The heart in Leber's optic atrophy

F. CLIFFORD ROSE*, A. N. BOWDEN, AND P. M. A. BOWDEN

The Royal Eye Hospital Medical Ophthalmology Unit, Lambeth Hospital, London

Patients with Leber's optic atrophy may have diffuse neurological disease with involvement of systems other than the nervous system (Ferguson and Critchley, 1928; Wilson, 1963; Bruyn and Went, 1964; Adams, Blackwood, and Wilson, 1966). These findings suggest that Leber's disease, although mainly affecting the optic nerves, is a multisystem disorder. Cardiac abnormalities have not been described in Leber's disease apart from an account of myocardial disease found *post mortem* in one patient (Wilson, 1963). This paper reports the electrocardiographic changes found in two patients with Leber's disease.

Case reports

Case 1, a capstan operator, was admitted to hospital in June, 1967, at the age of 24 years.

History

He had good vision until November, 1963, when he developed progressive painless blurring of central vision in the right eye over a period of 4 to 5 weeks, and 2 months later the vision in the left eye became similarly affected. He was admitted to hospital where he was found to have oedematous optic discs and dense central scotomata. The visual acuity in the right eye was counting fingers, and in the left eye 6/60.

Physical examination at that time showed no abnormality and investigations including x-rays, lumbar puncture, and air encephalography gave normal results. Since then the vision had remained poor in both eyes. He had no history of cardiorespiratory symptoms or other past illness. He had never smoked. Two maternal uncles had optic atrophy, with a similar history of rapidly progressive bilateral visual loss; one of them showed marked subsequent improvement. A male child of one of the affected uncles was born with a clubfoot deformity.

Examination

In June 1967, there was bilateral optic atrophy with dense central scotomata; the visual acuity in both eyes was hand movements at 1 m. The blood pressure was 120/80 mm. Hg, and the electrocardiograph was abnormal (Fig. 1; Table I), but further investigations, including chest x-ray and radiological screening of the heart, gave normal results. The electrocardiograph of the patient's father was normal; no other members of the family were available.

Case 2, a postgraduate research worker, was admitted to hospital in March, 1967, at the age of 28 years.

History

His vision had been good until December, 1961, when he developed simultaneous painless rapidly progressive blurring of the central vision in both eyes, while studying in Israel. He was admitted to hospital where he was found to have oedematous optic discs and central scotomata; the visual acuity in the right eye was counting fingers at 0.5 m., and in the left 3/60. Skull x-rays and lumbar puncture were normal, but air encephalography showed a doubtful abnormality in the chiasmatic

FIG. 1 *Electrocardiograph of Case 1*

Table I *Electrocardiographic findings in Cases 1 and 2*

Case no.	1	2
Rhythm	Sinus	Sinus
Rate/min.	60	60
P wave	Normal	Normal
PR interval (sec.)	0.12	0.16
Q wave	Prominent in I, II, AVL, V ₅ , 6	Prominent in II, III, AVF, V ₄₋₇
R wave	> 25 mm. in V ₄₋₆ RV ₁ > SV ₁	> 25 mm. in II, III, AVF, V ₅₋₇ Tall in V ₁
SV ₁ + RV ₅ (mm.)	45	41
QRS (sec.)	0.10	0.08
ST	Elevated V ₁₋₄	Elevated V _{2, 3}
T wave	Low voltage in I	Normal
QT _c (sec.)	0.40	0.40
Frontal plane axis	+55°	+70°

cistern. The vision failed to improve with ACTH injections. Craniotomy in February, 1962, was negative, the appearance of the optic nerves and chiasm being normal. In the 6 months after the operation the vision improved but had not changed since. In 1955, while in South Africa, the patient had had an episode of unconsciousness and had been kept in bed in hospital for 3 weeks. An electrocardiograph performed at that time was abnormal. He had no other cardiorespiratory symptoms or past illness. He had smoked fifteen cigarettes daily for 10 years. There was no known family history of eye or neurological disease; a brother, sister, and two maternal uncles were well.

Examination

In March, 1967, he was normal apart from bilateral optic atrophy and central scotomata; the visual acuity was 2/60 in both eyes. The blood pressure was 130/75 mm. Hg, and the electrocardiograph was abnormal (Fig. 2; Table I). Further investigations, including chest x-ray, gave normal results. The electrocardiograph taken in South Africa in 1955 was obtained and this was identical with the 1967 recording. No members of the family were available for examination.

FIG. 2 *Electrocardiograph of Case 2*

Electrocardiographs were obtained in four further unrelated male patients with Leber's hereditary optic atrophy and these were all normal.

Discussion

Leber's disease usually affects males in early adult life, who typically suddenly develop bilateral loss of central vision. Subsequently, vision may improve as optic atrophy develops. The family history is characteristic with unaffected females transmitting the condition to males who are affected but do not transmit. The exact mode of inheritance is not known (Rose and Friedmann, 1964; François, 1966). Of the present patients,

Case 1 has the classical features and family history of Leber's disease. The features in Case 2 are also typical but the family history is negative, though this is by no means excludes the diagnosis (Lundsgaard, 1944; Hierons and Lyle, 1959).

Although there have been several reports of cardiac involvement in hereditary familial neurological disorders, there has been only one in which the heart was involved in Leber's disease. This was a patient with Leber's disease and progressive dementia who had complained of breathlessness on exertion, chest pain, and palpitations for a few years before his sudden death at the age of 41 years. *Post mortem* examination revealed a dilated heart with abnormal myocardium and only slight coronary atheroma, and these features were thought to be consistent with cardiomyopathy (Wilson, 1963).

Syncopal attacks have been described in patients with Leber's disease in the absence of other evidence of heart disease, but electrocardiography was not performed in these patients (Ferguson and Critchley, 1928; Wilson, 1963).

The electrocardiographic abnormalities found in the two patients reported are very similar and occur in the absence of clinical or radiological evidence of cardiovascular disease. The main abnormalities are deep Q waves and tall R waves in limb and chest leads (Table I). Deep Q waves may be found in the normal in association with, and less than 25 per cent. of the height of, tall R waves, and less than 0.04 sec. duration; tall R waves are not in themselves abnormal, especially in the young (Goldman, 1964). Abnormally deep Q waves are found in myocardial infarction and ventricular hypertrophy, but there is no other evidence to support such diagnosis in these two patients. Abnormal Q waves are also found in association with hypertrophy of the interventricular septum in muscular subaortic stenosis (Braudo, Wigle, and Keith, 1964), when septal muscle is spared in the cardiomyopathy of progressive muscular dystrophy (Perloff, de Leon, and O'Doherty, 1966; Perloff, Roberts, de Leon, and O'Doherty, 1967), and in familial cardiomyopathy in which there is myofibrillar hypertrophy as well as patchy atrophy and fibrosis (Whitfield, 1961). It seems that the present patients might have a mild degenerative cardiomyopathy with sparing or hypertrophy of the interventricular septum and insufficient to produce clinical or radiological signs.

The hereditary familial neurological disorders which may have associated electrocardiographic abnormalities are summarized in Table II (overleaf). In those diseases in which bilateral optic atrophy occurs the cardiographic changes are unlike those in the present report, and are associated pathologically with disease of the myocardium, Purkinje fibres, or sinoauricular node.

Affected patients may have diffuse neurological disease with features of lower motor neurone, upper motor neurone, cerebellar, extrapyramidal, or cortical involvement (Ferguson and Critchley, 1928; Wilson, 1963; Lees, Macdonald, and Aldren Turner, 1964; Bruyn and Went, 1964; Adams and others, 1966). These associations suggest a link between Leber's disease and other hereditary familial neurological disorders in which optic atrophy occurs (Ferguson and Critchley, 1928; v Bogaert, 1948; Bruyn and Went, 1964). To explain the multisystem involvement in hereditary familial neurological disease it has been suggested that the abnormal gene is pleiotropic (Roth, 1948; Boyer, Chisholm, and McKusick, 1962; Rose, Fraser, Friedmann, and Kohner, 1966). Assuming a single gene abnormality in Leber's disease, the possibility that cardiac muscle may be involved provides evidence for pleiotropy of this gene. Since cardiac involvement occurs in other hereditary familial neurological diseases, the presence of electrocardiographic abnormalities in cases of Leber's disease lends some support to a relationship, however distant.

Table II Heredofamilial neurological syndromes associated with electrocardiographic abnormalities.

Syndrome	Inheritance	Optic atrophy	Cardiographic abnormalities	Reference
Friedreich's ataxia	Variable	+	Dysrhythmia T inversion	Boyer and others (1962)
Peroneal muscular atrophy	Variable	+	Dysrhythmia Flat T	Leak (1961)
Hereditary spastic paraplegia	Variable	+	Dysrhythmia Conduction defects	Sutherland (1957)
Refsum's disease	Recessive	—	Conduction defects T inversion	Gordon and Hudson (1959)
Congenital nerve deafness	Recessive	—	Prolonged QT _c Large T	Fraser, Froggatt, and James (1964)
Pseudo-hypertrophic muscular dystrophy	Sex-linked	—	Dysrhythmia Deep Q Tall RV ₁	Perloff and others (1966) Perloff and others (1967)
Ocular myopathy	Variable	—	Conduction defects	Kearns and Sayre (1958)
Dystrophia myotonica	Variable	—	Dysrhythmia T inversion Conduction defects	Cannon (1962)

Summary

Electrocardiographic abnormalities are reported in two patients with Leber's hereditary optic atrophy. Electrocardiographs in four further patients with Leber's disease were normal. The significance of these findings in relation to possible cardiac pathology and to the pathogenesis of Leber's disease is discussed.

We thank Dr. M. Harington, M.R.C.P., for advice on the interpretation of the electrocardiographs, and Mr. A. I. Friedmann, F.R.C.S., for his help and co-operation.

References

- ADAMS, J. H., BLACKWOOD, W., and WILSON, J. (1966) *Brain*, **89**, 15
 BOGAERT, L. VAN (1948) In "Modern Trends in Ophthalmology", ed. A. Sorsby, vol. 2, p. 317. Butterworth, London
 BOYER, S. H., CHISHOLM, A. W., and MCKUSICK, V. A. (1962) *Circulation*, **25**, 493
 BRAUDO, M., WIGLE, E. D., and KEITH, J. D. (1964) *Amer. J. Cardiol.*, **14**, 599
 BRUYN, G. W., and WENT, L. N. (1964) *J. neurol. Sci.*, **1**, 59
 CANNON, P. J. (1962) *Amer. J. Med.*, **32**, 765
 FERGUSON, F. R., and CRITCHLEY, M. (1928) *J. Neurol. Psychopath.*, **9**, 120
 FRANÇOIS, J. (1966) *J. Génét. hum.*, **15**, 147
 FRASER, G. R., FROGGATT, P., and JAMES, T. N. (1964) *Quart. J. Med.*, **33**, 361
 GOLDMAN, M. J. (1964) "Principles of Clinical Electrocardiography", 5th ed. Lange, Los Altos, California

- GORDON, N., and HUDSON, R. E. B. (1959) *Brain*, **82**, 41
- HIERONS, R., and LYLE, T. KEITH (1959) *Ibid.*, **82**, 56
- KEARNS, T. P., and SAYRE, G. P. (1958) *A.M.A. Arch. Ophthalm.*, **60**, 280
- LEAK, D. (1961) *Brit. Heart J.*, **23**, 326
- LEES, F., MACDONALD, A.-M. E., and ALDREN TURNER, J. W. (1964) *J. Neurol. Neurosurg. Psychiat.*, **27**, 415
- LUNDGAARD, R. (1944) *Acta ophthalm. (Kbh.)*, Suppl. 21, "Leber's Disease"
- , DE LEON, A. C., and O'DOHERTY, D. (1966) *Circulation*, **33**, 625
- PERLOFF, J. K., ROBERTS, W. C., DE LEON, A. C., and O'DOHERTY, D. (1967) *Amer. J. Med.*, **42**, 179
- ROSE, F. C., and FRIEDMANN, A. I. (1964) *J. med. Génét.*, **1**, 110
- , FRASER, G. R., FRIEDMANN, A. I., and KOHNER, E. M. (1966) *Quart. J. Med.*, **35**, 385
- ROTH, M. (1948) *Brain*, **71**, 416
- SUTHERLAND, J. M. (1957) *Lancet*, **2**, 169
- WHITFIELD, A. G. W. (1961) *Quart. J. Med.*, **30**, 119
- WILSON, J. (1963) *Brain*, **86**, 347