Acute optic neuritis: a prospective study of risk factors for multiple sclerosis

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SUMMARY Eighty two patients with isolated optic neuritis were studied prospectively to determine the frequency with which multiple sclerosis developed and the factors which increased its risk. Patients were followed for 6 to 264 months (mean, 57 months). Twenty six patients (32%) developed clinically definite or probable multiple sclerosis during the period of follow-up. Actuarial analysis predicted that 42% would develop multiple sclerosis by 7 years. Of those patients who developed multiple sclerosis, 92% had symptoms within 4 years of the first attack of optic neuritis. The highest incidence of multiple sclerosis occurred in the 21-40 year age group. There was an increased risk of MS in patients with HLA-DR2 and HLA-B7 tissue types. The frequency of HLA-DR4 was increased in patients with optic neuritis alone compared to controls and to patients with multiple sclerosis, but further studies are required to confirm this finding.

The frequency with which multiple sclerosis develops following an attack of acute optic neuritis varies widely in different series and has been reported to range from 11.5%¹ to 85%.² The variability of the findings may relate to the different methods of selection of patients and diagnostic criteria, geographical factors, duration of follow-up and design of study.³⁻⁵ Risk factors have been identified in previous studies which include recurrent attacks of optic neuritis^{3,4} association with certain HLA antigens^{4,6,7} and the presence of oligoclonal bands in the cerebrospinal fluid.⁸ There is general agreement that there is an increased risk associated with the HLA-DW2 antigen. The aim of the present investigation was to study prospectively 82 patients who presented with acute optic neuritis and were followed for a mean interval of nearly 5 years, in order to determine the frequency with which they develop multiple sclerosis and to identify risk factors. Patients were tissue typed and were examined clinically and had visual evoked potentials (VERs) performed at the beginning and end of the study period.

Methods

Patients

Eighty two patients with acute uncomplicated optic neuritis who had been examined and had had VERs performed in our department during the period 1975-1983 inclusive were reviewed. All patients had been referred by a neurologist or an ophthalmologist and conformed to the definition of optic neuritis as "a condition causing a relatively rapid onset of visual failure, in which no evidence for a toxic, vascular or compressive aetiology can be discovered and where local retinal lesions have been excluded".⁹ In most patients the initial VER and ophthalmological examination were performed by a neurologist within 1 month of the episode of acute optic neuritis. All patients with a history or signs of demyelination outside the optic nerves at the initial examination were excluded from the study. However, patients with a prior episode of optic neuritis alone were included. Patients were subsequently reviewed neurologically and ophthalmologically, and VERs were repeated. All patients were Caucasian and 71/82 had northern European ancestry.

Definitions

A diagnosis of multiple sclerosis was based on the criteria of Rose *et al.*¹⁰ Bilateral optic neuritis was defined as attacks of optic neuritis involving both eyes simultaneously or within 4 weeks of each other. Recurrent optic neuritis was defined as attacks of optic neuritis involving one or other eye at an interval greater than 4 weeks from the first attack.

Tissue typing

HLA typing was carried out using 120 sera for HLA-A, B

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and 60 sera for HLA-DR. All sera had been standardised against cells typed on the Ninth International Workshop¹¹ and previous workshops. For HLA-DR typing, B-lymphocytes were isolated by nylon-wool separation¹² followed by AET rosetting.¹³ Typing was carried out for HLA:—A1, A2, A3, A11, A23, A24, A25, A28, (Aw68 and Aw69), A29, Aw30/31, A32, Aw33, Aw34, B5, B7, B8, B13, B14, B18, B27, B35, B37, B38, B39, B41, B45, B48, B49, B50, Bw54, Bw55, Bw56, B57, B58, B60, Bw61, Bw62, Bw63, Bw70, DR1, DR2, DR3, DR4 (DRw11 and DRw12), DR5, DRw6 (DRw13 and DRw14), DR7, DRw8, DRw9 and DRw10.

Statistics

Statistical comparisons of results were made using the Chi-square (χ^2) test. Where applicable, the Bonferroni correction for multiple comparisons was applied. The relative risk (RR) of multiple sclerosis was calculated according to the formula of Svegaard *et al.*¹⁴ RR is increased for values greater than 1 and is decreased for values less than 1. To correct for the variable periods of follow-up an actuarial analysis was made to predict the probability of developing multiple sclerosis.¹⁵

Initial examination

Eighty two patients (59 females (72%) and 23 males (28%)) presented with acute optic neuritis. Their ages ranged from 10 to 50 years (mean 29.2). VERs were abnormal in 97 of 103 affected eyes.

Follow-up examination

Twenty six of the 82 patients (32%) progressed to clinically definite (22) or probable (4) multiple sclerosis (ON-MS) during the follow-up period of 7 to 144 months (mean 57 months; median 47 months). The remaining 56 patients with optic neuritis only (ON) were followed for 6 to 264 months, (mean 57 months; median 55 months). When life table analysis was used it was predicted that 42% would have progressed to multiple sclerosis by 7 years (fig).

There was no significant difference in the rate of progression to multiple sclerosis for males and females ($\chi^2 = 3.0$; $p > 0.5$) but the relative risk for females was increased (RR = 2.8). There was no significant difference in the mean ages of the ON (mean 29.4 years) and the ON-MS groups (mean 28.8 years). Twenty two of the 26 patients (85%) who progressed to multiple sclerosis were aged 21 to 40 years while 66% of the total patients studied were in this group. There is a significantly greater risk of developing multiple sclerosis for patients in the 21 to 40 year age group than those outside this age range ($\chi^2 = 6.0$; $p < 0.05$) (table 1). The interval between the initial episode of optic neuritis and the first manifestation of symptoms of demyelination outside the optic nerves ranged from one month to 7 years (mean 21 months; median 14 months). Sixteen of 26 patients (61.5%) had developed symptoms of multiple sclerosis by 24 months and 24/26 (92%) by 48 months.

Recurrent and bilateral optic neuritis

Twenty seven patients had recurrent attacks of optic neuritis in one or other eye prior to the onset of non-optic nerve symptoms. Recurrent attacks occurred in 48/56 (32%) patients in the ON group and 9/26 patients (35%) in the ON/MS group. The difference is not significant ($p > 0.05$) and the relative risk of multiple sclerosis for those with recurrent optic neuritis is only 1.1. Bilateral optic neuritis occurred in nine patients, four of whom developed multiple sclerosis (44%); the relative risk of developing multiple sclerosis was increased (RR = 1.9) but the difference was not significant ($p > 0.05$).

Tissue typing

The results of tissue typing are shown on table 2. The control group, obtained from the Sydney Red Cross Blood Transfusion Service, consisted of 552 people analysed for HLA-A and -B alleles and 225 people analysed for HLA-DR alleles. There was no significant difference between the ON, ON-MS and control groups for frequency of HLA-A3. The frequency of HLA-B7 was similar in the ON group to the control population but HLA-B7 was significantly increased in the group who developed multiple sclerosis when compared to controls ($\chi^2 = 11.3$; $p < 0.001$). HLA-DR2 was significantly increased in frequency in the ON-MS group when compared to controls, ($\chi^2 = 18.5$; $p < 0.001$) and to a lesser degree in ON compared to controls ($\chi^2 = 5.8$, $p < 0.05$). In an attempt to assess whether the frequency of HLA-DR2 was increased in the ON group because some of the patients may subsequently develop multiple sclerosis, the 32 ON patients who had been followed for greater than 4 years (range 54-264 months, mean 86 months) were compared with the control population: the frequency of HLA-DR2 remained significantly elevated ($\chi^2 = 12$; $p < 0.001$), and was not significantly different from ON-MS patients ($\chi^2 = 0.3$). A combination of HLA-B7/DR2 occurred more frequently in the ON/MS group than in those with ON alone ($\chi^2 = 8.9$; $p < 0.01$).

The relative risk of multiple sclerosis in patients with different tissue types was HLA-A3 (RR = 1.6), HLA-B7 (RR = 4.7), HLA-DR2 (RR = 2.7) and HLA-B7/DR2 (RR = 4.8). HLA-DR4 was present in 24/53 (45%) patients with ON and in 4/26 (15%) patients with ON-MS. The difference between ON

Table 1 Age at onset of optic neuritis

Age (years)	ON (n = 56)	ON-MS (n = 26)
<20	13	2
21-30	15	14
31-40	17	8
41-50	11	2

Table 2 Tissue typing results

Antigen	No positive		Antigen frequency		
	ON 53	ON-MS 26	ON	ON-MS	Controls 522
A-Locus					
A1	15	10	0.283	0.385	0.351
A2	28	7	0.528	0.269	0.489
A3	13	9	0.245	0.346	0.259
A11	6	0	0.113	0	0.128
A23	1	0	0.019	0	0.017
A24	11	1	0.208	0.038	0.167
A25	1	4	0.019	0.154	0.044
A26	7	1	0.132	0.038	0.165
A28	4	2	0.075	0.077	0.052
A29	0	0	0	0	0.094
Aw30/31	2	3	0.038	0.115	0.067
A32	4	1	0.075	0.038	0.073
Aw33	0	0	0	0	0.002
B-Locus					
B5	53	26			522
B7	10	0	0.189	0	0.100
B8	12	15	0.226	0.577	0.272
B13	12	11	0.226	0.423	0.266
B14	0	1	0	0.038	0.042
B17	5	0	0.094	0	0.075
B18	1	0	0.019	0	0.098
B27	3	0	0.057	0	0.094
B35	5	3	0.094	0.115	0.096
B37	8	6	0.151	0.231	0.130
B38	2	0	0.038	0	0.010
B39	1	0	0.019	0	0.034
B41	2	0	0.038	0	0.033
B44	1	0	0.019	0	0.015
B45	13	4	0.245	0.154	0.264
B48	1	0	0.019	0	0.002
B49	0	0	0	0	0.004
B50	4	0	0.075	0	0.013
Bw53	1	0	0.019	0	0.013
Bw54	0	0	0	0	
Bw55	1	0	0.019	0	
Bw56	3	0	0.057	0	
B57	2	0	0.038	0	
B58	2	1	0.038	0.038	
B60	5	1	0.094	0.038	
Bw61	3	1	0.057	0.038	
Bw62	3	0	0.057		
Bw63	0	0	0	0	
Bw70	0	0	0	0	
DR-Locus					
DR1	53	26			225
DR2	10	4	0.189	0.154	0.191
DR3	22	17	0.415	0.654	0.249
DR4	14	10	0.264	0.385	0.302
DR5	24	4	0.453	0.154	0.289
DRw6	7	2	0.132	0.077	0.178
DR7	11	2	0.208	0.077	0.222
DRw8	8	5	0.151	0.192	0.307
DRw9	0	0	0	0	0.036
DRw10	0	0	0	0	
B7/DR2	0	0	0	0	
A3/B7/DR2	8	12	0.151	0.462	0.08
	3	5	0.057	0.192	

and controls ($\chi^2 = 5.3$; $p < 0.05$) and ON and ON-MS groups ($\chi^2 = 6.8$; $p < 0.01$) did not reach levels of significance after application of the correction factor for multiple comparisons. The relative risk of multiple sclerosis in patients with HLA-DR4 was one fifth that of patients without HLA-DR4.

Actuarial analysis predicts that of all patients presenting with acute optic neuritis, 42% develop multiple sclerosis in 7 years. A greater proportion of patients who are HLA-DR2 positive (61%) develop multiple sclerosis, than those who are HLA-DR2 negative (30%) or HLA/DR4 positive (26%) (fig).

Fig Actuarial curves showing the percentage of patients who have not developed multiple sclerosis at each interval of follow-up.

Numbers studied at each interval:								
Months	0-6	7-12	13-24	25-36	37-48	48-60	61-72	73-84
Total	82	70	60	49	37	34	23	17
DR2 +ve	38	30	26	22	17	15	9	5
DR2 -ve	40	36	31	24	18	16	13	11
DR4 +ve	28	27	22	18	14	12	10	8

Combination of risk factors

Female sex, age 21-40, presence of HLA-DR2 or HLA-B7 tissue types add to the cumulative risk while HLA-DR4 decreases the risk regardless of sex. There is a slightly increased risk in patients with bilateral optic neuritis.

Discussion

There have been a number of previous studies of optic neuritis progressing to multiple sclerosis^{1 2 16-20} in some of which^{21 22} patients who had symptoms of demyelination in the central nervous system prior to the onset of the optic neuritis have not been excluded. In the present study patients with symptoms or signs of demyelination elsewhere in the central nervous system that preceded or were concurrent with optic neuritis were excluded.

The diagnostic criteria for clinically definite or probable multiple sclerosis were satisfied in 32% of patients after a mean follow-up of 57 months. Life-table analysis predicted that 42% of patients with optic neuritis would develop multiple sclerosis within 7 years. McDonald⁵ has suggested that geographical factors may be important in accounting for the variation in frequency of developing multiple sclerosis in the different reported studies. Another prospective

study from tropical and subtropical areas of Australia has reported a risk of 56%,²³ which is comparable to that of 50-60% in the United Kingdom.^{4 5 9 17} A somewhat lower incidence, similar to our own, of 30-40% has been reported from the United States.^{3 16 21} The unusually low frequency of 13% reported by Kurland *et al*¹ may be due to the fact that their study was confined to male patients. A recent study from Finland²² established that 19% of patients with optic neuritis develop multiple sclerosis during a follow-up period of 5 years; life-table analysis predicted that the probability of developing multiple sclerosis was 38% and 24% in 2 different provinces after 9 years. It does not appear from these studies that there is any clear association with latitude.

In the present study 92% of patients who developed multiple sclerosis had developed symptoms outside the optic nerves within 4 years. All of the patients who developed multiple sclerosis in the studies of Collis¹⁶ and Percy *et al*¹⁸ had done so by 4 years despite prolonged follow-up periods of 7-20 years and 2-33 years respectively. Bradley and Whitty¹⁷ stated that definite multiple sclerosis usually developed within the first 4 years and Landy *et al*²³ found that most of their cases who subsequently developed multiple sclerosis did so within 2 years of the onset of optic neuritis. Nevertheless it is clear that the longer patients are followed, the higher will be the incidence of multiple sclerosis.^{5 20}

Females presenting with optic neuritis outnumbered males in the present study, a finding consistent with other reports.^{17 23-25} There was a greater relative risk of progression to multiple sclerosis in females which is consistent with the observations of some workers^{3 16 25} but not those of others.^{9 17 23} The largest number of patients with optic neuritis were in the 21-40 year age group and they had a significantly greater risk of developing multiple sclerosis. The finding that patients in the younger adult age groups are more likely to develop multiple sclerosis is consistent with the reports of other workers.^{3 16 26} By contrast, Bradley and Whitty¹⁷ found the likelihood of developing multiple sclerosis greater in older age patients.

In the present study there was no statistically significant increase in the frequency of multiple sclerosis in patients with bilateral or recurrent optic neuritis, although the relative risk was increased in the former group. Parkin *et al*²⁷ found a very low risk of developing multiple sclerosis after simultaneous bilateral or recurrent optic neuritis in childhood and a relatively low risk in adults. Kinnunen²⁵ also found that recurrent optic neuritis did not increase the risk of multiple sclerosis. However, recurrent attacks of optic neuritis were a significant risk factor in the studies of Compston *et al*⁴ and Cohen *et al*.³ The frequencies of

HLA-A3 and -B7 antigens in ON patients did not differ significantly from the control population but HLA-B7 was significantly increased in the ON-MS group, a finding noted by other workers.²⁸ HLA-DR2 was significantly more frequent in ON-MS patients than in controls. It was also significantly elevated but to a lesser extent in the ON group. These findings are similar to those of others.^{4,28} The finding of Sandberg-Wollheim *et al*⁷ that all three histocompatibility antigens occurred at similar frequencies in ON and multiple sclerosis may be explained by their short follow-up period of 2-6 years. In our study there was a greater risk of developing multiple sclerosis if the HLA-B7 antigen was present in combination with HLA-DR2 than with HLA-DR2 alone. It is possible that HLA-DR2 is associated closely to a gene or genes that increase susceptibility not only to multiple sclerosis but also to optic neuritis that does not progress, and that other genetic and environmental factors lead to the development of chronic, recurrent demyelination.

It is of interest that in our study the frequency of HLA-DR4 is increased in patients with optic neuritis alone compared to controls and to ON-MS patients. It is thus possible that HLA-DR4 is not in linkage disequilibrium with the multiple sclerosis susceptibility gene(s) in this population of predominantly northern European extraction, although it is in Jordanian Arabs.²⁹ For this reason, the presence of DR4 may offer a reduced risk of disseminated demyelination, although the risk of optic neuritis in isolation appears to be increased. Further studies are required to verify this finding.

A close relationship between isolated optic neuritis and multiple sclerosis is apparent but the different HLA frequencies in the two groups suggest that different immunological factors may be active in allowing only some patients to progress to multiple sclerosis. In the present study female sex, young adult age and the presence of HLA-B7 or -DR2 increased the risk of developing multiple sclerosis and, in another study, the presence of oligoclonal bands.⁸ However, none of these features is a reliable guide to prognosis in individual patients.

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