

A Retrospective Review of Patients with Clinically Definite Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an uncommon disease in Singapore. We retrospectively reviewed our experience from a large single medical institution to identify prominent clinical features and forms of this disease. Of the 21 patients entered into the study, 10 patients developed optic-spinal symptoms over the course of their illness. None of these patients with optic-spinal symptoms had Devic's disease. Unusual clinical manifestations included paroxysmal symptoms either at presentation or during the course of their illness in 3 patients. While cerebrospinal fluid oligoclonal bands were present in only 4 patients, the majority of patients had abnormal neurophysiology and neuroimaging studies. Due to the presence of autoimmune markers in a significant number of cases, we recommend that as part of the initial evaluation for MS, an underlying collagen vascular disorder should be excluded.

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Introduction

Genetic susceptibility and environmental factors influence the prevalence and clinical manifestations of multiple sclerosis (MS). Since MS is rare in Southeast Asia, descriptions of this disease particularly as it occurs in Singapore have been sparse.¹⁻³ Situated 137 km north of the equator, Singapore's population of 2.7 million is approximately 77.7% Chinese, 14.1% Malays, 7.1% Indians, and 1.1% from a variety of other races. Singapore General Hospital, this country's largest acute care tertiary hospital with a total bed capacity of 1660, has a 93-bed inpatient neurology ward. This study is an analysis of the clinical and paraclinical findings of those patients with MS who presented to this hospital.

Materials and Methods

All patients examined at the Singapore General Hospital between January 1993 and December 1996 carrying an International Classification of Diseases (ICD) diagnosis of either MS or Devic's disease was retrospectively reviewed. Criteria published by Poser et al and the Schumacher committee were used to identify those patients with clinically definite MS.^{4,5} These criteria include objective central nervous system (CNS) dysfunction, two or more sites of CNS involvement, predominantly white matter involvement, a relapsing-remitting or chronic progressive course of more than 6 months, age between 10 to 50 years at onset and no better explanation of symptoms. Devic's disease or neuromy-

elitis optica, a syndrome of acute spinal-optic demyelination of which MS is one of the causes, is defined as bilateral visual impairment and a transverse myelitis which develops either concomitantly or within several weeks of each other with or without subsequent improvement. Functional status was graded using the Kurtzke expanded disability status scale.⁶ The patients' disabilities were assessed at last follow-up which was at the time of the last clinic visit, last hospitalisation, or death.

A full set of laboratory investigations were performed whenever possible to aid the diagnosis of MS and exclude other diseases particularly connective tissue disorders. Investigations included full blood counts, erythrocyte sedimentation rate (ESR), electrolytes, liver function tests, anti-nuclear antibody (ANA), and Venereal Disease Research Laboratory (VDRL) serology. Cerebrospinal fluid (CSF) was obtained to determine cell counts and the presence of oligoclonal bands. Neuroimaging by computed tomography (CT) or magnetic resonance imaging (MRI) of either the brain or spinal cord, and evoked studies (visual, brainstem, or somatosensory) were part of the evaluation.

Results

Of the 69 patients who carried an ICD diagnosis of MS or Devic's disease, 26 were thought to have clinically definite MS. Sufficient data were not available on 5 patients. Twenty-one patients with MS were entered.

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Although the 43 remaining cases initially carried a diagnosis of MS, further evaluation eventually led to other diagnoses: isolated transverse myelitis (9), isolated optic neuritis (3), stroke (7), cervical stenosis and myelopathy (4), lumbar spondylosis (1), underlying malignancy with metastases (3), periodic paralysis (1), metachromatic leukodystrophy (1), progressive spastic paraparesis (1), myopathy (1), peripheral vascular disease with aortic thrombosis (1), peripheral neuropathy (1), anxiety or functional weakness (2), infection (1), collagen vascular disorder (2), epilepsy (1), miscellaneous illnesses (4).

Clinical Features

As outlined in Table I, the 21 patients comprised of 14 (66.7%) Chinese, 3 (14.3%) Indians, 2 (9.5%) Malays and 2 (9.5%) Eurasians. There were no instances of familial occurrence. There were 16 females and 5 males with a female to male ratio of 3.2:1. The median age of onset for males was 23 years with a range of 20 to 50 years and the median age of onset for females was 30 years with a range of 13 to 48 years. Using the Mann-Whitney U test the age difference was not significant for the two sexes with a *P* value of 0.1990. The majority of patients presented by the age of 30. Table II shows the age of onset for males and females in greater detail.

Neurological signs and symptoms are outlined in Table III. Optic neuritis (43%) was the most common initial clinical presentation followed by transverse myelitis (19%). Sensory symptoms characterised by paresthesias or numbness, motor weakness, diplopia, ataxia, and sphincteric dysfunction occurred much less frequently. The predominant clinical symptoms occurring during the course of illness (Table IV) included transverse myelitis (67%) and optic neuritis (48%). Patients also had weakness characterised by hemiparesis (43%) and sensory complaints of paresthesias or numbness (29%). Ataxia (29%), diplopia (10%), and sphincteric dysfunction in the absence of transverse myelitis

(24%) occurred less frequently. Ten patients (48%) had optic-spinal symptoms manifest by optic neuritis and transverse myelitis. However, since the visual impairment and spinal symptoms did not develop either concomitantly or within a few weeks of each other this combination cannot be correctly called Devic's syndrome. Only 1 of the 5 males in our series suffered from optic neuritis. None developed optic neuritis as part of their clinical signs during the course of illness. In contrast 50% of females presented with optic neuritis and 63% had either one or more episodes of optic neuritis during their clinical course.

Of particular interest, 3 of the 21 patients (14%) had paroxysmal symptoms either at the onset or during the course of their illness. These patients are worthy of a more detailed description. One of the patients was a 27-year-old Malay woman who presented with abrupt episodes of paresthesias ascending from her toes to her arms followed by an inability to move the left side of her body resulting in falls. These symptoms occurred without warning while she was ironing, typing, or walking only to resolve within minutes without either concomitant clouding of consciousness or neurological sequelae. A second patient was a 28-year-old Chinese woman who had a 1½-year history of episodes of left optic neuritis, vomiting, bowel and bladder dysfunction, bilateral feet numbness and unsteady gait. Subsequently, she developed bilateral carpopedal spasms lasting several minutes occurring in the setting of normal calcium levels

TABLE I: ETHNIC COMPOSITION

Race	Female	Male
Chinese	12	2
Indian	2	1
Malay	2	
Eurasian		2

TABLE II: AGE OF ONSET IN WOMEN AND MEN

Age of onset (years)	Female	Male
11 to 20	2	1
21 to 30	7	3
31 to 40	3	
41 to 50	4	1

TABLE III: INITIAL CLINICAL SIGNS AND SYMPTOMS

	Female	Male
Initial clinical symptoms		
Optic neuritis	8	1
Transverse myelitis	4	
Sensory disturbances	1	2
Motor weakness	2	
Diplopia	1	
Ataxia		1
Sphincteric dysfunction		1

TABLE IV: CLINICAL SIGNS AND SYMPTOMS DURING THE COURSE OF ILLNESS

	Female	Male
Clinical symptoms during the course of illness		
Optic neuritis	10	
Transverse myelitis	13	1
Sensory disturbances	3	3
Motor weakness	5	4
Diplopia	1	1
Ataxia	3	3
Sphincteric dysfunction	2	3

and normal electroencephalogram. Figure 1 illustrates these spasms which are remarkably symmetric. Although these spasms looked like tonic fits, no loss of consciousness was observed. With carbamazepine these spasms resolved. A third patient was a Eurasian man who initially presented at the age of 21 years with episodes of incontinence, first of the bladder then the bowel. Subsequently, over a period of 3 years he had episodes of left arm weakness lasting half an hour and unassociated episodes of transient visual blurring lasting a few minutes. In the absence of a concomitant increase in body temperature either due to a fever or a hot bath, Uhthoff's phenomenon was thought to be unlikely.

In addition we had another patient with both MS and a demyelinating polyneuropathy who warrants further discussion. She was a 57-year-old Chinese woman who at the age of 23 developed optic neuritis, first in the right eye then the left eye. At the age of 27 she suffered from transverse myelitis. Subsequently, she had episodes of leg weakness, dysarthria, and optic neuritis. Twenty-six years after her initial presentation, she developed increasing bilateral leg weakness and hyporeflexia which progressed to areflexia. Supporting evidence for MS included a MRI scan of the brain which showed extensive plaques and CSF was notable for the presence of oligoclonal bands. Nerve conduction studies performed to evaluate her paraparesis and areflexia showed a severe motor neuropathy with reduced conduction velocities and diminished amplitude consistent with a demyelinating neuropathy (Table V & Fig. 2).

All patients were treated with steroids (prednisolone, hydrocortisone, or adrenocorticotrophic hormone) with variable responses and 1 of the recipients of steroids received additional azathioprine. One patient is currently being treated with and several others are being considered for beta interferon.

Previously proposed standardised definitions for common clinical courses of patients with MS were used to

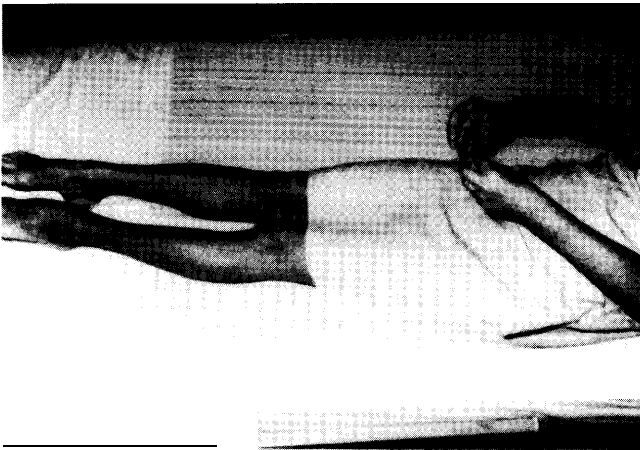


Fig. 1. Carpedal spasms in a patient with multiple sclerosis.

classify these patients.⁷ Adequate follow-up evaluations of at least 1 year were performed on 19 of the 21 patients. The mean follow-up period was 7.7 years with a range of 1 to 33 years. Of these 19 patients, the chronic progressive variety of this disease was found in 10 (53%) and the relapsing-remitting form in 9 (47%). One of the 10 patients who have been grouped in the chronic progressive category was periodically evaluated over 9 years. Initially he had a relapsing-remitting course. However, over the last 3 years he has suffered from secondary progression.

All patients were graded using the Kurtzke expanded disability status scale (EDSS)⁵ and the mean EDSS of the chronic progressive group was 8.3 with a range of 3.5 to 10 and of the relapsing-remitting group was 3.9 with a range of 1 to 10. Of the 21 patients, there were 2 mortalities in the chronic progressive group due to infections (urinary tract infection and pneumonia) that were the result of progressive disability. In the relapsing-remitting group

TABLE V: RIGHT PERONEAL NERVE CONDUCTION VELOCITY				
Segment number	Time (ms)	Distance (cm)	Conduction velocity (m/s)	
1-R	7.1	0.0	16.4	
2-1	20.4	33.5		
3-2		0.0		
Site number	Latency (ms)	Amplitude (mV)	Area ms X mV	Simulus (mA)
1	7.1	1.09	8.2	60.00
2	27.5	0.38	0.8	53.00



Fig. 2. Illustration of the rightperoneal nerve with a very slow motor conduction of 16.4 m/sec (normal conduction velocities 36.6 to 55.9 m/sec), reduced amplitude, and a splintered response.

the only mortality was the result of a fatal Stevens-Johnson reaction to carbamazepine that was administered for painful paresthesias.

CSF Findings

Twenty patients underwent a lumbar puncture. Cerebrospinal fluid results were available from 19 patients. Six had CSF pleocytosis ($>5/\text{mm}^3$) with a range of 6 to 16 cells/ mm^3 . Four had oligoclonal bands; of these 4, 2 also had CSF pleocytosis of 14 and 16 cells/ mm^3 , respectively.

MRI Findings

Of the 18 patients for whom MRI scan was performed, 18 patients had MRI scan of the brain and 14 had MRI scan of the spine. We considered a MRI abnormal if the T2 weighted images detected multifocal white matter lesions consistent with plaques.^{8,9} Since not all the patients received gadolinium, we were not able to adequately determine the nature of contrast enhancement in the setting of active or quiescent disease. Fifteen of the 18 MRI scans of the brain were abnormal and 10 of the 14 MRI scans of the spine were abnormal. Figure 3 shows MRI scans of the brain and spine with representative plaques. Fourteen patients had both MRI scan of the brain and spine. Of these 14 patients, 9 had abnormal MRI scans of both the brain and spine. Closer examination of these 9 revealed that 7 had a chronic progressive course. Two of the 3 patients with a normal MRI scan of the brain had a relapsing-remitting course.

Evoked Studies

Eighteen of the 20 visual evoked responses (90%), 10 of the 16 somatosensory responses (62.5%), and 5 of the 14 brainstem auditory responses (35.7%) were abnormal. These abnormalities were all characterised by prolonged latencies. Figure 4 compares a normal visual evoked study to a visual evoked study with a prolonged re-

sponse in the right eye.

Autoimmune Markers

Fifteen patients were tested for the presence of anti-nuclear antibodies (ANAs). Six (40%) had positive ANAs with serologies ranging from 1: 160 homogenous to 1:640 speckled. Of these 6, 3 had mildly elevated anti DS DNA (12.9 to 13.8 with our laboratory cut-off of 12.2). Four of the 6 cases with a positive ANA and all 3 with a mildly elevated anti DS DNA titres had a chronic progressive course.

Discussion

In performing this study we recognised both the clearly obvious disadvantages and deficits of a retrospective study and our small patient population. Nevertheless, our intention was to use this patient pool to identify trends and associations that are worthy of further study. Our main goal in this study was to draw attention to the



Fig. 3b.



Fig. 3. MRI scans of the brain (3a) and the spine (3b) with representative plaques delineated by arrowheads.

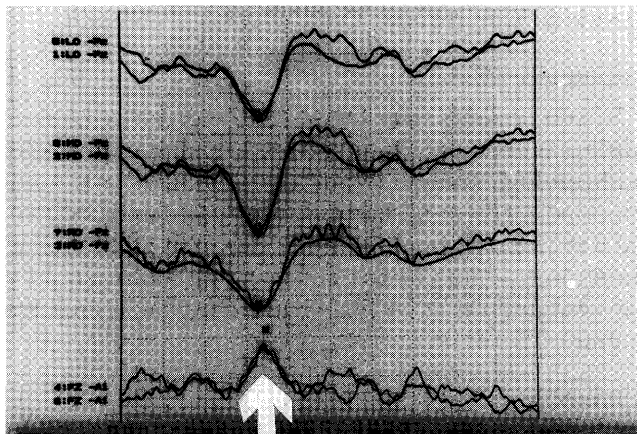


Fig. 4a.

Fig. 4. A normal visual evoked response (4a) had a P100 latency (arrow) of less than or equal to 100 ms. Note that the right visual evoked response in a patient with multiple sclerosis (4b) is poor and the P100 latency is prolonged at 146 ms.

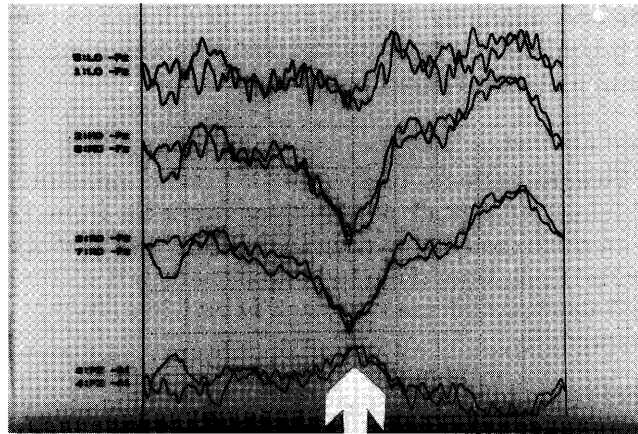


Fig. 4b.

fact that MS does exist in Singapore. Singapore, located close to the equator, has the potential to provide valuable data on the epidemiology of MS. The distribution of cases is a reflection of the percentages of each ethnic group. A larger series will allow us to determine if any particular ethnic group is prone to developing MS. The female preponderance and mean age of onset is similar to other studies.¹⁰⁻¹³

The predominant presenting symptom was optic neuritis. During the course of illness, transverse myelitis was the most frequent clinical manifestation. Optic-spinal symptoms were clearly the most common form of MS. Ataxia, a common symptom in Caucasian populations, only occurred in 29% of patients in our series. Paroxysmal symptoms were observed in 14% of our cases and were similar to other Oriental series, occurring with an increase in frequency in comparison to Caucasians.¹⁴⁻¹⁶ While a relationship between MS and either polyneuropathy or mononeuropathy multiplex has been described before, this combination is rare.^{17,18} In the case that we described the possibility of a coincidental occurrence is raised particularly since the time of onset between the signs and symptoms of MS and of demyelinating neuropathy is over two decades. Alternatively, this patient may be a compelling example of the common immunopathogenetic mechanisms that underlie both central and peripheral myelin dysfunction.¹⁹ In our series the majority of patients have a chronic progressive course. Nevertheless a significant percentage also have a relapsing-remitting course. The long-term survivors dispute a commonly held notion that MS as it exists in Southeast Asia has an inexorable progression.

In contrast to Caucasian populations which report an occurrence of 90%,²⁰ oligoclonal bands were observed in the cerebrospinal fluid in only 21% of our cases. Whether this is a function of test methodology or the disease process requires further study. Other laboratory meas-

ures highlight the use of MRI and evoked studies as aids in the diagnosis of MS.

Since collagen vascular disease can masquerade as MS, we emphasise the incidence of positive ANAs observed. The presence of ANAs has been reportedly associated with MS in 26.7% of the relapsing-remitting variant and 30.4% of the chronic progressive variant of MS. Most often the titres of ANAs in MS patients are less than or equal to 1:320.²¹ Other markers of collagen vascular diseases have also been observed. A recent report observes the presence of perinuclear antineutrophil cytoplasmic antibodies (pANCA) in 46.2% of 13 cases of MS whose clinical characteristics included an acute transverse myelopathy and severe optic neuropathy during the acute phase of their illness.²² The IgM antibody against cardiolipin has also been detected in elevated titres with a significantly higher frequency in patients with MS than in normal controls.²³ The incidence of these antibodies may imply that a broad spectrum of autoantibodies are produced in MS. Presumably, more antibodies related directly to MS pathogenesis have yet to be identified. While we reiterate that autoimmune markers only reflect systemic immune dysfunction and are not diagnostic of connective tissue disease, screening of these antibodies is an important component of the baseline evaluations performed.

Our study has identified and delineated some of the important clinical features of MS as it occurs in Singapore. We have highlighted the optic-spinal form as a common variant of the illness and paroxysmal symptoms as an interesting manifestation of the disease. With more treatment options available, systematic prospective study of patients with MS is crucial. Early identification of patients, particularly those with the chronic progressive form of MS, will lead to early administration of treatment that will likely affect the patient's quality of life.

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