

Cerebrospinal fluid analyses in Thai multiple sclerosis patients

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Abstract

Objective: To evaluate cerebrospinal fluid (CSF) patterns in Thai multiple sclerosis (MS) patients particularly oligoclonal bands compared with Western MS. **Methods:** Retrospective review of 72 patients from the MS Clinic, Siriraj Hospital, between January 1997 and June 2004. All were diagnosed MS using the Poser's criteria. **Results:** Seventy-six patients were evaluated. There were 62 female (86.1%), 10 male (13.9%) with a female:male ratio of 6.2:1. The mean age at onset was 33.11 ± 11.76 years. The mean duration of disease was 6.62 ± 5.9 years. Among the 56 MS patients, 52 patients (72.2%) had relapsing-remitting course, 3 (4.2%) had progressive relapsing course, 1 (1.4%) had secondary progressive course, none had primary progressive course. Eleven patients (15.3%) had possible MS and the remaining 5 patients had Devic's syndrome. Approximately 46% had CSF white blood cell (WBC) less than 5 cells/ μ L. Only 1 (2.3%) had CSF WBC count more than 50 cells/ μ L. However, both opticospinal form and classic form of MS similarly showed mononuclear cell predominant in differential CSF WBC count. Presence of CSF oligoclonal bands in definite MS patients was low in prevalence of only 27.3%.

Conclusion: The CSF of Thai MS patients have lower incidence of oligoclonal bands compared with the reports from western countries.

INTRODUCTION

Multiple sclerosis (MS) is a central demyelinating disease with a clinical course of acute exacerbation and remission phases which probably results from an aberrant immune response to myelin antigen.^{1,4} The cause of MS is unknown. At present, an association with immunogeneticity such as HLA-DRB1*1501 and DQB1*0602 in western countries⁵ and HLA-DPB1*0501 allele in eastern countries are reported.⁶ Immunological process may therefore play a major role. Previous studies suggested a shift towards an increase in production of interferon by CD₈-positive T cell in opticospinal MS throughout the relapse and remission phases.⁷ In addition, low titres of ANA are seen in some patients with MS, whereas antibodies specific for systemic or other organ-specific autoimmune disease are absent in most patients.⁶

Diagnostic criteria of MS have included a combination of both clinical and paraclinical evidences such as evoked response studies, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis.^{8,9} In the 1982 diagnostic criteria, diagnostic categories

were given as a range from clinical definite MS, laboratory-supported definite MS, clinically probable MS to laboratory-supported probable MS.¹⁰

In July 2000, the International Panel on MS Diagnosis revised the diagnostic criteria for MS. The objective demonstration of dissemination of lesions in both time and space was retained as necessary for diagnosis. MRI is integrated as part of the diagnostic work-up. In addition, abnormal results from CSF analysis can provide supportive evidence of the immunological and inflammatory processes which may be helpful when imaging criteria lack specificity as in older patients or when the clinical presentation is atypical. Nevertheless, CSF analysis cannot provide information about dissemination of lesion in space or time.¹¹ The outcome of this new diagnostic evaluation is either MS, possible MS or not MS. This criteria is intended for use by the practicing physicians

In previous studies, CSF profiles in western MS patients usually show normal cell count. If lymphocytic pleocytosis occur, it should be less than 50/mm.^{3,11} In Asian, CSF profiles are different from MS patients in western countries and also different among each form of MS (classic and

opticospinal type). CSF pleocytosis of more than 50 cells/ μ L was reported in 10% of Japanese MS patients whereas pronounced pleocytosis in the CSF is rare in MS patients in western countries.¹² Cell count and total protein concentration in the CSF were significantly higher in opticospinal than in classic MS.^{12,13} Moreover, the frequency of substantial CSF pleocytosis (>50 cell/ μ L) was much higher in opticospinal than classic MS. Moreover, neutrophilic pleocytosis in the CSF was observed in a few cases.⁶

Oligoclonal bands (OB) are reported in more than 90% of MS patients in western countries.¹⁴ In 2002 Nakashima et al reported that the CSF oligoclonal bands are less frequently observed in Japanese MS patients compared with Caucasian (55% Vs 90%). In the OB negative group, 50% of patients had the opticospinal form of MS.¹³

The objective of our study is to evaluate the CSF profiles of MS patients in Thailand, particularly the frequency of oligoclonal bands compared with MS patients in western countries.

METHODS

In this retrospective study, we collected demographic data as well as CSF profiles from 76 patients who attended MS Clinic, Division of Neurology, Department of Medicine, Siriraj Hospital, Mahidol University between January 1997 and June 2004. Most participants had given written informed consent. Patients were diagnosed using clinical data combined with paraclinical evidence such as MR, CSF analyses and evoked response studies according to the Poser's criteria.¹⁰ We reviewed clinical features such as gender, age at onset, duration of the disease, duration between onset of acute attack and results of lumbar puncture and CSF profiles including oligoclonal bands.

We obtained data of CSF samples from 64 patients. In 8 patients lumbar puncture (LP) was not consented during their admissions at Siriraj Hospital from acute relapses. Data from CSF analysis at the first LP of each patient were recorded. CSF data from patients with Devic's syndrome was analyzed separately.

CSF samples were sent to our neurologic laboratory for analysis comprised of appearance, cell count and differential count, protein content, sugar content (compared with blood sugar at the same time) and CSF oligoclonal bands in the CSF and in the serum for comparison.

Laboratory technique used for oligoclonal bands testing was isoelectric focusing (IEF)

electrophoresis. Interpretation of oligoclonal bands was divided into 2 main patterns: "Positive" in cases that oligoclonal bands were detected in the CSF but not in matched serum or two additional bands were seen in CSF compared to matched serum. "Negative" in other pattern rather than the previous. Data regarding oligoclonal bands in 17 patients were not available.

Other CSF serological tests in CSF would be performed if clinical diagnosis was doubtful and required other specific CSF analysis. For example Grams' stain, AFB, PCR for TB, India ink, cryptococcal Ag as well as VDRL if other diseases involving the CNS could not be excluded.

Statistical methods

Student t-test was used to compare quantitative data. Chi-square test and Fisher-exact test were used in comparing qualitative data. The following results were presented descriptively: gender, age at onset, duration of disease, duration between the relapse date and the LP date and finally the CSF profiles which mainly composed of WBC and differential cell count, protein content, sugar content which compared with simultaneous blood sugar samples and oligoclonal bands. SPSS version 11.5 software was used to analyze the data.

RESULTS

Demographic data

Initially, we had 76 patients whom were diagnosed of having MS. Thereafter, 4 patients were excluded due to subsequent diagnosis of other disease. The remaining 72 patients consisted of 62 female patients (86.1%), 10 male patients (13.9%) and the female to male gender ratio was 6.2:1. The mean age at onset was 33.11 ± 11.76 years (range 16 to 64 years). The mean duration of disease was 6.62 ± 5.9 years (range 0.5 to 32 years). None of the patients had a family history of MS.

Multiple sclerosis type

Among the MS patients in our clinic, 52 patients (72.2%) had a relapsing-remitting course (RR-MS), 3 patients (4.2%) had a progressive relapsing course (PR-MS), 1 patient (1.4%) had a secondary progressive course (SP-MS), none of our patients had a primary progressive course (PP-MS). 11 patients (15.3%) had possible MS and the remaining 5 patients were diagnosed as Devic's syndrome. If we classified our MS patients as

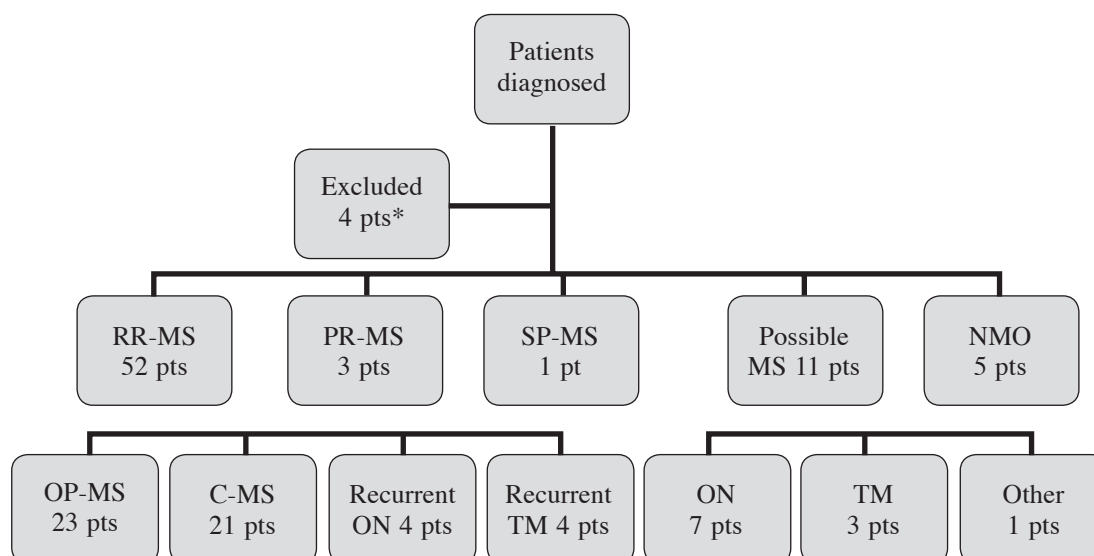


Figure 1. Patient ascertainment and classification

RR-MS: relapsing remitting MS, PR-MS: progressive relapsing MS, SP-MS: secondary progressive MS, NMO: neuromyelitis optica or Devic's syndrome, OP-MS: opticospinal MS, C-MS: classic MS, ON: optic neuritis, TM: transverse myelitis

*4 patients were excluded due to subsequent diagnosis of other disease.

opticospinal group and classic group, 23 patients (44.2%) would be opticospinal and 21 patients (40.4%) classic groups. The other remaining 8 patients composed of recurrent optic neuritis (4 patients, 7.7%) and recurrent transverse myelitis (4 patients, 7.7%). In Devic's syndrome (5 patients), there were 4 female patients and 1 male patient (Figure 1). The mean age at onset of this group was 38 ± 5.3 years.

CSF pattern

The mean duration between the onset of symptom and the time performing LP was 10 ± 9.88 days (range 1-60 days). The mean CSF WBC was 17.9 ± 32 cells/ μ L (range 0-200). This was further divided into 3 groups: a range of 0-5, 6-49, or > 50 cells/ μ L. In first group with WBC 0-5 cells/ μ L there were 20 patients (46.5%); in the second group with WBC 6-49 cells/ μ L, there were 22 patients (51.2%); in the third group with WBC > 50 cells/ μ L, there were 1 patient (2.3 %). The differential CSF WBC in MS patient group was predominantly mononuclear cells (38 of 41 patients). Only 3 patients showed predominantly polymorphonuclear cells. The mean CSF protein content in all MS patients group was 41.8 ± 39 mg/dL and CSF protein content of less than 45 mg/dL were found in approximately 80% of this patients group, only 1 patient had CSF protein of more than 100 mg/dL. Approximately two-thirds

of all MS patients group had a CSF to serum ratio of more than 0.5. Oligoclonal bands were positive in 27.3% in definite MS patients group.

When the MS patients were divided into classic and opticospinal forms, normal CSF WBC less than 5 cells/ μ L were present in approximately 60% in the opticospinal form MS versus approximately 40% in the classic form. Both classic form and opticospinal form showed a mononuclear cell predominant in the differential CSF WBC count. Oligoclonal bands was seen in 28% of the classical and 25% of the opticospinal patients respectively.

In the possible MS group which consisted of optic neuritis and transverse myelitis, mean CSF WBC were 5 ± 4.8 cells/ μ L and 36.5 ± 23 cells/ μ L respectively. The CSF WBC count of less than 5 cells/ μ L were found in 60% of the optic neuritis group, whereas none of the transverse myelitis group had less than 5 cells/ μ L. The protein concentration in transverse myelitis group was higher than the optic neuritis group, which were 75.5 ± 30.4 g/dL and 47.0 ± 51.3 g/dL respectively. All 6 patients in the optic neuritis group had no oligoclonal bands compared with 33% (1 in 3 patients) of the transverse myelitis group had positive oligoclonal bands.

In all 8 patients with recurrent optic neuritis, their CSF WBC count was less than 5 cells/ μ L, whereas none of the recurrent transverse myelitis group had CSF WBC count less than 5 cells/ μ L.

Table 1: Age at onset stratified by diagnosis

Diagnosis	RR-MS	PR-MS	SP-MS	PP-MS	Possible MS	Devic's syndrome	Total
Age at onset (yrs)							
<20	4	0	0	0	1	0	5
20-29	23	1	0	0	4	2	30
30-39	11	2	1	0	2	2	18
40-49	9	0	0	0	2	1	12
50-59	4	0	0	0	2	0	6
≥60	1	0	0	0	0	0	1
Total	52	3	1	0	11	5	72

RR-MS: relapsing remitting MS, PR-MS: progressive relapsing MS, SP-MS: secondary progressive MS, PP-MS: primary progressive MS

Table 2. CSF pattern in Thai MS patients

CSF- WBC	
Mean CSF WBC	17.9 ± 32 cells/μL
Range of 0-5 cells/μL	20 of 43 patients (46.5%)
6-49 cells/μL	22 of 43 patients (51.2%)
> 50 cells/μL	1 of 43 patients (2.3%)
The differential CSF WBC	
Mononuclear cell predominant	38 of 41 patients (92.7%)
Polymorphonuclear cells predominant	3 of 41 patients (7.3%)
Mean CSF protein	41.8±39 mg/dL
CSF to serum protein ratio > 0.5	63.3%
Presence of oligoclonal bands	27.3%

Table 3. Presentation of oligoclonal bands in each subtypes of MS patients

Subtype of MS	Oligoclonal band positive	Oligoclonal band negative
Opticospinal form	25%	75%
Classic form	27.8%	72.2%
Optic neuritis	0%	100%
Transverse myelitis	33.3%	66.7%
Recurrent optic neuritis	50%	50%
Recurrent transverse myelitis	25%	75%
Devic's syndrome	0%	100%

Oligoclonal bands were negative in one-half in the recurrent optic neuritis and 75% in the recurrent transverse myelitis.

In 5 patients with a distinct entity of Devic's syndrome, all 15 CSF samples had a mean CSF WBC count of 18.1 ± 11.86 cells/ μ L and CSF WBC count more than 50 cells/ μ L was found in 4 of 13 samples. Mostly, the differential WBC in CSF (7 of 9 samples) had predominantly mononuclear cells; polymorphonuclear cells > 5 cells/ μ L were found in 2 of 9 samples. In Devic's syndrome, CSF protein higher than 45 mg/dL was found in 5 of 12 samples. All patients in Devic's syndrome group had negative oligoclonal bands.

DISCUSSION

In several previous studies from Asians, it had been demonstrated that MS in Caucasian populations have many differences from MS in Asian populations,⁶ which are characterized by a lower prevalence, a rapid progression, no familial occurrence, more frequent attacks, severe involvement of visual system at onset as well as during the entire clinical course and more common occurrences of optic and spinal involvement.¹⁶⁻²⁵

Relapsing-remitting MS (RR-MS) can be clinically classified into two groups; classic or Western type of MS and opticospinal or Asian type of MS.¹³ Classic MS is characterized by multiple lesions in the CNS, including cerebral hemispheres, brainstem or cerebellum. Whereas, opticospinal MS is characterized by main lesions confined to only the optic nerve and the spinal cord with no evidence of lesion in the cerebrum or cerebellum except few lesions in the brainstem. Moreover, frequent relapses, severe disability, long lesion extending over many vertebral body segment, CSF pleocytosis and an absence of oligoclonal bands in the CSF are other features commonly found in Asian.⁶ Opticospinal MS seems to be the most common form in areas where there is a low prevalence of MS and is associated with a high proportion of female patients.

Opticospinal MS had a significantly higher age at onset, significantly higher Extended Disability Status Scale (EDSS) score, although the duration of the disease did not differ significantly.^{12,13} CSF analysis in previous studies found that cell count and total protein concentrations in the CSF were significantly higher in opticospinal than classic MS.^{12,13} The frequency of substantial CSF pleocytosis (>50 cells/ μ L) was much higher in the opticospinal group than in classic MS

group.¹² Neutrophilic pleocytosis in the CSF can be observed in a few cases.²⁵

Our study confirmed findings about the CSF WBC count and differential count in previous studies. Approximately 46% of our MS patients had CSF WBC count less than 50 cells/ μ L. Only 1 patient (2.3%) had CSF WBC count more than 50 cells/ μ L. Most CSF WBC type was predominantly mononuclear cell (38 in 41 patients or 93%) whereas neutrophilic pleocytosis was observed in few cases (3 in 41 patients or 7%). Protein concentration was normal (<45 mg/dl) in 80% of patients. Approximately two-thirds of the patients had a CSF to serum glucose ratio more than 0.5. Nevertheless, opticospinal form in our study showed a difference in CSF profile compared with previous studies in Asian. Among the opticospinal form our study, 60% of them had normal CSF WBC count less than 50 cells/ μ L and none of them had CSF white cell more than 50 cells/ μ L. However, both opticospinal form and classic form still showed a mononuclear cell predominant in differential CSF WBC count.

The possible MS patient group was subclassified into optic neuritis and transverse myelitis group. Interestingly, the latter showed higher CSF WBC count and higher protein concentration; 36.5 ± 30.4 cells/ μ L versus 5 ± 4.8 cells/ μ L and 75.5 ± 30.4 mg/dl versus 47.0 ± 51.3 mg/dl, in the optic neuritis and transverse myelitis group, respectively.

Regarding the oligoclonal bands, over 90% of MS patients is positive for oligoclonal band in western countries. In contrast, the frequency of oligoclonal bands in Asian countries is much lower when compared with western MS patients. In previous studies among Asian MS patients, positive oligoclonal bands were found in only 30-60% of MS patients.^{12,26} This discrepancy may be a result of differences in genetic backgrounds, especially with respect to the immune responses.²⁶

Moreover, Nakashima *et al* reported a significantly lower frequency of oligoclonal bands in patients with opticospinal MS than in those with classic MS.¹⁵ In the oligoclonal band negative group, 50% of patients had opticospinal form, but only 4.5% of patients in oligoclonal bands positive group had opticospinal form.¹⁵

In our study, oligoclonal band positive patients group showed no difference from other Asian patients. In the oligoclonal band negative group, approximately 50% (12 in 25 patients) had opticospinal form which is similar the report by Nakashima. Anyhow, approximately 50%

(4 in 9 patients) of the OB positive group had opticospinal form, which is much more common than in Nakashima's study.¹⁵

In the possible MS group, none of the patients with optic neuritis showed oligoclonal bands in the initial CSF samples. However, oligoclonal band was positive in one-half of the patients in recurrent optic neuritis group.

Neuromyelitis optica (NMO) or Devic's syndrome has been classified as a distinct entity from prototypic multiple sclerosis despite most of the patients in this group had a relapsing–remitting course which satisfied the diagnostic criteria for multiple sclerosis.^{27,28} Devic's syndrome is characterized by bilateral optic neuritis and myelitis occurring in rapid succession.²⁹ The patients were mostly female (90%), older age at onset, may coexist with autoimmune diseases including SLE³⁰, Sjogren's syndrome.³¹ Clinical presentation of Devic's syndrome was usually severe.³² It affects the optic nerve and spinal cord and could result in respiratory failure (approximately 30%) if the lesion involved high cervical level of the spinal cord. The most specific finding for neuromyelitis optica is longitudinal extensive involvement with gadolinium-enhancing lesion in MRI spinal cord whereas those findings were very rare in MS. In contrast, MRI brain was usually normal or showed non-specific findings.³³⁻³⁵ CSF also distinguished Devic's syndrome from MS. In which CSF WBC count of more than 50 cells/ μ L or neutrophilic pleocytosis was commonly found in Devic's syndrome but rare in classic MS.^{36,37} Oligoclonal bands, present in CSF up to 90% of MS patients¹⁴ were uncommon in Devic's syndrome.^{33,34} The prognosis of relapsing Devic's syndrome is relatively poor compared with classic MS.

In our study, there were only 5 Devic's syndrome patients and a female preponderance among them. The mean age at onset was higher than the MS patient group; 38 \pm 5.3 years Vs 33.11 \pm 11.76 years, respectively. CSF WBC count of more than 50 cells/ μ L in each CSF sample was found in approximately 30% (4 in 13 samples). Only 2 in 9 samples revealed neutrophilic pleocytosis and polymorphnuclear cells >5 cells/ μ L. And as in previous studies, no case of Devic's syndrome group showed positive oligoclonal bands.

In conclusion, Thai MS patients had many different features from western countries concerning the prevalence, patient characteristics, clinical presentation, neuroimaging findings and CSF profiles. There was lower incidence of

oligoclonal bands as compared with patients in western countries. In the oligoclonal band positive group, the opticospinal form was much more common than in previous studies from Japan.

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