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Bilateral simultaneous optic neuropathy in adults: clinical, imaging, serological, and genetic studies

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Abstract

To elucidate the cause(s) of acute or subacute bilateral simultaneous optic neuropathy (BSON) in adult life, a follow up study of 23 patients was performed with clinical assessment, brain MRI, HLA typing, and mitochondrial DNA analysis. The results of CSF electrophoresis were available from previous investigations in 11 patients. At follow up, five (22%) had developed clinically definite multiple sclerosis, four (17%) had mitochondrial DNA point mutations indicating a diagnosis of Leber's hereditary optic neuropathy (LHON). The remaining 14 patients (61%) still had clinically isolated BSON a mean of 50 months after the onset of visual symptoms: three of 14 (21%) had multiple MRI white matter lesions compatible with multiple sclerosis, three of 14 (21%) had the multiple sclerosis associated HLA-DR15/DQw6 haplotype, and one of seven tested had CSF oligoclonal IgG bands; in total only five (36%) had one or more of these risk factors. The low frequency of risk factors for the development of multiple sclerosis in these 14 patients suggests that few will develop multiple sclerosis with more prolonged follow up. It is concluded that: (*a*) about 20% of cases of BSON without affected relatives are due to LHON; (*b*) multiple sclerosis develops after BSON in at least 20% of cases, but the long term conversion rate is likely to be considerably less than the rate of over 70% seen after an episode of acute unilateral optic neuritis in adult life.

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Clinically isolated acute unilateral optic neuritis (AUON) is relatively common in adults. Long term follow up, at least in the United Kingdom, indicates that up to 75% of such patients will develop clinically definite multiple sclerosis.[1–4] At presentation with AUON, brain MRI shows multiple cerebral white matter lesions indistinguishable from those of multiple sclerosis in 50–70% of patients,[5–8] and follow up studies have shown that the risk of progression to multiple sclerosis is much higher in the presence of such lesions, at least in the first five years[7–11]; the results of longer term follow up are as yet unavailable.

Clinically isolated acute or subacute bilateral simultaneous optic neuropathy (BSON) is much less common that AUON in the adult age group, and its aetiology is often obscure. Some cases are due to toxic or metabolic factors—for example, tobacco-alcohol amblyopia and methanol poisoning. A currently unknown proportion has Leber's hereditary optic neuropathy (LHON), and a few will go on to develop multiple sclerosis, although at least one study has suggested that the rate of progression to multiple sclerosis is lower after BSON than after an episode of AUON.[12] There remains a large group of patients in whom the diagnosis is unclear.

Certain laboratory investigations may give clues to the aetiology of undiagnosed optic neuropathies. For example, LHON can be diagnosed by detecting specific mutations on mitochondrial DNA analysis,[13–16] and the findings on brain MRI, HLA typing, and CSF electrophoresis each influence the risk of subsequent progression to multiple sclerosis in patients with AUON.[3 10 17 18] To elucidate its causes further, we have studied 23 patients who had initially presented with BSON, by performing a clinical follow up, brain MRI, HLA typing, and mitochondrial DNA analysis; CSF examination was not performed as a part of the study, but results were available from earlier investigations in 11 cases.

Patients and methods

Medical records were obtained of patients attending the National Hospital for Neurology and Neurosurgery, London with a diagnosis of bilateral optic neuritis or optic neuropathy. The review was restricted to patients in whom onset of visual loss in the two eyes occurred within two weeks, and where the onset of visual loss was acute (less than 14 days to reach peak visual deficit) or subacute (between 14 and 120 days to maximal visual deficit). Cases were selected only if the cause of optic neuropathy had not been established at presentation. They were excluded if: (*a*) LHON had been considered to be the likely diagnosis on the basis of a positive family history or fundal changes in the early stages suggestive of LHON (increased vascularity around the optic discs[19]); (*b*) there had been exposure to toxins, or the history was suggestive of tobacco alcohol amblyopia; (*c*) there were any prior clinical features of multiple sclerosis. In addition, all patients had

a negative serological screen for collagen vascular disease and syphilis. It was also required that there be at least six months between the onset of visual loss and the study assessment.

We identified 27 adults (age 16 years or more) with clinically isolated BSON of unknown cause, of whom 23 attended for MRI, blood testing, and further clinical examination, and are the subject of this report. The other four cases declined to return for the follow up assessment; review of their records indicated that two had already developed multiple sclerosis.

MAGNETIC RESONANCE IMAGING

The whole brain was imaged with a 0·5 Tesla Picker MR system provided by the multiple sclerosis Society of Great Britain and Northern Ireland. A moderately T2 weighted sequence ($SE_{2000/60}$) was obtained in all cases with 5 mm thick, contiguous, axial slices. The magnetic resonance images were reported by an experienced neuroradiologist (IFM). The site and number of parenchymal brain lesions were recorded.

HLA TESTING

Genomic DNA was isolated from 30 ml venous blood by a phenol-chloroform extraction procedure. DR types were determined by restriction fragment length polymorphism (RFLP) analysis.[20] DNA (7 μg) was digested with TaqI restriction enzyme and the fragments were separated by electrophoresis and blotted on to nylon filters. The filters were hybridised sequentially with radiolabelled cDNA probes consisting of the 500 base pair (bp) Pst 1 fragment of pIIβ 4 (corresponding to the second domain, transmembrane, cytoplasmic, and 3′ untranslated portions of the DRβ gene) and the 750 bp ApaI fragment of pIIα5 (full length DQA1 gene). DR7 and DR9 were distinguished by HindIII digests hybridised with the former cDNA probe. DR3 and DR6 were distinguished with BamHI digests probed with the PstI/HindIII fragment of pIIβ (full length DQB1 gene).

DQA1 and DQB1 alleles were identified by sequence-specific oligonucleotide gene probing. The second exon of the DQA1 and DQB1 genes was amplified from 2 μg of genomic DNA using the polymerase chain reaction.[21 22] Amplified DNA (4μl) was dot-blotted on to nylon filters and probed with sequence-specific oligonucleotide probes to distinguish 7 DQA1 and 12 DQB1 alleles.[23]

MITOCHONDRIAL DNA ANALYSIS

DNA was extracted from leucocytes and analysed for three mitochondrial DNA (mtDNA) mutations that are associated with LHON. The mutations at bps 11778 and 3460 were investigated as previously.[15] The presence or absence of the 14484 bp mutation[16] was assessed by a mismatch primer method, using primers complementary to bases 14464–14483 (forwards) and 14664–14645 (reverse).[24] In primer 14664–14883 the cytosine at position 14482 was replaced by a guanine. This creates a restriction site for MboI in normal, but not mutant mtDNA. The polymerase chain reaction was performed with 30 cycles of denaturation (30 s at 90°C), annealing (30 s at 55°C), and elongation (30 s at 72°C) after initial cycles of four, three, and one minutes. The polymerase chain reaction product was digested with MboI; normal mtDNA is cut into two fragments of 180 and 20 bp whereas mutant mtDNA remains uncut.

CLINICAL EXAMINATION

All patients underwent a full neurological examination (by SPM) and neuro-ophthalmological assessment (by FXB). Multiple sclerosis was diagnosed at follow up by the Poser criteria.[25] A diagnosis of clinically definite multiple sclerosis was made in patients who developed symptoms and signs of new CNS lesions outside of the optic nerves.

CEREBROSPINAL FLUID

This had been collected during earlier investigations in 11 patients, for each of whom it had been examined for the presence of oligoclonal IgG bands by methods described elsewhere.[26]

Results (table)

There were 11 men and 12 women. Progression to maximal visual deficit was less than 48 hours in three patients, two to 14 days in 16, and 14 to 120 days in four. The mean age at onset of BSON was 31 (range 18–54) years, and at follow up 37 (range 23–66) years. For the whole group, the mean and median durations of follow up were 71 and 55 months respectively (range 7–324 months).

At follow up, 14 patients were still classified as clinically isolated BSON of uncertain cause; Their mean duration of follow up was 50 (range 7–151) months. Five patients had developed clinically definite multiple sclerosis[26]; their duration of follow up was longer (mean 121 (range 23–324) months), than those who had not developed multiple sclerosis, although review of their history and hospital records indicated that multiple sclerosis had developed between three and 72 (mean 28) months after the initial visual loss. In all five, the initial visual deficit took less than two weeks to evolve.

Three men had the mtDNA 11778 mutation and one the 14484 mutation, and therefore were diagnosed as having LHON. None had a positive family history and none had exhibited the characteristic fundal changes described in LHON at presentation.[19] Their mean age at onset of visual loss was 32 (range 18–54) years, and mean duration of follow up was 82 (range 55–150) months. In all four patients the initial visual deficit took more than two weeks to evolve.

BRAIN MRI

In all five patients with clinically definite multiple sclerosis, there were multiple periventricular and discrete cerebral hemisphere white

Clinical, MRI, serological, and CSF findings

Patient No and sex	Age of onset (y)	Duration of visual loss at follow up (months)	HLA DR15/DQw6 haplotype	Mitochondrial DNA point mutations	CSF oligoclonal bands	No of brain MRI lesions*	Diagnosis at follow up
1 M	43	55	–	–	ND	1	BSON
2 F	39	48	–	–	ND	0	BSON
3 F	32	7	–	–	–	0	BSON
4 F	21	39	–	–	ND	0	BSON
5 F	32	17	–	–	–	1	BSON
6 F	54	32	–	–	+	4	BSON
7 F	30	11	+	–	–	0	BSON
8 F	22	96	+	–	+	48	MS
9 M	27	72	–	–	+	57	MS
10 M	30	55	+	11778	ND	0	LHON
11 M	26	324	+	–	+	9	MS
12 F	41	23	+	–	+	3	MS
13 M	27	63	–	14484	ND	0	LHON
14 M	54	150	–	11778	ND	8	LHON
15 F	31	131	–	–	ND	0	BSON
16 M	31	20	–	–	–	1	BSON
17 F	22	29	+	–	ND	0	BSON
18 M	36	51	–	–	ND	0	BSON
19 F	27	51	+	–	ND	4	BSON
20 M	18	61	–	11778	ND	0	LHON
21 M	31	151	–	–	–	6	BSON
22 F	21	92	ND	–	ND	81	MS
23 M	28	55	–	–	–	0	BSON

*Lesions are intrinsic foci of high signal on T2 weighted MRI.
+ = present; – = absent; ND = not done; BSON = bilateral simultaneous optic neuropathy of unknown cause; MS = multiple sclerosis; LHON = Leber's herditary optic neuropathy.

matter lesions characteristic of multiple sclerosis, and four had additional infratentorial lesions. Brain MRI was normal in three of four patients with LHON; the fourth, a 66 year old man, had multiple cerebral white matter lesions, most of which were discrete (not periventricular), a frequent finding at this age and probably due to incidental small vessel disease.

Of the 14 patients who still had clinically isolated BSON at follow up, brain MRI was normal in eight, and showed only a single small white matter lesion in three others. In the remaining three patients there were multiple cerebral white matter lesions compatible with multiple sclerosis, although none had infratentorial lesions, a characteristic although not invariable feature of multiple sclerosis.

HLA TYPING

HLA typing was performed in 23 patients; it was not carried out in one, who had developed multiple sclerosis. The DR15/DQw6 haplotype was present in three of four who developed multiple sclerosis, one of four with LHON, and three of 14 (21%) of those with isolated BSON. Only one of the three patients with isolated BSON with more than one MRI lesion was HLA DR15/DQw6 positive.

CEREBROSPINAL FLUID

Oligoclonal IgG bands were present in four of four who developed multiple sclerosis, and in one of seven with isolated BSON.

VISUAL PROGNOSIS

Visual outcome was rated as good where visual acuity was 6/9 or better in both eyes, moderate where it was 6/9 or better in one eye, but < 6/9 in the other, and bad where it was < 6/9 in both eyes. Of the 14 with isolated BSON at follow up, a good outcome was seen in nine, a moderate outcome in three, and a poor outcome in two. In the five with multiple sclerosis, a good outcome was seen in four and a poor outcome in one. The four patients with LHON all had a poor outcome.

Discussion

This clinical and laboratory follow up study was performed a mean of 71 months after presentation with BSON of uncertain cause. A firm diagnosis was made in nine patients (39%).

Four (17%) had LHON on the basis of finding a specific mitochondrial DNA point mutation. The value of mitochondrial DNA analysis is emphasised by this finding. It should be performed in any patient presenting with BSON. As seen in the present study, the family history may be negative, fundal findings may be non-specific, and the range of age of onset may be wide.[14] The finding of LHON is more common in males, in whom it presents as a clinically isolated optic neuropathy, usually with normal brain MRI, or only non-specific age related changes.[27] In females LHON may, however, in addition to optic neuropathy, be associated with disseminated clinical features and cerebral MRI abnormalities indistinguishable from multiple sclerosis.[28]

Five (22%) patients in the present series had multiple sclerosis on the basis of clinical evolution, supported in all cases by typical MRI appearances and by the presence of CSF oligoclonal bands in the four in whom these were sought. The frequency of progression to multiple sclerosis is lower than that reported in adults presenting with AUON, even if we include the two cases not followed up (seven of 27; 26%). Several studies suggest that about 50% presenting with AUON will have developed multiple sclerosis after five years.[3 10] the conversion rate increasing to over 70% with more prolonged follow up.[4 29] The lower rate of progression to multiple sclerosis in patients with BSON in the present study is

similar to an earlier study in which clinical follow up after a mean of 19·2 (range 0·5–30) years found multiple sclerosis in only two of 11 patients.[12]

It is possible that with longer follow up, some patients in the present study with clinically isolated BSON will go on to develop multiple sclerosis. It should be noted that these 14 patients had been followed up for a shorter time (mean 50 months) than the five who had developed multiple sclerosis (mean 121 months). Multiple sclerosis had developed, however, within two years of visual symptoms in four, and after three years in the fifth, and other studies after AUON have also shown that conversion to multiple sclerosis is most often seen in the first two years.[3 4 30] Nevertheless, in evaluating the risk of future progression to multiple sclerosis, it is appropriate to consider the paraclinical investigations that have been shown to indicate risk in patients with AUON—namely, CSF electrophoresis, MRI, and HLA typing.

Oligoclonal IgG bands in CSF have been reported in 34–47% of patients presenting with AUON and their presence is associated with an increased risk of progression to multiple sclerosis.[17 18] By contrast, in the present group with isolated BSON, bands were seen in only one of seven patients in whom they were sought. This patient also had four cerebral white matter lesions compatible with multiple sclerosis, although at her age (57 years) these appearances are relatively non-specific.

Multiple white matter lesions compatible with multiple sclerosis were seen in only three of 14 (21%) patients with isolated BSON. By contrast, multiple white matter lesions are seen at presentation in 50–70% of adults with AUON,[5–11] in whom their presence is associated with an 82% risk of progression to multiple sclerosis over the next five years.[10] Three other patients with isolated BSON had a single small white matter lesion—in all this was small and in two subcortical. Such a finding is non-specific and not infrequent in healthy young adults.[31–33] A single, small, subcortical white matter lesion in patients presenting with AUON carries a much lower risk of progression to multiple sclerosis than the presence of multiple, periventricular lesions[11]; normal brain MRI also carries only a 5% risk of progression to multiple sclerosis after five years.[10]

The strongest HLA association with multiple sclerosis to date is with the DR15/DQw6 haplotype, which is present in over 60% of patients.[34] This association was confirmed in the present study where it was found in three of four patients with multiple sclerosis who were tested, compared with only three of 14 (21%) with isolated BSON. The frequency of DR15/DQw6 in the isolated BSON group is similar to that found in a normal healthy population of British Caucasians, and lower than that found in patients with clinically isolated AUON or spinal cord or brain stem syndromes suggestive of multiple sclerosis,[35] in whom its presence is associated with increased risk of progression to multiple sclerosis, at least over the first five years from onset of symptoms.[10 35]

Overall, the low frequency of recognised risk factors for multiple sclerosis in each of the paraclinical investigations—MRI, CSF electrophoresis, and HLA typing—suggests a low probability of future progression to multiple sclerosis in the isolated BSON group. If several more do develop multiple sclerosis (and further follow up of the patients with multiple white matter lesions and no clinical features of multiple sclerosis will be particularly interesting), the rate of conversion will increase from the present 20% for the whole BSON cohort, but it seems likely to remain well below the rate of over 70% seen after long term follow up of patients with AUON.

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NEUROLOGY IN LITERATURE

Some movement disorders

In previous centuries, patients with movement disorders were often accused of being possessed by the devil. Indeed the unfortunate victims came to believe it themselves, as the example from Malleus Maleficarum shows. Could she have had Gilles de la Tourette's syndrome? Some of the witches of Salem, incidentally, from the contemporary accounts available, seem to have had oculogyric crises. The examples from Fielding and Proust can be accepted as focal dystonias although both, one by inference, seem to have recovered. Mr Bates has blepharospasm, perhaps with spasmodic torticollis and spasmodic torticollis is probably the movement disorder being described by Tolstoy. Mr Rottcodd's movements are not accompanied by ataxia and probably represent the association of congenital nystagmus with head oscillation.[1] Hadden's papers are something of a ragbag of conditions, the first of the series having the privilege of following, in that issue of *The Lancet*, the second of David Ferrier's Croonian lectures.

Jacobus Sprenger and Heinrich Kramer, 1486, Malleus Maleficarum
"I cannot help myself at all, for he uses all my limbs and organs, my neck, my tongue, and my lungs, whenever he pleases, causing me to speak or to cry out; and I hear the words as if they were spoken by myself, but I am altogether unable to restrain them; and when I try to engage in prayer he attacks me more violently, thrusting out my tongue."

Henry Fielding, 1742, Joseph Andrews
A man in my circumstances, as he very well knew, had no choice. I accordingly accepted his proposal with his conditions, which were none of the most favourable, and fell to translating with all my might. I had no longer reason to lament the want of business; for he furnished me with so much, that in half a year I almost writ myself blind. I likewise contracted a distemper by my sedentary life, in which no part of my body was exercised but my right arm, which rendered me incapable of writing for a long time.

George Eliot, 1858, Scenes of clerical life
Mr Bates was further distinguished from the common herd by a perpetual blinking of the eyes; and this, together with the red-rose tint of his complexion, and a way he had of hanging his head forward, and rolling it from side to side as he walked, gave him the air of a Bacchus in a blue apron, who, in the present reduced circumstances of Olympus, had taken to the management of his own vines.

Leo Tolstoy, 1877, Anna Karenina (about Nicholas Levin)
But at the same moment he turned to look at the young man and convulsively jerked his head and neck as if his neck tie were strangling him, a movement Levin knew well, . . . "So you see, ..." Nicholas Levin continued with an effort, wrinkling his brow and twitching.

Marcel Proust, 1923–1927, Remembrance of things past. Volume 3
Morel was suffering at the time from violent cramp in the hand, and found himself obliged to contemplate the possibility of having to give up the violin. (Morel is a violinist—he recovers.)

Mervyn Peake, 1946, Titus Groan
His skull was dark and small like a corroded musket bullet and his eyes behind the gleaming of his glasses were the twin miniatures of his head. All three were constantly on the move as though to make up for the time they spent asleep, the head wobbling in a mechanical way from side to side when Mr Rottcodd walked, and the eyes, as though taking their cue from the parent sphere to which they were attached, peering here, there, and everywhere at nothing in particular.

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