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Multiple Sclerosis in Taiwan

Background. There is only 1 report about multiple sclerosis (MS) prevalence in Taiwan, and this was published in 1976 and involved only 25 patients. The clinical features and prevalence of MS in Taiwan still remain to be clarified. The aim of this study was to determine the prevalence and delineate the clinical features of MS in Taiwanese patients.

Methods. We retrospectively identified 43 ethnic Chinese multiple sclerosis (MS) patients over a 14-year period. The MS prevalence in Taiwan was estimated based on Bureau of National Health Insurance (BNHI) data. The clinical data (gender, family history, age at onset, initial symptoms, clinical course, disability and laboratory findings, evoked response and neuroimaging) were recorded, collected and analyzed.

Results. The MS prevalence in Taiwan was as low as 1.9 per 100,000. The distribution of most of the clinical features of our patients, like those in other Asian series, was different from Western series except for the percentage of the conventional form and sensory disturbances. Cerebrospinal fluid analysis for IgG index and OCB seemed to be less sensitive in the diagnosis of MS in our series.

Conclusions. The prevalence of MS in Taiwan, as in other Asian countries, was low; the optic-spinal form occurred very often, but predominant spinal cord involvement was not unusual, as well as there being less functional disability. A larger, prospective study is needed to provide more conclusive information.

Multiple sclerosis (MS) was first described as a clinical and pathological entity by Jean-Martin Charcot more than 100 years ago.¹ Its diagnosis was mainly based on the clinical course, which was characteristically “scattered in time and space” within the neuraxis. The worldwide distribution of MS was uneven, but mainly in the white populations. On the basis of the prevalence of MS, Kurtzke generally divided the world into zones of high frequency (more than 30 per 100,000), medium frequency (5-29 per 100,000), or low frequency (less than 5 per 100,000). Asia was in the low frequency area.² There is only 1 report about MS prevalence in Taiwan, and this was published in 1976 and involved only 25 patients.³ The clinical features and prevalence of MS in Taiwan still remain to be clarified. The aim of this study was to determine the prevalence and delineate the clinical features of MS in Taiwanese patients.

METHODS

Since 1995, all patients with MS in Taiwan have been registered with the Bureau of National Health Insurance (BNHI). For this study, Neurology specialists at the BNHI reviewed the detailed medical records of all patients with MS. Data from this review were utilized for the estimation of the prevalence. We also reviewed the charts of those patients with MS who had been admitted to Veterans General Hospital in Taipei, the tertiary referring medical centers in Taiwan from January 1985 to December 1999. Those patients who fulfilled the criteria established by Poser *et al.*⁴ were enrolled in this study. We arbitrarily classified the severity of the disability into 5 grades: I, still able to walk and independent in daily activity; II, walk with assistance (mild disability); III, confined to a wheelchair (moderate); IV, bedridden (severe); and V, dead.

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The clinical data (gender, family history, age at onset, initial symptoms, other neurological symptoms and signs, clinical course, disability and laboratory findings, including the results of lumbar puncture, evoked response and neuroimaging) were recorded, collected and analyzed.

RESULTS

In total, we identified 45 patients with MS. Two of them were Caucasians and thus were excluded from analysis.

Prevalence

In 1995, National Health Insurance (NHI), a government-run insurer with a single-payer insurance system, was established in Taiwan because of the desire to protect the health of the entire population and to avoid social problems caused by poverty and disease. The characteristics of NHI include: payroll-related premiums shared by employers, employees and the government, fee-for-service under the global budget and the requirement of co-payment for ambulatory care, inpatient care and medicine. In addition, there is mandatory enrollment. By March 2001, there were 22.405 million individuals nationwide enrolled in the program, with a coverage rate of 96%, up from 92% at the launching period. The Bureau of NHI contracted almost 92% of medical institutions nationwide, providing the public with comprehensive medical benefit coverage, such as hospitalization, day care for the mentally ill and social rehabilitation.

The Bureau of NHI also requires the registration of all cases of severe and major diseases, e.g., myasthenia gravis, cancer, multiple sclerosis, *etc.*, before certification for special medical aids can be granted. A group of Neurology specialist at BNHI reviewed the records of patients with MS under Poser's criteria. (In Taiwan, until the end of 2001, there were 30,818 registered Medical Doctors with 583 Neurology specialists and 93 MRI scanners). Until March 2002, only 429 patients with MS were identified in Taiwan, with a total population of 22,405,000. The prevalence was estimated at 1.9 per 100,000.⁵

Diagnosis of MS in Veterans General Hospital patients

Diagnosis was on the basis of Poser's criteria,⁴ and 37 with clinically definite MS A1 (CDMSA1), 2 with clinically probable MS C1 (CPMSC1), 1 with clinically probable MS C2 (CPMSC2), 1 with laboratory-supported definite MS B1 (LSDMSB1), and 2 with laboratory-supported definite MS B3 (LSDMSB3) were included in this analysis.

Age at onset, gender and family history

There were 36 females and 7 males (F/M ratio, 5:1). No patient had a family history of MS. The age at onset ranged from 11 to 70 years (mean age, 29.93 years). The mean age at onset of the optic-spinal and spinal forms was 41.88 years (*t*-test, *p* = 0.011 as compared with the average age at onset of other form).

Neurological symptoms and signs

The neurological symptoms and signs during the course of the illness are shown in Table 1. Most of the patients developed limb weakness (88.4%) and sensory disturbances (83.7%) during the course of the illness. Visual impairment, unilaterally or bilaterally, occurred in 58.1% of patients, and ataxia in 32.6%.

Table 1. Neurological symptoms and signs

Neurological S/S	No. of patients	%
Limb weakness	38	88.4
Hyperreflexia or Babinski sign	37	86.0
Sensory disturbances	36	83.7
Visual impairment	25	58.1
Bladder dysfunction	24	55.8
Spasticity	15	34.9
Ataxia	14	32.6
Painful tonic spasm	12	27.9
Depression	9	20.9
Nystagmus	8	18.6
Cranial nerve palsy	7	16.3
Vertigo	5	11.6
Tremor	5	11.6
Bulbar dysfunction	4	9.3
Fatigue	4	9.3
Cognitive abnormality	3	7.0
Lhermitte sign	2	4.7

S/S = symptoms and signs.

Table 2. Lesion site(s) involved according to the initial symptoms

Lesion site(s)	No. of patients	%
Spinal cord	20	46.5
Optic neuritis	14	32.6
Cerebrum	4	9.3
Cerebellum	3	6.9
Brain stem	2	4.7

Initial symptoms and lesion sites involved

The lesion sites involved according to the initial clinical symptoms are shown in Table 2. The initial symptoms referred to the symptoms occurring before the confirmed diagnosis of MS. The site most frequently involved at the onset of the illness was the spinal cord (48%), followed by the optic nerve (33%), either unilaterally or bilaterally. Only 6.9% of the patients had cerebellar involvement.

Clinical course and predominant clinical category

According to the clinical course definition of MS reported by Lublin *et al.*,⁶ 51 percent of the patients experienced a relapsing-remitting course, 30 percent a secondary-progressive course, and 19% a primary-progressive course. Four patients (9.3%) with secondary-progressive course expired during the course of the illness.

The categories were the conventional form 25/43 (58.1%), optic-spinal form 9/43 (20.9%), pure spinal form 4/43 (9.3%), brain stem 2/43 (4.6%), and brain stem and cerebellum 3/43 (6.9%). The systems involved were the spinal cord 29/43 (67.4%), optic nerve 28/43 (65.1%), cerebrum 16/43 (37.2%), brain stem 16/43 (37.2%), and cerebellum 9/43 (20.9%).

MRI, evoked response

The clinically determined lesion sites were reconfirmed by MRI and/or evoked potential changes. In our series, brain MRI done in 39 patients and spinal MRI in 30 patients all showed dissemination of white matter CNS lesions. Using different relaxation time constants (T1/T2), the calculated average number of lesions was 3.8. The percentage of abnormal results of visual evoked response (VER), brainstem auditory evoked response (BAER), and somatosensory evoked response (SSER) were 37.5% (12/32), 23.1% (6/26), and 68% (17/25), respectively.

Cerebrospinal fluid (CSF) findings

Abnormally increased IgG index was defined as a value of more than 0.67. Totally, 31 IgG index and oligoclonal band determinations were performed on specimens from 28 patients. Abnormally increased IgG index was detected in 42% and the presence of oligoclonal bands (OCB) in 29%. If the association between MS type and CSF parameters is considered, IgG index was increased in 47.4% of patients with the disseminated form and 33.3% with optic-spinal and spinal forms. Pleocytosis (more than 5/mm³) was noted in 45% of our patients and CSF protein value was increased (more than 45 mg/dL) in 47%.

Disability

Within 10 years after the first attack, 32.4% of our patients were grade I, 32.4% grade II (mild disability), 23.5% grade III (moderate disability), 11.8% grade IV (severe disability), and 9.3% (4 cases) with secondary progressive course expired during the course of the illness.

DISCUSSION

The prevalence of MS varies considerably around the world. Asia belongs to the low frequency area.² In Taiwan, there was only 1 report of MS in 1976, and the regional prevalence rate in northern Taiwan is estimated to be 0.8 per 100,000.³ In our series, the prevalence, similar to other Asian series, was 1.9 per 100,000. In our opinion, the mild increase of prevalence rate in Taiwan might be due to improvement in case detection. The mean age at onset, similar to that of the Malaysian series,⁷ was younger than that of the Japanese series.⁸ Previous studies had revealed preponderance of MS in females.^{3,7-8} We found that this phenomenon was especially pronounced in Taiwanese and ethnic Chinese from Malaysia, with female/male ratios of 5.1 and 7.0, respectively. The cause of this preponderance in these 2 countries remains to be elucidated. In addition, the most frequent initial symptom of our patients, like those in Malaysia⁷ but unlike those in Japan,⁸ was spinal cord syndrome rather than visual impairment. Although the reason for these similarities (in optic nerve and spinal cord involvement) between Taiwanese and Malaysian MS patients might be that both the ethnic

Chinese from Taiwan and Malaysia originated from mainland China, no patient had a family history of MS in our's or the other series.⁹

The neurological symptoms and signs of our patients were similar to those of other series,¹⁰ however, the frequencies varied in some aspects. The percentage of visual impairment at the onset of the illness in our series (33%) was intermediate between that of the Japanese (43%)⁸ and Western series (13-28%).⁹ In a comparative study of Japanese (Kyushu series) and British (Maida Vale series) patients, the most common symptoms during the course of the illness were visual impairment and numbness, respectively. In our series, somewhat similar to the Maida Vale series but different from the Kyushu series,¹⁰ the most common symptom was limb weakness (88.4%), followed by sensory disturbances (83.7%). Ataxia (32.6%), similar to the previous Asian series (30%),⁹ was less common than in the U.S. Army series (77%).¹¹ The percentages of painful tonic spasm (27.9%) and sphincter disturbance (55.8%), uncommon in Western MS patients, were similar to that of the previous Asian series (23% and 52%, respectively).⁹

Of the types of MS, the relapsing-remitting type has been reported to be most common and the primary progressive type, the least common.⁶ In our series, the percentage of the relapsing-remitting type (51%), although the most common type, was still lower than that in the Maida Vale (64%) and Kyushu series (85%).¹⁰ The percentage of the primary progressive type (19%), although the least common in our series, was nevertheless higher than that in the Maida Vale (5%) and Kyushu series (2%).¹⁰ Thus, in Taiwan, relapsing-remitting MS was less common, and primary progressive MS more common than in other countries. The cause remains to be determined.

The mortality rate due to MS has been reported to be as high as 20% and 36.7% in the previous Taiwan³ and Malaysia series,⁷ respectively. In the Maida Vale and Kyushu series, the mortality rate was 1.5% and 6.7%, respectively.¹⁰ In our series, the mortality rate of 9.3% was lower than that of previous Taiwan series. It was closer to that of Kyushu series,¹⁰ although still higher. The decline in mortality rate in Taiwan might be due to the advancement of medical care for this disease. The above data are summarized in Table 3. In previous studies, the greater

Table 3. Comparison of clinical features of different series

	Taiwan (Hung et al 1976)	Taiwan (Tsai et al.)	Malaysia 1988	Japan nationwide series 1975	Kyushu (Shibasaki et al. 1981)	Maida vale (Shibasaki et al. 1981)
No. of patients	25	43	30	1084	60	204
Mean age at onset	32.1	29.9	29.7	33.0	31.0	31.0
Gender ratio F: M	3.2:1	5:1	5:0	1:3	1:5	2:0
Family history	No	No	No	Yes (1-2%)	No	Yes (10%)
Most frequent initial symptom	Visual impairment	Spinal cord syndrome	Spinal cord syndrome	Visual impairment	Visual impairment	Numbness
Most common neurological symptom	Visual impairment	Limb weakness; sensory disturbances	-	Visual impairment	Visual impairment	Ataxia; paresthesia
Optic-spinal form Clinical course	44%	20.9%	53%	impairment	impairment	20.8%
R-R	-	51%	-	74%	85%	64%
S-P	-	30%	-	-	10%	31%
P-P	-	19%	-	-	2%	5%
Mortality	-	9.3%	36.7%	-	6.7%	1.5%

R-R = relapsing-remitting; S-P = secondary-progressive; P-P = primary-progressive; "-" = unknown.

functional disability in Asian patients was attributed to more severe spinal cord involvement. However, 64.8% of our patients had no or only slight disability within 10 years of their first attack, although most of our patients had spinal cord involvement. The reason might be that the follow-up period of our patients was not long enough.

The most common clinical forms of MS reported in previous Western and Oriental series was the conventional form and optic-spinal form, respectively.¹ In the Western and our series, the most common was the conventional form. Optic-spinal form (20.9% of our series) was not usual in the Western series. Furthermore, spinal involvement (67.4%) occurred very often but was not prominent (9.3%) in our patients. In our series, the abnormal SSER (68.0%) was the most common evoked response, and the abnormal BAER (23.1%) the least. These results are consistent with the fact that spinal cord involvement occurred more often in our patients, and indicated that SSER (but not BAER) was a useful adjunctive test in the diagnosis of MS in Taiwan.

Devic's syndrome (or Neuromyelitis Optica) is defined as the onset of acute transverse myelitis and optic neuritis within a short period.¹² Devic's syndrome appears to be extremely rare in Japan,¹³ and also our series did not include a typical case. We think that Devic's syndrome confuses the diagnosis of the optic-spinal form of MS by implying the existence of a separate disease entity.

In Japan, the frequency of the optic-spinal form was 36% in the 143 cases of MS diagnosed by clinical criteria collected from 1964 to 1998.^{10,14} Recently, 2 Japanese studies reported a decrease in the frequency of clinically diagnosed optic-spinal form of MS, and the conventional Western form of MS is increasing.^{15,16} In Taiwan, in 1976, most of the MS cases (44%) were reported to be of the optic spinal-form, but in our series, only 20.9% were of this form. Whether environmental factors (infectious agents, industrial poisons, *etc.*) are associated with the increase of the conventional form of MS or whether the difference is due to the use of improved diagnostic tools like MRI and CT remains to be investigated.

A study by Christenson *et al.*,¹⁷ using isoelectric focusing (IEF) with immunofixation, indicated that 87% of their MS patients showed significantly increased IgG index and 87.5% the presence of oligoclonal bands (OCB) that were significantly different from Ig patterns in con-

trol groups. In our series, using the same method, only 42% of our patients showed abnormally increased IgG index and only 29% showed the presence of OCB. CSF analysis for IgG index and OCB seemed to be less sensitive in the diagnosis of MS in our series. The results were similar to those of a previous Japanese study.¹⁸ Whether the presence of OCB is especially low in Asian MS patients still requires confirmation.

In summary, the prevalence of MS in Taiwan, as in other Asian countries, is low. Like other Asian series, our series differed from Western series with respect to most clinical features, except for the prevalence of the conventional form and sensory disturbances, which seemed to be intermediate between their prevalence in Japan and Western countries. The clinical pattern of MS in our patients was closer to that of Malaysian patients. In contrast to other Asian series, both our patients and the Malaysian patients were younger at disease onset and mainly female, and had disease characterized by initial spinal cord involvement. In addition, the optic-spinal form occurred very often but predominant spinal cord involvement was not unusual, as well as there being less functional disability. The percentage of relapsing-remitting type was less, and that of primary progressive type was more in our series than in other series. A larger and prospective study is needed to provide more conclusive information.

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