shew the family dystrophy (Fig. 3), though the dots are more highly refractile than usual, almost appearing crystalline. The visual acuity is 6/4 in each eye.

He has had attacks of pain in the eyes, but not so severe as his brothers. In a typical attack he awoke in pain with watering eyes at 2 a.m., but by 8 a.m. the trouble had passed. The last serious attack was in 1944, though he has had minor recrudescences. He attributes this comparative immunity to the care he now takes to avoid dry or smoky atmospheres; he avoids public vehicles and usually travels by bicycle. His wife is non-consanguineous; they have two children (IV. 3 and 4). The son suffers from asthma, but his eyes and skin are normal.

III. 6, female, aged 39 years, is an inmate of Darenth Park Hospital for mental defectives. She is a feeble-minded woman in whom there is no trace of corneal dystrophy, ichthyosis,

or asthma. She wears glasses to correct a refractive error but shews no other ocular abnormalities. Her case is interesting, as mental deficiency often occurs in isolated individuals in an ichthyotic family group.

*III. 7, male, examined by the author, a clerk aged 36 years, is less affected than his brothers. Corrected vision is 6/4 in each eye. There are similar epithelial and subepithelial corneal dots and endothelial nodules, but the distribution is sparse. So far he has never had the acute attacks of ocular pain. He is handicapped by a stammer but is of good intelligence. His skin is a little rough yet not to the extent of deserving such a label as ichthyosis. He gets "hay fever" badly, and attacks of asthma. He is sensitive to many allergens including his brother's cocker spaniel, and will always develop an attack of asthma when the animal is near. In 1951 he had a bad attack of asthma when the dog had previously been present without his knowledge. He is married and the father of an unaffected son (IV. 5).

III. 8, male, son of II. 6, was well known to III. 3 and 4 in their childhood, and at that time was normal as regards skin, eyes, and asthma. The London members of the family do not know his present whereabouts, so he could not be examined. Genetically he might have been expected to shew some of the family stigmata.

III. 9 and 10, females, daughters of II. 8, were normal in early childhood according to the evidence of III. 4. Present whereabouts not known.

III. 11, 12, and 13, females, daughters of II. 9, were known to III. 4 in childhood and were then normal.

Present whereabouts not known.

FOURTH GENERATION

IV. 1, female, aged 17 years, daughter of III. 3, examined by the author, is a clerical worker. Her skin is normal and she has no allergic troubles. Her left cornea shews a small "white ring" of subepithelial dots of the type described by Coats (1912). Both irides shew small tag-like remains of the pupillary membranes. No other abnormalities were discovered. Her vision is 6/5 in each eye.

IV. 2, female aged 12 years, daughter of III. 3, examined by the author, presents no ocular, skin, or allergic anomalies. Vision is 6/5 in each eye.

IV. 3, male, aged 5 years, son of III. 5, examined by the author, has in the left optic disc a crescent resembling the type found in myopia, though the eye is in fact emmetropic. Vision is 6/4 in each eye. His skin is normal, but he suffers severely from asthma.

IV. 4, female, aged 7 years, daughter of III. 5, examined by the author, has normal eyes and skin, and has not had hay fever or asthma.

IV. 5, male, aged 6 years, son of III. 7 is the patient of the Hon. G. J. O. Bridgeman who kindly furnished details. His eyes are normal save for refractive error and a convergent squint now successfully treated by operation. His skin is normal and there is no history of asthma or allergy.

Discussion

Corneal Dystrophy.—This occurred in four members of the family, always in male members, and always associated with ichthyosis or allergy or both. III. 7 presented the dystrophy in a mild form, so that it was only discovered on slit-lamp examination. Similar symptomless dystrophic changes may well therefore have been overlooked in other members of the family group who were not examined ophthalmologically, particularly the two ichthyotic members (II. 8 and 9). On the other hand three of the four known cases of corneal dystrophy have presented acute ocular exacerbations with pain,

lacrimation, and photophobia. The histories are so similar to those of recurrent erosion and treatment with lubricant (paroleine) is so effective that in the acute attacks one cannot help postulating a breach of epithelial continuity as the most likely explanation. No such epithelial disruption has in fact so far been observed. No direct transmission of the dystrophy from parent to child has been noted. The corneal "white ring" of IV. 1 is an isolated instance, and on the present evidence is presumed to be a chance occurrence.

Ichthyosis Simplex.—The factor of ichthyosis simplex has only been found in male members of the group. Cockayne (1933) noted that mental deficiency may occur in isolated individuals of an ichthyotic family group, possibly as an alternative manifestation of the ichthyosis factor. Therefore the mentally defective female patient (III. 6) in this family conforms to precedent, possibly the factor of ichthyosis as manifested in a female. In this family group ichthyosis can be transmitted to males by apparently unaffected females (I. 4 and II. 7). The first of these cases is particularly striking; by her first marriage she transmitted ichthyosis through her apparently unaffected daughter (II. 7) to three ichthyotic grandsons (III. 3-5); by her second marriage she transmitted it directly to her two sons (II. 8 and 9). The skin condition is of relatively benign type in the group, and there is no tendency to eczematous exacerbations as in "Besnier's prurigo"; this is interesting as "Besnier's prurigo" is also associated with asthma and allergy.

Allergic Manifestations.—All the allergic manifestations in this pedigree are found in male subjects, either as "hay fever" or as asthma. In three patients the allergy is associated with ichthyosis (II. 8, III. 3, III. 4). Allergy occurs with corneal dystrophy in III. 3, 4, and 7. Asthma occurs alone in IV. 3, who is the child of III. 5, a patient suffering from ichthyosis and corneal dystrophy but not from asthma. All the allergic subjects are descended from an apparently unaffected female subject (II. 4), who by her first marriage transmitted allergic manifestations through her unaffected daughter (II. 7) to three grandsons (III. 3, 4, and 7), and a greatgrandson (IV. 3), who suffers from asthma, and by her second marriage transmitted asthma to her son (II. 8).

Mode of Genetic Inheritance.—Most of the facts disclosed in this genetic study are explicable on the hypothesis of three recessive genes, separate but adjacent on the X-chromosome, and carrying the phenotypic counterparts of corneal dystrophy, ichthyosis, and allergy. This would explain the frequent recurrence of these characteristics, often in association, but sometimes independently. The hypothesis would explain why positive manifestations of the syndrome are practically confined to male members of the family group. As the genes are recessive, an externally unaffected female carrier, *e.g.*, I. 4, married to a normal husband might have sons either normal or unaffected for each individual characteristic. Daughters would remain

externally unaffected, but might be carriers of the affected gene, which would reappear in turn in affected sons (I. 4 and II. 7).

There are however several points in this study which are difficult to reconcile with the attractively simple hypothesis just propounded:

(1) There are anomalies in two female members of the family. III. 6, the mentally defective female, would be readily explained as a chance occurrence were it not for similar findings in other ichthyosis families (Cockayne, 1933). Possibly, as suggested, idiocy is an alternative manifestation of the ichthyosis gene in females, but if this be so the simple hypothesis of inheritance must be expanded. Probably the "white ring" in the cornea of female subject IV. 1 is fortuitous; but further research might conceivably shew it as a female alternative to corneal dystrophy.

(2) Asthma has been noted in male subject IV. 3. His father suffers from ichthyosis and corneal dystrophy but not from allergic manifestations. Should the asthma in this case be considered fortuitous or is it inherited? Geneticists point out that part of the X-chromosome has its counterpart on the Y-chromosome, and considerations of this sort might easily account for the asthma in IV. 3.

Final judgements are probably impossible without further data from other members of the family (III. 1, 2, 8, 9, 10, 11, 12, and 13). As the fourth generation increases in numbers and age further cases may appear and necessitate reconsideration of the mode of inheritance of the syndrome.

Summary

A family is described in which certain male members suffer from corneal dystrophy, ichthyosis simplex, and allergic manifestations. The syndrome is not complete in every case. Ichthyosis and atopy have often been previously described in association. The eye complications of ichthyosis are usually those attributable to exposure of the cornea from ectropion of the eyelids, a complication which did not appear in this series. Slit-lamp examination of the corneae of ichthyotic patients might possibly disclose other latent or manifest cases of corneal dystrophy. It is hard to believe that the defect is confined to one family of ichthyotic patients.

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