LEBER'S OPTIC ATROPHY AND ITS RELATIONSHIP WITH THE HEREDO-FAMILIAL ATAXIAS.*

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INTRODUCTION.

THE purpose of this paper is to draw attention to the existence of an atypical variety of Leber's disease, wherein positive neurological signs were present in addition to the optic atrophy.

Since the publication of Leber's original paper¹ in 1871, we have been accustomed to regard the form of optic atrophy which bears his name as a pure clinical entity uncomplicated by other morbid conditions in the nervous or other systems. We have regarded this disease, moreover, as one which breeds true; that is to say, there is no variation in the clinical features as appearing in successive generations. Furthermore, no characteristic mental or physical anomaly is known to occur among members of the family who themselves show no optic atrophy. The monographs of Habershon², Nettleship³, Favier⁴ and others who have carefully reviewed the literature, on the whole confirm this view.

The clinical picture of Leber's disease is fairly well-defined. It comprises a heredo-familial type of optic atrophy in which both males and females are affected, but is transmitted through the females alone. Symptoms commence at puberty or shortly afterwards, often with a rapid onset; one eye may be affected before the other. Vision deteriorates, but complete blindness is exceptional. There is a central scotoma with little or no peripheral constriction of the visual fields. The disc changes in the earliest stages are those of a neuritis, but the later appearances are those of a definite optic atrophy. There may be a slight degree of improvement in the state of vision, after which the condition remains stationary. No obvious etiological factor can be traced and physical examination reveals no abnormality in any region outside the optic nerve.

Although the symptomatology of Leber's disease is comparatively clear-cut, opinions are divided on the question of pathogenesis. We may briefly mention the hypotheses of an inherited temporary disorder of the pituitary gland; of meningeal inflammation round the optic foramina; of toxic retrobulbar neuritis due to some neighbouring sepsis and affecting tissue which bears an inherent vulnerability. Lastly, there is the conception of a primary neuronc degeneration localised to the optic nerve.

Leber quite definitely excluded from his cases all instances of optic atrophy associated with nervous disorders. But, in the family about to be described, one member showed the additional features of epilepsy and mental defect, while another showed signs of a marked neurological affection, sufficiently

* Carried out under the auspices of the Medical Research Council.

severe to cause her to seek advice at a nerve hospital. Despite these added unorthodox features there is no doubt whatever that the familial affection is one of Leber's disease.

THE N. FAMILY OF KILBURN.

The four cases recorded in this paper are those of the surviving offspring of Mrs. Ada N. (née D.). One son died about the age of six months from "curvature of the spine and convulsions." There were no miscarriages. Mrs. Ada N. herself is one of a family of seven (two sisters and four brothers). They were all of normal mentality and average intelligence. We have not been able to obtain any information which would lead us to suspect that any of them suffered from defective sight or any nervous disease (See genealogical table.)

Mrs. N.'s husband and his parents did not show any ocular or neurological abnormality. Mr. and Mrs. N. were not related prior to marriage.

CASE 1. Minnie N., age 30.

History: Symptoms commenced at the age of fourteen with gradual impairment of vision in both eyes. In the course of the next few months the sight grew worse, but it has remained approximately the same ever since. Nine months after the onset of the visual defect she was admitted to the Maida Vale Hospital under the late Dr. Guthrie.

Examination at that time showed a slight swelling of both discs passing into atrophy, with bilateral central scotomata. There is no record of any other abnormality in the central nervous system and the diagnosis of familial optic atrophy was made. While she was an in-patient her vision somewhat deteriorated.

Apart from her visual defect she is perfectly well and works as a housemaid.

Physical examination, August 8, 1928.—Normal appearance and speech; no psychological defect.

Visual acuity 1/60 in both eyes. The fields of vision show large bilateral central scotomata with slight peripheral constriction (see chart I.). There is no field for red or

green. The optic discs are atrophic and of bluish-white colour, especially on the temporal sides; the edges are sharp and the laminae cribrosae are not visible. The fundi are otherwise normal.

Pupils: Left slightly larger than right, react normally. Ocular movements full; no nystagmus.

The other cranial nerves are normal.

No abnormality was demonstrated in complete examination of the rest of the body.

CASE 2. Charles James N., age 27.

Is at present an in-patient in Caterham Mental Hospital, Surrey, and we are much indebted to Dr. Leslie Gordon and Dr. Turnbull for permission to examine the patient and for details of his history.

History: A normal child at birth, he talked at 12 months and walked at 18 months; teething normal. During early life he appeared to be a perfectly normal boy and went to school at the age of five; while at school he was given glasses because he could not see very well. At the age of 12 his eyesight failed very rapidly; he became abnormal mentally and ceased to learn. In consequence, he was taken from school and "put to work." He is said to have fallen in with bad companions and was unable to keep in employment for any length of time.

About this time, his sister Minnie was an in-patient at the Maida Vale Hospital; Charles—in common with the other members of the family—was examined and reported to have optic atrophy secondary to optic neuritis. There is also a note to say that he "carried himself stiffly."

Because of his inability to keep in employment, he was medically examined and sent to Darenth colony in August, 1919.

At that time he is described as having been backward and ignorant (able to count to 100, but unable to name the King of England). His pupils were dilated and sluggish, his fundi myopic and the general appearance suggested blindness. In 1920 he had an epileptic fit. In March, 1921, he was transferred to Caterham Mental Hospital and was classed as an imbecile with epilepsy. Glasses were ordered for him but they did not improve his visual acuity. In 1924 he had several syncopal attacks and valvular disease of the heart was diagnosed.

The Hospital records state that he has very occasional fits (none for fifteen months), that he works well, quietly and willingly and that his general conduct is excellent.

The patient himself says that he could see fairly well until he was twelve or thirteen; about that time his vision became rapidly worse, but since then it has remained the same.

Physical examination, August 18, 1928: Well developed and well proportioned young man, staring vacant appearance, prominent eyes, marked overaction of the frontalis muscles; the head is tilted over towards the right shoulder. Speech—lalling, childish and slightly dysarthric. Co-operation good.

Counts fingers at 2 metres with the right eye and at 1 metre with the left eye. Both eyes, especially the left, show a high degree of myopia. The right optic disc is greyish white all over, but it is definitely paler on the temporal aspect. There is some accumulation of pigment round the disc, the edges of which appear clear-cut. The lamina cribrosa is not visible. The blood vessels are not reduced in calibre and the macular region is normal. The left optic disc is "paper white" all over, its edges are rather indistinct in outline and there is no pigmentary disturbance round it. The blood vessels are not reduced in calibre and the macula is normal.

The patient co-operated remarkably well in testing the fields of vision and showed a definite central scotoma for a white object in both eyes, together with some constriction

of the peripheral fields (see chart II.). Examination of colour vision revealed central scotomata for red, green and blue, with a narrow field for each colour round the scotoma. The red field was larger than the green and the green larger than the blue. In the upper and outer portions of the field, vision for blue was almost absent.

The pupils were moderately dilated, equal, circular, central and reacted to light normally. Convergence and reaction on accommodation good. No nystagmus.

There was bilateral exophthalmos and marked overaction of the frontales muscles, but otherwise the cranial nerves were normal. No abnormality was detected in the muscular or sensory systems. The reflexes and gait were normal. No trophic changes or stigmata of degeneration were present and the testes were descended. The pulmonary, cardio-vascular, alimentary and genito-urinary systems showed no abnormality.

X-ray of skull, relative opacity of the sphenoidal sinus, otherwise normal. The cerebro-spinal fluid was clear and colourless; cells, 0 per cm.; total protein, 0.04 per cent.; globulin, weakly positive; Lange, no change. Wassermann reaction, negative in the cerebro-spinal fluid and blood.

CHART II.

CASE 3. Nellie N., age 25.

History: She was normal in every respect until the age of eleven years. During the course of the routine eye examination at school, it was found that she could only read the "big letters on the card." When tested three months previously she had read the letters perfectly well. The patient herself had not noticed the visual defect and had no other symptoms. On the school doctor's advice she attended regularly at the Western Ophthalmic Hospital, where the diagnosis of Leber's atrophy was made.

The vision, however, deteriorated until five years ago, since when it has remained stationary. In other respects she is well and is in regular employment as a housemaid.

Physical examination, August 12, 1928: Healthy looking girl of normal appearance. Psychologically normal. No defect in speech or articulation. Visual acuity, right 1/18; left 1/60. Both optic discs are pale with clear cut edges; fundi otherwise normal. Fields

of vision : right, caecal scotoma for white and colours with slight peripheral constriction ; in left eye there is a large central scotoma for white and colours, with some peripheral constriction (see chart III.).

Pupils and ocular movements normal ; no nystagmus. No abnormality in the other cranial nerves.

Examination of the rest of the central nervous system is completely negative.

No trophic changes ; no stigmata of degeneration.

The cardio-vascular, pulmonary, alimentary and renal-reproductive systems are normal.

CASE 4. Florence N., age 17.

Was admitted to the National Hospital, Queen Square, in June, 1928, under the care of Dr. Grainger Stewart. She complained of pains in the legs and unsteadiness in walking, which had come on six months previously, and of defective vision of five years' duration.

CHART III.

History of present illness : She felt perfectly well except for defective sight until December, 1927. During the Christmas vacation she noticed an aching in both legs ; this persisted on and off until March, 1928, when the legs began to tremble. She found that she could not walk properly and that she was reeling about. The legs felt very tired from the feet up to the hips ; they were " full of pins and needles " and almost too heavy to move.

In April, 1928, she attended the out-patient department of the National Hospital and saw Dr. Purdon Martin. There has been no headache and no abnormality of the bowels or micturition.

Previous history : At the age of seven she had a corneal ulceration of the right eye and attended hospital for about a year ; as a result, the eyes became perfectly normal again.

In 1923, at the age of twelve, her sight suddenly became worse—both eyes were very misty, but she complained of no pain. She was examined by Sir William Lister, who considered her case to be one of Leber's atrophy. Her vision at that time was 2/60 in both eyes and ophthalmoscopic examination showed marked papillitis in the right eye and in the left eye optic atrophy with slight swelling. Sir William tells us that four years previously Florence had been examined and her visual acuity was then 6/6 in both eyes, with correction.

In 1923, Dr. Gordon Holmes examined her and could find no evidence of other disease of the nervous system. An X-ray of the sella turcica showed no abnormality.

Her vision has remained practically stationary since 1923 and has not altered during her recent illness.

From the age of 14 to 16 she was at a residential school in Norwood. About a year ago she went to a school belonging to the London Association for the Blind and worked there until her admission to the National Hospital.

Physical examination, August, 1928: Pale-faced, well-nourished girl; speech a little hesitant, otherwise normal.

Psychologically normal, intelligence fair.

Visual acuity $1/36$ right eye; perceives movement of fingers at 1 metre left eye.

The right optic disc is small and white with clear-cut edges; the vessels are diminished in calibre. The left disc is also white with clear-cut margins; laminae cribrosae not visible in either eye. Both retinæ have a "peppery" appearance, probably due to the fact that the girl is a blonde.

The right field of vision shows a definite peripheral constriction with a centro-caecal scotoma and there is a well-marked central scotoma with peripheral field constriction in the left eye (see chart IV.). In the right eye there is a central scotoma for red with a small colour field round it, otherwise there is no field in either eye for red, green or blue.

The pupils are small but equal and react to light and accommodation through a small range. Ocular movements are full except that convergence is poor. Fairly coarse horizontal nystagmus is present, more marked on looking to the right.

The other cranial nerves show no abnormality.

The upper extremities are normal in power and tone. A slight jerkiness is observed in performing the finger-finger and finger-nose tests, but there is no intention-tremor or dysmetria. The tendon reflexes are brisker than normal, but equal. Power in the legs is fairly good and equal; tone is normal and there is no wasting. A similar jerkiness to that observed in the arms is seen in the legs in performing co-ordination tests. The knee and ankle jerks are brisk and equal. The abdominal reflexes are sluggish but present in all quadrants. Both plantar responses are extensor.

Sensory examination reveals a marked diminution in the sense of passive movement and position and in vibration sense appreciation in both lower extremities, but is otherwise normal. She walks slowly on a broad base with a general unsteadiness and a tendency to sway from one side to the other. Rombergism is well-marked. Slight titubation is present and all her movements are characterised by a jerky action such as one sees in marionette figures.

There is no tenderness, rigidity or deformity of the spine. Both feet show some degree of pes cavus, and the hands are fine, with tapering fingers.

No stigmata of degeneration are present.

X-ray: Stereoscopic views of the skull show no abnormality.

Cerebrospinal fluid: Clear, colourless; cells, 15 per c.mm. (15 per cent. mononuclear); total protein 0.06 per cent., globulin positive; Lange colloidal gold curve 2113321000; Kahn test negative. Wassermann reaction, negative in the cerebrospinal fluid and blood.

The blood sugar curve was as follows:

Resting	..	..	..	..	..	0.088	per cent.
$\frac{1}{2}$ hour after ingestion of 50 gms. glucose	..	..	..	..	..	0.157	„ „
1	„	„	„	„	..	0.195	„ „
$1\frac{1}{2}$	„	„	„	„	..	0.141	„ „
2	„	„	„	„	..	0.146	„ „

Her condition and signs have varied somewhat during her stay in hospital, but the condition at present (August) is practically the same as in June.

DISCUSSION.

We have no doubt that the family described is one of Leber's optic atrophy. The familial incidence, the onset at puberty, the presence of optic neuritis leading to atrophy, the characteristic fields and the course of the disease are all typical.

In two members the condition is uncomplicated and conforms entirely to Leber's original description. One member (Charles) also shows some degree of mental defect and infrequent epileptic attacks, features which, as we shall see, may occasionally be present. The fourth patient (Florence) shows, in addition to the characteristics of Leber's atrophy, the development of additional features of pyramidal disease, ataxia and sensory loss. The chief purpose of this paper and the main object in placing these family cases on record is to determine the nature of the spasto-ataxia exhibited by our fourth patient. We are naturally unwilling to diagnose a combination of two disorders in the same patient, although we feel that we cannot straightway dismiss the possibility of a co-existent disseminated sclerosis. In many respects the findings in this patient, eye changes apart, are compatible with such a diagnosis. These same features, however, including the eye changes and the cerebrospinal fluid changes, also occur in some of the heredo-familial disorders of the nervous system.

We realise, moreover, that in the case of one other member of the family (Charles) the symptomatology has shown a tendency to display features in addition to the optic atrophy. We are, therefore, tempted to regard the pathological condition in this family as an example of a neurone degeneration,

which has affected not only the optic nerve but also some other structures of the nervous system. In this way it would form a connecting link between Leber's atrophy and the wide group of the heredo-familial ataxies.

THE OCCURRENCE OF OTHER NERVOUS OR MENTAL SYMPTOMS AND SIGNS IN CASES OF LEBER'S ATROPHY.

Although the general statement holds true that Leber's disease is unassociated with any characteristic mental or physical defect, nevertheless we realize that some of the affected families are of what we might term degenerative stock. Leber himself called attention to this point; in his original paper he wrote "in many of our families there occurred neurological appearances, chiefly of minor degree, so that these individuals are referable to the group of neuropaths (in the sense of Griesinger)*." He mentions that the patients and even the unaffected members of a family may suffer from periodic headaches, migraine, vomiting, giddiness, weakness, palpitations and teichopsia. They may be nervous and easily tired.

If one reviews a large series of cases of this disease, other positive findings, such as epilepsy or mental defect, may occasionally come to light. In his Bowman Lecture, Nettleship (1909) gave an account of all the cases of Leber's disease recorded to date. In nine instances (Leber, Story⁵, Habershon, Snell⁶, Higier⁷, Keersmaecker⁸, Stzeminski⁹, Taylor¹⁰, Lawford¹¹), epilepsy occurred in families with Leber's disease, among either affected or unaffected members.

To these may be added the family recorded in 1821 by Travers¹², wherein three members became blind and epileptic at puberty. In this case, however, legitimate doubt may arise whether the familial disorder was not a cerebromacular degeneration, although usually quoted as an instance of Leber's disease.

Insanity occurred in the family recorded by Story (associated with epilepsy) and also in an unpublished instance of French, quoted by Nettleship.

In the family recorded by Johnson Taylor one of the afflicted members suffered from "pins and needles" in the legs and cramps in the calves; the tendon jerks were exaggerated. The brother—who also showed optic atrophy—likewise complained of *dysæsthesiæ*. The father was epileptic, but did not show any ocular signs.

Two of Taylor and Holmes¹³ patients complained of vague pains and *paræsthesiæ* in the legs and also showed some defect of bladder control. One of these also proved to be suffering from a co-existent tabes.

Out of six brothers with Leber's disease, recorded by Pines and Tron¹⁴, three also showed nystagmus, tremor of the hands and brisk tendon reflexes. One patient was also peculiar in his behaviour and was of low grade intelligence.

* "Bei vielen unseren Kranken bestanden noch sonstige Erscheinungen von Seiten des Nervensystems, allerdings zum grössten Theil leichteren Grades, aber desart, dass die Individuen in die Klasse der Neuropathischen im Sinne Griesinger's zu rechnen sind."

Various degenerative anomalies were present in the members of this family—such as facial asymmetry, adherent lobes of the ear, forked tongue, syndactyly, and absence of hair from the face.

The first indication in the literature of any definite association of Leber's atrophy with nervous disease is to be found in a communication by Carl Behr¹⁵ (1909). Under the title of "Complicated heredo-familial infantile optic atrophy" he gives details of six children in whom symptoms had been present since the earliest childhood. The main clinical features common to all his cases were:—

- (1) *Optic atrophy*; one case was observed definitely to develop after a retrobulbar neuritis; fields of vision peripherally restricted; central scotomata.
- (2) *Pyramidal signs*, comprising slight rigidity, increased tendon reflexes. Babinski responses, but no definite diminution of muscular power.
- (3) *Cerebellar signs*: nystagmus, inco-ordination, reeling gait, slow and monotonous speech.
- (4) Slight intellectual defect.
- (5) Weakness of bladder control.
- (6) Presence of degenerative stigmata (cryptorchismus, adherent lobules of the ear, facial asymmetry, congenital cataract).
- (7) In two cases there was some weakness of the extrinsic eye muscles.

Behr looked upon his cases as representing a transition type (Unterart) between Leber's disease and Strümpell's spastic paralysis on the one hand and the heredo-ataxias on the other.

Four years later another communication emanated from Behr's clinic in the paper of Takashima¹⁶, who recorded six fresh cases of this anomaly. One of his patients was indeed the sister of two of Behr's original subjects. Takashima was able to throw further light upon Behr's cases by determining the stationary character of the disease. The commencement of the morbid process, he suggested, occurred in foetal life or else during the first year of infancy.

Under the title of "Familial optic atrophy with tremor and intellectual deterioration" Imamura and Ichikawa¹⁷ reported a Japanese family who showed positive neurological signs superimposed upon a Leber's atrophy. Their patients consisted of a brother and sister whose symptoms started in early adolescence. The brother (Monta) developed at the age of 18 misty vision which grew progressively worse. The optic discs were atrophic; there were bilateral central scotomata, while the peripheral fields were full. Examination of the nervous system revealed some weakness of the right face; eye movements inco-ordinate and jerky; convergence poor; nystagmus on extreme lateral deviation. No mental defect.

His sister (Tazu) developed at the age of 24 defective vision with some headache. Ophthalmoscopy revealed some hyperæmia of the disc and hazy outlines, but there was no swelling; immediately round the disc was some pigmentary disturbance. She could count fingers at three metres

with the left eye and four metres with the right. There were central scotomata in both eyes. Fifteen months later the discs were atrophic; the vision had deteriorated still more, and some peripheral restriction of the visual fields was demonstrable in addition to the scotomata. Her mentality was abnormal in several respects; she was "euphoric, nonchalante, insouciant and almost always smiling." Cerebration was slow, memory poor and orientation vague. There was slight weakness of the right face; fibrillary tremors were present round the lips and eyes, especially on emotional movement. On distant fixation, one or other eye tended to swing outwards. Convergence was poor. Nystagmus was absent. Tremor was present in the trunk, tongue, and fingers, and was aggravated by voluntary movements. The limbs were rigid, especially the arms, and fine movements were inco-ordinate in execution. The reflexes were normal.

Imamura and Ichikawa were inclined to regard their cases as exemplifying a type intermediate between Leber's disease and Behr's optic atrophy.

So far, the cases described bear some resemblance to each other and also to that of our fourth patient, in that visual defects due to optic atrophy occupied the centre of the clinical picture. In this respect the cases of Behr and of Imamura and Ichikawa probably constitute the solitary examples in the literature. The age of onset in the twelve recorded cases of Behr's atrophy obviously constitutes a distinct differentiation from that of our fourth patient; from the standpoint of history as well as of symptomatology the two Japanese patients bear a closer resemblance to Florence N.

Apart from these clinical types just mentioned there are of course several other varieties of heredo-ataxia or hereditary combined diseases of the cord in which optic atrophy is a characteristic finding. Thus the cases in the families recorded by Freud¹⁸, Nonne^{19,20}, Bach²¹, Sanger Brown²² (which may all, if desired, be considered under the comprehensive category of Marie's ataxia²³) bear in their complete form some resemblance to our fourth case. But in each of these instances the optic atrophy occupies a comparatively unimportant place in the symptomatology, and disorders of gait or of movement antedate and outweigh the defects of vision. Our fourth patient is rather a case of Leber's disease with neurological signs than of familial ataxia with an incidental optic atrophy.

It is obvious that in many cases it is almost impossible to place a particular case into a definite class—features of more than one disease apparently co-existing. At one end of the scale there is the simple, uncomplicated heredo-familial optic atrophy; thence we pass through a stage where the family shows a neuropathic tendency or where there is a definite tendency to migraine or epilepsy. Next come those cases (Behr, Takashima) where optic atrophy and neurological signs co-exist, both appearing early in infancy. Parallel with these are the cases in which optic atrophy and neurological signs co-exist but appear in early adolescence (so far represented alone by our fourth patient and by Imamura and Ichikawa's family). By this process of transition we are

GENEALOGICAL TABLE OF THE N. FAMILY.

led up to the well-defined heredo-familial ataxias (Marie) in which optic atrophy occurs, but the motor phenomena are the outstanding features. At the extreme end of the scale one may place Friedreich's ataxia as representing a type of cerebellar disease in which optic atrophy occasionally occurs.

CONCLUSIONS.

Apart from its intrinsic rarity, the familial condition recorded in this paper is of importance in that it may throw some light upon one or two neurological problems of interest. In the first place, by representing a probable transition type between Leber's disease and Marie's ataxia, it tends to support Raymond's unitary conception of the heredo-familial affections of the nervous system.

Secondly, the association of neurological findings may contribute to our knowledge of the etiology of Leber's disease, by suggesting that the essential pathogenic process is a neuronie abiotrophy, limited—in typical cases—to the optic nerve. The presence of a neuritis in the early stages may appear to argue against this conception of a degenerative origin, but there are two further possibilities which will reconcile these apparently contradictory views. Thus the products of degeneration may of themselves be of such a toxic nature as to cause a superadded inflammation to the affected optic nerve; or, the optic nerves may possess merely an inherent vulnerability which requires the intervention of some added factor (such as sepsis in the adjacent structures) to develop neuritis and consequent atrophy. Both hypotheses are compatible with our conception of Leber's disease as a familial abiotrophy of the optic nerve which may in rare instances be accompanied by degeneration in other parts of the nervous system.

We beg to acknowledge our thanks to Dr. Grainger Stewart for permission to publish the case under his care, and to Sir William Lister for his kindness in so readily giving us information concerning the N. family.

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