Tapeto-retinal Degenerations with Varying Clinical Features in Åland Islanders

H. FORSIUS* and A. W. ERIKSSON†

During the period 1959–1962, we investigated families afflicted with blindness in the Åland archipelago, situated in the northern Baltic Sea between Finland and Sweden. Among the natives of the Åland islands we observed various types of tapeto-retinal degeneration: Leber's congenital amaurosis, degeneratio retinae pigmentosa juvenilis, and retinitis punctata albescens.

In 1969 we again surveyed the occurrence of poor sight on the Åland islands, and found new cases of dystrophic changes of the fundus in young subjects. We also observed progression in some of the cases we had on record. Some patients were also studied by electroretinography (ERG), electro-oculography (EOG), electronystagmography (ENG), anomaloscopy, the Farnsworth 100 Hue Test, fluorescein angiography, etc.

The question arose as to whether these clinically different retinal abiotrophies of autosomal recessive type could be due to the same mutant gene, causing a great diversity of clinical manifestations, depending partly on pleiotropy (polypheny) and partly on progression of the tapeto-retinal degeneration.

This hypothesis was corroborated by the genealogical data. Many probands showing different kinds of tapeto-retinal degeneration were found to have ancestors in common, particularly in the more distant ascendancy, though some of them were born in quite different parts of the Åland archipelago. (Water excluded, this archipelago comprises 1505 sq. km., water included about 6,000 sq. km., and the distance between some of the inhabited islands is as much as 100 km.)

Furthermore it seemed unlikely that the small population of Åland (about 21,000 subjects) would show so many different recessively inherited tapeto-retinal diseases, which are all rare, both in Sweden and in Finland. It should be borne in mind that the atypical forms of degeneratio retinae

pigmentosa reported in the literature show a great variety of clinical features (for references see Forsius and Eriksson, 1964a).

Kökar Pedigree (Families I–V)

During 1960–1962 we examined almost all the permanent population of about 420 in the highly isolated island community of Kökar; in addition we examined many who had emigrated and returned to Kökar on holidays. The total number of subjects examined was 565.

On scanning the detailed and well-preserved church registers going back to the 1650's we found many persons with a record of night blindness, poor vision, or blindness, often belonging to the same sibship or closely related in different ways.

As manifested in the Kökar families, the disease is characterized by night blindness, usually congenital, and relatively early impairment of vision, which may result in blindness at the age of 10–40 years. In the older age-groups, cases resembling atrophía gyrate were observed (Fig. 1). We have interpreted the great diversity of clinical forms of tapeto-retinal degeneration as variants of retinitis punctata albescens, and we believe that the difference in age of the patients is one of the main causes of the differences in clinical picture (for details on pedigree, etc. see Forsius and Eriksson (1964a) and Eriksson and Forsius (1964)).

Family I

Agnes J.-R. Female, born in 1920, IV/4* children. Has always had night blindness. Reading vision lost at the age of 36. In 1963, visual acuity in both eyes 0.1 (–1.0 D). Fundus degenerated, obvious choroidal sclerosis. ERG extinct. Diagnosis: degeneratio tapeto-retinalis of the type gyrate (Fig. 1).

A brother (Arnold, J.) became blind at the age of about 38, a sister (Astrid, J.) at the age of 10–12 years. The latter shows Turner's syndrome: 45,X/46,XX mosaicism (de la Chapelle, 1962; Case 15, p. 58).

Family II

Gunnevi F. Female, born in 1945, I/1 child, birth-weight 2490 g. Hearing somewhat impaired, probably as a result of bilateral middle ear inflammation at the age of 7–8. Has shown a squint since birth. On ophthalmological examination for squinting, changes of the

* IV/4 etc., means 4 h born of 4 sibs.

* Address: Department of Ophthalmology, University of Oulu, Eye Hospital, Uusikatu 50, Oulu, Finland.

† Address: Folkhälsan Institute of Genetics, Tölögatan 12, Helsinki 10, Finland.

FIG. 1. Family I (Agnes J.-R.) Left eye of 42-year-old woman with hemeralopia, showing degeneration of the fundus resembling atrophía chorioidea gyrata. ERG extinct.

fundus were observed. State in 1969: V. o.dx. 1.25 (−3.5 D). V. o.sin. 1.2 (−0.5 D). Fundus: pale papillae, normal blood vessels. Everywhere in the fundus were abundant small pigment spots. Dark adaptation (Goldmann-Weekers), normal in both eyes. Diagnosis: atrophía nervi optici, degeneratio retinae pseudopigmentosa?

Family III

Anna L.-L. Female, born 1883, II/5 children. Investigated in 1959 (she died soon afterwards), showed polar cataract and pronounced choroidal sclerosis and bone cell pigments in the totally destroyed fundus. Vision 1/∞, no light projection. Diagnosis: final picture of tapeto-retinal degeneration.

Family IV

Yngve S. Male, born in 1947, III/4 children. Examined by us in 1962 and 1967. No definite progression. Has always shown poor night vision. Slight subjective impairment of vision during the past few years. V. o.dx. 1.2 (+1.0 D cyl −3.75 ax 6°). V. o.sin. 0.9 (+1.25 D cyl −3.5 ax 3°). Fundus: papillae somewhat prominent, pale. Except at the outermost periphery and the central area, abundant small white spots in the fundus, and abundant very small pigmented areas in the retina (Fig. 2). Fovea and blood vessels normal. Dark adaptation much impaired (Goldmann-Weekers).

Visual fields normal. Colour vision: secondary dyschromatopsia varying in type. ERG: b-wave normal. Diagnosis: retinitis punctata albescens.

A sister (Inga S.) was diagnosed by Dr. M. Zewi as a case of retinitis punctata albescens. Another sister (Carola S. born in 1957) had also shown night blindness since infancy. State in 1968 (Dr. Zewi): V. o.dx. 0.2 (cyl +3.0 D ax 90°). V. o.sin. 0.25 (cyl +3.0 D ax 100°). Abundant small light spots in the equatorial region of the fundus. Diagnosis: retinitis punctata albescens.

Family V

Agnes E.-N. Female, born in 1900. Parents closely related. A sister (Anna E.), diagnosed by us as a case of retinitis pigmentosa, became blind at the age of 47 years. V. o.dx. 1.0 (−1.25 D cyl −0.25 ax 90°). Somewhat narrow retinal blood vessels. V. o.sin. 1.0 (−1.75 D). Somewhat narrow blood vessels. Drusen papilla. Sector-shaped choroidal sclerosis with bone-cell like pigments temporally of the fovea, extending to the periphery. Visual field defect in this area. After 60 minutes of dark adaptation the final light threshold of both eyes was about $10^4 \mu\text{L}$, which is about 1 log unit poorer than normal. Subnormal ERG. (The case has been previously described by Elenius, Forsius, and Eriksson 1961.) Diagnosis: degeneratio retinae et chorioideae o.sin. Drusen papilla o.sin. Glaucoma simplex o.a.

FIG. 2. Family IV (Yngve S.) Male, 20, with retinitis punctata alba. Abundant white spots superficially in the retina and small pigment particles in the deep layers.

Main Island Pedigree (Families VI–X)

Family VI. According to the parents, the affected subjects showed relatively normal vision up to the age of 2–4 years, when obvious impairment in the form of 'near-sightedness' set in. The three sibs described below have all visited a school for the blind in Helsinki.

FIG. 3. Family VII (Dorrit M.) Female, 14. Large central retinal degeneration with round pigment spots in both eyes. Narrow blood vessels, pale yellow papillae. Peripherally some white-greyish spots and occasional bone-cell pigments. Diagnosis: late form of amaurosis congenita (Leber)?

Carl Johan L. Male, born in 1948, I/6 children. Just managed reading at elementary school up to the age of 12, after which he visited a school for the blind. No subjective night blindness. State in 1959: V. o.dx. finger counting in front of the eyes (+7.0 D). V. o.sin. hand movements (+6.0 Dcyl +1.0 ax 90°). Fundus yellow papillae, narrow blood vessels. Abundant bone-cell like pigments peripherally and round ones centrally. Rapid jerky nystagmus. Diagnosis: amaurosis congenita (Leber).

Birgitta L. Female, born in 1953, V/6 children. Poor sight since birth, continuously impaired. Has always shown night blindness. State in 1969: vision (1959 and 1969) in both eyes finger counting 0.5 m. (+6.0 Dcyl +4.0 ax 90°). Central visual field lacking. Papilla pale, swollen—'drusen papilla'. Narrow blood vessels. Very heavy bone-cell pigmentation extending to the periphery. Dark adaptation much impaired (10^5 – 10^6 $\mu\mu\text{L}$ Goldmann–Weekers). ENG: ocular nystagmus. Diagnosis: amaurosis congenita (Leber).

Bern L. Male, born in 1956, VI/6 children. Impairment of vision was observed before he was 1 year old. Vision problems particularly in the dusk. State in 1963: V. o.dx. finger counting 3 m. (+8.0 Dcyl +2.5 ax 90°). V. o.sin. finger counting 20 cm. (+2.0 Dcyl +2.0 ax 90°). Reddish-yellowish papillae, narrow arteries, normal veins. All over the fundus, but least in the macular region, pigment spots and streaks, some the shape of bone cells. Abundant small white or yellow spots peripherally in the retina. State in 1969: V. o.a. hand movements. Fundus: pale atrophic papillae, narrow blood vessels in the superficial retinal layer. Fluorescein angiography revealed total atrophy of the retinal pigment layer. Adaptation much impaired (10^5 $\mu\mu\text{L}$, Goldmann–Weekers). ENG: ocular nystagmus. Diagnosis: amaurosis congenita (Leber).

Family VII

Dorrit M. Female, born in 1955, I/2 children. Night vision always poor. State in 1969: V. o.a. 5/50. Refraction: +4.0 Dcyl +1.0 ax 90° o.dx. +4.0 Dcyl +1.5 ax 90° o.sin. Fundus: narrow blood vessels. Pale yellow papillae. Centrally in the fundus choroid vessels clearly visible. Choroid shines through especially on fluorescein angiography. Peripherally the retina shows milky degeneration with occasional bone-cell pigments. Some white-greyish spots in the central portion of the periphery (Fig. 3). Adaptation impaired $1\frac{1}{2}$ log unit (Goldmann–Weekers). Obvious secondary dyschromatopsia. ENG: latent nystagmus of a type suggesting a lesion of the cerebellum. Vision and fundus appearance in 1963 and 1969 about the same. Diagnosis: late form of amaurosis congenita (Leber)?

Family VIII

Gunnel P. Female, born in 1937, I/2 (II/3). Parents are cousins of fourth degree and related to Families VI and VII. Dizygotic twin, the other twin, a girl, died at the age of 17 days. Birthweight 1500 g. Convulsive fits during the first 2–3 weeks of life and at the age of 3½ years. At the age of 27 years an attack of epileptic

grand mal. EEG: suggestive of frontal brain lesion. Normal development of speech; started walking at the age of 4. Has visited a school for the blind. Shows mental retardation and weakness of the left extremities. In 1959, vision in both eyes finger counting 0.5–1 m. (+2.0 D). Ocular nystagmus. Fundus: papillae white, pale, borderlines sharp; blood vessels normal; retina normal. Diagnosis: atrophía nervi optici secundaria.

Family IX

Elmar O. Male, born in 1934, I/7 children. Blind since birth. In 1969 vision o.a. O. Central corneal opacities and keratoconus in both eyes. Pale yellowish papillae, very narrow vessels. Obvious choroidal sclerosis. Scanty bone-cell pigmentation all over the fundus. Ocular nystagmus. Diagnosis: amaurosis congenita (Leber).

Family X

Jack C. Male, born in 1962, II/2 children. Blind since birth. Nystagmus observed at the age of 2 months. From time to time he rubs his eyes frantically. State in 1969: vision in both eyes 1/∞. Mature cataract in right eye. Posterior capsular opacity in left eye. Fundus: pale papilla, narrow arteries, no pathological pigmentation. Keratoconus with central corneal opacities in both eyes. Diagnosis: amaurosis congenita (Leber).

Kumlinge Pedigree (Families XI–XII)

Family XI

Fjalar H. Male, born in 1915, IV/7 children (the proband's eldest sister was born with only locomotor vision; died of 'Spanish disease' at the age of 13). Parents were cousins of second degree in two different ways. Congenital night blindness. Vision poor already before school age. State in 1969: V. o.d. 1/∞ (−0.25 D cyl −0.5 ax 90°). V. o.sin. 1/∞ (−0.25 D cyl +0.75 ax 0°). Lens clear. ENG: latent nystagmus. Irregular pendular deviations with eyes open suggestive of ocular nystagmus. Extremely pale papillae and narrow blood vessels. Obvious choroidal atrophy. Diagnosis: amaurosis congenita (Leber).

Family XII

Fanny E. Female, born in 1900, VII/8 children. Parents were cousins of second degree. She and the mother in Family XI are cousins. The patient and her youngest sister showed endogenous depression at times. Had night blindness and poor vision as long as she could remember, but when she was 20 could still read with the aid of a magnifying glass. State in 1969: V. o.d. 1/∞ (−2.25 D). V. o.sin. 0 (+0.25 D cyl +1.25 ax 90°). Ocular nystagmus. Cataracta polaris posterior. Atrophic papillae, abundant bone-cell pigmentation. Marked choroidal sclerosis. Diagnosis: degeneratio retinae pigmentosa juvenilis. Late form of amaurosis congenita (Leber).

Föglö–Sottunga Pedigree (Families XIII–XVII)

Family XIII

Dailis P.-L. Female, born in 1930, IV/4 children. Became aware of impairment of vision at the age of 22. An ophthalmologist noted haemorrhages in the retina. State in 1969: V. o.d. finger counting 3 m (−3.25 D). V. o.sin. 0.2 (−4.75 D cyl +1.25 ax 90°). Centrally in the fundus there was obvious atrophy of the retina and choroid; occasional retinal pigment spots visible at the outermost periphery, though the severity of the changes steadily decreased towards the periphery. Some pigment was seen along the retinal blood vessels. The visual field showed a large central defect. Adaptation much impaired (by two log units), EOG subnormal, ERG subnormal (Fig. 4).

When this patient was first examined by us in 1963, vision was 0.25 on both eyes. There was an atrophic area of the same size as in 1969, but the margin of the degeneration had peculiar semitranslucent vascularized grey foci, which were the size of the papillae, and clearly raised from the remainder of the retina (Fig. 5a). These pseudotumours were still visible in 1969, though they were less prominent than previously (Fig. 5b). New large choroidal blood vessels were seen. We have not seen published reports of such pseudotumours. For fluorescein angiographic findings see Fig. 5c. Occasional white–yellowish spots were seen near the margin of the focus. We have noted haemorrhages only once (Fig. 5a). Diagnosis: degeneratio retinae et chorioideae centralis.

Family XIV

Anni Paulina L. Female, born in 1898, VII/9 children. Subjectively, she has not been night blind. In 1968 ablatio retinae was seen in the left eye, with numerous peripheral ruptures in a very atrophic retina.

FIG. 4. Family XIII (Dailis P.-L.) Female, born in 1930. ERG of left eye, recorded with a Techonix 502A oscilloscope. Before examination the patient spent half an hour in the dark. After coupling the electrodes the eye was exposed to a total of 10 steadily strengthened flashes at about 1-minute intervals. Maximum value of b-wave 0.9 mV. The curves show the growth of the b- and a-waves with increasing stimulation. ERG is within the normal range.

FIG. 5. (Dailis P.-L.) Female, born in 1930, with degeneration retinae and chorioideae centralis (and see opp.)

5a. Left eye on 17 September 1963. Extensive choroidal sclerosis. Normal retinal blood vessels. Haemorrhage in papilla (arrow). Grey, raised semitranslucent pseudotumour, the size of the papilla, medially at the border to the normal tissue (arrow), showing large choroidal vessels.

Normal vision in the right eye. One year later progressive haemorrhagic macular degeneration was seen covering a large proportion of the central fundus and surrounded by white exudate. V. o.d.x. 0.25. Treated at the University Eye Hospital, Turku. Diagnosis: degeneratio maculae senilis haemorrhagica o.d.x. Ablatio retinae totalis o.sin.

Family XV

Gerhard L. Male, born in 1953, birthweight 2680 g. Admitted to hospital because of vomiting and poor general condition at the age of 6 weeks. Died at the age of 3 months. Diagnosis: Gaucher's infantile lipidosi.

Gertrud L. Female, born in 1955, birthweight 3080 g. Admitted to hospital for loose mucous stools.

The abdomen was swollen, and there was frequent flatulence and vomiting. The patient died at the age of 3½ months. Tissue preparations were subjected to thorough lipid chemical investigations and were also submitted to Prof. H. F. Thannhäuser, Boston. These studies as well as patho-anatomical investigations performed by Dr. L. Meurman, were clearly indicative of Gaucher's infantile lipidosi.

The parents of these patients and two living sibs were examined by us in 1969: they were ophthalmologically normal.

Family XVI

Bengt T. Male, born in 1951, I/4. Poor vision was observed at the age of 10 on examination performed in

school, and since then there has been gradual impairment. Night vision always satisfactory. State in 1969: V. o.d.x. finger counting 3 m. V. o.sin. O-1. Emmetropia. Centrally in the fundus an area the size of the papilla, in which the retinal pigment epithelium is destroyed and the choroid shines through (Fig. 6). Occasional pigments along the blood vessels in the equatorial region. In an area at a distance from the fovea equal to the diameter of the papilla, numerous grey spots seen in the

5b. Detail of grey pseudotumour laterally of the macular region in the right eye (September 17, 1963). From 19 January 1963, to 25 February 1964, the pseudotumour showed no photographic changes.

5c. Same area as in Fig. 5b on 25 April 1969. The pseudotumour is much less prominent than six years earlier. Many of the choroidal vessels have disappeared and new vessels have developed.

5d. Same area as in Fig. 5b and c, on 25 April 1969. Fluorescein angiography in initial phase. Retinal artery only weakly filled, whereas the dilated choroidal blood vessels in the pseudotumour are obviously filled. Choroidal sclerosis, especially to the right.

5e. Same area as in Fig. 5b, c, and d, 18 seconds later than in 5d. Centrally, a large choroidal blood vessel, not filled during angiography, appears dark against the light background. This vessel, which is seen below in Fig. 5c, was lacking in 1963–1964.

FIG. 6. (Bengt T.) Male, 18. Fluorescein angiography 20 seconds after the dye has reached the retina. Retinal pigment also injured outside the macular region.

deep layers of the retina. Normal visual fields. EOG subnormal. Dark adaptation: one log unit poorer than normal. ERG normal; maximum of the b-wave 0.7 mV, maximum of the a-wave 0.2 mV. Obvious secondary dyschromatopsia predominantly in the tritan axis (Farnsworth panel D-15 test). Anomaloscopic equation in the protanomalous direction. Diagnosis: degeneratio retinae centralis; Stargardt's macular dystrophy?

Börje T. Male, born in 1954, II/4 children. Poor sight noted at the age of 6. Has passed elementary school. Night vision always satisfactory. State in 1969: V. o.d.x. 0.1 (-0.25 D cyl $+0.5$ ax 90°). V. o.sin. 0.15 (-0.75 D cyl $+1.25$ ax 90°). Centrally in the fundus a dystrophic focus, in which the choroidal vessels shine through in an area with a cross-section of $1\frac{1}{2}$ papillary diameter (Fig. 7a). Under the vascular layer in the retina, about one papillary diameter outside this area and extending to the equator, there are whitish-grey spots, hardly distinguishable from the surrounding tissue. Centrally the pigment in the deep retinal layers is disintegrated into spots. Above the pigment layer, a strongly light-reflecting layer is seen. Fluorescein angiography clearly showed that the pigment defect area in the retina was larger than shown by ophthalmoscopy (Fig. 7b). Adaptation (Goldmann-Weekers): one log unit poorer than normal. Visual field peripherally normal EOG subnormal. ERG within the normal range Maximum of the b-wave 0.5 mV, maximum of the a-wave 0.2 mV. Diagnosis: degeneratio retinae centralis; Stargardt's dystrophy?

FIG. 7. (Börje T.) Male, 15. (a) Foveal area in a patient with central chorioretinal atrophy. The five dark spots are marks for stereogrammetric analysis. (b) Same eye as in Fig. 7a. Fluorescein angiography in initial venous phase. Pigment epithelium also injured outside the central area.

Family XVII

Nandor G. Male, born in 1906, has experienced vision problems in the dusk and dark since childhood. Became totally blind in less than a week at the age of 48. State in 1959: V. o.a. finger counting 1 m. No nystagmus. Pupils react to light. Snow-white papillae with sharp borders. Narrow blood vessels. Diagnosis: atrophie nervi optici l.a.

Discussion

Many reports have been published on the occurrence of various forms of degeneration of the fundus within the same pedigree or even the same family unit. Choroidal sclerosis and retinitis punctata albescens have been observed in the same family

(e.g. Guglianetti, 1950). This is in good agreement with our clinical findings in Families XVI and IV. These two families come from the communities of Föglö-Sottunga and Kökar, respectively, which are both situated in the south-eastern part of the Åland archipelago. However, genealogical studies covering the last 200–300 years did not reveal any blind ancestors in common (Fig. 8–10).

The white spots in retinitis punctata albescens and fundus albipunctata disappear with advancing age (Franceschetti, 1953). This may perhaps explain the variations in our findings in related families in the Kökar isolate. On the other hand, to the best of our knowledge no case of typical retinitis punctata albescens (as observed, for instance, in Family

FIG. 8. Part of the pedigree of the subjects from the Åland main island showing tapeto-retinal degeneration. Third from left, generation VII, Family XIII, is identical with twelfth, generation VII, in the Föglö-Sottunga pedigree (Fig. 10). The first subject from the left (born in 1734) in generation V in Family VII moved with her husband from Kumlinge to the Åland main island in the middle of the 1770's. She is the sister of one of the ancestors in Family XII in the Kumlinge pedigree (fourth from left, generation V). The proband in Family II is also found in the Kökar pedigree (Forsius and Eriksson, 1964a). Her ancestor in the main island pedigree—ninth from left, generation VII—was a pilot who moved from Kökar to the northern part of the main island during the latter half of the 18th century.

FIG. 10. Part of the pedigree of the subjects from the neighbouring island communes of Föglö and Sottunga showing tapeto-retinal degeneration. The pedigree shows the close relation between Family XV, in which infantile lipidosi was observed, and the families having central retinal degeneration. The connexions to the Kumlunge pedigree are shown to the left (cf. text and key to Fig. 8 and 9). Cases in the ascendancy, which, according to official records, e.g., parish registers, have poor sight, are indicated by thick circles (◐).

from the fundus findings in Families XIII and XVI. In both cases the central retino-choroidal sclerosis was the predominant feature. The EOG, ERG, and adaptation were found to be relatively normal in Family XVI, in which the first symptom was observed at school age or somewhat later, and the clinical picture resembled most that described in atrophio chorioidea centralis, a disease occurring in a recessively inherited form (Waardenburg, 1952), or in the related Stargardt's dystrophy, which has also been described as recessively inherited (François and Verriest, 1956). We have also considered the possibility of Sorsby's inflammatory dystrophy, which has likewise been described in a recessive form (Sorsby, 1940; Sorsby and Mason, 1949).

In occasional cases a normal ERG has been observed in Leber's disease (Alström and Olson, 1957;

Bamatter, Franceschetti, and Klein, 1961; François and De Rouck, 1961) and in central choroidal sclerosis (François and De Rouck, 1961). All these patients were, however, young.

With regard to the patients showing atrophic changes of the fundus classification is difficult. In Family II it seems possible that viral degeneratio retinae pigmentosa is involved, whereas in Family VIII the condition may be due to cerebral injury caused by prematurity or infection (meningitis?). However, considering the kinship between these individuals and the families showing tapeto-retinal degeneration, the possibility cannot be excluded that these two cases and the case in Family XVII represent deviating *formes frustes* or heterozygotic manifestations of the same mutant gene.

Ammann and Marty (1962) described a large

pedigree from a Swiss Alpine isolate showing various clinical manifestations, e.g. fundus albipunctatus (a stationary form of retinitis punctata albescens), degeneratio retinae pigmentosa atypica, degeneratio maculae senilis, and central dystrophy of the fundus.

Tapeto-retinal degeneration occurs in association with congenital disorders of sphingolipid metabolism. In pedigrees with Niemann-Pick's disease and Tay-Sachs' disease, tapeto-retinal degeneration has been encountered (Hanhart, 1956; Fraser and Friedmann, 1967). Degenerative retinal changes have also been noted in patients with the infantile form of Gaucher's disease (Eyb, 1952). Hence, the concurrence of Gaucher's infantile lipidosis and tapeto-retinal degeneration in the Föglö-Sottunga pedigree is not perhaps accidental. Gaucher's disease is rare. Only 300 cases have been reported (Hsia, Naylor, and Bigler, 1962), even including the Jewish cases.

In regard to the degenerations of the fundus seen in the pedigrees described in this study a classification into the following variants seems justified: (1) a variant corresponding to Leber's congenital amaurosis, and (2) a variant manifesting itself as retinitis punctata albescens or as central atrophic degeneration of the fundus, just as in the pedigree described by Ammann and Marty (1962) (cf. also Fraser and Friedmann, 1967).

With the above-mentioned two sibs with Gaucher's infantile lipidosis and two cases of typical ocular nerve atrophy excluded (Families VIII and XVII), a total of 23 cases of definite degeneration of the fundus was thus diagnosed in 14 families in the Åland archipelago in 1959-1969.

The tapeto-retinal degeneration occurring on the Åland islands does not seem to be combined with disorders of a neurological or psychiatric nature. Impaired hearing was observed in two of the affected subjects (Families I and II), but this was probably due to otitis media. No accumulation of deafness or deaf-muteness was observed in the pedigrees of the probands. With the exception of the proband in Family VIII, who showed prematurity, epilepsy, and mental retardation, the patients studied, as well as their families, showed at least normal intelligence. Hormonal disturbances were only observed in a case of Turner's syndrome (Family I). Tests for toxoplasmosis and syphilis were negative in all investigated cases. Twin births occurred in 6 of 15 families showing abiotrophies. However, considering the scantiness of the series, this must be attributed to chance and to the fact that the frequency of twin births has been relatively high on the Åland islands (Eriksson, 1964). Ammann, Klein, and Franceschetti (1965) reported typical cases of

retinitis pigmentosa and congenital tapeto-retinal amaurosis (Leber) occurring in the same family: in this instance 3 of the 24 maternities were twin pairs.

Emigration to the outer Åland archipelago began about 700 years ago, chiefly from the main island. It seems probable that these island populations are descended from a small number of immigrants, who moreover may have been related to each other. Owing to the hardships of daily life in these communities there has been little migration to them later. This is true in particular for the last few centuries. The part played by founder effect and isolation in the Åland archipelago is corroborated by the fact that neighbouring insular communities show extreme gene frequencies deviating very much from each other (Eriksson and Forsius, 1964).

Provided that there were among the first immigrants some subjects with a recessive mutant gene not involving any significant handicap in heterozygous form, the smallness of the original population (founder effect) and the isolation, perhaps in connexion with random genetic drift, would account for a high frequency of this gene, notwithstanding the growth of the population.

When the relationship between two relatives in a large panmixed population becomes remote, the probability that they share a common gene (identical by descent) becomes very small. However, inhabitants in small isolates have often, particularly in earlier generations, so many common ancestors that their marriages may well be compared to marriages between cousins in a panmixed population. Consequently, marriage partners in small isolated populations are quite likely to have genes in common. Therefore, the probability that the offspring will be homozygous is much greater, as dictated by chance. The heavy accumulation of blindness and poor sight in the pedigrees in the outer Åland archipelago is evidence in favour of the above hypotheses, considering in particular that trachoma has not been reported in these communities, and that we have not observed any accumulation of severe myopia or juvenile cataract or glaucoma. The cases of defective vision detected among the ancestors or their sibs are therefore helpful from the standpoint of tracing the path of the mutant gene in the pedigrees.

It may be suggested that the different clinical manifestations are due to one and the same gene mutation. In an equally large panmixed population this would mean a gene frequency of about 0.034. On the assumption that both parents of the affected subjects are heterozygotes, another estimate of the gene frequency is obtained. Apart from the

14 families with definite tapeto-retinal degeneration discovered, there may be others in which both parents are heterozygotes, though the defect allele has not manifested itself in any of the children. Presuming full penetrance of the monogenic recessive autosomal gene, there ought to be further 9.2 parent pairs with this mutant gene. If these 23.2 families are compared to the total number of married couples with at least one child living on Åland during the period 1881–1960 (totalling about 8000), a gene frequency of 0.027 is obtained. Notwithstanding the simplified premises, the two methods of estimation give gene frequencies which in any event are of the same order. The above-mentioned gene frequencies for Åland are 5–7 times higher than these obtained by Alström and Olson (1957) for Sweden, and about 8 times higher than those obtained for the regions bordering on Åland, i.e. the counties of Stockholm and Uppsala. It is noteworthy, however, that in Sweden the highest gene frequency (0.011) was obtained for the island of Gotland. There is historical evidence of intensive contacts between the Swedish-speaking populations on Åland and Gotland, in particular during and after the time of the Vikings (Dreijer, 1960).

On the assumption that the different clinical manifestations are due to three different mutations in different loci, the total gene frequency would be much higher, i.e. 0.055. Even when the isolate effect with consanguineous marriages etc. is taken into account, it seems very unlikely that several tapeto-retinal diseases, which are exceedingly rare in areas bordering on Åland, would occur in this archipelago independently of each other, and that all would exhibit such high frequencies of manifestation.

Of those admitted to a school for the blind in Sweden, 10% showed hereditarily congenital (Alström and Olson, 1957). In our series from Åland, no less than 60% of the subjects who showed poor sight or blindness when young belonged to families with tapeto-retinal degeneration. Among 16 patients not showing autosomal recessive tapeto-retinal degeneration, 7 males had the X chromosomal Åland eye syndrome (Forsius and Eriksson, 1964b; Waardenburg, Eriksson, and Forsius, 1967; Eriksson, Waardenburg, and Forsius, 1969). Irrespective of whether the number of subjects with tapeto-retinal degeneration is compared to the total population or to the number of individuals showing other types of blindness, the frequency of tapeto-retinal degeneration on Åland is very high.

The investigation of isolates offers a useful

approach to the study of rare hereditary diseases. When a large population is screened for vision defects, for instance, the sample is selective and severe cases are predominant. Provided that the total population of an isolate is examined, a more exact picture is obtained of penetrance and phenotypic expression (e.g. *formes frustes*, degree of manifestation among heterozygotes) as well as of the age of manifestation, the progression, etc. of the defect involved. In various ways these factors may be suggestive of genetic differences, as in cases of tapeto-retinal degeneration, though the latter may be due to the same mutant gene. Follow-up studies of affected families and more thorough and extensive investigations of isolates may contribute significantly to a more adequate classification of the tapeto-retinal degenerations and to a better understanding of their associations with other affections.

Summary

Families in the Åland archipelago showing tapeto-retinal degeneration varying in type are described. Subjects coming from the same district and in some instances from the same pedigree showed different retinal abiotrophies: Leber's congenital amaurosis with or without keratoconus, atrophie chorioideae centralis, senile macular degeneration with haemorrhages, retinitis punctata albescens, atrophie nervi optici, and Gaucher's infantile lipidosis. The majority of the cases were investigated using Goldmann-Weekers' adaptometer, fluorescein angiography, ERG, EOG, ENG, etc. Genealogical studies of the pedigrees of the probands covering the past 200–300 years revealed many ancestors in common. In 11 of the 16 families studied, the parents were cousins of 1st to 4th degree. The possibility that the very variable clinical pictures of tapeto-retinal degeneration shown by Åland islanders are caused by the same mutation is discussed.

We are greatly indebted to Dr. A. G. M. van Vliet, Rotterdam, for the nystagmographic investigations, to Dr. P. Tuomaala, Oulu, Finland, for the ERG and EOG investigations, to J. Fellman, M.Sc., Helsinki, for statistical consultations, and to Mr. H. Nieminen, Oulu, for the clinical photographs.

These studies were supported by grants from the National Institute of Health, Public Health Service (NB-06368-02), Bethesda; the Association for the Aid of Crippled Children, New York; the Sigrid Jusélius Foundation; and the Finnish Council for Medical Science.

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