A PEDIGREE SHOWING AN ATYPICAL FORM OF HEREDITARY OPTIC ATROPHY EXHIBITING APPARENT POLYMORPHISM.

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INTRODUCTION.

HEREDITARY optic atrophy was first described and defined by Leber¹ in 1871 and since that date over two hundred pedigrees have been reported in detail. The condition is, of course, well-known and the clinical picture and inheritance appear to be remarkably constant.

The examples here described differ in various ways from the typical form; and a further interesting feature is the occurrence of retinitis pigmentosa in some members of the pedigree in an association that, as far as can be ascertained, has not been described before. It appears worth recording in that it suggests some kind of relation between the two conditions; and also there seem some grounds for supposing that this may be a form of hereditary optic atrophy distinct from that originally described by Leber.

It may be as well to summarize briefly, for comparison, the principal features of hereditary optic atrophy and retinitis pigmentosa.

Leber's atrophy is a heredofamilial disease, usually sex-limited, transmitted by the female and appearing in the male. The onset, sometimes with a preliminary phase of neuritis coming under observation, occasionally one eye preceding the other by some weeks, is most commonly at 24 years. There is considerable impairment of vision, non-progressive and occasionally improving slightly, usually a central scotoma for form and colour and, rarely, a peripheral contraction of the fields. Direct vision is the first to suffer, but it is not possible to say whether the degeneration is primarily in the papillomacular bundle or in the retinal ganglion-cell layer. One case only has been described post-mortem by Rehsteiner². An atrophy of the retinal ganglion-cell layer with degeneration of the medullary sheaths and axis-cylinders of the optic nerve, most marked in the papillomacular bundle, was found. The author considers that the changes suggest a primary degeneration of the retina and optic nerve directly conditioned by the germ-plasm; he does not suggest which may have occurred first.

Retinitis pigmentosa presents a sharply contrasted picture. Although the symptoms alone allow of this, it was not until the invention of the

ophthalmoscope that the syndrome was delimited from congenital night-blindness: the main features are night-blindness, progressive contraction of the visual fields, and peripheral retinal pigmentation. Complete sex-limitation is less frequent than in hereditary optic atrophy, the age of onset is earlier, usually in childhood, and the condition is progressive, the disability increasing slowly to almost complete blindness at about 40 years. Many cases have been examined histologically; the changes found comprise an atrophy of the nervous elements of the retina, sclerosis of retinal vessels, hyperplasia of connective-tissue and a migration of pigment from the pigment-cell layer into the areas of atrophy. The original view that the changes are essentially inflammatory (De Wecker³, etc.) is now no longer held, and it is thought that the process is degenerative, affecting, primarily, either the vessels or the nervous elements of the retina. Collins⁴ regards the condition as abiotrophic, the process being one of a primary degeneration of the neuroepithelium followed by atrophy of nerve-fibres and increase of connective-tissue.

It appears, therefore, that while both may be regarded as primary degenerations of retinal and nervous elements, they are distinct in pathology and symptomatology.

DESCRIPTION OF PEDIGREE.

The H. family (Cases I 1, 2; II 1-9; III 1-5; IV 1, 2) has no history of eye trouble. Unfortunately it was not possible to see the surviving members, but the information obtained was fairly detailed; its members are of a higher social status than the rest of the pedigree and more closely in touch with each other, and the accounts obtained are probably reliable. It seems justifiable to exclude the occurrence of any eye condition in any way comparable to those shown in the rest of the pedigree. Cases II 4 and II 6 were twins, probably identical. The patient whose case is II 9 died in a mental hospital of ? mania; her eyes were normal.

Case II 10: E. W., has been dead for many years. He was an engine-driver and at about 45 years lost his job on account of colour-blindness; as this occurred when tests were first instituted on the railways, it does not necessarily represent the time of onset of the condition. He had no serious defect of vision, nor was he night-blind. It appears likely that this was a mild case of Leber's disease of the form exhibited by other members of the family, but of course the possibility that the defect was simply one of congenital colour-blindness cannot be excluded. He is said to have confused red and green and to have called blue white. His father is also thought to have been colour-blind and to have suffered with his eyes.

Case II 12: eyes reported normal.

Case II 13: said to have been 'mental' and to have committed suicide.

Case II 14: died young of tuberculosis.

Case II 15: is said to have had bad sight and to have been colour-blind. It is probable that he suffered from optic atrophy.

Case II 17: W. W., 73 years, is the only surviving member of this generation; he is a sufferer from Paget's disease. There is no history of night-blindness, or defect in colour-vision; his eyesight began to fail at 50 years and has progressed until he can now only count fingers at 1 m. He has been almost completely deaf for many years.

On examination, the lenses are clear; both fundi show a large patch of pigmentation in the papillomacular region, which is superficial (retinal), and the edges are serrated. There is a fine superficial pigmentation extending 2 disc diameters around the disc, not well-marked, but more definite in the left eye. There is no peripheral pigmentation. The discs are well-coloured, the retinal vessels being perhaps rather small. This, of course, bears no resemblance to the picture of retinitis pigmentosa.

Case III 6: E. W., 55 years. His sight began to fail gradually, being noticeably bad at 18 years; night-blindness was the first prominent symptom. Later, constriction of the peripheral fields was complained of. The condition gradually progressed until now he can only detect hand movements. On examination his pupils are equal and react to light, nystagmoid jerks are present, there are extensive opacities of the posterior portion of the lens and there is typical and extensive peripheral retinal pigmentation with atrophy of the retinal vessels and of the greyish disc. The patient is very deaf. He is below the average in intelligence.

Case III 9: in Canada. She is said to have normal eyesight, and her children also are said to be normal.

Case III 10: C. W., 52 years. His sight was good at school, but gradually became affected, first noticeably so at 20 years. The symptoms complained of were night-blindness and difficulty with peripheral fields in the day-time. Upon examination, a refractive error was found in both eyes; pupils are equal and react to light, there is no nystagmus, both lenses show posterior opacities; there is extensive peripheral pigmentation of the retinitis pigmentosa type, while the disc is pale and the retinal vessels are narrow and atrophic. He can count fingers at 1 m. and is also very deaf. He is below the average in intelligence.

Cases III 12 and 13: died in infancy: cause unknown.

Case III 14: is a policeman. He and his family are normal.

Case III 16: is normal.

Case III 18: A. W., 38 years, had one depressive attack three years ago, lasting three months, during which he was in the Maudsley Hospital. He

became night-blind at 14 years, being unable to drive his father's cart home in the evenings. His sight gradually became worse until now he can distinguish hand movements only. His pupils are equal and react to light, there is a slight refractive error, and marked opacities in the posterior layer of both lenses. On examination, there are typical cortical cataracts in the right eye obscuring the disc, and very marked peripheral pigmentation; the discs are dirty grey and there is an atrophy of the retinal vessels. He is deaf, but this is not so marked as in the other cases. He is also below the average in intelligence.

Case III 21: is in Australia. She and her family are reported normal.

Cases III 22, 25, 26: they and their families are normal.

Case III 27: H. W., 50 years, has always had very bad eyes, but there has been no progression of his disability. He tried glasses at school and found them useless. He has always been known to be colour-blind. There is no night-blindness and he is not deaf. Upon examination, visual acuity is 2/60 in both eyes. The visual fields are normal, no central scotoma or constriction of the fields being found. He is practically completely colour-blind, recognizing only the deep red of the Edridge-Green lantern at 1 m. Both lenses are clear, the discs are very pale, not grey, cupped, with a well-marked lamina cribrosa. Vessels are not particularly contracted and there is no peripheral pigmentation. There are horizontal nystagmoid jerks of both eyes. He is an abnormal personality, and periodically deserts his family.

Cases III 29, 32 and 34: are normal. The last married an unrelated deaf-mute who deserted her.

Cases III 36-43: are normal.

Cases IV 3-6: are normal.

Cases IV 8 and 10: are normal.

Case IV 9: A.W., 18 years, is always known to have weak eyes, this being definitely remarked upon at the medical inspection when he started school. There is no night blindness. Upon examination, there is a slight refractive error, V.A.R. (corrected) 6/60, V.A.L. (corrected) 6/36. Lenses are clear, pupils react to light; there is definite optic atrophy, and slight disparity between the sizes of veins and arteries. There is no peripheral pigmentation, no scotoma and no constriction of visual fields. Colour-blindness is present, the patient being unable to read Ishihara's tables, but it is not so marked as in the other cases.

Case IV 14: is a difficult child and at times unmanageable at home. There is no mental defect.

Cases IV 15, 16, 17: are normal.

Cases IV 18-22: are normal.

Cases IV 23-27: are normal.

Case IV 28: is normal.

Case IV 29: E. W., 30 years, has always suffered from her eyes. Upon examination, visual acuity is 6/60 in both eyes, pupils are equal and react to light, lenses are clear, no peripheral pigmentation or constriction, no scotoma, no nystagmus. Both discs show optic atrophy, being very pale. Vessels are slightly constricted. She is very colour-blind, being unable to distinguish reds and greens on the Edridge-Green lantern at 1 m.

Case IV 30: L. W., 27 years, has always had bad eyes and a noticeable nystagmus. Two years ago she complained of giddiness and weakness of the left leg. The spinal fluid was normal. She was considered to be a case of disseminated sclerosis. A year ago she was admitted to the Maudsley Hospital. Upon examination, she showed a visual acuity of 6/36 in both eyes, pupils equal and active to light, lenses clear, pallor and definite atrophy of the discs, and retinal vessels slightly reduced in size. There was no peripheral pigmentation or contraction and no central scotoma. She was very colour-blind, finding great difficulty with blue and yellow at 1 m. with the Edridge-Green lantern. She showed a weakness of the left leg and stocking and glove anæsthesia on that side. These latter symptoms cleared up after some weeks in hospital, but her eye condition remained the same. She was considered to be a case of hereditary optic atrophy with additional symptoms of conversion hysteria.

Case IV 31: is normal.

Cases IV 32-57: are normal, except for Case IV 41 and Case IV 44 who have strabismus, and Case IV 53 who is a congenital mental defective.

In the fourth generation Cases IV 1, 2, 5, 6, 10, 14-17, 25, 26, 27, 28, 39-47, 49-57 are all under 15 years, so that it is not possible to exclude a subsequent development of retinitis pigmentosa with an onset comparable to the other cases.

There is no consanguinity. No marked over-indulgence in alcohol or tobacco was reported.

DISCUSSION.

The cases in the above pedigree, described as hereditary optic atrophy, while resembling each other very closely, differ from the typical example of the condition in their very early, probably congenital, onset, the absence of a central scotoma, the occurrence of transmission through the male and of the comparatively high female incidence. A consideration of the literature reveals that, though uncommon, none of these features are unknown. To quote Bell's⁵ detailed analysis of the available literature, she finds that 5.5 per cent. of European cases show an onset up to 7 years of age; 11.9 per cent. males and 18 per cent. females show no central scotoma; in males 4 per cent. of cases show the father affected, 9 per cent. the father's stock,

4.9 $\pm$ 0.6 per cent. transmission through the father; in females, father affected in 13.6 per cent, the father's stock 2.3 per cent., transmission through the father 15.9 $\pm$ 2.6 per cent.; 15.2 per cent. is the female sex incidence.

The question arises whether cases which show exceptional features have enough in common to permit of their separation into a group distinct from the ordinary cases of Leber's disease. It has been suggested that this may be true of cases showing a very early, or congenital, onset, such as those of Clemesha, Doynes, Jakobsohn, Gunn, Hutchinson, Posey and Snell. Snell's⁶ case may be quoted in more detail as it shows various points in common with this pedigree.

The parents and grandparents were normal. Case III 1: 33 years, male, unaffected. Case III 2: female, 32 years, had R.V. = 3/36, L.V. = 3/60, discs pale, colour-sense feeble. Case III 3: male, 31 years, had good sight and normal fundi but was colour-blind, confusing dark green with red and pale blue with pink. Case III 4: male, 29 years; R.V. = L.V. = 8/200, discs white, vessels normal. Sight always the same; children normal. Case III 6: male, 27 years; R.V. = L.V. = 6/60 with -1 D. Discs pale, especially temporal half, colour-vision weak. Case III 7: female, 25 years, unaffected. Case III 8: male, 24 years; R.V. = L.V. = 6/60, discs pale, colour-sense defective. Case III 9: female, 21 years; R.V. = L.V. = 6/24 with -6 D. Discs pale, crescents noted, colour-sense normal. In all cases the condition has been present since earliest recollection, there was no scotoma and no peripheral contraction of the fields. This case has been referred to (Cargill⁷) as an example of an atypical variety of Leber's disease, but other cases of early onset do not appear to have any of its unusual features. Nettleship⁸ saw no justification for regarding cases with congenital onset as a distinct group, and Bell⁵, with a larger available literature, concurs with him.

In our pedigree the occurrence of three typical cases of retinitis pigmentosa is difficult to interpret. The only other reported pedigree in which this occurs is that of Mann⁹. Here, a brother and sister were found to show optic atrophy; no eye disease occurred in the grandparents, parents or siblings, but a maternal aunt had eight children of whom four had retinitis pigmentosa and four had changes in the fundus suggestive of this condition; but as it was found that the man she married came of a stock in which retinitis pigmentosa had occurred, it is evident that the association of the two conditions is apparent only.

The only possibility that in the family here described the association of Leber's disease and retinitis pigmentosa is in the same way a chance one, is that Case II 4 may have transmitted the retinitis pigmentosa into a stock showing Leber's atrophy. This appears most unlikely in that there is no history of the condition in the H. family; and the twin sister, Case II 6, had

many healthy descendants. Also it is possible that Case II 17 shows a condition definitely related to the cases in the family showing retinitis pigmentosa (Cases III 6, III 10, III 18). This is suggested by the occurrence of deafness in this case, a condition found elsewhere in the pedigree only in the examples showing the typical eye picture, as it is found that when one case of retinitis pigmentosa in a given pedigree is deaf, the correlation of the two in that particular pedigree is exceedingly high (as shown in Usher's pedigrees¹⁰). It does not, of course, follow because a patient with retinitis pigmentosa is deaf that any other deaf person in the family is necessarily also a case of retinitis pigmentosa; but in this particular case the association is interesting in view of the eye picture, and it tends to support the argument that retinitis pigmentosa was not introduced into the family through Case II 4.

In the literature there are various associations of optic atrophy and indefinite pigmentary changes. Coste¹¹ reports a family in which four males show optic atrophy while a brother of one of them shows pigmentary choroiditis, and in one of Usher's¹² cases in which there are seven males and one female with optic atrophy in three generations, there are unioocular pigmentary changes in two individuals, while one of them has in addition a black-pepper appearance at the yellow spot in both eyes. In families exhibiting retinitis pigmentosa the only ones in which other cases occurred suffering from optic atrophy are those of Usher¹³ and Schmidt¹⁴. In both of these the condition was unioocular and confined to one individual. It seems justifiable to assume that in none of these cases is there any reason to consider that any relation is shown between hereditary optic atrophy and any case of definite retinal pigmentation.

Retinitis pigmentosa, although usually exhibiting a clear-cut picture, appears at times definitely related to other conditions. Polydactylism and glaucoma may be combined with it in the same way as deafness in particular families. The Laurence Biedl syndrome, of which the first example was recorded by Laurence and Moon¹⁵ in 1866, in which polydactylism, atresia ani, mental defect, obesity with genital hypoplasia, are combined with an atypical retinitis pigmentosa is a familial condition which appears related. Retinitis pigmentosa sine pigmento, first described by Leber¹⁶ in 1871 occurring in families showing the typical condition, is also a recognized variant; choroideræmia (see Smith and Usher's case¹⁷) appears to be closely allied. Retinitis punctata albescens, distinguished first by Mooren¹⁸ in 1882, occurs most frequently in families showing retinitis pigmentosa, and once with atypical retinitis pigmentosa in a case described as an example of the Laurence Biedl syndrome (Lisser¹⁹). There is nothing to suggest, through these diseases, any indirect connexion between Leber's disease and retinitis pigmentosa.

Pedigrees of both hereditary optic atrophy and retinitis pigmentosa show frequently other defects. Epilepsy and mental defect are the commonest examples; some fifteen pedigrees with epilepsy and Leber's disease, five of epilepsy and retinitis pigmentosa, five of mental defect and Leber's disease, twenty-five of mental defect and retinitis pigmentosa have been reported. Other defects occurring with Leber's disease, but much less frequently, such as syndactylism, congenital night-blindness and albinism, occur also in pedigrees of retinitis pigmentosa. But whatever the explanation of the frequency of other defects in pedigrees showing the two conditions no conclusion as to any specific relationship between hereditary optic atrophy and retinitis pigmentosa can be drawn from this, as such defects are also of frequent occurrence in other hereditary diseases.

CONCLUSIONS.

While Leber originally defined this condition as a hereditary optic atrophy without other neurological signs, thus differentiating it from other varieties of nervous diseases in which optic atrophy is but one of many prominent symptoms, there are various intermediate forms in which, while optic atrophy is the distinctive feature, other definite neurological signs are present. The best known variety is that of Behr²⁰, described as complicated heredofamilial infantile optic atrophy, which shows in addition to optic atrophy, pyramidal and cerebellar signs, further cases of which have been recorded by Takashima²¹, who established definitely the stationary character of the condition. Ferguson and Critchley²² describe a case in which two of a sibship show typical Leber's atrophy, a third shows atrophy complicated by mental defect and epileptic attacks, while a fourth has optic atrophy, pyramidal disease, ataxia and sensory loss. In their discussion they suggest that it may be possible to trace a transition between the uncomplicated hereditary optic atrophy on the one hand to Marie's heredofamilial ataxia on the other, through Behr and Takashima's cases as the first stage; and Imamura and Ichikawa's²³ cases (those of a brother and sister with optic atrophy combined with weakness of the right face, poor convergence, and in the former nystagmus on lateral deviation, in the latter, tremor of the trunk, tongue and fingers, some rigidity of the limbs and incoordination of fine movements) and their own fourth case as the second stage. Their own pedigree is of particular interest in that not only is there a rare example of complicated hereditary optic atrophy, but that it occurs in the same sibship as two cases of typical Leber's atrophy, and may thus be regarded as a possible polymorphic variety of the latter condition. Whether this is so or not can only be determined by subsequent investigation of their descendants, as the previous family history is negative.

It appears possible that the case here recorded may also form one of a group of a distinct variety of optic atrophy and that this group may also represent a transition between Leber's hereditary optic atrophy and retinitis pigmentosa. Apart from the age of onset, the most striking anomalous feature is the manner of transmission. In considering the recorded examples of transmission through the male, while it is found that, in the majority, this occurs as an isolated instance in a pedigree exhibiting otherwise the normal inheritance, there are pedigrees in which it seems to be the rule, forming thus a striking contrast to the usual pedigree. The following are examples of this.

Griscom²⁴ records a family with eight affected males and six affected females in three generations comprising 16 males and 16 females. Four affected and one unaffected male transmit the condition and one affected female has two unaffected sons and one unaffected daughter. The other example of this in the literature is the case recorded by Yo-Kansyo²⁵ of ten affected males and two females in four generations; here five affected males transmit the condition and one affected female. On one occasion an affected male has a normal family, but it is stated that the latter is too young to be certain that some members of it may not show the condition later. It is noteworthy that in the former pedigree several members show, in addition to the optic atrophy, abnormal retinal pigmentation; a female, aged 34, had a complete narrow ring of choroidal atrophy surrounding the disc, the vessels were thread-like in size, the macula showed a fine pigment disturbance and in the periphery there were a few spicule-like pigment areas overlying the retinal vessels; a male, 32 years, had vessels about one-half normal size and fine granular pigmentation throughout the retina; a male, 30 years, had vessels almost thread-like in size, retinae finely granular throughout and a few pin-point glistening spots and fine pigment deposits seen in the macular region. The recorder concludes that the pigment disturbance and atrophic vessels are evidence of a low-grade retinal degeneration resulting from nutritional disturbances from a toxæmia affecting the optic nerve and retina; but whatever the explanation of the local happenings it is the inheritance of the specific weakness of these structures that is of particular interest. Unfortunately, in Kawakami's abstract of Yo-Kansyo's case there is no detailed description of the fundi of the members of this pedigree.

In the pedigree recorded here it seems probable that the appearance of retinitis pigmentosa in one sibship is more than a chance association, for the reasons given above, and that it may be regarded as a polymorphic manifestation of Leber's disease occurring here, the sequence of Cases II 10, III 10, and IV 9 being particularly suggestive in this connexion; while the condition shown by Case II 17 may also possibly be related to the two conditions.

Here, therefore, are three pedigrees in which the manner of inheritance is absolutely different from that of other cases of Leber's optic atrophy: (1) in Yo-Kansyo's case male transmission is invariable except for one instance in which an affected female transmits the condition; (2) in Griscom's case male transmission is the rule and definite instances of retinal pigmentation occur; and (3) in the case here recorded, there is male transmission only, three cases of typical retinitis pigmentosa and one of atypical pigmentation. There seems, therefore, some justification for regarding these as a distinct group, possibly intermediate between Leber's hereditary optic atrophy and retinitis pigmentosa.

The rarity of examples of predominantly male transmission of any hereditary disease has rendered the factors responsible for this very obscure; at any rate no comparable cases appear to have been recorded in the literature of retinitis pigmentosa except possibly a type of case, represented by pedigrees of Nettleship²⁶ and Snell²⁷, in which the defect occurs with extreme frequency and is invariably transmitted by affected members, whether male or female.

SUMMARY.

This pedigree differs from that typical of Leber's hereditary atrophy in several respects. The defect is congenital, there is no central scotoma and females are affected. It is stated, on the best authority, that there is no reason for regarding cases of congenital onset as forming a group distinct from Leber's atrophy and there are certainly no other features common to the cases; in the present instance the only other pedigree resembling this one in these particulars is that of Snell.

In the pedigree there are three cases of typical retinitis pigmentosa and one case with retinal pigmentation in the region of the macula. While it is possible that the retinitis pigmentosa was introduced by marriage and that the fourth case is a coincidence, it seems on the whole unlikely and that there is a real connexion between these and the cases of optic atrophy.

The last point of importance is that in every case in the pedigree transmission is through the male. Whether, as has been suggested, it is justifiable to regard pedigrees with predominantly male transmission as forming a distinct group of hereditary optic atrophy, related on the one hand to Leber's atrophy and on the other to retinitis pigmentosa, in the same way as Behr's variety may be so regarded with its comparable relations, or not, this pedigree appears worthy of record on account of features which are of interest not only from the clinical aspect and with regard to the definition of Leber's disease, but also from the genetic point of view.

In conclusion, I wish to thank Mr. J. N. Tennent for examining Cases II 17, III 10, III 27, IV 9, and IV 29 with me and giving me the benefit of his opinion on them, and also to express my indebtedness to the monographs of Bell^{5, 28} whose analysis of all available literature and her conclusions based upon them are invaluable when any new pedigree has to be considered. I also wish to thank Dr. Edward Mapother for kindly allowing me to use clinical material at the Maudsley Hospital.

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