INVITED REVIEW ARTICLE

A Review of Multiple Sclerosis with Asian Perspective

H T Chong, FRCP, C T Tan, FRCP

Division of Neurology, Department of Medicine, University of Malaya, 50603 Kuala Lumpur, Neurology Laboratory, University Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia

SUMMARY

Multiple sclerosis, although a rare disease in Asia, often presents significant diagnostic challenges to clinicians. There has been rapid advancement in the understanding of the underlying genetic influence, pathophysiology, investigation and treatment recently. This paper reviewed the latest development of various aspects of the disease and examined the differences between the manifestations of Asian and Western patients. The implications of these differences to investigation and treatment were also touched upon.

KEY WORDS:
Multiple sclerosis, Neuromyelitis optica, Asian

INTRODUCTION

Multiple sclerosis is an idiopathic, autoimmune, demyelinating disease affecting the central nervous system. It is commonest among women in their 20s to 40s, and it is the commonest non-traumatic cause of disability among young people in Western countries. The prevalence of multiple sclerosis varies mainly with gender, ethnicity and latitude, especially the latitude of the place where the patient spends the first 15 years or so of life. Regions with high prevalence (> $30/10^5$) include Western Europe, North America, Southeast Australia and the whites of New Zealand. Regions with medium prevalence (between $5/10^5$ to $29/10^5$) include Eastern Europe, southern shores of the Mediterranean, Mexico, South Africa, southern parts of South America and the rest of Australia. The rest of Asia, Africa and northern South America have low prevalence (< $5/10^5$). The illness is commoner among whites and the female to male ratio varies from 2:1 to 3.8:1[1-3]. The prevalence of multiple sclerosis was 1.39/105 in Shanghai, China, 4 and $7.7/10^5$ in Japan[5].

In Malaysia, even as late as the 1980s, the disease was thought not to exist here. The first detail description of multiple sclerosis, and thus the proof of its existence in Malaysia, was published in 1988[6,7]. Since then, it was found that its prevalence, computed in comparison to that of amyotrophic lateral sclerosis, which has a stable worldwide prevalence, is about 2 to $3/10^5$, and it is commoner among the Chinese than the Malay[2, 6, 7]. It was thus estimated that there are currently about 500 – 750 patients in Malaysia. However, a recent survey conducted among the Ministry of Health hospitals in Malaysia suggested that perhaps the difference in prevalence rates among the races was less pronounced than previously thought (personal communication: Dr. Shanthi V, Hospital Kuala Lumpur). Recent study also suggested that the prevalence of the disease, especially the classical, Western form, is on the rise at least in northeast Asia[5].

AETIOLOGY

The actual cause of multiple sclerosis is not known and is probably multifactorial as both environmental and genetic factors have been proven to be important. The concordance rates are nearly 30% in monozygotic twins and 2% in siblings or dizygotic twins, compared to the highest population prevalence of 0.1 – 0.2%. Since 1972, association with HLA-DRB1 gene on chromosome 6p21 has been established and it is still the single most important genetic locus found to be associated with multiple sclerosis. Meta-analyses of large genetic studies have suggested additional minor loci on 5p, 17q and 19q[8]. Recent genome-wide analysis of 12,000 subjects for single nucleotide polymorphism markers indicated minor involvement of two additional genes, IL2RA on chromosome 10p15, which encodes the alpha subunit of interleukin-2 receptor (CD25), and IL7RA on chromosome 5p13, which encodes the alpha subunit of interleukin-7 receptor[9]. These findings suggest that cell mediated immunity plays a key role in the immunopathogenesis of multiple sclerosis.

Latitudinal variation in the prevalence of multiple sclerosis and migration studies suggested that environmental factors are as, if not more, important as genetic factors. A dramatic increase in the incidence of multiple sclerosis in the Faroe Island after the deployment of British garrison during the Second World War suggested that infective agents may be the causative or precipitating factor of the disease[10]. Recent studies have implicated Epstein-Barr virus as one such possible culprits[3]. Serum vitamin D levels had been shown to have a significant negative correlation with the risk of multiple sclerosis;[11] and vitamin D supplement was also shown to be associated with lower risk of the disease,[12] although the exact mechanism of how vitamin D supplement reduces the risk of multiple sclerosis is not known.

PATHOLOGY AND PATHOPHYSIOLOGY

The pathological hallmark of multiple sclerosis is the focal, well delineated demyelinating plaques, with myelin destruction on a background of inflammation and later, glial scarring. Macroscopically, the plaques appear to be sharply demarcated within the white matter tracts of the brainstem, spinal cord, within the periventricular regions and the optic nerves. Within the active plaques, the inflammatory cells consist mainly of T lymphocytes with extensive macrophages

This article was accepted: 10 November 2008
Corresponding Author: Tan Chong Tin, Division of Neurology, Department of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
Email: chongvictor@gmail.com

and microglial activation and a small number of B lymphocytes and plasma cells[13]. Axonal transaction, however, is found to present extensively in active and chronic active lesions even in patients who were diagnosed recently and in normal appearing white matter[13, 14].

The inflammation in these plaques is associated with an up-regulation of a variety of cytokines and chemokines, such as interleukin-2, α-interferon and α–tumour necrosis factors. Other active participants in this process include CD8+ T cells and antibodies to myelin proteins, such as myelin oligodendrocytes glycoprotein (MOG) and myelin basic protein (MBP)[13]. After the inflammatory process subsides, remyelination and gliosis follow. A systematic review of demyelinating plaques suggested four immunopathological patterns:

Pattern I: T cells/macrophages-mediated demyelination
Pattern II: Antibody/complement-mediated demyelination
Pattern III: Oligodendrocyte dystrophy with myelin dysregulation and oligodendrocytes apoptosis
Pattern IV: Primary oligodendrocytes degeneration.

Although the pattern of demyelination tend to be the same in multiple lesions in the same patients at any one time, the pattern varies from patient to patient, and it does not correlate well with the clinical course, except for pattern IV, which has only been identified in patients with primary progressive disease[13, 15].

Increasingly, neurodegeneration is thought to play an important role early in the course of the illness, and inflammation may not be the initiating trigger in lesion formation, suggesting that pattern III lesions may be the precursors to the typical pattern I and/or II plaques. Current evidence suggests that oligodendrocyte apoptosis occurs before the setting in of inflammation, and is likely to be the trigger of inflammation. The cause of oligodendrocyte apoptosis is yet unknown, though some authors have suggested that viruses such as the human retrovirus, HERV-W, may be the cause[16 - 18].

Clinical Features

The mean age of onset is 31 years[2]. The commonest presenting symptoms in classical multiple sclerosis include sensory disturbance in the limbs (33%), unilateral visual loss (16%), motor deficits (14%) and diplopia (7%). The sensory disturbance often involves one limb then the other, however, it may vary from ascending numbness mimicking Guillian-Barré syndrome to radicular pain, dysaesthesiae and paraesthesiae. Another less common sensory symptom is Lhermitte's phenomenon, which is described as an electric shock-like sensation traveling down the back to the legs upon flexion of the neck[19]. Other symptoms include acute motor deficits, diplopia, cerebellar disturbance and cranial nerve palsy. In Asia, the commonest presenting symptoms are myelitis (33%), optic neuritis (29%), brainstem (14%) and cerebellar symptoms (4%)[2].

In a joint Asian study, 45% of patients had at least a clinical episode of acute transverse myelitis[2]. The onset often progresses over a few days. The initial complaint is numbness and weakness of the lower limbs, progressing to incontinence, loss of proprioception and walking difficulty. Examination showed variable loss of strength. The tone and reflexes may be normal initially, but the limbs would become hypertonia and hyperreflexic over the next few days. The cervical cord is the commonest site of involvement, followed by the thoracic cord. Initial attacks of myelitis tended to recover rapidly and completely. However, with recurrent attacks, the recovery tended to become less complete. Severe weakness and loss of proprioception herald poor recovery. During recovery, a significant proportion of patients develop paroxysmal tonic spasm; a frequent, intermittent, painful motor spasm of the affected limbs which may spread from one muscle group to another. The spasm is often over within minutes, but may recur numerous times in a day. The spasm responds to carbamazepine, and is good indicator that the myelopathy is of demyelinating etiology. Regionally, 28% of the patient complained of paroxysmal tonic spasm during the course of their illness[2, 20].

Optic neuritis is also a very common presenting symptom, occurs in about 15-35% of patients in the Western countries. In a joint Asian study, 48% of patients had at least a clinical episode of optic neuritis[2]. Bilateral optic neuritis is also not rare and subclinical optic neuropathy is relatively common in Malaysia. The presenting complaint is sudden onset of vision loss or blurring, often, though not always, accompanied by pain. Pupillary reflex may be spared in mild cases. In severe cases, the involvement of the afferent pathway of the pupillary reflex arc results in the Marcus-Gunn pupil. Upon recovery, the patients most often had impairment of contrast sensitivity, and less often visual field and colour vision defect. Therefore, even those without visual field defect may complain of loss of colour brilliance upon recovery. The visual field defect was highly variable, ranging from central scotoma to hemianopia. Like myelitis, initial attacks tend to recover rapidly and completely, though with recurrent attacks, blindness is not uncommon[21].

About 80% of patients present initially with a relapsing remitting course; however, after a number of years, most of the patients enter the secondary progressive phase, during which the neurological deficits progress relentlessly even during remission of relapses. This occurs in 12% of patients after 5 years, 40% after 10 years and 66% after 25 years[22]. The other 10 – 20% of patients have continual progression of symptoms independent of relapses from the onset of the disease; those with relapse are termed progressive relapsing multiple sclerosis, and those without are termed primary progressive multiple sclerosis. Progressive disease is less common in Asia; in a recent survey, in which the mean duration of illness was 9.3 years, 79% of patients remained in the relapsing remitting phase and only 7% of patients progressed to secondary progressive phase. Eleven percent of these patients had relapsing progressive disease and 3% had primary progressive disease[2].

DIAGNOSIS AND INVESTIGATIONAL FINDINGS

The diagnosis of multiple sclerosis hinges on demonstrating that the attacks of presumed central nervous system demyelination are disseminated in space and time and there is no better explanation for these attacks. The differential

Table I: Symptomatic treatment

Symptoms	Treatment
Fatigue	Fatigue management programme
	Amantadine
	Modafinil
	Calcium channel blockers
Spastic bladder	Pelvic floor exercises
	Clean intermittent self-catheterisation
	Oxybutynin
	Tolterodene
Nocturia	Intranasal desmopressin (DDAVP)
Detrusor hyperreflexia	Intravesical capsaicin
Constipation	High fibre diet
	Osmotic laxative such as lactulose & polyethylene glycol
	Senna
	Bisocodyl
	Erectile dysfunction Sildanefil
	Intracorporeal alprostadil
Spasticity	Physiotherapy
	Avoidance of noxious stimuli (such as poor posture, fecal impaction, ingrown toenail, urinary tract infection)
	Baclofen (10 – 80 mg daily in 3 doses)
	Tizanidine (6 – 32 mg daily in 3 doses)
	Dantrolene
	Gabapentin
	Memantine
	Viagabatrin
	Cannabis
	Botulinum toxin injection for focal spasticity
	Intrathecal baclofen infusion
	Paroxysmal tonic spasm Carbamazepine
	Phenytoin
	Lamotrigine
	Gabapentin
	Chronic pain Transcutaneous electrical stimulation
	Amitriptylene
	Eye movement disturbances Prisms
	Baclofen
	Gabapentin
	Isoniazid
	Memantine
Vertigo	Physiotherapy
	Prochlorperazine
	Cinnarizine
Dysphagia	Percutaneous endoscopic gastrotomy tube feeding

diagnoses of multiple sclerosis are varied and many, including multiple stroke, multiple metastases and central nervous system lymphoma. Clinically, evidence of dissemination in time can be obtained by taking a detail history, and that of dissemination in space by showing that on neurological examination the signs are localized to more one site in the central nervous system. When the clinical history could not prove that the attacks were disseminated in time, serial MRI showing occurrence of new T2 or gadolinium enhanced lesions is sufficient to prove dissemination in time. Similarly, when neurological examination does not show evidence of multiple lesions, the presence of subclinical MRI lesions is sufficient to prove dissemination in space as in modified McDonald criteria[23].

Therefore, among all the paraclinical tests, MRI is the most important. Its sensitivity approaches 95% in Western patients, and specific lesions are best seen in T2 or FLAIR weighted images. The typical findings are multiple small, round or ovoid, discrete lesions in the juxtacortical, periventricular, callosal or pericallosal regions. Acute lesions are often enhanced with gadolinium.

The typical cerebrospinal fluid findings include the presence of oligoclonal bands, normal or mildly elevated protein and normal cell counts, though in Asian patients, only 27% of patients were found to have positive oligoclonal bands and lymphocytic pleocytosis is not rare[2].

In Asian patients, though the MRI findings were found to be largely similar to those of the Western patients in terms of lesion distribution and appearance, there were significant differences as well. Asian patients had fewer brain lesions and longer, more severe spinal cord lesions and rare involvement of the cerebellum[24]. The MRI findings were also less likely to fulfill McDonald's criteria on dissemination in space[25]. Therefore, we recently proposed that future diagnostic criteria should take these into account by reducing the number of MRI brain lesion necessary for diagnosis, inclusion of long spinal cord lesions, or cord lesions involving the entire cross sectional area, as consistent with MS plaques. It was further proposed that relapses restricted to clearly separate lesions of the spinal cord be accepted as sufficient to demonstrate dissemination in space[26].

NEUROMYELITIS OPTICA, OPTIC-SPINAL MULTIPLE SCLEROSIS AND MULTIPLE SCLEROSIS IN ASIANS

Since the 1970's it was recognised that MS patients in Asia have different clinical features compared to those in North America and Europe. The main differences are lower prevalence, rare familial occurrence, higher female to male ratio, more severe optic nerve and spinal cord attacks, fewer brain and cerebellar lesions, higher proportion of optic nerve and spinal attacks, lower proportion of progressive disease and lower incidence of positive oligoclonal bands[2]. Those patients in Asia who have clinical relapses (though not necessarily radiological or pathological lesions) limited to the optic nerves and the spinal cord are said to have optic-spinal MS (OSMS). Shibasaki et al differentiated OSMS from Devic disease or neuromyelitis optica in that the former is a polyphasic or relapsing condition while the latter monophasic[27].

Pathologically, NMO lesions showed necrosis and cavitation associated with the demyelinating plaques[28]. A series of reports in the 1990's also found that the MRI of patients with NMO showed a paucity of brain lesions, but the spinal cord lesions were longer than the usual MS lesions. Unfortunately, these reports did not differentiate monophasic from polyphasic disease[29-31]. Recently, it was found that both NMO and OSMS were associated with an autoantibody directed against the water channel, the anti-aquaporin-4 antibody. The autoantibody test was found to be 73% sensitive and 91% specific for NMO and 58% sensitive and 100% specific for OSMS[32]. It was therefore claimed that OSMS is NMO but not MS[33].

However, a joint American-Japanese pathological study on multiple sclerosis did not find any substantial differences in the histopathology of multiple sclerosis lesions in Northern American and Japanese patients with MS. What was noted to be different was the distribution of the lesions[34]. A recent MRI studies of MS patients in the Asia Pacific region showed that the MRI findings were the same as Western patients and a significant proportion of those with OSMS fulfilled the MRI dissemination in space diagnostic criteria for multiple sclerosis. The paucity of brain lesions and the presence of long spinal cord lesions were not specific to OSMS, but was seen in Asian patients with classical MS[35]. Recent reports from Asia contradicted some the initial findings on anti-aquaporin-4 antibody – the sensitivity was only 5.6 – 27.1%, and up to 25% of patients having other neurological conditions (such as idiopathic transverse myelitis) were positive. More importantly, the autoantibody was found to be associated with the severity and frequency of relapses rather than with NMO or OSMS – the autoantibody was more likely to be positive in patients who fulfill MRI criteria for MS, who had long spinal cord regardless of the underlying diagnosis and who had more frequent relapses[36]. The nature of NMO and OSMS, the pathogenesis of these diseases and their association with MS are still topics of intense debate currently.

TREATMENT

The management of patients with multiple sclerosis can be divided into the management of acute relapses, disease modifying therapy, symptomatic treatment and rehabilitation.

Except for minor sensory relapses, the treatment of acute relapses is intravenous methylprednisolone at doses of 1000 mg daily for 3 to 5 days. Tapering doses of oral prednisolone has not been shown to improve results, and may increase the risk of side effects. It is important to remember that paroxysmal symptoms such as Uhthoff phenomenon may mimic relapse, and these should not be treated with high dose steroid. Moreover, steroid only hastens the speed of recovery and has not been shown to improve on the eventual disability[36]. Since paroxysmal symptoms seldom last longer than a few hours and that actual relapse lasts more than 24 hours (but does not continue to deteriorate for more than 30 days), it is therefore worthwhile to observe the patient for a day or two when the cause of neurological deterioration is uncertain. In patients with disabling relapses and who do not respond to high dose steroid, plasmapheresis has been shown to be effective in improving outcomes in two randomized, double-blind, controlled trials[37].

The definitive treatment of relapsing remitting disease that reduces relapse rate, MRI burden of disease and disease progression are the β-interferons, the naturally occurring immunomodulatory cytokines. β-interferon 1a and 1b are mostly given as subcutaneous injection weekly or every other day. Generally, they reduce relapse rate by about a third on intention-to-treat analysis, reduce lesion areas on MRI and delay progression to sustained disability by up to 18 months[38]. The effect was sustained even after 10 years[39, 40]. There is a dose-response relationship, in that high dose β-interferon has been shown to be more effective than low dose or less frequent dose regime[41]. Glatiramer acetate, on the other hand, has only been proven to reduce relapse rate and the burden of disease on MRI, but not the progression of the disease[42]. The main limiting factor to the widespread use of β-interferon locally is the prohibitive cost.

There are recent recommendations that β-interferon treatment should be started as early as possible, even as soon as the first attack if the patient has MRI changes. However, these trials used slightly different MRI criteria[43-46]. This is further confounded in Asia where the overall prevalence of multiple sclerosis is very low, the MRI changes are not as florid, and the conversion rate of a single isolated demyelinating event to multiple sclerosis is not known.

Older immunosuppressants have not been found to be as useful. Sulfasalazine and cladribine do not reduce relapse rate, though mitoxantrone, azathioprine and intravenous immunoglobulin could possibly do. None of these, perhaps with the exception of mitoxantrone, delay the progression to disability[42]. Other newer agents that have been proven useful includes the monoclonal antibodies, natalizumab,[47-49] alemtuzumab,[50] daclizumab[51] and rituximab,[52] as well as other immunosuppressant such as fingolimod, [53] monthly pulse methylprednisolone or intravenous immunoglobulin[52].

The treatment of progressive disease is more controversial. β-interferon, monthly intravenous immunoglobulin and cladribine were not shown to delay disease progression. Mitoxantrone, and possibly monthly pulse methylprednisolone, methotrexate and cyclophosphamide could stabilize disease progression, but the toxicity of these compounds limit their long term use[54]. Future therapy for

relapsing and progressive disease may focus on neuroprotective agents or neuronal stem cell transplantation[55].

Given that current therapy is not able to cure or totally arrest the progression of disabilities, symptomatic and rehabilitation therapy forms an important aspect of the management of multiple sclerosis. Many of the symptoms are amenable to pharmaceutical and surgical intervention, while others are better managed with rehabilitation (see Table I)[56].

PROGNOSIS

The progression of multiple sclerosis is well studied. The median time to reach irreversible disability milestones, such as Disability Scale scores of 4 (limited walking ability, but without aid or rest for more than 500m), 6 (ability to walk with unilateral support no more than 100 m without rest) and 7 (ability to walk no more than 100 m with aid), which is 8, 20 and 30 years respectively, is consistent in many studies worldwide. Important prognostic factors include gender, age of disease onset, characteristics of relapses and the occurrence of progressive disease in the first years of the disease. Younger age of onset, female gender, monosymptomatic onset (such as optic neuritis), complete recovery from the attacks, a long interval between the first two relapses and a low number of relapses within the first year have been consistently associated with a better prognosis in the past[57]. Recent studies of large patient databases, however, are beginning to shed new light on this. In the London, Ontario, study, it was found that patients with primary progressive disease, single attack followed by disease progression sometimes later and patients with secondary progressive disease reached the progressive stage at the same age (38.6, 40.9 and 39.2 years respectively), though the onset ages were different (38.6, 33.3 and 29.8 years respectively). Similarly, Confavreux *et al* found that in the Lyon, France, database, the initial course of disease and the number of relapses did not substantially influence the age at disability milestone – specifically, the number of relapses and the initial course of relapsing or progressive disease did not influence the interval of reaching DSS of 7 from 4 or 6, though the disease duration was longer in those with relapsing disease[58]. These data suggest that degeneration characterizes the later phase of the disease and the progression of disability continues even in the absence of relapses. Along the same vein, it has been proposed that perhaps different phenotype and course of multiple sclerosis (relapsing and progressive) are the perhaps same disease manifested at different phases[57].

The natural history of multiple sclerosis in Asia is less well studied. In Malaysia, 54% of patients with myelopathy without a definite cause went on to develop multiple sclerosis after 5.5 years of follow with the female sex as the only risk factor[59]. In those with established MS, the frequent attacks of optic neuritis and myelitis impacts negatively on the patients' prognosis, hence it was not surprising that Asian patients reached the same level disability 5 to 10 years earlier than their Western counterparts. It was also not surprising to find that the number of relapses did not affect the level of disability; but on logistic regression analyses, progressive course of illness, a history of transverse myelitis, incomplete recovery from the first attack and abnormal somatosensory evoked potential study were associated with more severe disability[60]. Long term disability study similar to those from London, Ontario, and Lyon, France, will be invaluable in determining the nature of various types of multiple sclerosis in Asia, including that of optic-spinal multiple sclerosis.

CONCLUSION

Over the last twenty years, an explosion of knowledge has impacted every aspect of our understanding of multiple sclerosis. The genome-wide survey, the findings of early axonal injury, the importance of neuronal degeneration as elucidated by both pathological and long term clinical studies and the early occurrence of oligodendrocyte apoptosis as the trigger of inflammation had revolutionized our understanding of multiple sclerosis. The advent of MRI has given us a sharp tool in diagnosis; and that of cytokines and monoclonal antibodies has for the first time enabled us to alter the course of the illness without much side effect. The future looks even brighter with a host of drug going through the phases of trials which will add to our armamentarium of treatment. Finally, the understanding of the pathophysiology and the availability of sensitive diagnostic imaging tools will not only enable us to prognosticate better, but also allow us to better assess the effectiveness and efficacy of new treatment.

REFERENCES

1. Kurtzke JF and Wallin MT. Epidemiology. In Burks JS and Johnson KP (ed) Multiple Sclerosis: Diagnosis, Medical Management and Rehabilitation. Demos, New York. 2000.
2. Chong HT, Li PCK, Ong B *et al*. Severe spinal cord involvement is a universal feature of Asians with multiple sclerosis: A joint Asian Study. Neurol J Southeast Asia 2002; 7: 35-40.
3. Román GC, Castellanos-Mateus P. Multiple Sclerosis in Feigin VL and Bennett DA. (ed) Handbook of Clinical Neuroepidemiology. Nova Science Publisher, New York, 2007.
4. Cheng Q, Miao L, Zhang J *et al* A population-based survey of multiple sclerosis in Shanghai, China. Neurology 2007; 68: 1495-500.
5. Kira J. Epidemiology of multiple sclerosis in Japanese: with special reference to opticospinal multiple sclerosis. Rinsho Shinkeigaku – Clinical Neurology 2006; 46(11): 859-62.
6. Tan CT. Multiple sclerosis in Malaysia. Arch Neurol 1988; 45: 624-27.
7. Tan CT. Multiple sclerosis in Malaysia. Neurol J Southeast Asia 1997; 2: 1-5.
8. Peltonen, L. Old suspects found guilty – The first genome profile of multiple sclerosis. N Eng J Med, 2007; 357 (9): 927-29.
9. The International Multiple Sclerosis Genetic Consortium. Risk alleles for multiple sclerosis identified by a genomewide study. N Eng J Med, 2007; 357(9): 851-62.
10. Kurtzke JF and Hyllested K. Multiple sclerosis in the Faroe Island: Clinical and epidemiological features. Ann Neurol, 1979; 5 (1): 6-21.
11. Munger KL, Levin LI, Hollis BW *et al*. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006; 296: 2832-38.
12. Munger KL, Zhang SM, O'Reilly S *et al*. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004; 62: 60-65.
13. Brück, W. Clinical implications of neuropathological findings in multiple sclerosis. J Neurol 2005; 252 (Suppl 3): III 10 – III 14.
14. Trapp, BD, Peterson J, Ransohoff RM *et al*. Axonal transaction in the lesions of multiple sclerosis. N Eng J Med, 1998; 338: 278-85.
15. Kornek B and Lassmann H. Neuropathology of multiple sclerosis – new concepts. Brain Research Bulletin 2003; 61: 321-26.
16. Lisak RP. Neurodegeneration in multiple sclerosis. Neurology 2007; 68 (Suppl 3): S5-S12.
17. Barnett MH and Prineas JW. Relapsing and remitting multiple sclerosis: Pathology of the newly forming lesion. Ann Neurol 2004; 55: 458-68.
18. Matute C. and Pérez-Cerdá F. Multiple sclerosis: Novel perspective on newly forming lesions. Trends in Neurosciences 2005; 28(4): 173-75.

19. Paty DW. Initial Symptoms. In Multiple Sclerosis: Diagnosis, Medical Management and Rehabilitation by Burks JS and Johnson KP. Demos, New York, 2000.
20. Tan CT. Paroxysmal tonic seizures in demyelinating disease. Singapore Med J, 1986; 27(3): 256-8.
21. Ho JSF and Tan CT. Visual function among multiple sclerosis patients in Malaysia. Neurol J Southeast Asia 2000; 5: 35-40.
22. Bitsch A and Brück W. Differentiation of multiple sclerosis subtypes. CNS Drug 2002; 16(6): 405-18.
23. Polman CH, Reingold SC, Eden G *et al*. Diagnostic criteria for multiple sclerosis: 2005 Revisions to the "McDonald's Criteria". Ann Neurol 2005; 58: 840-46.
24. Chong HT, N Ramli, KH Lee *et al* Magnetic resonance imaging of Asians with multiple sclerosis was similar to that of the West. Neurol Asia 2004; 9: 47-53.
25. Chong HT, N Ramli, KH Lee *et al* Low sensitivity of McDonald MRI criteria in the diagnosis of multiple sclerosis among Asians. Neurol Asia 2006; 11: 129-33.
26. Chong HT, Li PCK, Singhal BJ, Kira J, Saida T, Kim BJ, Lee KH, Ong BKC, Tsai CP, Prayoonwiwat N and Tan CT. Proposed modifications to McDonald diagnostic criteria for Asians with multiple sclerosis. Neurol Asia 2006; 11: 87-90.
27. Cree BAC, Goodin DS and Hauser SL. Neuromyelitis optica. Seminar in Neurology 2002; 22(2): 105-22.
28. de Seze J. Neuromyelitis optica. Arch Neurol 2003; 60: 1336-38.
29. O'Riordan JI, Gallagher HL, Thompson AJ, Howard RS, Kingsley DP, Thompson EJ, McDonald WI, Miller DH Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. J Neurol Neurosurg Psychiatry 1996; 60(4): 382-7.
30. Fazekas F, Offenbacher H, Schmidt R *et al*. MRI of neuromyelitis optica: evidence for a distinct entity. J Neurol Neurosurg Psychiatry 1994; 57(9): 1140-2.
31. Filippi M, Rocca MA, Moiola L, Martinelli V, Ghezzi A, Capra R, Salvi F, Comi G. MRI and magnetization transfer imaging changes in the brain and cervical cord of patients with Devic's neuromyelitis optica. Neurology 1999; 53(8): 1705-10.
32. Lennon VA, Wingerchuk DM, Kryzer TJ *et al*. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004; 364: 2106-112.
33. Weinshenker BG, Wingerchuk DM, Nakashima I *et al*. OSMS is NMO, but not MS: proven clinically and pathologically. Lancet Neurology 2006; 5: 110-111.
34. Ikuda F, Koga M, Takeda S *et al*. "Comparison of MS pathology between 70 American and 75 Japanese autopsy cases" in Kuroiwa Y and Kurland LT (ed) Multiple Sclerosis East and West: Proceedings of the Asian Multiple Sclerosis Workshop and Satellite Symposium, Multiple Sclerosis, 12th World Congress of Neurology. Karger, Basel 1981.
35. Chong HT, Kermode A and Tan CT. The role of anti-aquaporin-4 antibody in Asian patients with multiple sclerosis: Confusions and controversies. Neurology Asia 2007; 12: 135-39.
36. Murray TJ. Diagnosis and treatment of multiple sclerosis (Clinical Review). BMJ 2006; 332: 525-7.
37. Lehmann HC, Hartung H-P, Hetzel GR, Stüve O and Kieseier BC. Plasma exchange in neuroimmunological disorders. Arch Neurol 2006; 63: 930-35.
38. Calabresi PA. Considerations in the treatment of relapsing remitting multiple sclerosis. Neurology 2002; 58(Suppl 4): S10-S22.
39. Tourbah A and Lyon-Caen O. Interferons in multiple sclerosis: Ten years' experience. Biochimie 2007; 89: 899-902.
40. Pozzilli C, Prosperini L, Sbardella E and Paolillo A. Inteferon after 10 years in patients with multiple sclerosis. Neurol Sci 2006; 27: S369-72.
41. Durelli L, Verdun E, Barbero P *et al*. Every other day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002; 359: 1453-60.
42. Goodin DS, Frohman EM, Garmany GP *et al*. Disease modifying therapies in multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002; 58: 169-78.
43. Comi G. Future therapies in multiple sclerosis: Early treatment. Neurol Sci 2006; 27: S8–S12.
44. Jacobs LD, Beck RW, Simon JH *et al*. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. N Eng J Med, 2000; 343: 898-904.
45. Comi G, Filippi M, Barkhof F *et al*. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001; 357: 1576-82.
46. Kappos L, Polman CH, Freedman MS *et al*. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006; 67: 1242-49.
47. Rudick RA, Stuart WH, Calabresi PA *et al* for the SENTINEL investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Eng J Med, 2006; 354: 911-23.
48. Miller DH, Khan OA, Sheremata WA *et al* for the International Natalizumab Multiple Sclerosis Trial Group. N Eng J Med, 2003; 348: 15-23.
49. Kappos L, Bates D, Hartung H-P *et al.* Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurology 2007; 6: 431-41.
50. Coles AJ, Cox A, Le Page E *et al*. The window of therapeutic opportunity in multiple sclerosis: Evidence from monoclonal antibody therapy. J Neurol 2005; online publication: DOI 10.1007/s00415-005-0934-5.
51. Rose JW, Burns JB, Bjorklund J, Klein J, Watt HE and Carlson NG. Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. Neurology 2007; 69: 785-89.
52. Rizvi SA and Bashir K. Other therapy options and future strategies for treating patients with multiple sclerosis. Neurology 2004; 63 (Suppl 6): S47-S54.
53. Kappos L, Antel J, Comi G *et al*. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Eng J Med, 2006; 335: 1124-40.
54. Rovaris M, Confavreux C, Furlan R, Kappos L, Comi G and Filippi M. Secondary progressive multiple sclerosis: Current knowledge and future challenges (review). Lancet Neurology 2006; 5: 343-54.
55. Karussis D, Grigoriadis S, Polyzoidou E, Grigoriadis N, Slavin S and Abramsky O. Neurprotection in multiple sclerosis. Clinical Neurology and Neurosurgery 2006; 180: 250-54.
56. Thompson AJ. Symptomatic management and rehabilitation in multiple sclerosis. J Neurol Neurosurg Psychiatry 2001; 71 (Suppl II): ii22-ii27.
57. Vukusic S and Confavreux C. Natural history of multiple sclerosis: risk factors and prognostic indicators. Current Opinion in Neurology 2007; 20: 269-74.
58. Confavreux C, Vukusic S, Moreau T and Adeleine P. Relapses and progression of disability in multiple sclerosis. N Eng J Med, 2000; 343: 1430-8.
59. Tan CT. Prognosis of patients who present with an episode of myelopathy of unknown origin in Malaysia: a retrospective study of 52 patients. Aust NZ J Med 1989; 19: 297-302.
60. Chong HT, Li PCK, Ong B *et al*. Long term outcome of multiple sclerosis in Asia. Neurol Asia 2006; 11: 49-53.