SHORT REPORT

A prospective study on the predictive value of CSF oligoclonal bands and MRI in acute isolated neurological syndromes for subsequent progression to multiple sclerosis

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Abstract

A prospective study in patients with a clinical acute isolated brainstem or spinal cord disorder was undertaken. The aim was to evaluate the predictive value of IgG intrathecal synthesis (through the detection of oligoclonal bands in CSF) and MRI lesions at presentation, for the subsequent progression to multiple sclerosis. Forty four patients took part in this study: 22 had a brainstem disorder and 22 a spinal cord disorder. After a mean period of 26 (SD 22) months, 30 patients (68.2%) developed clinically definite multiple sclerosis. The remaining 14 patients were followed up for more than seven years. Twenty six (59.1%) patients had oligoclonal bands in CSF, with a sensitivity of 80.0%, specificity of 85.7%, and a predictive value of 92.2%. Magnetic resonance imaging showed disseminated white matter lesions in 22 patients (50.0%), with a sensitivity of 60.0%, a specificity of 71.4%, and a predictive value of 81.7%. The difference between patients with multiple sclerosis and patients without the disease was statistically significant for the findings of an IgG intrathecal synthesis ($P < 0.001$). It was only borderline for the MRI findings ($P = 0.052$). Thus the detection of an intrathecal IgG synthesis at presentation seemed to be a better prognostic indicator of the progression to multiple sclerosis in patients affected by acute isolated brainstem or spinal cord syndromes.

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Over the past few years, interest has been focused on the occurrence of laboratory abnormalities in early multiple sclerosis, as it is associated with oligoclonal bands (OCB) in CSF and increased CSF IgG concentration evaluated by several indices and formulas.¹⁻¹² In addition, MRI shows cerebral and spinal

cord lesions which are highly suggestive of the demyelinating white matter typical of multiple sclerosis.¹³⁻¹⁵

Studies so far carried out mainly concern patients with clinically definite multiple sclerosis or acute unilateral optic neuritis.¹⁶⁻¹⁸ Only a few report such a paraclinical diagnostic approach in monosymptomatic clinically suspected multiple sclerosis—namely, patients with isolated brainstem and spinal cord syndromes. Results indicate that half of these patients show typical CSF and MRI abnormalities and that more than two thirds of them have a progression to clinically definite multiple sclerosis.¹⁹⁻²³ These studies are either based on short periods of clinical observation—generally less than two years—or they take into account, in the final evaluation, the paraclinical criteria to support the diagnosis of multiple sclerosis.²⁴ This, however, may be misleading if the final aim is to evaluate the real impact and predictive value of CSF OCB and MRI findings in the early phases of multiple sclerosis.

To verify the progression to clinically definite multiple sclerosis of monosymptomatic brainstem and spinal cord syndromes in patients with suspected multiple sclerosis, we undertook a prospective study, seven years ago, to evaluate sensitivity, specificity and predictive value of CSF analysis and MRI, by using, as a reference mark, only clinical criteria.²⁵

Patients and methods

This study included 66 consecutive patients with a monofocal acute or subacute clinical lesion of the brainstem or spinal cord at the time of their first hospital presentation. The study was restricted to patients under 50 years of age. All neurological diseases other than clinically suspected multiple sclerosis were excluded by means of clinical and paraclinical tests. All underwent a CSF and MRI examination, performed within 15 days from the onset of neurological symptoms and signs and before modulator or suppressor immunotherapy was begun.

We excluded six patients because of inadequate paraclinical evaluation (refusal of lum-

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bar puncture or MRI).

Patients who were subsequently diagnosed as having clinically definite multiple sclerosis according to the McAlpine criteria,²⁵ had a minimum of seven years of clinical follow up.

Twelve other patients were dropped from the study because their follow up was less than seven years. None of the patients with acute isolated unilateral or bilateral optic neuritis were included as it is difficult to be sure of the aetiology of this disorder basing the diagnosis only on clinical and paraclinical tests.

When acute intercurrent bouts did not occur, the patients did not require any urgent medical help, so we examined them regularly every three months and, if necessary, blood and CSF analysis and MRI were repeated (15 patients). In this way, we found another four patients without multiple sclerosis, who were dropped from the studied population. These patients were excluded because three were found to be affected, at follow up, by systemic lupus erythematosus, and one by cyanocobalamin deficiency which caused a subacute combined sclerosis. At the moment of inclusion their serological tests were negative and, therefore, these diagnoses were not suspected.

Thus only 44 patients fulfilled the inclusion criteria. Twenty two patients were affected by brainstem isolated syndromes and complained of diplopia, ataxia, and vertigo at the onset. Clinical signs were gaze palsies, nystagmus, cranial nerve impairment, and involvement of the cerebellum and long tract ascending and/or descending ways, indicating various typical complete or incomplete brainstem crossed syndromes. The remaining 22 patients, affected by spinal cord isolated syndromes, had either tetraparesis or tri paresis, which often showed a Brown-Séquard syndrome at cervical or dorsal level and usually had an acute or subacute onset (from a few days to two weeks). No patient had a clear acute myelitis that could be shown by an adequate clinical evaluation of signs and symptoms and laboratory tests (positive or negative diagnostic findings).

Serum and CSF albumin and IgG concentration were assayed by a nephelometer method. To detect IgG OCB, we examined unconcentrated CSF and paired diluted serum on agarose isoelectric focusing followed by silver staining. Two or more definite bands in the γ region were needed to diagnose an oligoclonal pattern.²⁶

At presentation, all patients underwent brain and spinal cord MRI studies with a 0.5 Tesla Philips Gyroscan (double spin echo technique—TE 50 and 100 ms; TR 2000 ms).

Five mm contiguous axial and 4 mm sagittal slices were obtained in all the brain images. The spinal cord (cervical, thoracic, and lumbosacral) was generally investigated in the two major projections, whereas contiguous axial studies were performed only when a reasonable and pertinent diagnostic uncertainty was present. T2 weighted images were found to be more sensitive than T1 weighted images in detecting demyelinating lesions compatible with multiple sclerosis. The presence of three

or more (multifocal) lesions in the cerebral white matter or in the spinal cord was considered to be strongly indicative of multiple sclerosis. We excluded lesions explaining the presenting syndrome from the MRI analysis.

Data from CSF and MRI were blind tested, and patients were divided into four groups according to the pattern found in the final clinical diagnosis: true positive (TP), false negative (FN), true negative (TN), and false positive (FP), so that we were able to calculate sensitivity (TP/TP + FN) and specificity (TN/TN + FP). The predictive value (PV)—the probability that a patient may have multiple sclerosis at follow up—was estimated from the formula:

$$PV = \frac{P \times S}{(P \times S) + (1 - P) \times (1 - Sp)}$$

where P is the prevalence of the disease in our series, S is sensitivity, and Sp is specificity.

We also estimated the odds ratios (ORs) with the formula:

$$OR = \frac{\text{Group A NIS/MS}}{\text{Group B NIS/MS}} \times \frac{\text{Group B NIS only}}{\text{Group A NIS only}}$$

where group A represents patients with neurological isolated syndromes (NIS) in the brainstem or spinal cord with CSF OCB and/or disseminated MRI lesions at presentation, and group B shows those patients without CSF OCB or MRI lesions. "MS" and "only" represent the progression or otherwise to the disease.

Statistical evaluation was by Fisher's exact test.

Results

Forty four patients (13 males and 31 females; mean age at onset: 30.39 (SD 10.2) years) took part in this prospective study.

At presentation, there was an isolated brainstem syndrome in 22 patients and an isolated spinal cord syndrome in the other 22. After a mean period of 26 (SD 22) months, 30 patients (68.2%) developed clinically definite multiple sclerosis. There were 11 males and 19 females, mean age at presentation 32.1 (SD 10.5) and at clinical diagnosis 34.3 (SD 11.3) years. The remaining 14 patients, two males and 12 females, without clinically definite multiple sclerosis, were followed up for a mean of 80 (SD 5) months.

All except two of the patients with an isolated brainstem syndrome developed clinical relapses outside the brainstem and were therefore classified as having clinically definite multiple sclerosis (90.9%), whereas an initial spinal cord disorder evolving to clinically definite multiple sclerosis was found in only 10 patients (45.4%). The difference between isolated brainstem syndromes and isolated spinal cord syndromes evolving to clinically definite multiple sclerosis was statistically significant ($P < 0.005$; table 1).

Ten patients (33.3%) developed clinically definite multiple sclerosis within one year, eight in the second year (total percentage =

Table 1 Clinical and paraclinical features at presentation in patients with isolated brainstem or spinal cord syndromes

Characteristics	Male patients	Female patients	Total
No of patients	13 (29.5)	31 (74.5)	44
Mean age (SD) (y)	31.8 (11.5)	29.6 (9.6)	30.3 (10.2)
Brainstem isolated syndromes (22/44; 50.0%)	7 (31.8)	15 (68.2)	22
Spinal cord isolated syndromes (22/44; 50.0%)	6 (27.3)	16 (72.7)	22
Presence of CSF IgG OCB (26/44; 59.1%)	7 (26.9)	19 (73.1)	26
MRI detected disseminated cerebral and spinal cord lesions (22/44; 50.0%)	11 (50.0)	11 (50.0)	22
Patients with progression to multiple sclerosis (30/44; 68.2%)	11 (36.7)	19 (63.3)	30
Patients with brainstem isolated syndrome and multiple sclerosis (20/22; 90.9%)*	7 (35.0)	13 (65.0)	20
Patients with spinal cord isolated syndrome and multiple sclerosis (10/22; 45.4%)*	4 (40.0)	6 (60.0)	10

Values in parentheses are % (apart from mean age (SD)).

*P < 0.005; 20/22 (90.9%) v 10/22 (45.4%).

CSF IgG OCB = Cerebrospinal fluid immunoglobulin G oligoclonal bands.

Table 2 Number of patients with progression to multiple sclerosis at follow up compared by means of predictive value and the odds ratios (ORs) of CSF oligoclonal bands (CSF OCB) and MRI disseminated lesions at presentation

Test and findings at presentation	Outcome after a seven year follow up		OR	Predictive value
	Multiple sclerosis (n = 30)	Non-multiple sclerosis (n = 14)		
CSF OCB:				
Positive***	24	2	24 (95% CI = 4.2-137.2)	92.2
Negative***	6	12		
MRI lesions:				
Positive*	18	4	3.7 (95% CI = 0.9-14.6)	81.7
Negative*	12	10		

*P = 0.052; 18/30 (60.0%) v 4/14 (28.6%).

***P < 0.001; 24/30 (80.0%) v 2/14 (14.3%).

60.0%), and four in the third year (total percentage = 73.3%). The remaining eight who developed definite multiple sclerosis required a mean period of clinical observation of at least five years.

Twenty six (59.1%) patients had CSF OCB and 22 (50.0%) had MRI disseminated white matter lesions at initial presentation. If we refer these data to the 30 patients who developed a clinically definite multiple sclerosis, 18 of the patients with an isolated brainstem syndrome showed CSF OCB (18/20; 90.0%) and a positive MRI was found in 13 patients (13/20; 65.0%). Moreover, in patients with isolated spinal cord syndromes we found six CSF OCB (6/10; 60.0%) and five MRI positive patients (5/10; 50.0%; table 1). The difference, however, was not statistically significant for either of the tests.

Thus in total, 24 out of the 26 patients with CSF OCB (92.3%) and 18 of those with disseminated lesions on MRI (81.8%) developed a clinically definite multiple sclerosis. There were two false positives for the CSF analysis and four for the MRI, and six and 12 false negatives respectively.

Therefore, we estimated a sensitivity of 80.0% and a specificity of 85.7% for CSF OCB, and a sensitivity of 60.0% with a specificity of 71.4% for MRI. The predictive value was 92.2% for the initial presence of CSF OCB and 81.7% for disseminated MRI lesions (table 2). The difference between patients with multiple sclerosis and those without was statistically significant only for the findings of an IgG intrathecal synthesis (P < 0.001) and

not for the MRI (P = 0.052). These results were also confirmed by the ORs.

Discussion

In this study, we have found that a progression to clinically definite multiple sclerosis in patients affected by acute isolated neurological syndromes may be predicted early from CSF and MRI studies. Our results differ slightly from those reported elsewhere,¹⁹⁻²³ as they are higher and statistically significant only for the evidence of CSF OCB (P < 0.001) and borderline for the MRI findings (P = 0.052).

In other studies^{27,28} it is reported that MRI is the better predictor for the progression to multiple sclerosis. This may be because our study plan is in part different. Firstly, we did not include optic neuritis in the series as it is difficult to be sure of its aetiology when only clinical and paraclinical tests are used in its diagnosis. Secondly, we chose to consider the MRI abnormal only when three or more lesions in the cerebral white matter or in the spinal cord were present. On the other hand, the other studies^{27,28} confirm that this choice was correct as a higher rate of progression to multiple sclerosis was seen only when four or more MRI lesions were found at presentation.

In our series, half the patients had an isolated brainstem disorder and 90.9% of this half developed a clinically definite multiple sclerosis. The remaining 50% presented a spinal cord syndrome and only 45.4% of these progressed to clinically definite multiple sclerosis, thus showing a highly significant difference (P < 0.005).

We know that, compared with cerebral MRI, spinal cord MRI has less resolution in showing adjunctive demyelinating lesions even if, sometimes, it may be useful for diagnosing other neurological diseases mimicking multiple sclerosis. On other hand, in many patients a definite intrathecal immunoglobulin synthesis may be found even in the first manifestation of the disease, in any isolated area involved, including the brainstem or spinal cord.^{1-12,19-23,29}

However, test positivity of MRI and CSF analysis is similar in both brainstem and spinal cord syndromes. It is the greater rate of progression to multiple sclerosis of patients with an affected brainstem which determines a significant CSF OCB finding in comparison with the morphological analysis.

It must be noted that the CSF profile does not always give a clear picture for diagnostic purposes, even when performed on patients with clinically definite multiple sclerosis. In fact, quantitative and qualitative CSF pictures, in our experience, may vary in the different phases of the disease. In many patients we found a poor or scarcely definite CSF OCB pattern at onset. However, in the successive relapses that define the disease, CSF abnormalities give clearer patterns, which become more and more evident and remain unchanged for many years in the course of the disease. In the final or chronic stages, when the disease shows less clinical sharpness, the CSF profile may be similar to that at the onset,

as if the intrathecal immunological reaction had exhausted itself. This could be related to a burning out phenomenon.

Because our series includes only cases at onset, this could account for the fact that CSF analysis did not reach greater expected predictive percentages in clinically suspected multiple sclerosis. Furthermore, in the initial phases of some systemic diseases a neurological disorder may possibly mimic multiple sclerosis, as we have shown recently.³⁰

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