OPTIC ATROPHY IN WOLFRAM (DIDMOAD) SYNDROME

TIMOTHY G. BARRETT[1], SARAH E. BUNDEY[1], ALISTAIR R. FIELDER[2] AND PETER A. GOOD[3]

Birmingham and London

SUMMARY

Wolfram syndrome is the association of diabetes mellitus and optic atrophy, also called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness). Incomplete characterisation has caused diagnostic confusion; we therefore undertook a nation-wide cross-sectional case finding study. We identified 45 patients with Wolfram syndrome, median age 29 years. All patients fulfilled the ascertainment criteria (juvenile onset diabetes mellitus and optic atrophy). Optic atrophy presented in 38 patients with reduced visual acuity and colour vision defect (median age 11 years), progressing to visual acuity of 6/60 or less in 35 patients (median time 8 years, range 1–25 years). Visual field examinations recorded before acuity deteriorated showed central scotomas with peripheral constriction. Blind patients had absent pupillary reflexes. Horizontal nystagmus was seen in patients with other signs of cerebellar degeneration. There was no pigmentary retinal dystrophy; only 3 patients had background diabetic retinopathy, despite a median duration of diabetes of 24 years. Electroretinography was normal in 3 patients and showed reduced amplitude in 3 patients; visual evoked responses were abnormal (10/10 patients: reduced amplitude to both flash and pattern stimulation). Magnetic resonance imaging showed generalised brain atrophy with reduced signal from the optic nerves and chiasm. A postmortem brain specimen from one patient revealed atrophy of the optic nerves, chiasm, cerebellum and brainstem. We found no evidence of mitochondrial genome defects or rearrangements. This primary neurogenerative disorder presents with diabetes mellitus and progressive optic atrophy, probably due to pathology in the optic nerve.

From: [1]Department of Clinical Genetics, Institute of Child Health, University of Birmingham; [2]Academic Unit of Ophthalmology, Imperial College School of Medicine at St Mary's, London; [3]Birmingham and Midland Eye Hospital, City Hospital NHS Trust, Birmingham, UK.

Correspondence to: Dr T. G. Barrett, Clinical Genetics Unit, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG, UK.

Optic atrophy and diabetes mellitus were described in four siblings by Wolfram and Wagener in 1938, and have been taken as essential features of Wolfram syndrome.[1] The acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness) has been used synonymously with Wolfram syndrome to indicate two other complications commonly found. In a literature review, diabetes mellitus and optic atrophy were consistently present, diabetes insipidus and deafness were present in 51% of cases, and all four complications present in 13%.[2] Despite extensive literature reviews,[2–4] the syndrome is poorly understood. In particular, the natural history of the optic atrophy, its site of pathology and the pathogenesis are all unclear.

In Wolfram's original description, the two eldest siblings developed poor vision at 6 and 8 years respectively, and when examined 10 years later, acuity was reduced to counting fingers. Case reports of the syndrome have contained too few patients to make generalisations; literature reviews have not clarified whether the optic atrophy is preceded by a period of normal vision or is always progressive and, if so, over what time period.

There has been confusion over the site of pathology in the visual pathway: in a series of 7 patients, one was found to have pigmentary retinal dystrophy.[5] A later review of electroretinographic (ERG) findings in 19 patients concluded that the visual disorder was mainly due to a lesion in the ganglion cell and nerve fibre layer.[6] Eleven further patients had normal ERGs but abnormal visual evoked potentials, suggesting that the retina is not involved in the pathogenesis.[7] A postmortem study of one patient revealed atrophy, severe axonal destruction and demyelination of the optic nerve, chiasm, tract and radiations, and shrunken nerve cells in reduced numbers in the superior colliculus and lateral geniculate body.[8]

As more cases of Wolfram syndrome have been described, its neurodegenerative nature has become recognised, with the onset of cerebellar signs and absent lower limb reflexes in some patients. Magnetic resonance imaging (MRI) scans in 2 patients have shown widespread atrophic changes throughout the brain, including the cerebellum, optic nerves and chiasm.[9] It is not clear whether other ophthalmic signs such as nystagmus are related to an afferent defect or underlying cerebellar degeneration.

Although all patients with Wolfram syndrome have diabetes mellitus, there have been very few descriptions of diabetic retinopathy. It is not known whether Wolfram patients die before developing retinopathy, or have a lower risk of microvascular complications.

The inheritance of Wolfram syndrome is thought to be autosomal recessive, and a nuclear-encoded gene has recently been mapped to chromosome 4p.[10,11] However, the presence of pigmentary retinal dystrophy in at least some patients together with other complications commonly seen in mitochondrial disorders (deafness, optic atrophy, diabetes mellitus, ataxia) led to suggestions that some cases might be due to mitochondrial gene abnormalities.[12]

We recently undertook a nationwide cross-sectional casefinding study to characterise Wolfram syndrome.[13] In this present paper we aim to describe the ophthalmic complications of our cohort of patients, and provide accurate data on the natural history, site of pathology and pathogenesis of optic atrophy.

METHODS

Patients were recruited nationally from major referral centres and a national DIDMOAD register that had been set up under the auspices of the British Diabetic Association. Minimum ascertainment criteria for identification of patients were juvenile onset diabetes mellitus (under 30 years) and optic atrophy, which were chosen as the only features consistently present and earliest to develop in 166 of 168 case reports.[4] The two main referral sources were all consultant ophthalmologists and physicians.

All living patients were visited at home for clinical history taking and examination; hospital records were also studied. All affected patients had been examined, with pupils dilated, by experienced ophthalmologists; the results of these examinations, and information on visual acuity, colour vision testing, examination of visual fields, ERGs, and visual evoked potentials (VEP), were obtained wherever possible from hospital records. Cranial MRI scans were also available for some patients.

Visual function tests were performed in some patients at Birmingham and Midland Eye Hospital. The 2 Hz transient VEPs were recorded to flash and reversing black and white chequerboard patterns, recorded monocularly using a two-channel montage. Pattern ERGs were recorded using a 6 Hz reversing black and white chequerboard, and gold foil electrodes.

A polymerase chain reaction (PCR) *Apa*1 restriction site assay was used to screen for the mitochondrial tRNA Leu (UUR) A to G (3243) mutation.[14] The final cycle of PCR was labelled with ^{33}P-dATP, permitting detection of the mutation at levels of heteroplasmy below 1%. Mitochondrial DNA was also analysed for the presence of major rearrangements by a standard method:[15] PCRs were performed in a final volume of 50 μl with 0.25 μl each of primers L1 (nt2695–2720) and H3 (nt16459–16436), 2.5 mM $MgCl_2$, 0.25 mM of each dNTP, 1 × Bio-Optiform 111 buffer (Bioline) and 1.5 units Bio-X-ACT *Taq* polymerase (Bioline). PCRs were hot-started at 80 °C by the addition of 20–50 ng DNA and denatured at 95 °C for 10 seconds, and 68 °C for 10 minutes plus 30 seconds for each subsequent cycle (25 cycles). PCR products were run on 0.7% Seakem agarose gels.

RESULTS

Fifty-four patients were referred with the minimum ascertainment criteria of juvenile onset diabetes mellitus and optic atrophy. Nine patients were excluded: 2 had congenital rubella syndrome, 1 had Leber's hereditary optic neuropathy,[16] 4 had thiamine-responsive megaloblastic anaemia with diabetes and deafness (thiamine-responsive anaemia syndrome), and 2 were unclassified (one had retinal dystrophy and diabetes mellitus; the other presented at 14 months with ketoacidotic coma, hypoxia and seizures, and then secondary optic atrophy and anterior pituitary failure).

The remaining 45 patients were classified as having Wolfram syndrome. There were 29 index patients (14 male, 15 female) and 16 secondary patients (all siblings; 7 male and 9 female). Thirty-five patients were alive during the study (median age 29 years, range 5–46 years). Thirty-six patients presented with diabetes mellitus, 6 with optic atrophy, and 3 with diabetes insipidus. No patient presented with deafness.

The clinical features of this cohort have been described,[13] and are summarised in Table I. The ascertainment criteria were validated by comparison of index with secondary patients as shown in Table I. All secondary patients also had diabetes mellitus and optic atrophy; there was no significant difference in the ages of onset or prevalence of complications between the two groups ($p>0.02$).

Fig. 1 shows schematically the natural history of Wolfram syndrome. Of the 26 patients with renal tract abnormalities, 20 also had symptomatic

Table I. Age of onset and prevalence of complications in 45 patients with Wolfram syndrome

	Index cases (n = 29)		Secondary cases (n = 16)		Total (n = 45)	
	Prevalence	Age[a]	Prevalence	Age[a]	Prevalence	Age[a]
Diabetes mellitus	29 (100%)	6 (3 wk–16 yr)	16 100%)	6.5 (4–15)	45 (100%)	6 (3 wk–16 yr)
Optic atrophy	29 (100%)	10 (6 wk–19 yr)	16 (100%)	11.5 (3–15)	45 (100%)	11 (6 wk–19 yr)
Diabetes insipidus	21 (72%)	15.5 (2–39)	13 (81%)	12 (3 mo–40 yr)	33 (73%)	14 (3 mo–40 yr)
Deafness	19 (66%)	16 (5–32)	9 (56%)	15 (6–39)	28 (62%)	16 (5–39)
Renal tract abnormality	16 (55%)	22 (10–44)	10 (62%)	20 (10–33)	26 (58%)	20 (10–44)
Neurological abnormality	19 (66%)	32 (5–44)	9 (56%)	30 (16–36)	28 (62%)	30 (5–44)

[a]Median and range in years unless otherwise shown.

deafness, and 23 had cranial diabetes insipidus. Of the 28 patients with neurological abnormalities, 22 had symptomatic deafness and 25 had diabetes insipidus. One patient had renal and neurological complications without symptomatic deafness or diabetes insipidus. There were 6 patients with optic atrophy and diabetes mellitus only (median age 16 years, range 5–28 years).

Generalised optic atrophy was observed in all patients at a median age of 11 years (range 6 weeks to 19 years), and was the presenting feature of Wolfram syndrome in only 2 patients. The presenting symptoms were decreasing visual acuity and loss of colour vision, patients typically complaining that everything was going grey.

In 42 patients there was a documented period of normal vision before optic atrophy became symptomatic. Out of these 42 patients, 24 had documented progression to a visual acuity of 6/60 or less in the better eye over a median of 8 years (range 1–25 years). One 28-year-old patient had a rapid onset of decreasing visual acuity over weeks aged 15 years, to 6/24 in the better eye, and no progression since then; this patient has diabetes mellitus and optic atrophy only. Thirty-four patients were registered blind, and 7 patients partially sighted. Most of the patients registered as blind had residual vision allowing perception of light and dark, human shapes or a hand in front of the face. Two unrelated girls, aged 15 and 17 years, had visual acuities of 6/18 biaterally, diabetes mellitus, and no other complications.

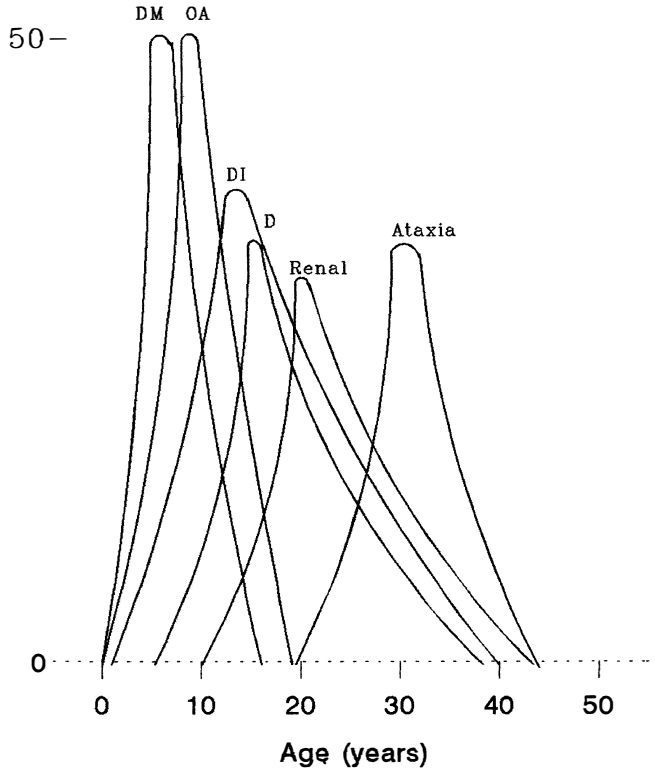


Fig. 1. *Natural history of Wolfram syndrome.*[13] *DM, diabetes mellitus; OA, optic atrophy; DI, diabetes insipidus; D, deafness; Renal, renal tract abnormalities; Ataxia, neurological abnormalities (2 patients presented in the first decade). The y-axis shows the frequency (%).*

The remaining 3 patients (of 45) presented in infancy and were diagnosed as having congenital optic atrophy. Two of these 3 are brothers, aged 16 and 18 years respectively, and have a non-progressive optic atrophy and diabetes mellitus only.

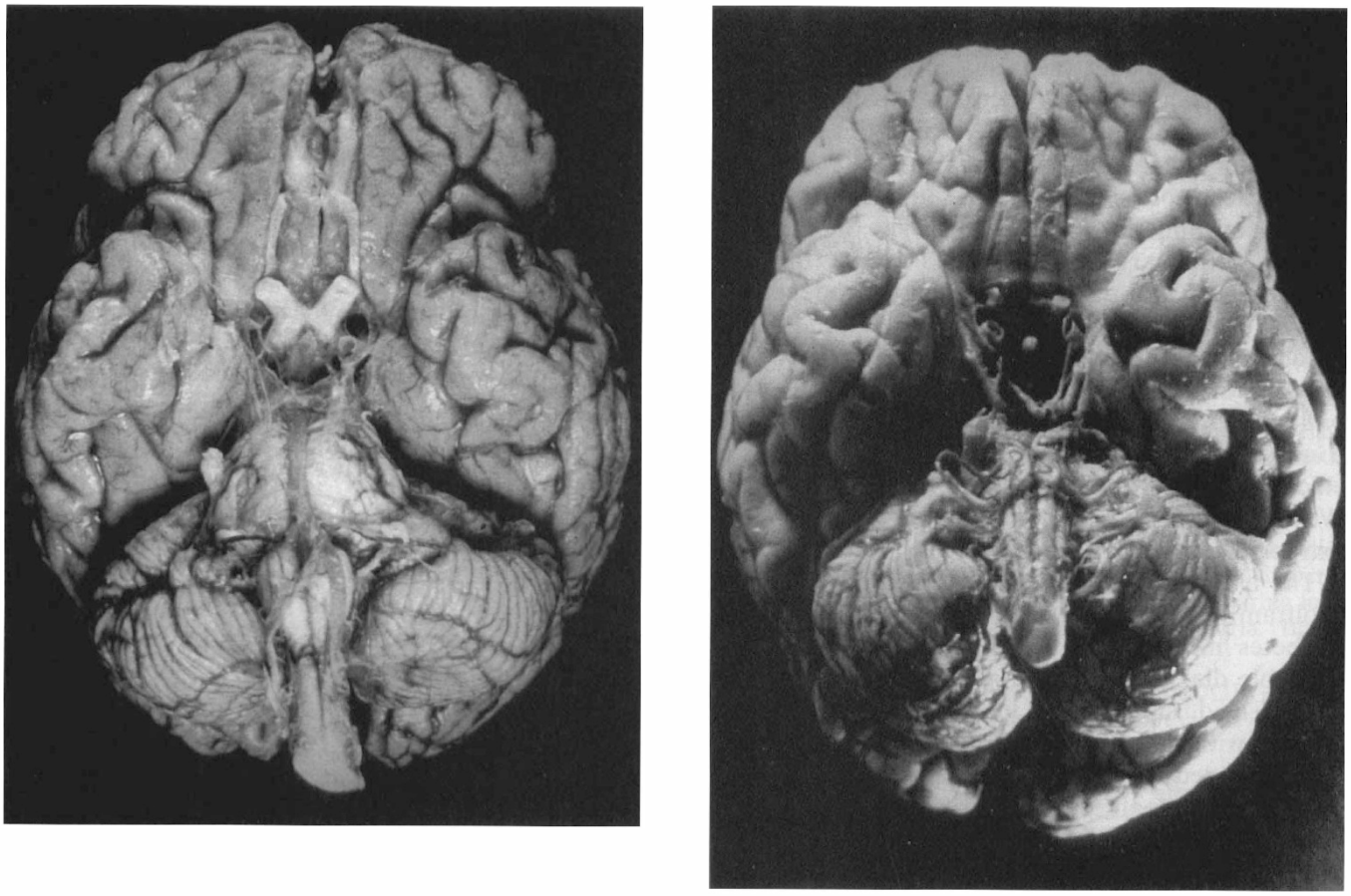
Colour vision was mentioned in the records of 22 patients: the commonest defect was blue–yellow, the Farnsworth error scores for 2 patients being grossly abnormal at 844 and 914 respectively.

Visual fields were recorded for 15 patients before the onset of severely reduced acuity; they consistently showed bilateral paracentral scotomas, with some peripheral constriction in 5 patients.

Absent pupillary responses to light were found in all 11 patients with acuities less than 6/60 who were tested. Nine of these patients also had horizontal nystagmus; these were older patients with other cerebellar signs including ataxia and dysarthria.

Three patients had evidence of cataract formation. No pigmentary retinal dystrophy was seen on ophthalmoscopy. Five patients had definite evidence of background diabetic retinopathy out of 34 for whom a recent ophthalmic examination was recorded; the median duration of diabetes mellitus in these 5 patients was 33 years (range 20–36 years), compared with the median duration in the whole cohort of 24 years (range 2–44 years).

Visual evoked responses were abnormal in all 10 patients tested, typically showing no responses to flash or pattern stimulation. ERGs were undertaken in 6 patients. Three of these were normal; in 3 there was a reduction in amplitude of response without significant change in latency.



(a) (b)

Fig. 2. *Macroscopic appearance of the undersurface of a normal brain (a) and the brain of a patient with Wolfram syndrome aged 45 years (b).*

Cranial MRI showed abnormalities in 8 of 11 patients: the commonest finding was a generalised atrophy, particularly of the brainstem and cerebellum. In addition there was reduced signal from the optic nerves, chiasm and tracts. The brain of one patient was available for postmortem study: this clearly showed macroscopic atrophy of the optic nerves and chiasm (Fig. 2).

Eighteen patients were screened for the mitochondrial tRNA Leu (3243) mutation; all screened negative. In addition, no major mitochondrial rearrangements were found in DNA extracted from whole blood of 40 patients.

CASE HISTORY

A previously well girl presented with insulin-dependent diabetes mellitus at 4 years of age. Her older brother had been diagnosed with Wolfram syndrome aged 6 years; consequently she was referred to an ophthalmologist who found bilateral optic atrophy, reduced visual acuity (6/18 bilaterally) and poor colour vision. Cranial CT scan was normal, as was ultrasound of her renal outflow tracts. She continued to have thirst and polyuria despite good glycaemic control, and a raised serum sodium (148 mmol/l). Cranial diabetes insipidus was diagnosed, and she responded to intranasal Desmopressin spray (Ferring).

At 7 years she was seen at the Birmingham and Midland Eye Hospital. Her visual acuity had deteriorated to 6/60 bilaterally, and she had a marked afferent pupillary defect, with a refractive error +2.5 in both eyes. Visual field testing revealed bilateral centrocecal scotomas, worse in the right eye. The Farnsworth 100 Hue test showed a gross tritanopic defect binocularly, with an error score of 392 (normal <100). Fundoscopy confirmed bilateral optic atrophy, with normal retinal vessels. An audiogram showed a high tone loss greater than 50 dB above 2000 Hz. Visual evoked responses were of PNP waveform (neg) in both eyes. Pattern responses were markedly delayed in both eyes, with reduced amplitude from the right eye. Pattern ERGs showed a normal P50 (preganglionic) component; the N95[14] (ganglion cell component) was absent from the right eye and grossly reduced in the left eye.

Over the next year she developed unsteadiness with occasional falls. On examination she had mild intention tremor of her hands, with an ataxic gait but no nystagmus. Cranial MRI showed reduced signal from the optic nerves.

DISCUSSION

We have shown that the visual defect in Wolfram syndrome is a progressive optic atrophy, with a median age of onset of 11 years; this leads to perception of light and dark only, over a median of 8 years. Electrophysiology, cranial imaging and post-mortem examination all point to the site of pathology as the optic nerve; this appears to be the first manifestation of a more generalised neurodegeneration. We have found no evidence of an underlying mitochondrial genome mutation or rearrangement.

A limiting factor of the study was the spread of patients across the country; thus visual function tests could not all be performed in one centre. Results of electrophysiological testing from patients outside the West Midlands NHS region have therefore been extracted from hospital records.

The ascertainment criteria and natural history of Wolfram syndrome have already been discussed.[13] Diabetes mellitus and optic atrophy are the best available diagnostic criteria as they were present in all affected siblings of index patients. Patients present with diabetes mellitus and optic atrophy in the first decade, cranial diabetes insipidus and sensorineural deafness in the second, dilated renal tracts in the third, and multiple neurological abnormalities in the fourth decade, particularly cerebellar ataxia, dysarthria and startle myoclonus. Eight of 11 male patients had biochemical evidence of primary gonadal atrophy. Premature death may occur from respiratory failure associated with brainstem atrophy. This is a primary neurodegenerative disease process presenting with the unusual combination of diabetes mellitus and optic atrophy. The differential diagnosis includes other causes of neurodegeneration.

The median age of onset of optic atrophy of 11 years is in general agreement with the results of other studies, which range from 8 years[2] to 13 years.[17] It is usually preceded by a period of normal vision, as most patients in the UK would have had their vision tested at school entry. In this condition most have developed insulin-dependent diabetes mellitus by the time optic atrophy is diagnosed, and have to cope for many decades with a combination of handicaps not usually experienced by individuals with isolated diabetes mellitus.

The presenting features of reduced visual acuity not due to a refractive error and colour vision defect suggest a site of pathology in the visual pathway proximal (posterior) to the eye. Blue–green colour vision loss is a recognised feature of optic nerve atrophy.

The rate of progression of visual loss shows a wide variability (1–25 years), but distinguishes Wolfram syndrome from more acute causes of vision loss such as Leber's hereditary optic neuropathy (weeks/months). We found one patient with an acute onset then non-progression, and 3 patients with apparent non-progressive, congenital optic atrophy. It is unclear whether this clinical heterogeneity represents the involvement of several different genes or the variable manifestations of a single pleiomorphic gene.

The involvement of both the central and peripheral visual fields in patients investigated with perimetry, is in agreement with the findings of Neimeyer and Marquardt[6] and again points to a site of pathology in the visual pathway proximal to the retina.

Absent pupillary responses to light were found in patients with the most severe vision loss. This finding is more likely to be related to an afferent system disorder or underlying generalised neurodegeneration than a complication of diabetes mellitus. Patients with diabetic autonomic neuropathy would be expected to have severe small vessel disease, which was not seen in this cohort. The horizontal nystagmus is also probably related to the underlying neurodegeneration as it was seen in patients with other cerebellar signs.

It is surprising that only 5 patients had background diabetic retinopathy; the median duration of diabetes mellitus of these 5 patients was 33 years, compared with the median duration of diabetes mellitus in the whole cohort of 24 years. This suggests that Wolfram patients eventually develop diabetic retinopathy but that the rate of progression is slower than in type 1 diabetics. It has been suggested that 90% of a population of conventionally treated type 1 diabetics would be expected to develop retinopathy after 20 years.[18] All Wolfram patients required insulin, were insulin deficient, and had relatively poor glycaemic control as assessed by glycated haemoglobin measurements. Our finding cannot be explained by the higher mortality in Wolfram syndrome compared with type 1 diabetics, as many of the Wolfram cohort patients have survived long enough to develop retinopathy. Retinal vessel attenuation secondary to optic atrophy could conceivably protect the retina from hypertension and glucose toxicity.[19] Retinal vessel abnormalities associated with optic atrophy usually require a direct retinal insult such as retinal dystrophy; in optic atrophy due to damage to the retrolaminar optic neve (as in Wolfram syndrome), retinal vessels are unaffected.[20] Animal studies have shown that diabetes-induced increases in vascular permeability in retinal vessels are prevented by castration;[21] our finding of reduced levels of sex hormones in Wolfram patients with primary gonadal atrophy may indicate a hormonal modulation of the development of diabetic retinopathy.[13] Alternatively there may be a direct gene effect. Conditions in diabetics known to be associated with reduced

prevalence of diabetic retinopathy include carotid stenosis, glaucoma and high myopia.[22] To this list should be added Wolfram syndrome.

The electrophysiological tests confirm previous work[7] suggesting that the pathogenesis of the optic atrophy does not lie in the retina, but primarily affects the optic nerve. The absent visual evoked responses to flash and pattern stimulation, together with colour blindness, indicate a probable optic nerve pathology. Reduced ERG responses in 3 of 6 patients is compatible with another report of retinal function in Wolfram syndrome:[6] the authors found slight reduction in ERG responses in 2 patients, not accounted for by diabetic retinopathy, which was absent. The ERG changes could not account for the profound reduction in visual function. The authors concluded that the ganglion cell and optic nerve fibre layer were predominantly affected, and hypothesised that retrograde transsynaptic degeneration may be responsible for involvement of the ganglion cell layer.

Cranial MRI scans in our patients confirm previous reports of reduced signals from the sites of the optic nerves,[9] and demonstrate the wider underlying neurodegeneration seen in this syndrome. This is demonstrated most vividly in the macroscopic appearance of the undersurface of the brain of a patient with Wolfram syndrome (Fig. 2): atrophy of the optic nerves, chiasm and tracts is part of a wider atrophy that includes the medulla and pons, cerebellum and vermis.

Wolfram syndrome shares some clinical characteristics with disorders of the mitochondrial genome, which mediate their effects through disruption of the respiratory chain enzymes and energy production in the form of ATP. Shared clinical features include diabetes mellitus, deafness, optic atrophy, ataxia and myoclonus. However, we have found no evidence of a mitochondrial genome mutation or rearrangement in this cohort of patients. It may be that Wolfram syndrome is caused by a nuclear-encoded energy supply defect – either underproduction or inefficient use of ATP, perhaps in maintaining membrane integrity. Our recent improved localisation of a Wolfram syndrome gene to chromosome 4p[11] should permit identification of the gene product and better understanding of this disorder.

T.G.B. was funded by a Price-Hall fellowship from the United Birmingham Hospitals Trust, and the Royal National Institute for the Blind.

Key words: Optic atrophy, Wolfram syndrome, DIDMOAD.

REFERENCES

1. Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Mayo Clin Proc 1938;9:715–8.
2. Gunn T, Bortolussi R, Little J, Andermann F, Clarke FC, Belmonte M. Juvenile diabetes mellitus, optic atrophy, sensory nerve deafness and diabetes insipidus: a syndrome. J Pediatr 1976;89:565–70.
3. Cremers CW, Wijdeveld PG, Pinckers AJ. Juvenile diabetes mellitus, optic atrophy, hearing loss, diabetes insipidus, atonia of the urinary tract and bladder, and other abnormalities (Wolfram syndrome). Acta Pediatr Scand 1977;264(Suppl): 1–16.
4. Blasi C, Pierelli E, Rispoli E, Saponara M, Vingolo E, Andreani D. Wolfram's syndrome: a clinical, diagnostic, and interpretive contribution. Diabetes Care 1986; 9:521–8.
5. Rose FC, Fraser GR, Friedmann AI, Kohner EM. The association of juvenile diabetes mellitus and optic atrophy: clinical and genetical aspects. Q J Med 1966; 353:385–405.
6. Niemeyer G, Marquardt JL. Retinal function in a unique syndrome of optic atrophy, juvenile diabetes mellitus, diabetes insipidus, neurosensory hearing loss, autonomic dysfunction, and hyperalaninuria. Invest Ophthalmol 1972;11:617–24.
7. Mtanda AT, Cruysberg JRM, Pinckers AJLG. Optic atrophy in Wolfram syndrome. Ophthalmic Paediatr Genet 1986;7:159–65.
8. Carson MJ, Slager UT, Steinberg RM. Simultaneous occurrence of diabetes mellitus, diabetes insipidus, and optic atrophy in a brother and sister. Am J Dis Child 1977;131:1382–5.
9. Rando TA, Horton JC, Layzer RB. Wolfram syndrome: evidence of a diffuse neurodegenerative disease by magnetic resonance imaging. Neurology 1992;42:1220–4.
10. Polymeropoulos M, Swift R, Swift M. Linkage of the gene for Wolfram syndrome to markers on the short arm of chromosome 4. Nature Genet 1994;8:95–7.
11. Collier DA, Barrett TG, Curtis D, Macleod A, Arranz MJ, Maasen JA, Bundey S. Linkage of Wolfram syndrome to chromosome 4p 16.1 and evidence for heterogeneity. Am J Hum Genet 1996; 59:855–63.
12. Bundey S, Poulton K, Whitwell H, Curtis E, Brown IAR, Fielder AR. Mitochondrial abnormalities in the DIDMOAD syndrome. J Inher Metab Dis 1992; 15:315–9.
13. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 1995;346:1458–63.
14. Goto Y, Nonaka I, Horai S. A mutation in the tRNA Leu (UUR) gene associated with the MELAS subgroup of mitochondrial encephalopathies. Nature 1990;348:651–3.
15. Li YY, Hengstenberg C, Maisch B. Whole mitochondrial genome amplification reveals basal level multiple deletions in mtDNA of patients with dilated cardiomyopathy. Biochem Biophys Res Commun 1995;210: 211–8.
16. Pilz D, Quarrell OW, Jones EW. Mitochondrial mutation commonly associated with Leber's hereditary optic neuropathy observed in a patient with Wolfram syndrome (DIDMOAD). J Med Genet 1994;31:328–30.

17. Kinsley BT, Swift M, Dumont RH, Swift RG. Morbidity and mortality in the Wolfram syndrome. Diabetes Care 1995;18:1566–70.
18. Krowlewski AH, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR. Risk of proliferative diabetic retinopathy in juvenile-onset type 1 diabetes: a 40-yr followup study. Diabetes Care 1986;9: 443–52.
19. Kohner EM, Patel V, Rassam SMB. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. Diabetes 1995;44:603–7.
20. Millar NR, editor. Walsh and Hoyt's clinical neuro-ophthalmology. Vol 2. Baltimore: William and Wilkins, 1985.
21. Williamson JR, Chang K, Tilton RG, Prater C, Jeffrey JR, Weigel C, *et al.* Increased vascular permeability in spontaneously diabetic BB/W rats and in rats with mild versus severe streptozotocin-induced diabetes: prevention by aldose reductase inhibitors and castration. Diabetes 1987;36:813–21.
22. Becker B. Diabetes mellitus and primary open-angle glaucoma. Am J Ophthalmol 1971;71:1–16.