

## OPTIC ATROPHY AND NERVE DEAFNESS IN DIABETES MELLITUS

BY

D. A. SHAW and L. J. P. DUNCAN

*From the Royal Infirmary of Edinburgh and the Department of Therapeutics, Edinburgh University*

The belief, once held, that an aetiological relationship exists between diabetes mellitus and optic atrophy is not now generally accepted. The observations of early authors such as Allbutt (1871) and von Noorden (1917), who regarded optic atrophy as a diabetic complication, may have been partially vitiated by the fact that both visual loss and changes in the optic discs may result from other ocular complications of diabetes and need not be an expression of primary nerve degeneration.

Waite and Beetham (1935), in a comprehensive survey of the visual mechanism in diabetes, reported optic atrophy in 27 (0.69%) of the 3,915 fundi that they were able to examine in 2,002 diabetic patients, and in four (0.44%) of the 901 visible fundi of 457 non-diabetic persons. These findings have, however, been repeatedly misinterpreted by subsequent authors (Wagener, 1938; Tunbridge and Paley, 1956) who, by overlooking the fact that the percentage figures related to individual fundi and not to patients, quote a higher incidence of optic atrophy in both groups than was actually recorded. It is not possible to derive from these data the percentage of patients in each group having optic atrophy in one or both eyes. On the basis of their findings Waite and Beetham (1935) considered the two conditions to be fortuitously associated: that no aetiological relationship exists between them is the view now generally accepted. The development of both optic atrophy and diabetes in two or more members of a family is thus of special interest.

Wolfram (1938) reported a family of eight children, four of whom, two boys and two girls, developed diabetes mellitus and bilateral optic atrophy by the age of 12. Tyrer (1943) described an 18-year-old boy who suffered from infantilism with goitre, diabetes mellitus, mental defect, and bilateral primary optic atrophy. One sibling suffered from diabetes and epilepsy and had pronounced bilateral primary optic atrophy; another, who was only 5 years old when examined, was also diabetic and epileptic and had pallor of the optic discs. A third family was reported by Tunbridge and Paley (1956) in which two members, brother and sister, were dia-

betic and had primary optic atrophy; they had, in addition, bilateral nerve deafness. We report here a fourth family in which the association of diabetes mellitus with optic atrophy and nerve deafness is again encountered but in which, unlike the other three, more than one generation is involved.

### Report of Cases

Two of the patients are sisters, the youngest members of a family of 13, born of non-diabetic parents in whom there was no consanguinity. The third patient is the only daughter of their eldest sister who herself is not diabetic. All of these patients have diabetes mellitus and bilateral nerve deafness. Two have bilateral optic atrophy and one a neurogenic bladder.

**Case 1.**—Harriet N., born in 1928, is now aged 29. Her mother was aged 37 at the time of the child's delivery which was at full term after an uncomplicated pregnancy. The patient contracted whooping cough when aged 2 and measles when 3 and shortly afterwards her tonsils and adenoids were removed. At the age of 4 it became apparent that her hearing was defective and bilateral deafness has since become progressively marked. When aged 8 she was admitted to hospital on account of weight loss, thirst, and polyuria and the diagnosis of diabetes mellitus was established by the demonstration of glycosuria and impaired glucose tolerance. Control was readily achieved by dietary measures and the daily administration of small doses of insulin but since puberty it has been less satisfactory, the present requirement of insulin being 104 units.

On physical examination she is of healthy appearance and, although unresponsive and monotonous in speech because of her deafness, is not mentally backward and lip-reads moderately well. No neurological abnormality can be demonstrated apart from the deafness, and the blood Wassermann reaction is negative. The optic discs are normal and the only ocular abnormality is a true diabetic cataract in the left eye. Both tympanic membranes show minimal scarring but they are intact and quite mobile. There is no congenital malformation of external or middle ear and nose and throat are healthy. With eyes closed she is unresponsive to the spoken word. Rinné's test is positive in both ears and Weber's test shows indefinite lateralization to the left. Absolute bone conduction is markedly diminished. On audiometric examination only residual hearing is present in both ears from 500 to 1,000 c.p.s. and no bone conduction is recordable.

**Case 2.**—Betty N., born in 1930 prematurely, is now aged 27 years. After measles and bronchopneumonia in infancy she progressed normally until aged 9 when she started to lose weight and to complain of thirst and polyuria. Hyperglycaemia, defective glucose tolerance, and glycosuria confirmed the diagnosis of diabetes. At that time she had no abnormality of vision or hearing and the diabetes was well controlled by dietary restriction and the administration of insulin in modest daily dosage (24 units). The following year her vision was noticed to be defective and her hearing impaired. That these defects were attributable to bilateral optic atrophy and nerve deafness was established two years later and both have become progressively marked over the years. Although never having complained of urinary symptoms, she was found, when aged 17, to have a markedly distended bladder and to be capable of voiding as much as 900 ml. of urine at a time without any preceding sensation of fullness. Cystometric studies at that time showed that bladder tone remained at 15 cm. to 18 cm. throughout filling to 450 ml. and at 500 ml. voluntary contractions produced a rhythmic series of increases in tone, with an amplitude extending to 40 cm. There was no sensation of fullness throughout. No other neurological abnormality was demonstrable and the cerebrospinal fluid was normal in all respects. It was concluded that she had an atonic neurogenic bladder. The diabetes has remained well controlled, although the insulin requirement has gradually increased to 72 units daily.

She is of average build and stature and, although handicapped by grossly defective vision and hearing, is alert and not mentally backward. The bladder is distended. Visual acuity is reduced to perception of hand movements on both sides. There is bilateral optic atrophy with well-defined disc margins but no retinopathy. The ear drums are intact, unscarred, and freely mobile and there is no congenital malformation. Rinne's test is positive on both sides and absolute bone conduction is markedly shortened. On audiometric examination there is severe loss of hearing throughout the entire frequency range with no hearing above 6,000 c.p.s. and no bone conduction is recordable. Apart from these abnormalities and uniform depression of the deep reflexes the nervous system is intact. The blood Wassermann is negative and urinary amino-acid pattern normal.

**Case 3.**—Catherine R., now aged 13, is the only child of the eldest sister of the two previous patients. Her mother was 31 when the patient was born in 1944, the pregnancy being uncomplicated. The child's development was normal until the age of 4 when she was noticed by her parents to be hard of hearing; tonsils and adenoids were removed but without benefit. During convalescence from measles the following year, she failed to gain weight and developed polyuria, nocturia, and thirst. The diagnosis of diabetes mellitus was established on the basis of hyperglycaemia, impaired glucose tolerance, and slight ketonuria. Control was achieved by dietary restriction and the injection of approximately 20 units of insulin daily and has since been well maintained, although her daily insulin requirement has now risen to 64 units. The auditory defect has become progressively marked and the diagnosis of bilateral nerve deafness was

established in 1953 when the patient was aged 9. In the last two years her vision has also gradually become defective.

She is a well developed child who, because of her disability, is unresponsive and at times sullen and difficult although not mentally backward. The otological findings are similar to those described in the previous patient and confirm the presence of bilateral nerve deafness. Her visual acuity in both eyes is reduced to 4/60: near vision to N 36. Optic atrophy with clearly defined disc margins is present in both eyes but there is no retinopathy. The nervous system is otherwise intact and the blood Wassermann reaction is negative.

#### Other Members of the Family

The mother of Cases 1 and 2 and grandmother of Case 3 is presently aged 62. She has no glycosuria (a single post-prandial blood glucose value was 110 mg./100 ml.) and there is no ocular or auditory abnormality. None of her six siblings, or their progeny, has or had diabetes, or visual or auditory defect. Her husband died recently in hospital from pulmonary heart disease and his case records state that the urine contained no sugar and that the optic fundi and hearing were normal. Of his 12 siblings none had diabetes but his youngest sister had an illegitimate male child, now aged 27, a high-grade mental defective, who was found to have diabetes when admitted to an institution at the age of 17. His diabetes has been well controlled by diet and insulin and examination shows no evidence of optic atrophy or nerve deafness. Nothing is known of his father or of his father's family.

The sibship, of which Cases 1 and 2 are the youngest two members, consisted of eight girls and five boys. The seventh child was prematurely born and died in the immediate post-natal period. The tenth, who was one of twins, died in hospital at the age of 3 but the cause of death was not established. The oldest of the family, now aged 44 and the mother of Case 3, has neither glycosuria nor post-prandial hyperglycaemia and her optic fundi and auditory function are normal. There is no history of diabetes in her husband's family. In the other eight brothers and sisters, who are living, and in their offspring, who number 23, there are no instances of diabetes mellitus, optic atrophy, or nerve deafness.

#### Discussion

The coexistence of diabetes mellitus and optic atrophy in the same individual need not imply a causal relationship and it is not suggested that the development of the ocular or auditory lesions in these patients is the consequence of the altered metabolism of diabetes. Indeed, in two of the cases recorded, the onset of nerve deafness antedated the clinical manifestation of diabetes; in one instance (Harriet N.) the interval was four years and in the other (Catherine R.) two years. Nevertheless, it is of interest and significance that a relationship between diabetes and optic atrophy should have been encountered amongst members of four unrelated families in different parts of the world and that other

features, namely, nerve deafness and neurogenic bladder dysfunction, should have been common to some of them.

Tunbridge and Paley (1956), who contrasted their own patients with those described by Wolfram (1938), expressed the view that "when there was enough well studied material, a statistical analysis might allow geneticists to distinguish biotypes within the range of hereditary optic atrophy." The importance of reporting details of family groups, in which inherited conditions occur simultaneously, was stressed by Roberts (1945). Indeed he went so far as to say that "it may easily happen that a single small pedigree may be decisive in regard to whether or not there is close or moderate linkage between the genes, thus making possible a solid contribution to the task of mapping the human chromosomes, and, if the chance is missed, so rare an opportunity may not recur for centuries". As Crew (1947) puts it, "a storehouse of pedigrees is an essential requirement in clinical medicine". It is from this aspect that it is considered important to study these patients in light of those previously recorded and to note the various points of contact.

The four families now recorded contained 12 diabetic members. A feature common to them all is the early age of onset of the disease. The average age at which the diagnosis was established was 7 years and in all diabetes had developed by the age of 12, although in no instance was there a high incidence of the disease among the antecedents. In the families reported by Tyrer and Tunbridge and Paley there was no history at all of diabetes in earlier generations and in each of the other two families only one diabetic relative was traced.

The presence of optic atrophy has been established in 10 of the 12 individuals under consideration. In one of the other two, Harriet N. described above, it was definitely lacking: she, however, has unilateral juvenile cataract, a true complication of diabetes. The other patient is one of the diabetic siblings of the case described by Tyrer in whom pallor of the optic discs was recorded but it is uncertain whether or not vision was impaired; the child was only 5 years old at the time of examination and there is no information as to subsequent developments. From the details available it appears that optic atrophy was of similar type in all the patients involved; none had central scotomata and in this respect and in its invariable failure to remit, the type of atrophy differs from the classically described hereditary optic atrophy of Leber.

Although less striking than optic atrophy in the frequency of its occurrence among these patients, nerve deafness is nevertheless recorded in five of them—all those of the present group and both of

Tunbridge and Paley's cases. However, it is now known (Tunbridge and Paley, 1956) that three of Wolfram's patients had subnormal hearing as tested by a watch tick, although this was not recorded in his original description and the nature of the auditory defect is not known.

The last feature in this constellation of defects is neurogenic bladder atony. It may be that its occurrence in Betty N. as an isolated neurological lesion with no other evidence of myelopathy is quite fortuitous, but it is interesting to note in Tunbridge and Paley's paper their reference to the development of cord bladder in two of Wolfram's patients.

There are thus many features common to the members of those four diabetic families described to date. Despite the fact that the pattern is not identical in all cases, the overlap is sufficient to raise the possibility that they constitute a genetic entity. Tyrer inclined to the view that his original description was of a new and previously unrecorded clinical syndrome and it is suggested that the three cases here recorded may be further examples of the same genetic type.

#### Summary

Three members of a family are described, two sisters, and a niece, in whom the coexistence of diabetes mellitus, bilateral optic atrophy, and bilateral nerve deafness is encountered. All three conditions are present in two of them but the third member, although suffering from diabetes and nerve deafness, has normal vision. With the exception of one male relative who is diabetic, there is no history of diabetes mellitus, optic atrophy, or nerve deafness in other members of the family.

Current views on the relationship between diabetes and optic atrophy are discussed and the cases are contrasted with the three other families previously recorded in which an association between these conditions has been described.

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