DOMINANTLY INHERITED OPTIC ATROPHY*

BY

RUBY JOSEPH AND J. B. DAVEY

*Ophthalmological Research Department
Royal College of Surgeons and Royal Eye Hospital, London*

LEBER'S disease, with its sudden onset in adolescence or early adult life, its rapid course, and puzzling mode of inheritance, has overshadowed other forms of inherited optic atrophy. The early literature contained many cases of "atypical" Leber's disease, but the continued emphasis on the established form, even in the monumental review by Bell (1931), hampered the emergence of other forms as separate clinical entities.

Waardenburg (1913) drew attention to the incidence of consanguinity in reported pedigrees of infantile optic atrophy suggestive of the existence of a recessive autosomal form. Rather more evidence for a dominant autosomal type is suggested by several reports in the early literature, such as the cases recorded by Knapp (1904), Lawson (1907), Nettleship (1909), Griscom (1921), Ginzburg (1923), Kawakami (1926), Alsberg (1927), Riedl (1935), and others; onset in childhood or infancy was common in such cases. Dominant optic atrophy is in fact not particularly uncommon; Lodberg and Lund (1950) have even suggested that in Denmark this type of optic atrophy is more common than Leber's disease. Recently attempts have been made to separate dominant optic atrophy into different forms. Thus Lodberg and Lund (1950) and Sorsby (1951) suggested a congenital and a post-natal form, while Jaeger (1954) suggested a third variety: dominant optic atrophy with nystagmus. The reports in the literature appear to fall into two main groups:

(1) The type which has been referred to as "congenital" has been infrequently reported. The largest family in this group, with twelve affected members, is that reported by Thompson and Cashell (1935) and by Dorrell (1932), which, as pointed out by Sorsby (1951), is the same family as that previously described by Nettleship (1909). Other similar families are those of Herzog (1930) and one of the three reported by Lodberg and Lund (1950). Although the affection has not in fact been seen at birth, Dorrell observed optic atrophy at 8 months. Some of Nettleship's patients speak of good vision up to the age of 3 or 4 years, although this in itself does not preclude the existence of optic atrophy as a congenital lesion. Visual acuity in these three families ranged from 6/24 to hand movements, the poorer levels of vision being common. Progressive deterioration appears to have been experienced by some patients, as in two cases recorded by Lodberg and Lund. Divergent strabismus and contraction of the peripheral field were noted in some members of each of these three families. Thompson and Cashell observed nystagmus in nine out of ten cases; a generalized pallor of the optic disc

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was a common finding in their cases, and was sometimes accompanied by attenuation of the retinal blood vessels. Taking these three family groups together—the Nettleship-Dorrell-Thompson-Cashell group, the Herzog family, and the Lodberg and Lund family—it is evident that, though there is a fairly definite pattern, there are considerable individual variations, especially in the degree of vision and the presence of nystagmus.

(2) The second type has been termed the “infantile” or “juvenile” form, or the “acquired” form. The largest study is that of Kjer (1956), who reported twenty families with at least 200 affected individuals. Kjer emphasized that there was wide variation in the degree of manifestation in any one family. Visual acuities ranged from 6/6 to 2/60, but vision was apparently never entirely lost. Progress with age is not constant. In 51 cases the disease appeared stationary, while in 43 there was slow progression. The age of onset is usually in childhood. The youngest case found by Kjer was aged 2 years, and by Scott (1941) 4 years. Lodberg and Lund (1950) give details of three siblings whom they re-examined while the disease was progressing. The first was passed as normal at the age of 7, but 3 years later there was marked temporal pallor and the visual acuity had fallen from 6/6 to 6/36. The second at the age of 9½ years showed temporal pallor and the visual acuity was recorded as 6/18; 4½ years later the visual acuity was reduced to 6/36 in the right eye and 6/24 in the left, with bilateral temporal pallor of the discs. The changes in the third were less striking; between the ages of 7 and 12 “light fading” of the temporal side of the disc became “pronounced” and the visual acuity fell from 6/24 to 6/36. Progressive deterioration with age is also suggested by the following analysis:

Visual Acuity in Better Eye	Scott (1941)		Kjer (1956)	
	Adults	Children	Adults	Children
6/6–6/18	—	—	76	15
6/24–6/60	11	5	57	6
6/60–2/60	13	—	27	—
No data	—	—	7	12

Ophthalmoscopically, pallor is commonly confined to the temporal side, or is more marked on this side; in severe cases it is generalized. Contraction of the peripheral fields is rare, but in severe cases it may be gross, the temporal field being the more affected (Kjer). Enlargement of the blind spot was reported by Jaeger (1954), and a paracentral scotoma by Kjer. Poor colour vision and constriction of the colour fields was noted by a number of observers (Knapp, 1904; Scott, 1946; Lodberg and Lund, 1950; Jaeger, 1954). The reduction of the field for blue observed by Scott (1941) was confirmed by both Jaeger and Kjer, the latter drawing attention to the hemianopic nature of the colour fields, the temporal side being lost first. Kjer stressed the psychic anomalies and mentioned poor night vision.

PERSONAL OBSERVATIONS

(1) D. Family (Pedigree Chart I).

There were five affected persons in two generations:

Case 1, Laura D—(I, 4, Pedigree Chart I).—This patient was first seen at the age of 65 years when the visual acuity was 1/60 in each eye. She had had defective sight “all her life” and had always been “bad at colours”. The Ishihara test was not practicable because of the low visual acuity. The fundi showed myopic changes at the maculae and temporal pallor of the optic discs.

Case 2, Frederick D—, aged 62 (I, 7).—The refraction was: Right +3 D sph., -2 D cyl., 95°; Left +4 D sph., -2 D cyl., 95°. He had had poor vision since his school-days and had been aware of a steady deterioration. In 1951 the visual acuity was 3/36 in the right eye, and 3/60 in the left. By 1956 this had fallen to counting fingers at 2 m. in the right eye, and at 1 m. in the left. The fundi showed marked pallor of the discs, especially on the temporal side (Fig. 1a).

(a) A severely affected man aged 62. The right disc had retained some pink colour on the nasal side, but otherwise the discs were grey. Visual acuity was reduced to counting fingers.

(b) A son (aged 37) and a daughter (aged 30) both had poor vision.

FIG. 1.—Appearances of the optic nerve in the D. family.

Case 3, Frederick John D—, aged 37 (II, 9), a son of Case 2.—His visual acuity was 6/36 in each eye in 1951 and 5 years later it had not altered. This man was illiterate and mentally subnormal, and as a child had been subject to epileptic fits. His response to the Ishihara test was poor. The anomaloscope showed him to have poor matching ability with a tendency towards protanopia. Colour fields were restricted, that for blue being absent. The field for white is shown (Fig. 3a, opposite), and the enlarged blind spot will be noted. His dark-adaptation curve was substantially the same as his father's (Fig. 2, Curve c). Temporal pallor was present in both optic discs (Fig. 1b).

Case 4, Mrs. Christina G—, aged 30 (II, 12), a daughter of Case 2.—She had had poor vision since her school-days and was not aware that there had been any recent deterioration. For the past 5 years her visual acuity had been 6/60 in each eye. She failed completely on the Ishihara test and on the anomaloscope could only detect changes in luminance. As with her father (Case 2), it was not possible to plot fields of vision on a screen. Her dark-adaptation curve was normal except for a minimal restriction in the cone curve. Temporal pallor was present in the optic discs, but the nasal sides appeared normal (Fig. 1(c), opposite).

FIG. 1(c).—A son (aged 37) and a daughter (aged 30) both had poor vision.

FIG. 1(d).—A younger daughter (aged 22) retained visual acuity of 6/24 and 6/18. Temporal pallor was present in all three siblings, but the coloration of the nasal side remained good.

(a) Case 3, right eye. The field for blue was absent, and the other colour fields were restricted. Note the enlarged blind spot.

(b) Case 5, left eye. Colour fields; note the severe restriction.

(c) Case 5, left eye. Fields for white; note the enlarged blind spot and restriction of the nasal field for a 2/2000 stimulus (---), while the 10/2000 field (—) was full.

FIG. 3.—Fields of vision in the D. family.

Case 5, Doreen D—, aged 22 (II, 13), proband.—The refraction was: Right -3.25 D sph., -0.5 D cyl., 65° ; Left -3 D sph., -0.25 D cyl., 80° . In 1951 the visual acuity was 6/12 in each eye and this had fallen by 1956 to 6/24 in the right eye and 6/18 in the left. The colour vision was normal but the colour fields were severely restricted on the temporal side (Fig. 3b), the upper temporal quadrants of the fields being absent. The field for white showed an enlarged blind spot for a 2/2000 stimulus (Fig. 3c), and restriction of the nasal field. The optic discs showed a mild temporal pallor (Fig. 1d).

(2) P—, Family (Pedigree Chart II).

There were four affected persons in two generations:

Case 6, John Alfred P—, aged 57 (II, 1, Pedigree Chart II), proband (Royal Eye Hospital record number, 33/1104).—He had had poor sight since his school-days and in 1916 was rejected by the Army on this account. In 1933 his visual acuity was 6/60 in each eye and by 1946 this had fallen to 3/60 in the right eye and 4/60 in the left; 5 years later it was 3/60 in each eye. The fields for white had not altered markedly between 1933 and 1951 (Fig. 4, opposite). Colour vision was almost completely lacking in 1951 but it was possible to plot a small field with a blue stimulus (Fig. 4). This response was present on the nasal side only. Dark adaptation was markedly restricted both for rod and cone vision (Fig. 6b, overleaf). Temporal "atrophy" of the optic discs was observed in 1933, and this is now considerable (Fig. 5a, opposite) but some colour remains on the nasal sides.

Case 7, George P—, aged 45 (II, 4), brother of Case 6.—His visual acuity was 6/9 in each eye. The Ishihara test showed complete colour blindness and the anomaloscope showed the hue discrimination to be much reduced. Pallor of the temporal side of the discs was observed and there was the same considerable reduction in his night vision (Fig. 6c, overleaf) as was seen in his brother (Case 6). This patient was uncooperative and it was not possible to plot his fields of vision.

Case 8, Lilian P—, aged 34 (II, 7), sister of Case 6.—Her visual acuity was 6/24 in the right eye, and 6/18 in the left. At the age of 18 years she was admitted to a mental hospital suffering from schizophrenia. She knew her sight had always been poor and that she was colour blind. However, she thought that when she first entered the hospital she could see colours better. She failed completely on the Ishihara test. It was not possible to plot her visual fields but the manner in which she turned her head to the side

FIG. 4.—Case 6, right and left eyes. The colour fields show that only a small field for blue remained on the nasal side. The fields for white show enlargement of the blind spot. The peripheral fields were first plotted in 1933 (—) and, as will be seen, were little changed on examination in 1951 (---).

FIG. 5 (a).—Case 6, a man aged 57 with 3/60 vision each eye, left eye. Some pink coloration was still present on the nasal side of the disc.

FIG. 5 (b).—Case 8, a sister, aged 34, of Case 6, left eye. The nasal side of the disc still retained some pink coloration. Visual acuity 6/18.

when she wanted to regard an object was suggestive of a central scotoma. The optic discs showed considerable temporal pallor (Fig. 5b).

Case 9, Rose P.—, aged 26 (III, 1), daughter of Case 6.—She attended the Royal Eye Hospital in 1946 (46/3713), when the visual acuity was 6/18 in each eye. The visual fields were normal and the discs were pale, but not so pale as her father's. Defective vision had been first noticed at the age of 15 years.

Analysis

Mode of Inheritance.—In the D. family affected individuals occur in two generations. In the first generation, two out of the three individuals seen were affected. There had been seven in this sibship, but three are now dead and a fourth could not be traced. All the six children of I, 7, an affected

man, were seen, with the exception of II, 11, who was killed while flying in the R.A.F. in 1944 aged 22, and whose sight was presumably normal. Of these six siblings, three were affected and three normal (if II, 11, be included as a normal). The two children of II, 12, an affected woman, aged 5 and 7 years, are both normal.

In the P. family two generations included four affected individuals. There was hearsay evidence which suggested that I, 1, had also been affected (his sons reported that he had had poor sight all his life and was unable to learn to drive on account of this defect). Generation II included seven individuals of whom three were affected. In Generation III one woman was affected; she was one of three children of an affected man.

The pattern of inheritance seen in both families strongly suggests dominant autosomal inheritance. If I, 1, in Pedigree Chart II is accepted as an affected

individual, then the evidence for dominance is conclusive. Sex-linkage is obviously excluded.

Visual Acuity.—The nine cases are arranged according to age in the Table.

TABLE
VISUAL ACUITY IN RELATION TO AGE

Case No.	Examination								
	First			Second			Third		
	Age (yrs)	Visual Acuity		Age (yrs)	Visual Acuity		Age (yrs)	Visual Acuity	
		Right	Left		Right	Left		Right	Left
5	17	6/12	6/12	22	6/24	6/18			
4	25	6/60	6/60	30	6/60	6/60			
9	26	6/18	6/18						
3	32	6/36	6/36	37	6/36	6/36			
8	34	6/24	6/18						
6	39	6/60	6/60	52	3/60	4/60	57	3/60	3/60
7	45	6/9	6/9						
2	57	3/36	3/60	62	Finger counting at 2 m.	Finger counting at 1 m.			
1	65	1/60	1/60						

(a) The visual acuity in individual cases tends to diminish although at varying rates. In 5 years Cases 2 and 5 showed an appreciable reduction while Cases 3 and 4 showed no change. Case 6 showed a gradual reduction over 18 years.

(b) The visual acuity of different cases bears little relation to their age. Case 7 had visual acuity of 6/9 at the age of 45, while Case 4 had visual acuity of 6/60 at the age of 25.

Fundus Appearances.—Pallor of the optic disc was the only ophthalmoscopic sign observed. This ranged from temporal pallor with good coloration on the nasal side, as in Cases 4 and 5, to a more general whitening of the discs as in Cases 2 and 6. The amount of pallor is only an approximate guide to the degree of visual handicap.

Dark Adaptation.—Poor night vision was found in five affected individuals, in one of whom the defect was minimal (Case 4). The dark-adaptation curves for the remaining four are given in Figs 2 and 6. The two cases in the P. family showed a marked restriction of both cone and rod vision (Fig. 6, Curves b and c). The point at which rod vision became more

sensitive than cone vision was delayed by some 5 minutes. Case 7 had good visual acuity (6/9), but the other cases with poor night vision had low visual acuity.

Colour Vision and Colour Fields.—Of the eight cases examined by the Ishihara and anomaloscope tests, seven showed evidence of defective colour vision. The one case with normal colour vision, a girl aged 22, showed a quadrant, almost hemianopic field defect. It was possible to plot the colour fields in only two other cases and these were severely constricted. In Case 3 only the plotting of red and green fields was possible, the blue field being absent (Fig. 3a), and in Case 6 only the blue field could be plotted (Fig. 4). This last was an unexpected finding, since other workers have emphasized early loss of the blue field with the retention of the red and green fields. The hemianopic shape agrees with previous findings. In three patients low acuity and gross colour vision defects rendered the procedure impracticable. Of the rest, two declined to be tested and another was a patient in a mental hospital which lacked the necessary equipment.

Fields for White Stimuli.—In the three cases in which fields for white were plotted an enlargement of the blind spot was observed (Figs 3a, 3c, and 4). The periphery of the field is not markedly contracted. In Case 6 the fields for white were plotted in 1933 and again in 1951 and the change was small; in the same period his visual acuity fell from 6/60 to 3/60 in each eye. In Case 2 a confrontation test revealed no marked constriction of the periphery of the fields, although the visual acuity at the time was only 3/36 in the right eye and 3/60 in the left.

Psychic Abnormalities.—These were noted in one patient in each family, and one of these was a patient in a mental hospital.

Discussion

(1) **Onset and Course.**—Like previous studies, the present records show dominant optic atrophy to be an insidious affection. In two of our cases the anomaly was not discovered until the ages of 15 and 17, when the visual acuity was 6/18 and 6/12 respectively. The success with which patients overcome their visual difficulties is possibly accounted for by the fact that, although their visual acuity may be low, the periphery of their fields is largely intact. In addition, the gradual reduction in visual acuity, unaccompanied by any marked contraction in the field for white allows the patient to become adapted to his failing vision. Even though his vision was below 6/60, Case 2 was still working. In three of the six cases examined on more than one occasion a fall in visual acuity was detected. Since one of these is 22 years of age and another 62 it seems probable that a gradual diminution occurs throughout life.

(2) **Functional Disturbances.**—Defective colour vision has been reported by several other observers as one of the more consistent findings among affected adults and this was the case in at least seven of our patients. The contraction of colour-fields stressed by Kjer (1956) as especially marked on the temporal side and most definite for blue was also found in two of those patients who could be examined. In a third (Case 6) an anomalous finding was the persistence of a somewhat hemianopic field for blue when all other colour fields had already been lost.

Kjer noted defective night vision in some of his cases. The present study confirms that this defect is not an uncommon feature. The anomaly is more than a mere raising of the final threshold. The curves of both cone and of rod adaptation are late in appearing and both are restricted.

(3) **Psychic Abnormalities.**—These were noted by Kjer in about 10 per cent. of his cases, and were seen in two cases in the present study.

(4) **Outstanding Issues.**—The significance of poor dark adaptation in dominant optic atrophy still requires elucidation. Whether involvement of both rod and cone curves is characteristic of this particular affection or an aspect of any optic atrophy needs to be determined.

The present case reports show how difficult it is to establish in any particular family whether the affection is congenital or post-natal in origin, and whether indeed this distinction with its implications as to severity and prognosis is valid. Investigations are needed in suitable families specially studied for this possible distinction.

Summary

Two families with inherited optic atrophy were examined. The following characteristics were observed:

- (1) The mode of inheritance is almost certainly dominant and autosomal.
- (2) The visual acuity of affected adults diminishes slowly throughout life.
- (3) The visual fields show an enlarged blind spot, a good peripheral field for white, but contracted fields for colour, usually especially marked for blue (an exception was a case in which the blue field was retained while those for red and green were lost). The field defect may be quadrantic or hemianopic, the temporal side being the more severely affected.
- (4) Colour vision among the adults is usually defective or absent.
- (5) Poor dark adaptation is often seen, usually with a marked restriction of both the rod and the cone portions of the dark-adaptation curve.
- (6) Pallor of the disc, most marked on the temporal side, is a constant finding in affected individuals, but the degree of pallor is only an approximate guide to the amount of visual defect.

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