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A retrospective study of multiple sclerosis in Thailand

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Abstract

Objectives: To determine the prevalence of Thai demyelinating diseases regarding demographic data, symptoms and signs, associated diseases, disease progression, cerebrospinal fluid analysis and imaging findings. *Methods:* A multicenter retrospective study of 107 MS patients attending the Neurological Centers in Thailand during June and December 2004 was performed. Each had an initial diagnosis of demyelinating diseases. *Results:* From 107 patients, there were 78.5% female and 21.5% male with the female: male ratio of 3.7:1. The age at onset was 32.7±11.5 years. The mean disease duration was 3.8±5.1 years and the mean number of relapses was 4.6±4.4 with annual relapse rate of 1.5±1.3 times. None reported a family history of MS. Recurrent optico-spinal form was 27.1% followed by 17.8% of spinal form and 15% of western form of MS. The most common presenting symptom was visual impairment (51.4%). Only 24.1% demonstrated oligoclonal bands in CSF. The median score of EDSS at their latest visits was 3.0 with mean score of 3.8±3.0.
Conclusions: MS in Thailand is different from Western countries. There were no occurrence of MS in families, higher incidence of visual impairment at onset, more common recurrent optico-spinal form and lower incidence of oligoclonal bands in the CSF.

INTRODUCTION

Multiple sclerosis (MS) is the most common demyelinating diseases and it is a chronic, inflammatory, autoimmune demyelinating disease of the central nervous system. MS is characterized by plaques of demyelination and remyelination, leaving scars on the brain and spinal cord.[1-3] Since 1860s, after Professor Jean Martin Charcot first described and named the disease 'sclerose en plaques". We now know more about the disease.[1-16]

Manifestations of MS, however, seem to be different among Eastern and Western countries in many aspects such as the prevalence, MS types, clinical presentations, magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) analyses.[9,17-32] Moreover, an updated diagnostic criteria proposed by McDonald incorporated MRI criteria for diagnosis, which may not be practical in some regions in Asian countries because of the inaccessibility to MRI.[33-34]

Thailand has no prior study for the incidence of demyelinating disease. Estimated incidence of MS in Thailand was thought to be the same rate as in other Asian countries, which is around 1-2/100,000 population. The objective of our study is to determine the prevalence of the demyelinating diseases in particular MS, as well as to describe the demographic data, symptoms and signs, CSF findings, initial data of the imaging in Thai patients.

METHODS

In this retrospective study, data were collected

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from 8 centers; 5 from Bangkok, 2 from the northern and one from the southern part of Thailand. Each site was a tertiary care hospital responsible for recruiting MS patients up to 25-100 kilometers away from the center.

One hundred and thirty patients with the initial diagnosis of demyelinating disease were recruited within 6 months during 1June 2004 and 31 December 2004. Baseline data recorded were: history, presenting symptoms and signs, investigations including immune profiles, initial imaging studies, visual evoked potentials (VEPs), CSF analysis and oligoclonal bands (OCB). All patients met the current international criteria for a diagnosis of MS which includes "no better explanation". Diagnosis of MS was made according to the Poser criteria and the 2005 McDonald criteria.[34,35] Acute transverse myelitis was defined as an acute illness with onset of less than 4 weeks, with both sensory and motor involvement, motor involvement being severe and bilateral.[36-37] Recurrent optico-spinal form of MS was defined among patients whose clinical relapses were limited to optic nerve and spinal cord. Western form of MS was defined among patients whose neurological deficits involved beyond optic nerve and spinal cord.[34] Because of the inaccessibility of the NMO-IgG antibody, in this study, Devic's syndrome was based on the 1999 Wingerchuk criteria.[38]

Matched CSF and plasma samples were analyzed using isoelectric focusing (IEF) and IgG specific immunofixation to test for the presence of intrathecal specific OCB and the results compared directly with serum. Positive OCB was defined as ≥2 bands present in CSF but absent in the corresponding serum.

The ethic committee of each center approved the study and every patient gave written informed consent.

Statistical analysis

Results were analysed by using Student's t-test for quantitative data; Chi-square tests and Fisher's exact test for qualitative data. Kruskal-Wallis test was used to find a correlation between MS-type and Extended Disability Status Score (EDSS).[39] Mann-Whitney-U test was used to analyse a relationship between the outcome and the location of an attack. Spearman correlation was used to analyse an association between the number of attacks and outcome. SPSS version 14.0 software was used to perform the statistical analysis.

RESULTS

Demographic data:

From 130 patients initially diagnosis with demyelinating disease, we excluded those who had positive VDRL (6 patients), anti-HIV (4 patients) or FTA-ABS (6 patients). Also 17 patients who did not have brain MRI for brain dysfunction and who had not have cervical and thoracic spine MRI for spinal syndrome were not included. The remaining 111 patients with demyelinating disease were defined as having MS in 107 patients and NMO in 4 patients were included. In this paper we only analysed the patients who had multiple sclerosis and clinically isolated syndrome or early MS.

Of the 107 MS patients, there were 84 female (78.5%) and 23 male (21.5%) with the female:male sex ratio of 3.7:1. The age at onset was 32.7±11.5 years (range 5-60). Most of the patients (53.3%) had their first presenting symptoms at age 20-40 years (Table1). None reported having family history of MS. The average length of follow-up was 10.2 months. The mean disease duration was 3.8±5.1 years (range 0-27), the mean number of relapses was 4.6±4.4 times (range 1-25) with the mean annual relapse rate of 1.5±1.3 times (range 0.1-7).

Clinical courses and MS types

Regarding the clinical course of MS, there were 64 (59.8%) relapsing-remitting (RR-MS) patients, 6 (5.6%) secondary progressive (SP-MS) patients,

Table 1: Age at onset and sex

Parameter	Age range (years)				Total
	<20	20-40	>40-60	>60	
Female	4	46	33	1	84
Male	4	13	6	0	23
Total	8	59	39	1	107

Table 2: Clinical courses

Clinical course	Frequency	Percent
PP-MS	1	0.9
SP-MS	6	5.6
RR-MS	64	59.8
PR-MS	3	2.8
Early MS presentation	33	30.8
Total	107	100.0

PP-MS: Primary progressive MS
SP-MS: Secondary progressive MS
RR-MS: Relapsing remitting MS
PR-MS: Progressive relapsing MS

3 (2.8%) progressive relapsing (PR-MS) patients and only 1 (0.9%) primary progressive (PP-MS) patient, respectively (Table 2). Furthermore, 33 patients (30.8%) had clinical isolated syndrome, described as following; 4 patients (3.7%) suffered from myelitis, 3 patients (2.8 %) had single attack of optic neuritis, 13 patients (12.1%) had recurrent myelitis, 10 patients (9.3%) had recurrent optic neuritis, 1 patient (0.9) had recurrent brain attacks, 1 patients (0.9 %) had recurrent brainstem attacks and 1 patient (0.9%) had recurrent cerebellar symptoms.

Recurrent optico-spinal form of MS was found in 29 patients (27.1%) among all MS types followed by 19 patients (17.8%) of spinal form and 16 patients (15%) of classic (western) form of MS.

If the patients were classified according to

Table 3 Diagnosis according to Poser criteria

Poser criteria	Frequency	Percent
CDMS A1	65	60.7
CDMS A2	4	3.7
LSDMS B1	2	1.9
LSDMS B3	2	1.9
CPMS C1	21	19.6
CPMS C2	3	2.8
LSPMS D1	1	0.9
Possible MS	9	8.4
Total	107	100.0

CDMSA1: Clinically definite MS having 2 attacks and clinical evidence of 2 separate lesions
CDMSA2: Clinical definite MS with 2 attacks, clinical evidence of one and paraclinical evidence of another separate lesion
LSDMSB1: Laboratory supported definite MS with 2 attacks, and either clinical or paraclinical evidence of 1 lesion, and cerebrospinal fluid (CSF) immunological abnormalities
LSDMSB3: Laboratory supported definite MS with 1 attack, clinical evidence of 1 and paraclinical evidence of another seperate lesion, and cerebrospinal fluid (CSF) abnormalities
CPMSC1: Clinically probable MS with 2 attacks and clinical evidence of 1 lesion
CPMSC2: Clinically probable MS with 1 attack and clinical evidence of 2 separate lesions
LSPMSD1: Laboratory supported probable MS with 2 attacks and CSF abnormalities

Schumacher criteria, approximately 60-85% satisfied for each separated criterion. Interestingly, only 47 patients (43.9%) fulfilled all of the 6 criteria. Using Poser criteria, sixty-five patients (60.7%) were categorized as a clinically definite MS having 2 attacks and clinical evidence of 2 separate lesions (CDMSA1), 4 patients (3.7%) had clinical definite MS with 2 attacks, clinical evidence of one and paraclinical evidence of another separate lesion (CDMSA2), 4 patients (3.7%) had laboratory supported definite MS (LSDMSB1+LSDMSB3), 24 patients (22.4%) had clinically probable MS (CPMSC1+CPMSC2), only 1 patient (0.9%) had laboratory supported probable MS (LSPMSD1) and 9 patients had possible MS (8.4%) (Table 3).

When classified by the McDonald 2005 criteria, most patients (82 patients; 76.6%) had diagnosis with MS and 25 patients (23.4%) had clinical isolated syndrome (CIS) (Table 4).

Therefore 74 patients (69.2%) were categorized in definite MS based on Poser criteria. However when using McDonald 2005 criteria, 82 patients (76.6%); additional 7.4%, would satisfied MS diagnosis.

Symptoms and signs

Among the first attacks, the most common location of involvement was visual pathway, predominantly the optic nerve (51.4%), which was persistent in any age group; followed by spinal cord, brainstem, cerebrum, cerebellum and optic-spinal by 26.2%, 21.5%, 8.4%, 7.5% and 2.8%; respectively (Table 5). There were 17.8% had multifocal attacks at first presentation. Corresponding to the locations involved, the common initial presentations were visual impairment (50.5%), weakness predominantly paraparesis (39.3%), sensory loss (33.6%), gait ataxia (9.3%), diplopia (8.4%), painful tonic spasm (6.6%), trigeminal neuralgia 1.9% and dysarthria (0.9%), respectively (Table 6). Except for painful tonic spasm, paroxysmal symptoms and others such as trigeminal neuralgia, abnormal sensation described as burning sensation in the feet were seldom seen as the first presenting symptoms (6.5%, 1.9%; respectively). Among those with RR-MS, the most common presentation was still visual impairment.

Investigations

Ninety-five patients (88.7%) underwent lumbar puncture. All had MRI brain and at least cervical spinal cord. Visual evoked potential (VEPs) was performed in 50 patients (46.7%). Thirty-seven patients (34.6 %) received all three investigations.

Table 4: Diagnosis according to McDonald criteria

Criteria	Frequency	Percent
≥ 2 attacks, objective evidence of ≥ 2 lesions	65	60.7
≥ 2 attacks, objective evidence of 1 lesion Plus MRI for dissemination in time[1]	11	10.3
1 attack, objective clinical evidence of 2 lesions plus MRI for dissemination in space[2]	3	2.8
1 attack, objective clinical of 1 lesion Plus MRI for dissemination in time[1] and space[2]	2	1.9
Progressive neurological deficit suggestive of MS	1	0.9
Clinical isolated syndrome	25	23.4
Total	107	100.0

[1] Dissemination in time: MRI evidence of a Gs-enhancing lesion detected in scan at least 3 months after onset of initial clinical event at a site different from initial event or a new T2 lesion detected in a scan done at any time compared to a reference scan done at least 30 days after initial clinical event.

[2] Dissemination in space: MRI compatible with 3 out of 4 of the following; 1Gd-enhancing brain or cord lesion or 9 T2 hyperintense brain and/or cord lesions if there is no Gd-enhancing lesion, 1 or more infratentorial or cord lesions, 1 or more juxtacortical lesions, 3 or more periventricular lesions.

Table 5: Location of the first attacks

Location	Number of patients	Percentage
Optic pathway	55	51.4
Brain	8	7.5
Brainstem	23	21.5
Cerebellum	9	8.4
Spinal cord	28	26.2
Optic-spinal cord	3	2.8

* There were 17.8% had multifocal attacks at first presentation

CSF analysis

Eighty-two patients (76.6%) had available CSF data. Analysis for CSF-OCB was performed in 58 patients (70.7%). Only 14 of 58 patients (24.1%) demonstrated positive OCB detected only in the CSF but not in the serum. There were 53.7% with the CSF-WBC less or equal 5 cell/mm^3, 25.6% with CSF-WBC between 6-20 cell/mm^3 and 20.7% with CSF-WBC more than 20 cell/mm^3. The mean CSF protein was 43.4±37.1 mg/dl, and the mean CSF sugar from was 63.2±21.3 mg/dl (Table 7). No correlation was found between cell count, level of CSF protein, positive OCB, location of the attacks or any symptoms. Positive result of CSF-OCB could support a diagnosis for 4 LSDMS and 1 LSPMS.

Other blood tests

Immune profiles including ESR, LE, ANA profiles, Anti-DNA, FTA-ABS, Anti-HIV and B12 level were performed for all patients. No one in the report had clinical suspected Sjogren's disease. There were ANA positive in 22 patients (20.6%), most at low to moderate titer; 1:40-1:160, of speckle pattern.

Outcome

The Kurtzke's Expanded Disability Status Score (EDSS) was available in 23 patients (21.5%). The mean score was 3.8±3.0 (median 3); ranging from 0-9 with a score of 3 or less in 9 patients (39.1%), a score of more than 3 but less than 6 in 7 patients (30.4%), and a score more than 6 in 7 patients (30.4%).

EDSS was not shown to have any correlation with the location of attacks, symptoms nor number of attacks.

Table 6: Initial clinical presentations

Symptoms	Number of patients	Percentage
Blurred vision	54	50.5
Diplopia	9	8.4
Weakness	42	39.3
Stiffness	1	0.9
Abnormal sensation	3	2.8
Sensory loss	36	33.6
Ataxia	10	9.3
Dysarthria	1	0.9
Tonic spasm	7	6.6
Trigeminal neuralgia	2	1.9

Table 7: Analysis of cerebrospinal fluid

Parameters	Number of samples with available result (percentage)
Cell count (cell/HFP)	82
0-5 cell	44 (53.7)
6-20	21 (25.6)
21-50	10 (12.2)
51-100	5 (6.1)
>100	2 (2.4)
Differential count (cell/HPF)	
Lymphocyte	68
100	41 (60.3)
>60	49 (72.1)
Neutrophil	61
<5	54 (88.5)
5-50	2 (3.3)
>50	5 (8.2)
Protein (mg/dl)	82
≤45	57 (69.5)
>45	25 (30.5)
Glucose (ratio of CSF /blood sugar)	50
<1/3	2 (4)
>1/3-2/3	34 (68)
>2/3	14 (28)

DISCUSSION

This study adds to the established evidence that there are many differences between Eastern and Western MS, corresponding to the earlier report from Thailand.[40] Data from this study showed differences in several aspects regarding a lower prevalence, a rare occurrence of family history, slightly higher female to male sex ratio, higher incidence of visual impairment at the onset of the illness, high frequency of paroxysmal tonic spasm, less frequent involvement of the cerebellum, rare presentation of PP-MS, more common optico-spinal recurrent form of clinical manifestation and lower incidence of positive CSF-OCB.

This is the first multicenter study of MS patients in Thailand, the earlier case series reported that Thailand should have low prevalence of MS.[23] However, real prevalence has not been evaluated in Thailand. The prevalence of MS in Asia varies depending on locations to be very low, low and medium, in the south, east and west Asian populations, respectively.[23-25,31,41] This apparent increase could simply reflect an increase in disease awareness as well as technological improvements, particularly applying MRI as a diagnostic tool, however, genuine increase the occurrence of MS is still possible. It is important to verify similar trends in other Asian populations.

In this study, the female to male sex ratio was 3.7:1 which slightly higher than the ratio of 2-3:1 among Western populations. As compared to the previous report which found 6.2:1[40] we have no clear explanation for that. But the preponderance of female patients was still higher than that in western country. Similar to our study, many Asian countries reported higher female to male ratio,

varying from 2:1 to 5:1.[6-10]

The proportion of MS patients with main lesions confined to the optic nerve and the spinal cord is much higher among our patients. Unlike in western countries, cerebellar involvement was relatively uncommon in our study; therefore the clinical manifestation of optico-spinal form was far more common than the classic form of MS (optic-brainstem/cerebellum-spinal cord). In Japanese study, however, the proportion of patients diagnosed clinically as classic type MS is increasing.[22-23] Another consistent difference is the rarity of chronic progressive MS in our patients. Only one patient with primary progressive MS was found in our series. Moreover, secondary progressive MS comprised only 5.6% of our cases, compared with 40-70% in Caucasian populations.[9] Also in the present study, there was no report of familial MS. Whether the environmental, immunological and genetic factors are responsible for the differences are immensely important and needed to be clarified.[5-8,42-44]

Optic neuritis in Asian patients are different from western population.[45] In our study, visual impairment was the most common initial presentation. Simultaneous or almost simultaneous optic neuritis in both eyes were more common compared to the Optic Neuritis Treatment Trial from North America with almost all of the patients in the study presented with unilateral optic neuritis.[24-25,45]

There were reports of a higher incidence of tonic spasm in Asian MS patients.[17-18,30] This may be explained by the common involvement of the spinal cord. Similarly, we observed that 6.5% of our patients had paroxysmal tonic spasm, even in patients who did not have spinal cord involvement. This finding is poorly understood; and no clear explanation for the mechanism could be offered.

Part of our study will be presented elsewhere which confirmed some distinct characteristics of MRI findings in Asian MS.[46] Chawalparit *et al* demonstrated the preponderance of spinal cord involvement, particularly the cervical cord.[46] Moreover a lesion involving more than 2 vertebral body segments which is not characteristics for western MS was commonly found. Furthermore, swelling and atrophy of the involved spinal cord segment were also more common.[30,33,44,47-48,50] Moreover, typical MRI brain lesion compatible to Barkhof 's criteria for diagnosis of MS were found in a smaller percentage rendering this test relative insensitive. Application of MRI criteria proposed in McDonald's diagnostic criteria may need to be evaluated among Asian countries.[27,33,47]

Oligoclonal bands were positive in low frequency; being only 24.1% compared with 80-90% in western countries.[25,32] This low prevalence was similar among other Asian countries which should not be interpreted as technical errors from the laboratory processes. Same as in MRI, this investigation seemed to offer little help in diagnosis of MS in Thai patients particularly in questionable patients presenting with features not typical for MS.

We recognize that application of MRI and CSF oligoclonal bands in the diagnostic criteria for MS may not be practical in Thai MS patients.[21,26,30,32] However positive results might help in problematic cases.

Very few studies have explored the natural course of progressive disability in Asian MS patients or compared it with natural course of the disease in western patients among different MS subtypes.[4,10-12] A major problem in our study was the high dropout rate and the inaccessibility public transportation.

Focusing on the effects of different diagnostic criteria benefit in our patients, we found that the McDonald 2005 criteria which incorporated MRI findings increased the sensitivity for early diagnosis of MS from 69.2% based on Poser criteria to 76.6% using McDonald criteria. In contrast, Schumacher criteria had lower power to detect MS compared with the Poser or the McDonald criteria. However, as East Asian patients have fewer brain MRI lesions, and a smaller percentage have positive CSF-OCB compared with the Western MS, the application of McDonald criteria in Asian population may not be suitable. A more reliable diagnostic criteria based on information from this regions would be necessary.

There are several limitations in our study. Firstly, we have a much smaller number of patients compared to the western population.The definition of Devic's syndrome from previous publications differed. Most of them included patients with optic neuropathy and myelopathy, either as a monophasic disease or part of a multiphasic illness; and the myelopathy may or may not be severe.[49-50] In Asian literatures, Devic's syndrome has been commonly defined as a monophasic illness with severe bilateral optic neuritis and transverse myelitis occurring consecutively within several weeks.[29,38] Those patients with multiphasic episodes may have been alternatively classified as having optic-spinal recurrent form of multiple sclerosis in the Asian literature. As optic-spinal

recurrent form is common among Asians, the recent trend to loosen up the definition for Devic's syndrome raises the question of whether recurrent optic-spinal involvement is a distinct disease entity from multiple sclerosis. This implication is important for the Asian neurologists in practice. The terminology and diagnostic criteria for non-classic types of MS, in particular optic-brainstem/cerebellum-spinal MS, also need unifying.

Application NMO-IgG, the most recent diagnostic tool in clinical practice needs to be studied. Although, a large scale study of the Asian population is needed, it would be quite difficult to accomplish due to the lower prevalence of MS. It is therefore important to find an alternative way to evaluate the usefulness of NMO serology in this region. Collaborative multicenter studies among Asian countries may be necessary.

In conclusion, MS in Thailand is different from western countries in the following regards: a lower prevalence, rarity of family history, higher female to male sex ratio, higher incidence of visual symptom at presentation, high frequency of paroxysmal tonic spasm, less cerebellum involvement, rare presentation of PP-MS, more common recurrent form of optico-spinal and lower incidence of positive CSF-OCB.

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