REVIEW

Multiple sclerosis in Malaysia

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Abstract

The prevalence multiple sclerosis (MS) is estimated to 2/100,000 population in Malaysia. It is seen in all the three main ethnic groups; Chinese, Malays and Indians, but with higher prevalence among ethnic Chinese. There is high F:M ratio of 6.6:1. None has a family history of similar illness. The average age of onset of symptom was 31 years. 50% of patients presented with a myelopathy, 59% of the relapses involved the spinal cord, 97% of patients had myelopathy at sometime of the illness. Acute transverse myelopathy was seen in 45% of cases and paroxysmal tonic spasm in 30%. Optic-spinal recurrence was the most common form, seen in 53% of cases and disseminated recurrence in 21%. Relapsing myelopathy accounted for 20% of clinically probable and definite MS combined. Devic’s disease was seen in one patient only. The annual relapse rate was 0.58. The mortality rate was high at 29% over 7.1 years. There was characteristic severe motor and visual disability. At the time of last examination, 34% had bilateral optic atrophy with severe impairment of vision and were also bedridden or wheelchair bound. 52% of patients who presented with acute transverse myelitis went on to develop MS. High total protein and pleocytosis in CSF was not uncommon. The evoked potential studies detected subclinical abnormalities in VEP (32%), BAEP (27%), and median nerve SSEP (31%). 75% of patients showed abnormality of cerebrum in the CT scan, mostly asymptomatic. 38% had positive hot bath test although none of the patients complained of Uhthoff’s phenomenon.

Key words: multiple sclerosis, Malaysia; myelopathy; myelitis, transverse; optic neuritis, evoked potential, CT scan.

Although multiple sclerosis (MS) is not as frequently encountered in Asia as compared to the West, it nevertheless is an important neurological disease in Asian neurological practice because of the high morbidity and mortality. MS is characterized pathologically by multiple lesions affecting principally the white matter of brain and spinal cord, with predilection for the periventricular region of the brain, the optic nerve, optic chiasma, spinal cord, brainstem and cerebellar peduncle. Histologically, the recent lesions show a partial or complete destruction and loss of myelin with sparing of axons, and perivasal para-adventitial infiltration with mononuclear cells and lymphocytes. The chronic lesion is relatively acellular, with some loss of axis cylinders occurs with partial remyelination.

MS is an inflammatory disorder accompanied by immunological disturbance, though the exact mechanism is not clear. The experimental allergic encephalomyelitis, which is an autoimmune phenomenon, closely simulates MS. The plethora of immunomodulatory treatment is also supportive of the immunological mechanism of the disease. The pathogenesis is believed to be an interplay between the genetic and environmental factors. The over representation of certain histo-compatibility antigen in MS, the higher concordance rate for identical twins are supportive of the genetic factor. The epidemic of MS described in the Faroes Islands and the migration study showing a difference in the prevalence of MS as determined by the age of migration are supportive of environmental factor.

It is now clear that there is difference between the MS seen among the Caucasian populations and that seen among the Asian populations. The MS described in the neurology textbook is seen among the Caucasian population. In contrast, the MS seen among the Asians has the following characteristics: low prevalence (<5/100,000 population), rare occurrence of similar family history, a higher incidence of visual failure at the onset of the illness; a more severe visual impairment during follow-up; a more frequent occurrence of acute transverse myelopathy, with Devic’s disease being more common; and a more severe involvement of spinal cord with greater functional disability and less frequent involvement of the cerebellum.
Singapore and Malaysia have strong historical and cultural links, the Medical School of the University of Malaya used to serve both countries and was located in Singapore. It was the traditional teaching in the medical community that MS was not seen in Singapore (and Malaysia). A case of MS in a patient of ethnic Chinese origin with autopsy confirmation seen in Singapore in 1985 proved beyond doubt that MS does exist in this region. We have also undertaken studies to better understand the behaviour of the disease. Our studies of MS in Malaysia was based on the patients seen in the University of Malaya Medical Centre (UMMC). UMMC was until recently, one of the two institutions in the country providing neurological services. For the purpose of the study, the diagnostic criteria for clinically definite MS was: (1) remitting and relapsing history with two or more episodes; (2) evidence of lesions at two or more sites in the central nervous system; (3) lesions predominantly in the white matter; (4) age of onset of symptoms, 10 to 60 years; (5) history of signs or symptoms for one year or longer and (6) no better explanation of the observed abnormality. The diagnostic criteria closely follow those of McDonald and Halliday. The more recent criteria rightly include laboratory findings. However, due to problem of facilities, only some of our patients had accurate data on the cerebrospinal fluid immunoglobulin level and the evoked response study. Active efforts, including home visits, were made to obtain the latest follow up status.

PREVALENCE, RACE, SEX, FAMILY HISTORY

From the period 1968-88, 38 cases of clinically definite MS was seen. In summary, the clinical features of MS seen in Malaysia was largely similar to the non-Caucasian MS elsewhere. Based on comparison with amyotrophic lateral sclerosis, the prevalence of MS in Malaysia was estimated to be 2/100,000. This falls into low-frequency area in the world wide distribution of MS. There appears to be a relative predisposition of ethnic Chinese for MS. The ethnic composition of MS was 84% Chinese, 11% Malays and 5% Indians, whereas ethnic Chinese accounted for 33% of the population in Malaysia (1980 census) and 48% of non-obstetric admissions to the medical centre from 1979-85. The relatively low prevalence of Malay MS patients may partly explain the very few reports of MS from Indonesia, which consists of large ethnic Malay population.. The female to male ratio was 6.6:1. The F:M sex ratio of the ethnic Chinese patients was even higher at 10:1. The corresponding sex ratio for ethnic Chinese patients from Taiwan was 4.5:1. Zhao et al reported a F:M ratio of 1.12:1 for their patients from mainland China. The ethnic Chinese from Malaysia, like those from Taiwan, mainly originated from the southern coastal provinces of China whereas the mainland Chinese series were form the northern cities of Beijing, Changchun and Harbin. Other areas that have reported high F:M ratios were Hawaii, South Africa, Western Australia, Okinawa and Thailand. Despite the large family size (average of 6 siblings), none had a family history of similar problems. As mentioned above, the rare occurrence of a positive family history is a characteristic of Asian MS. The usual incidence of a positive family history in patients with MS is approximately 15%.

CLINICAL FEATURES

The age of onset of symptom was 31 years. This is similar to most series. 50% of the patients presented with a spinal cord syndrome, 26% presented with optic neuritis, mainly unilateral. In general, most patients recovered from the initial motor weakness whereas the visual loss was more permanent. 9% of patients presenting with motor involvement became permanently wheelchair bound; whereas 56% of the patients presenting with visual failure had residual blindness or visual acuity <3/60. Optic-spinal recurrence was the most common form, as seen in 53% of cases. Disseminated recurrence (more than four sites of lesion) was the next common form, seen in 21% of cases. 97% of patients had involvement of the spinal cord at sometime during the course of the illness (average 7.1 years). 59% of the relapses involved the spinal cord. 45% had acute transverse myelopathy at some time during the course of the illness. Paroxysmal tonic spasm occurred in 30% of patients. The high frequency of paroxysmal tonic spasm among Asian MS patients has also been noted previously. 84% had optic nerve involvement sometime during the course of the illness, 65% of the relapses involving the eye were unilateral. In general, the brainstem, cerebellum and cerebral involvement were less persistent, with only 3% of patients each having residual persistent severe ataxia, ophthalmoplegia, dementia and dysphasia.
PROGNOSIS
The average duration of illness was 7.1 years. The annual relapse rate was 0.58 with the average interval between relapse of 1.7 years. In terms of motor activities and visual outcome, the disease was generally very disabling. At the time of last examination, 21% were bed ridden, 26% were confined to a wheelchair, 24% were ambulant but with daily activity affected, 11% had neurological signs without disturbance of daily activity, and 18% were clinically normal. The visual outcome on last examination was blindness in 26% of the eyes, visual acuity <3/60 in 21%, visual acuity from 6/60 to 6/24 in 8%, visual acuity between 6/18-6/9 in 1% and normal in 43% of the eyes. At the time of last examination, 34% had bilateral optic atrophy with blindness or severe impairment of vision with visual acuity <3/60. 26% were blind or had severe impairment of visual acuity in both eyes and were also bedridden or wheelchair bound. There were 29% mortality. All the deaths occurred in the context of severe disability, with spinal cord involvement resulting in severe tetraplegia and urinary incontinence. Some patients had respiratory paralysis as well. The high mortality rate is in contrast to that from England and Japan, which were 1.5% and 6.7% over 12 and 8 years respectively. 7 The common and severe spinal cord involvement explained the high mortality as well as morbidity among our patients.

RELAPSING MYELOPATHY FORM OF MS
Over the same period of study, 12 patients fulfilled the diagnostic criteria for clinically probable MS. The criteria used were: (1) remitting and relapsing course; (2) evidence of only one lesion associated with MS; or (1) single episode suggestive of MS; and (2) evidence of lesions at two or more necessary sites in the CNS. 10 of the 12 patients had a syndrome of relapsing myelopathy. The average age of onset of these 10 patients was 32 years. The annual relapse rate was 0.45 with an average duration of illness of 6.9 years. There was a F:M sex ratio of 2.3:1. Three of these 10 patients had paroxysmal tonic spasm. All these features are closely similar to the clinically definite MS cases indicating that they are caused by same disease. In fact one of the patients, a Chinese women (NSN) had her first episode of acute transverse myelitis in 1968 at the age of 44 years. After that, she had 9 other episodes of relapsing myelopathy over 26 years of follow up (1968-94). She passed away in 1994 at home due to complication related to bed ulcer. In 1988, she developed paroxysmal tonic spasm for the first time. In 1990, after 22 years and 10 episodes of relapsing myelopathy, she developed right optic neuritis, from which she became permanently blind in the right eye. CT scan then showed right frontal periventricular hypodense lesion consistent with a demyelination plaque. This patient illustrates that when followed up long enough, some of these patients with relapsing myelopathy would develop lesions elsewhere. Relapsing myelopathy should thus be recognized as an important clinical form of MS in Malaysia, accounting for 20% of the clinically definite and probable MS patients combined.

RISK OF DEVELOPING MS IN PATIENTS WITH MYELOPATHY OF UNKNOWN ORIGIN AND ACUTE TRANSVERSE MYELITIS
As mentioned above, myelopathy is common in both the clinically definite and probable MS. We have studied 52 patients who presented with an episode of myelopathy with no definite aetiology. 53% subsequently developed relapsing disease consistent with clinically probable or definite MS during the follow up of 5.5 years. 17 A subgroup of 27 patients had a presentation indicative of acute/subacute transverse myelopathy defined as those with an acute illness of <4 weeks with both sensory and motor involvement. The motor involvement was severe and bilateral. 52% went on to develop clinically definite or probable MS during follow up. This is far higher proportion than the 1.6% to 7.7% previously described in the literature 18,19, which is the basis of the belief that acute transverse myelitis do not give rise to MS. Berman et al 18 also pointed out that none of their 747 MS patients had acute transverse myelitis as an initial symptom. The much higher risk of developing MS in patients presenting with acute transverse myelitis in Malaysia indicates that the long term prognosis of acute transverse myelitis vary with different geographical location and racial group

UITHOFF'S PHENOMENON
Transient deterioration of neurological signs with temperature change (Uithoff's phenomenon) is a well known phenomenon in MS said to occur in up to 35% of MS patients. 21 There is no mention of such phenomenon among Asian MS
patients despite the extensive medical literature. No one of our patients complained of neurological symptoms related to temperature change such as from a febrile illness. We subjected 13 clinically definite MS patients to a hot bath test with evoked response studies before and after heating. \(^{20}\) Five patients (38\%) developed neurological changes with the rise in body temperature. There was an average of 0.46 new signs per patient. Four patients had motor disturbances attributed to aggravation of spinal cord function. Two patients had additional visual deterioration. Thus, when subjected to vigorous testing and close observation, our patients also demonstrated an abnormal sensitivity to temperature change. However the rate of abnormal hot bath test and the number of new signs was much lower than those previously reported. Mrathora & Goren reported 93\% of their MS patients had positive hot bath test with an average of 2.6 new signs per patient. Most of the abnormalities occurring with application of temperature previously reported have involved the bulbar structure and the eyes rather than the spinal cord. \(^{22}\) The hot bath test further demonstrate the Malaysia MS patients is essentially similar to MS among Caucasians, yet there are differences.

**DEVIC'S DISEASE**

Kuroiwa defined Devic's disease (neuromyelitis optica) as acute bilateral visual impairment and transverse myelitis occurring successively within an interval of less than several weeks.\(^{23}\) Following this widely accepted modern classification, only one case of Devic's disease has been seen in the UMMC. It was a 39 years old Chinese women (LHS) from Penang seen in 1988, who died a year later. Devic's disease as defined above is thus uncommon in Malaysia. Previous reports mentioning that Devic's disease was seen regularly in Singapore and Malaysia never gave a clear definition of the disease.\(^{24}\)

It is possible that the same patients would have been classified as optic-spinal form of MS according to modern criteria as adopted in this paper.

**LABORATORY INVESTIGATIONS**

The CSF studies showed a high percentage of patients with high total protein and leukocyte count. 14\% of CSF examinations of clinically definite MS patients has a total protein of >108mg\%, and 32\% among the clinically probable MS patients has a leukocyte count of >50 cells per cu mm. The rate of abnormal IgG index was 36\% among the clinically definite MS cases. All these features has been previously reported in the Asian studies of MS patients.\(^{10}\) As for the use of evoked potential studies, the rate of abnormality was high for the patients who were symptomatic, reaching 100\% for VEP, 83\% for nerves in median nerve SSEP, 31\% in BAEP. The rate of abnormality among those who are asymptomatic was lower, varying from 32\% of eyes in VEP, 27\% of patients in BAEP, and 31\% of nerves in median nerve SSEP. Three out of 10 patients with optic spinal form of MS have abnormal BAEP. These show the usefulness of the evoked potential studies in confirming the clinical lesions as well as demonstrating subclinical involvement. The rate of abnormal evoked responses for the asymptomatic patients is generally lower than that published elsewhere.\(^{25}\) Using high dose infusion CT scan, 75\% showed abnormality of the cerebrum, mostly asymptomatic. The abnormality is more florid in patients with clinically disseminated forms of the disease. It shows that asymptomatic cerebral involvement is common Asian patietsns with MS and CT scan is a useful tool in the overall assessment and diagnosis of Asian MS patients.\(^{26}\) 11 patients with MS and 2 patients with acute transverse myelitis were tested for HTLV-I antibody which was all negative. There is thus no evidence to date to implicate HTLV-I in MS in Malaysia. The prevalence of HTLV-I in the general population in Malaysia is estimated to be <0.1\%.\(^{27}\)

**REFERENCES**