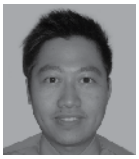


Benjamin K-T Tsang
Richard Macdonell

Multiple sclerosis

Diagnosis, management and prognosis

Background

Multiple sclerosis is the most common chronic disabling disease of the central nervous system in young adults.

Objective

This article summarises the diagnosis, management and prognosis of multiple sclerosis.

Discussion

Multiple sclerosis usually starts with an acute episode of neurological disturbance, termed a 'clinically isolated syndrome', followed by an illness phase punctuated by relapses and remissions which may transition after 10 years to a phase of progressive accumulation of disability without relapses. Fifteen to 20% of patients will have a progressive course from the onset. There is significant interpatient variability in prognosis. The main diagnostic criteria are clinical, supported by investigations including magnetic resonance imaging and lumbar puncture and evoked potentials. First line disease modifying agents for relapsing remitting multiple sclerosis include interferon-ß and glatiramer. First line treatment for relapses is usually intravenous methylprednisolone for 3 days. Troublesome symptoms may include spasticity, parasthesias, tremor, erectile dysfunction, depression and anxiety, fatigue and pain. After excluding differential diagnoses, symptomatic management includes pharmacological agents, allied health consultation and continence strategies. Although pregnancy reduces disease activity, there is a higher risk of relapse in the postpartum period.

Keywords: multiple sclerosis

CPD

Multiple sclerosis (MS) is a multifocal central nervous system (CNS) disorder characterised by inflammatory demyelinating lesions affecting white and grey matter; thought to be mediated by autoreactive T cells.[1,2] In addition to demyelination, irreversible axonal injury occurs from the outset. It is the steady accumulation of damage to the CNS over time that leads to the irreversible disability that characterises the advanced stages of the disease.[1]

Aetiology

Multiple sclerosis arises from a complex interaction of environmental and genetic factors. Environmental factors include place of residence in pre-adult years, age of exposure to Epstein-Barr virus, and smoking. Later age of exposure to Epstein-Barr virus infection is associated with a higher incidence of the disease while seronegative individuals have a very low risk of developing MS.[3] Genome wide association studies have now identified 52 risk alleles for the development of MS, but HLA-DRB1 status retains the strongest correlation.[4]

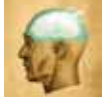
Epidemiology

The epidemiology of MS in Australia shows that it varies with latitude. It is more common in Tasmania (approximate prevalence 100 per 100 000 and incidence 4 per 100 000) and becomes progressively less common as one travels further north.[5] There are approximately 13 000 people with MS currently in Australia, females comprise approximately 73% of cases. Mean age at symptom onset and diagnosis is the mid 30s.[6]

Natural history and disease phases

Clinically isolated syndrome (first demyelinating event)

Eighty-five percent of people who later develop MS start with an episode of neurological disturbance, usually evolving over days or weeks.[7] This is known as a 'clinically isolated syndrome' (CIS), or 'first demyelinating event'. A review of a large database of patients with MS found that 21% started with a clinically isolated syndrome of optic neuritis, 46% with long tract symptoms and signs (motor or sensory deficits), 10% with a brainstem syndrome and 23% with multifocal abnormalities (*Table 1*).[8–10]



Relapsing remitting multiple sclerosis

Most patients with MS experience an initial disease phase punctuated by relapses and remissions. This is termed relapsing remitting MS (RRMS). A relapse is defined as symptoms or objective signs typical of an acute inflammatory demyelinating event in the CNS which last at least 24 hours (*Table 1*).[9] Complete resolution may occur, but mild residual symptoms or signs persist in up to 40% of attacks.[11] A major increase in disability due to a single relapse is uncommon. In untreated patients new relapses occur erratically with a mean rate of 0.65 attacks per year.[12] Fatigue in isolation or transient fever related worsening of symptoms are not considered to be relapses and are termed pseudorelapses.[9]

Secondary progressive multiple sclerosis

After 10 years, 40–45% of patients with RRMS will have transitioned to a phase of progressive accumulation of disability without relapses, termed, secondary progressive MS (SPMS).[12] The lifetime risk of this transition is greater than 80%.[12] In this phase, occasional plateaus and temporary minor improvements may be observed, however the overwhelming trend is toward progressively increasing disability.

Primary progressive multiple sclerosis

Fifteen to 20% of patients have a progressive course from disease onset, without relapses or remissions. This is termed, primary progressive MS (PPMS).[13] The most common presentation of PPMS is a slowly progressive spastic paraparesis, followed by cerebellar or hemiplegic syndromes.[13] Primary progressive MS does not respond to current treatment.

Investigations and diagnosis

Multiple sclerosis remains a clinical diagnosis supported by magnetic resonance imaging (MRI), laboratory findings from cerebrospinal fluid (oligoclonal bands and raised IgG index), and evoked potential studies (delayed evoked response with preserved waveform).[9,14] Ultimately it can only be confirmed histopathologically, but the need to resort to biopsy is rare. Over recent years diagnostic criteria for clinically definite, probable and possible MS have evolved from the purely clinically based definitions,[15,16] which emphasised dissemination in space and in time of lesions, with exclusion of alternative diagnoses. The advent of MRI led to the McDonald criteria[9] (most recently revised in 2010) which are now the accepted criteria for a diagnosis of MS. These criteria still allow for a diagnosis of clinically definite MS if a patient has objective clinical evidence of two lesions that are disseminated in space and time and there is no better explanation for the clinical presentation. However in reality, MRI correlation is usually sought. Importantly, if imaging or other tests (eg. cerebrospinal fluid) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS and alternative diagnoses must be considered. The McDonald criteria also allow for a diagnosis of MS without objective clinical evidence of two lesions disseminated in space and time. If one of these criteria are not met the presence of the other can be inferred from contrast enhanced MRI findings (*Figure 1*), which has sensitivities in the range of 95% for patients with clinically definite MS.[8] Typical locations of MS lesions on MRI are listed in *Table 2*.[8,9] Primary progressive MS is diagnosed by recognising the clinical syndrome of 1 year of disease progression,

Table 1. Common sites, signs and symptoms of acute inflammatory demyelinating events (clinically isolated syndrome or multiple sclerosis relapses)[8–10]

Site	Condition	Symptoms	Signs
Optic nerve	Optic neuritis	Pain on eye movement, blurred vision	Reduced monocular visual acuity, colour desaturation
Cerebellum	Cerebellar disease	Unsteadiness	Limb or gait ataxia; horizontal or torsional gaze evoked nystagmus
Spinal cord (usually multifocal and asymmetric)	Partial myelitis affecting pyramidal tracts	Upper or lower limb weakness	Pyramidal distribution weakness
	Partial myelitis affecting spinothalamic tract and posterior columns	Unilateral or bilateral limb numbness or paraesthesias L'Hermitte's phenomenon (short electric shock-like sensation on neck movement)	Sensory level
Brainstem			
• Medial longitudinal fasciculus	Internuclear ophthalmoplegia	Blurred or double vision	Internuclear ophthalmoplegia
• Pyramidal tracts	(Similar to conditions described in spinal cord)		
• Spinothalamic tract and posterior columns	(Similar to conditions described in spinal cord)		
Bowel/bladder	Loss of upper motor neuron control	Constipation, urinary frequency, urge incontinence, erectile dysfunction	

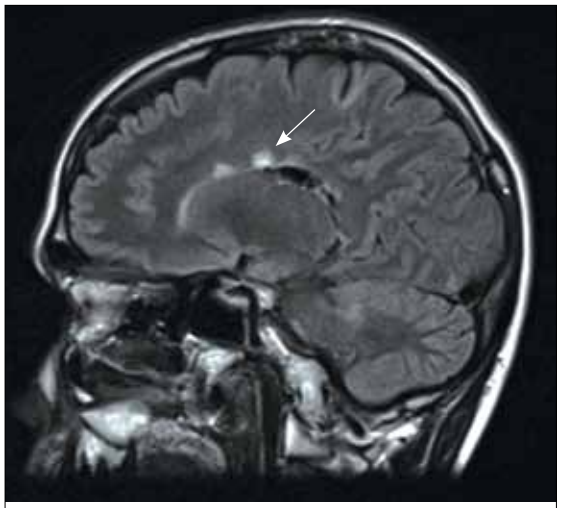


Figure 1. Sagittal view of the brain, showing multiple pericallosal hyperintense lesions (arrow) on fluid attenuation inversion recovery (FLAIR)

an MRI showing evidence of inflammatory lesions with dissemination in space and positive oligoclonal bands in the cerebrospinal fluid.[9]

Differential diagnoses

The most problematic differential diagnoses are other demyelinating illnesses such as neuromyelitis optica (Devic

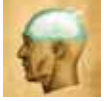
Table 2. Typical sites of lesions on MRI[8,9]

- Periventricular white matter (if at right angles to the corpus callosum, these are referred to as 'Dawson fingers')
- Juxtacortical white matter
- Corpus callosum
- Optic nerve (with gadolinium enhancement in acute neuritis)
- Infratentorial structures (pons, cerebellar peduncles and cerebellum)
- Spinal cord

Table 3. Disease modifying treatments for multiple sclerosis available on the PBS[20,21]

Drug	Mode of action	Indications	Route and recommended dose
Interferon-ß-1a (Avonex®, Rebif®)	Immunoregulatory including antagonism of gamma interferon, reduction of cytokine release and augmentation of suppressor T cell function	Reduction of relapses in ambulatory RRMS	Avonex®: IMI 30 µg once per week Rebif®: SC 44 µg three times per week
Interferon-ß-1b (Betaferon®)	Immunoregulatory including antagonism of gamma interferon, reduction of cytokine release and augmentation of suppressor T cell function	Reduction of relapses in ambulatory RRMS SPMS with relapses	SC 250 µg every 2 days
Glatiramer acetate (Copaxone®)	Synthetic polypeptide; possibly blocks presentation of myelin antigens to T lymphocytes	Reduction of relapses in RRMS	SC 20 mg once daily
Natalizumab (Tysabri®)	Recombinant humanised monoclonal antibody to alpha-4 integrins, inhibiting leucocyte migration from blood to CNS	Reduction of relapses in RRMS	IV 300 mg over 1 hour, once a month
Fingolimod (Gilenya®)	Sphingosine 1-phosphate receptor modulator	Reduction of relapses in RRMS	Orally 0.5 mg/day
Mitoxantrone (Onkotrone®)	Anthracenedione derivative that inhibits DNA and RNA synthesis by intercalation of DNA base pairs. Prevents DNA repair by inhibiting topoisomerase II	RRMS	IV 12 mg/m^2 every 3 months up to a total cumulative dose of 140 mg/m^2 (100 mg/m^2 in patients with cardiac risk factors)
Cyclophosphamide (Endoxan®, Cycloblastin®)	Cytotoxic effect on lymphocytes	RRMS	IV – multiple different regimens

IV = intravenous; SC = subcutaneous; IMI = intramuscular injection



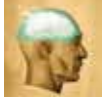
disease) and acute disseminated encephalomyelitis. Neuromyelitis optica can present with relapsing CNS demyelinating disease characterised by involvement of optic nerves, often severe myelopathy with MRI evidence of longitudinally extensive spinal cord lesions and serum aquaporin-4 autoantibodies.[9] This phenotype has a different clinical course and prognosis and is poorly responsive to MS disease modifying therapies (DMTs). Acute disseminated encephalomyelitis is a monophasic autoimmune demyelinating illness of the CNS typically seen in paediatric populations. However, it is also seen in adults and can be indistinguishable from an acute MS attack.[17] Typical acute disseminated encephalomyelitis tends to have a more explosive course associated with alterations in mental status. Triggers such as recent viral infection or vaccination may be present. Other important differential diagnoses include[1,9,10]:

- migraine
- cerebral neoplasms (primary and secondary)
- nutritional deficiencies (eg. B12 or copper)
- compressive lesions of the spinal cord
- infections (eg. syphilis, HIV)
- amyotrophic lateral sclerosis
- steroid sensitive relapsing disorders (eg. systemic lupus erythematosus, neurosarcoidosis)
- recurrent infarcts
- paraneoplastic syndromes
- psychiatric disease/functional symptoms.

Treatment of acute relapses

Intravenous methylprednisolone (1 g/day for 3 days) is the treatment of choice but is only necessary if the relapse impacts significant on quality of life. This treatment has been shown to hasten the recovery from a relapse but not the likelihood of recovery, frequency of further attacks or any permanent disability resulting from an attack.[18,19] Side effects may include mood changes, psychosis, aseptic hip necrosis and hyperglycaemia.[20] Plasma exchange is considered in steroid unresponsive patients with severe relapse.[19] Pseudorelapses may

Precautions	Adverse effects	Other comments
May worsen seizures, depression, psychiatric illnesses, and cardiac disease	Common: injection site reactions, flu-like illness, headache, depression, nausea, abdominal pain, raised liver function tests (LFTs), anaemia, leucopenia Uncommon: interferon-ß neutralising antibodies, hypertension Rare: heart failure, cardiomyopathy, suicidal thoughts, lymphadenopathy, autoimmune disease, hepatotoxicity, thyroid dysfunction, hypersensitivity, alopecia	Dose titration recommended Paracetamol may reduce flu-like symptoms Presence of neutralising antibodies may reduce response Monitor full blood examination, LFTs periodically
Asthma, history of anaphylaxis – risk of allergic reactions	Common: injection site reactions, nausea, arthralgia, oedema, hypertonia, tremor Rare: anaphylaxis	Antibodies to glatiramer develop in all patients and are not associated with adverse effects or decreased efficacy
Caution if history of progressive multifocal leukoencephalopathy, immunosuppression Treatment with other DMTs contraindicated	Common: infusion reactions, (headache, dizziness, fever, arthralgia, rigors, flushing), neutralising antibodies Rare: progressive multifocal leukoencephalopathy, hepatotoxicity	Persistent neutralising antibodies associated with reduced efficacy and increased risk of allergic reactions
Caution in diabetic patients due to increased risk of macular oedema	Common: bronchitis, lymphopenia, bradycardia, LFT abnormalities Uncommon: prolongation of QT interval, bronchospasm, macular oedema, disseminated varicella in the nonimmunised	
Caution in hepatic disease (dose reduction) and elderly (increased risk of myelosuppression)	Common: lassitude Infrequent: taste disturbance, gastrointestinal bleeding, dyspnoea, rash, nail pigmentation, conjunctivitis, cardiomyopathy, acute myeloid leukaemia	
Caution in renal impairment (dose reduction)	Common: myelosuppression, alopecia, anorexia, haemorrhagic cystitis, nasal congestion, taste disturbance Rare: heart failure, pulmonary fibrosis	Mesna (a cytoprotective agent) is used for prophylaxis of cystitis



occur as a result of sepsis and fever and treatment should be geared toward the infectious agent rather than using steroids.

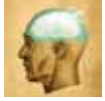
Disease modifying treatments

Disease modifying treatments are approved by the Therapeutic Goods Administration for use in patients with clinically isolated syndrome and RRMS but are only available on the Pharmaceutical Benefits Scheme (PBS) for RRMS (*Table 3*).[20,21] Suppression of relapses and their surrogates (new lesions on imaging) have been used as the endpoints for evaluating efficacy of these drugs. Suboptimal response is indicated by an unchanged relapse rate or ongoing MRI activity after continuous therapy for at least 6 months compared with pretreatment. The patient should first be evaluated to identify secondary causes for suboptimal response including noncompliance or the development of neutralising antibodies to interferon-ß.

Table 4. Therapy directed at the symptoms of multiple sclerosis[20,21]

Symptom	Drug	Dosage	Common side effects	Comments
Spasticity	Baclofen	If predominantly nocturnal symptoms: 10–25 mg nocte; if continuous symptoms: 5–25 mg tds	Weakness, drowsiness, dizziness, fatigue, headache, insomnia, confusion, ataxia, frequency, urgency, dysuria, constipation	If ceased, needs to be withdrawn slowly over 2 weeks to avoid agitation, delirium, convulsions
	Diazepam	2–10 mg tds	Drowsiness, ataxia, dependency	Can be used as add-on therapy to baclofen
	Dantrolene	Starting dose 25 mg/day (maximum 50 mg qid)	Muscle weakness, drowsiness, hypertension, drooling, enuresis, diarrhoea, nausea, abnormal LFTs	Mainly useful in bed-bound patients
Paroxysmal symptoms of MS*	Carbamazepine	Initially 100 mg bd increasing slowly to 300 mg bd	Fatigue, weakness, ataxia	
Fatigue	Amantadine	100–200 mg/day in two divided doses	Nervousness, depression, nightmares, hallucinations, insomnia, dizziness, headache, blurred vision, orthostatic hypotension, peripheral oedema, dry mouth, gastrointestinal side effects	Should be gradually withdrawn after 3–4 months because of likely spontaneous improvement
Intention tremor	Clonzepam	0.5 mg/day increasing slowly to 6 mg/day	Drowsiness, ataxia, dependency	
	Propranolol	40 mg bd	Nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, bradycardia, hypotension	
	Carbamazepine	100 mg bd, can be increased to 300 mg bd	See above	Increase slowly until symptoms resolve
Urinary urgency	Oxybutynin	2.5–5 mg bd to tds	Dry mouth, constipation, nausea, vomiting, dyspepsia, blurred vision, dry eyes, tachycardia, facial flushing	
	Propantheline	15–30 mg tds	Dry mouth, constipation, nausea, vomiting, dyspepsia, blurred vision, dry eyes, tachycardia	
	Amitriptyline or imipramine	25–75 mg nocte	Dry mouth, constipation, nausea, vomiting, dyspepsia, blurred vision, dry eyes, tachycardia	
Erectile dysfunction	Sildenafil	25–100 mg 1 hour before intercourse	Rash, diarrhoea, urinary tract infections, abnormal vision	

* Paroxysmal symptoms of MS include trigeminal neuralgia and paraesthesias
bd = twice per day; tds = three times per day; qid = 4 times per day; nocte = at night



First line treatments

The interferon-ßs and glatiramer acetate have been used as first line DMTs for RRMS for over a decade. They have roughly equivalent efficacy; double blind, placebo controlled trials demonstrate a relapse reduction of around 30% and reduction in the number of active lesions on brain MRI for both groups.[22,23] Studies have also shown these drugs delay the progression from clinically isolated syndrome to clinically definite MS.[24] However, they are not approved for this use on the PBS.

Second line treatments

Natalizumab has been demonstrated to reduce the rate of disability progression, the annualised relapse rate and the number of new lesions on MRI by 54%, 68% and 92% respectively.[25] Although these relative risk reduction figures appear greater than those seen with interferon-ß and glatiramer acetate, its use is limited due to the potentially devastating complication of progressive multifocal leukoencephalopathy due to a brain infection with JC virus. The risk of progressive multifocal leukoencephalopathy overall is estimated at one case per 600 patients treated[26] and an increased risk is associated with longer treatment duration, prior immunosuppressant use and presence of antibodies against JC virus.[27] Natalizumab has generally been used to treat patients who have a suboptimal response to first line DMTs or in those who have a particularly aggressive initial disease course.

Fingolimod (FTY720), the first oral treatment for RRMS, was listed on the PBS on 1 September 2011.[28] This drug has a unique mode of action through the sphingosine 1-phosphate receptor which prevents lymphocyte trafficking through the lymph node and causes a reversible lymphopenia.[29] With regards to the efficacy of fingolimod in clinical trials, the annualised relapse rate was approximately 50% lower compared to placebo. Approximately 70–75% of the fingolimod groups were relapse free for 2 years compared with 46% of the placebo group.[30] Despite being a 1 year trial, fingolimod has also been shown to have greater efficacy compared to interferon with respect to relapse rate and proportion who are relapse-free. However, discontinuation rates were higher in the fingolimod arm.[31] The drug is given 0.5 mg/day and is generally well tolerated. Possible side effects include first dose bradycardia, macular oedema, liver function abnormalities and increased risk of infections. It should not be used in patients without prior exposure to varicella zoster infection or immunisation.

Other oral therapies currently undergoing preclinical trials include laquinimod, teriflunomide and BG12. The long term safety and exact role of these oral therapies in MS are yet to be established.

Third line and salvage therapeutic options

In patients with aggressive disease who do not respond to treatment, other options include immunosuppression with cyclophosphamide or mitoxantrone, or high dose chemotherapy followed by autologous haematopoeitic stem cell transplant. The use of these strategies is limited by their lower tolerability and potentially serious adverse events.

Table 5. Early clinical features affecting prognosis in multiple sclerosis[35–38]

Better prognosis	Poor prognosis
• Optic neuritis or isolated sensory symptoms as the CIS • Initial relapsing remitting course • Long interval to second relapse • No disability after 5 years • Normal initial MRI • Female gender • Younger age at onset • Complete recovery from the first neurological episode	• Efferent systems affected in the CIS or 'multifocal' CIS • High relapse rate in first 2–5 years • Substantial disability after 5 years • Abnormal initial MRI with large lesion load

Symptomatic treatment

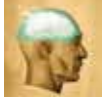
Troublesome symptoms may include spasticity, parasthesias, tremor, erectile dysfunction, depression and anxiety, fatigue and pain. Symptomatic management includes pharmacological agents (*Table 4*), allied health consultation and continence strategies. It is important to exclude differential diagnoses before instituting treatment (eg. urinary infection in patients with new urinary symptoms).

In addition to the medications outlined in *Table 4*, spasticity may respond to physiotherapy and muscle stretching. Cerebellar intention tremor is difficult to treat pharmacologically, however wrist weights can be tried. A pre- and post-void bladder scan will help direct continence strategies: urinary urgency due to a small capacity 'spastic' bladder may respond to anticholinergic drugs. If the bladder is atonic, intermittent urinary catherterisation is more appropriate.

Depression and anxiety are very common in MS, but psychoses are rare. Management options include counselling with a psychologist familiar with MS and antidepressants.[21] Fatigue is common and may respond to amantidine 100 mg in the morning and at midday. Importantly, depression should always be considered as a cause in any MS patient complaining of fatigue. Pain is common and often under-recognised in MS and management includes counselling and medications (eg. amitriptyline, carbamazepine, gabapentin, pregabalin).

Pregnancy and multiple sclerosis

All drugs listed in *Table 3* are Australian Drug Evaluation Committee pregnancy category D, except glatiramer (Category B1) and natalizumab (Category C). Pregnancy reduces disease activity, particularly in the third trimester when it is around 70% lower than the year preceding pregnancy.[32] In the postpartum period, there is a higher risk of relapses in the first 3 months after delivery when up to 30% of patients may relapse.[32] The decision when to stop treatment and when to recommence after delivery should be individualised, depending on disease activity in the months leading up to the time when the woman plans to conceive.



Prognosis

Multiple sclerosis is characterised by considerable interpatient variability in prognosis. Less than 5% of patients have very severe disability within the first 5 years after onset and 10–20% of patients remain unimpaired without therapy over 20 years.[12] In the pre-DMT era, the median time from disease onset to cane requirement, bedbound status and death, was roughly 15, 26 and 41 years respectively.[12] The median survival time is approximately 5–10 years shorter for MS patients than for the age matched general population.[33] The degree to which DMTs alter this timeline of progression is still to be determined.[34] Early clinical features of MS reported to affect prognosis are listed in *Table 5*.[35–38]

In PPMS and other progressive forms of MS, the median time from disease onset to reaching irreversible disability scores is significantly earlier compared to RRMS, with most patients having developed mild to moderate disability by time of diagnosis.[12] Cognitive impairment occurs at all stages and in all subtypes of MS, with the more severe levels of cognitive impairment occurring in the progressive phase.[39] The typical profile of impairment is in information processing speed, memory and executive skills. This often impacts on the employability of the patient with MS, even when physical disability is low, and should be factored in at the other end of the spectrum when end-of-life issues are raised.

Summary of important points

- Multiple sclerosis usually starts with an acute episode of neurological disturbance.
- There is significant interpatient variability in prognosis.
- The main diagnostic criteria are clinical, supported by investigations including MRI and lumbar puncture and evoked potentials.
- First line disease modifying agents for relapsing remitting MS include interferon-ß and glatiramer.
- First line treatment for relapses is usually intravenous methylprednisolone for 3 days.
- Troublesome symptoms including spasticity, parasthesias, tremor, erectile dysfunction, depression and anxiety, fatigue and pain can be managed with pharmacological agents, allied health consultation and continence strategies.
- Pregnancy reduces disease activity. However, there is a higher risk of relapse in the postpartum period.

Resources

- Multiple Sclerosis Society of Australia: www.msaustralia.org.au
- Multiple Sclerosis Research Australia: www.msra.org.au
- The Brain Foundation: www.brainaustralia.org.au.

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Conflict of interest: Professor Macdonell has served on advisory boards for Biogen Idec, Novartis, Sanofi-Aventis and Merck-Serono. The MS service at Austin Health has received honoraria, travel support, and research and clinical service sponosrhip from Biogen Idec, Novartis, Sanofi-Aventis, Merck-Serono and Bayer-Schering.

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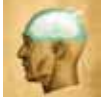

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