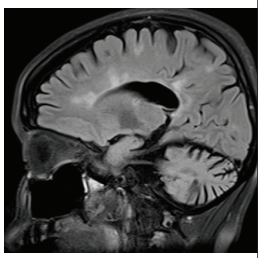
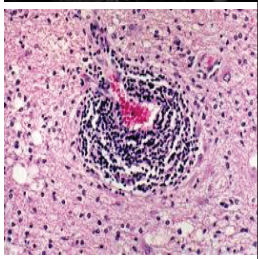
QUICK REFERENCE FOR HEALTHCARE PROVIDERS

MANAGEMENT OF MULTIPLE SCLEROSIS





Ministry of Health Malaysia

Malaysian Society of Neurosciences

Academy of Medicine Malaysia

KEY MESSAGES

1. Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disorder characterised by neuroinflammation & neurodegeneration. The hallmark of MS is attacks or exacerbations affecting different parts of the central nervous system (CNS) which are separated in time & space in the absence of any other better explanation. It is a disease of the young (20s to 40s) & commoner among women.
2. An attack/relapse/exacerbation in MS is defined as a patient-reported symptom or objectively observed signs typical of an acute inflammatory demyelinating event within the CNS either current or historical of at least 24 hours in the absence of fever or infection.
3. Clinically isolated syndrome (CIS) is the first clinical episode in which a patient has symptoms & signs suggestive of an inflammatory demyelinating disorder of the CNS. Patients with CIS need to be stratified according to risk of conversion to Clinically Definite Multiple Sclerosis (CDMS).
4. The commonest type of MS is relapsing-remitting disease (85%).
5. The McDonald criteria 2010 should be used in the diagnosis of MS.
6. Magnetic resonance imaging (MRI) of the brain & spine utilising the MRI Diagnostic Criteria should be used in the diagnosis of MS. Cerebrospinal fluid oligoclonal bands & evoked potentials may be useful in the diagnostic workup.
7. In the diagnosis of MS, it is important to rule out other possible mimickers of MS [idiopathic inflammatory demyelinating disease (IIDD) such as neuromyelitis optica spectrum disorder, vasculitis, sarcoidosis and small vessel disease] & identify the “Red Flags” that may suggest an alternative diagnosis to MS.
8. Patients with clinical features highly suggestive of MS should be referred to a neurologist.
9. Disease progression in MS should be assessed clinically by using Kurtzke's Expanded Disability Status Scale upon diagnosis & follow-up. MRI should be done at baseline, annually & earlier if clinically indicated. Neuroimaging parameters in monitoring MS disease activity are T2-weighted & gadolinium-enhancing T1-weighted lesions.
10. The management of MS involves:
    - treatment of acute attacks (this includes CIS & relapses in CDMS)
    - prevention of relapses
    - multidisciplinary interventions for MS-related symptoms

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Multiple Sclerosis.
Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:
Ministry of Health Malaysia: www.moh.gov.my
Academy of Medicine Malaysia: www.acadmed.org.my
Also available as a mobile app for Android & IOS platform: MyMaHTAS

CLINICAL PRACTICE GUIDELINES SECRETARIAT
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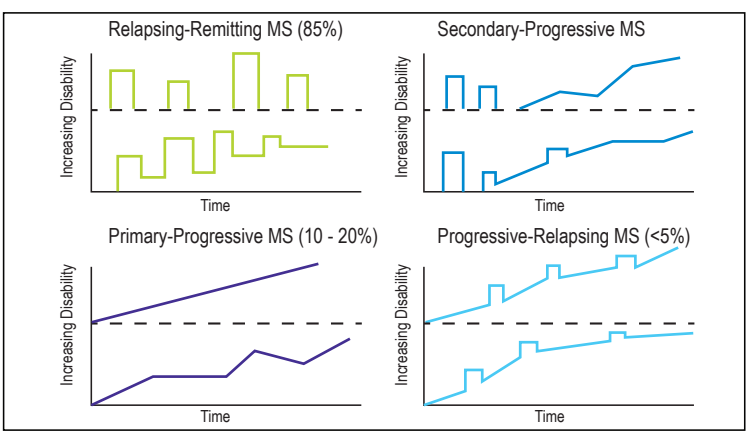
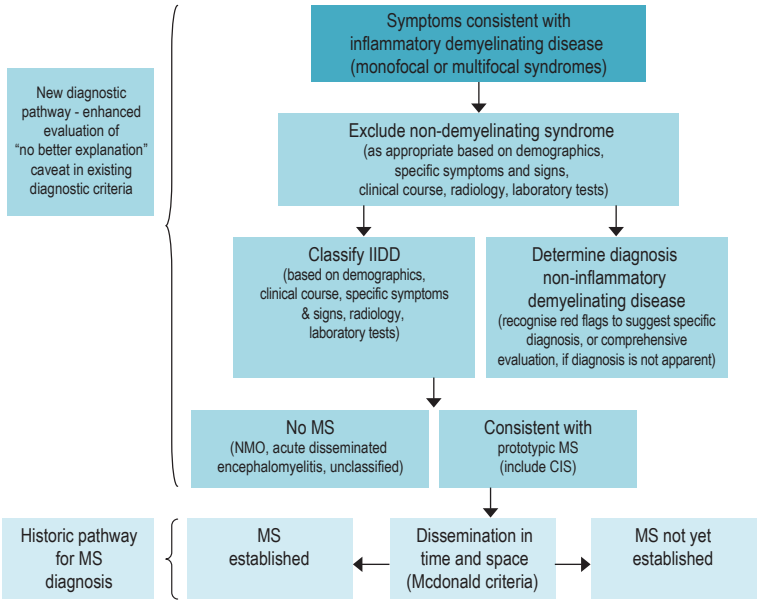
SUMMARY OF THE HIGHLY VARIABLE CLINICAL PRESENTATIONS IN MS

Site	Symptoms	Signs
Cerebrum	Cognitive impairment Sensory & motor deficits Affective features (mainly depression) Epilepsy (rare) Focal cortical deficits (rare)	Deficits in attention, reasoning, & executive function (early), dementia (late) Upper motor neuron signs
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, loss of colour vision & relative afferent pupillary defects
Cerebellum & cerebellar pathways	Tremor Clumsiness & poor balance, diplopia, oscillopsia	Postural & action tremor, dysarthria Limb incoordination & gait ataxia
Brainstem	Diplopia, oscillopsia Vertigo Impaired speech & swallowing Paroxysmal symptoms	Nystagmus, internuclear & other complex opthalmoplegia Dysarthria & pseudobulbar palsy
Spinal cord	Weakness, stiffness & painful spasms Bladder dysfunction Erectile impotence Constipation	Upper motor neuron signs, spasticity
Others	Pain Fatigue Temperature sensitivity & exercise intolerance	

NATURAL HISTORY OF MS



STEPS IN MS DIAGNOSIS



THE 2010 MCDONALD CRITERIA FOR MS DIAGNOSIS

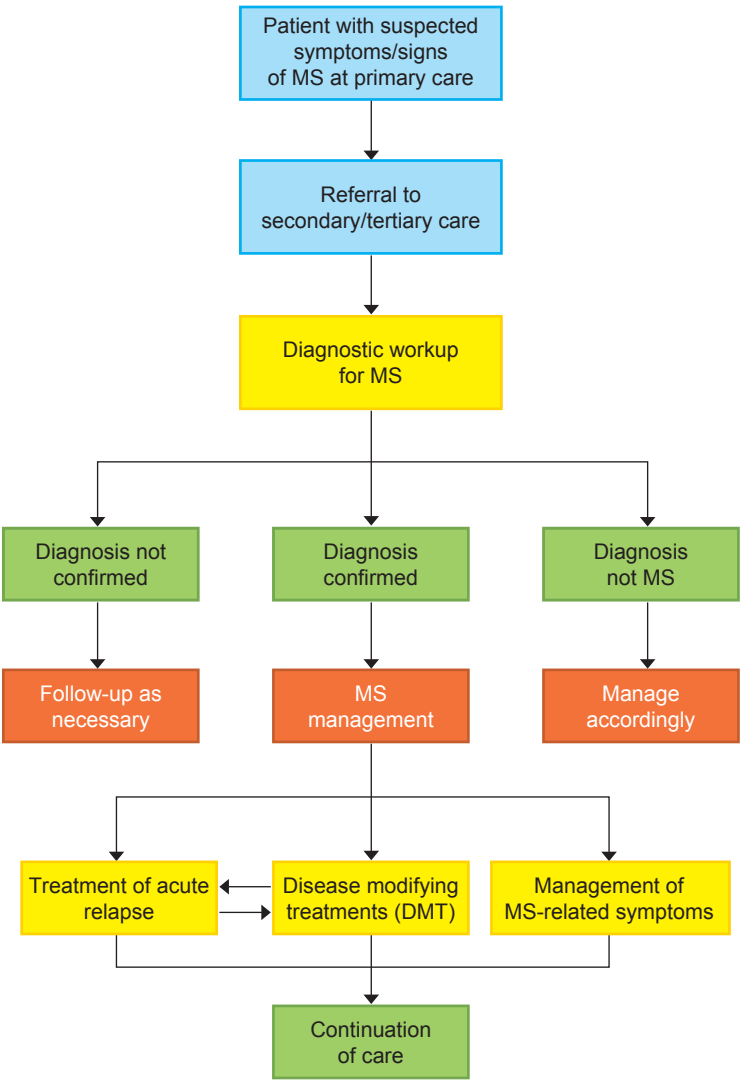
Clinically definite RRMS requires the presence of ≥2 attacks with objective clinical evidence of ≥2 lesions/objective clinical evidence of 1 lesion (corroborated by examination) with reasonable historic evidence of a prior attack. If the definition for CDMS is not/partially fulfilled, MRI criteria for DIS and DIT can help to substitute for earlier diagnosis (refer below).

Dissemination in Space (DIS) Requirements
≥1 lesion in ≥2 of 4 CNS location
• Periventricular
• Juxtacortical
• Posterior fossa
• Spinal cord

Dissemination in Time (DIT) Requirements
1. Simultaneous presence of asymptomatic gadolinium-enhancing lesion & a separate non-enhancing lesion at any time
or
2. A new T2 &/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to baseline scan, irrespective of timing of baseline scan

Lesions in symptomatic regions excluded, especially in brainstem & spinal cord syndromes

CARE PATHWAY FOR REFERRAL & MANAGEMENT OF MS



TREATMENT

Intravenous (IV) methylprednisolone 500 - 1000 mg daily for 3 to 5 days

DISEASE MODIFYING THERAPIES USED IN THE TREATMENT OF MS

Drug	Pregnancy Category	Route	Dosages & Frequency	Side Effects
Interferon beta-1a	C	IM	30 µg once weekly	Injection site reactions, flu-like symptoms, depression, increased liver enzymes, thyroid dysfunction
Interferon beta-1a	C	SC	44 µg 3 times/week	
Interferon beta-1b	C	SC	250 µg every other day	
Alemtuzumab	C	IV	12 mg daily for 5 consecutive days, followed by 3 days infusion at 12 & 24 months	Infusion-related reactions, idiopathic thrombocytopaenia, thyroid disorder
Cyclophosphamide	D	IV	First year: 700 - 800 mg/m^2 monthly, second year: bimonthly. Re-evaluation every 6 months. Maximum lifetime dose: 80 - 100 g	Haemorrhagic cystitis, oral mucosal ulceration, leucopaenia, anaemia, thrombocytopaenia, myelosuppression, gonadal suppression, skin & nail pigmentation, alopecia, dermatitis
Dimethyl fumarate	C	Oral	120 mg twice daily for 7 days, then increase to 240 mg twice daily	Flushing, rash, abdominal pain, diarrhoea, nausea, vomiting
Fingolimod	C	Oral	0.5 mg daily	Bradycardia, lymphopaenia, liver function test (LFT) elevation, macular oedema, infections (influenza, herpes-varicella zoster virus)
Mitoxantrone	D	IV	12 mg/m^2 every 3 months up to 140 mg/m^2 lifetime cumulative dose	Infection risk, nausea, anorexia, fatigue, weakness, alopecia, amenorrhoea, leukaemia, LFT elevation, blue urine, diarrhoea
Natalizumab	C	IV	300 mg every 4-weeks	Infusion-related reactions, anaphylaxis, hepatotoxicity, progressive multifocal leukoencephalopathy, immune reconstitution syndrome, herpes virus infection of the CNS
Rituximab	C	IV	1 g at Day 1 & 1 g at Day 15 every 6 - 12 months	Infusion-related reactions, fever, headache, angioedema, rashes, thrombocytopaenia, neutropaenia
Teriflunomide	X	Oral	7 or 14 mg daily	Hair thinning, diarrhoea, nausea, LFT elevation, influenza, agranulocytosis, pancytopaenia, thrombocyto-paenia

MULTIDISCIPLINARY INTERVENTIONS OF MS-RELATED SYMPTOMS

Symptoms	Non-pharmacological	Pharmacological	Surgical
Ataxia	Physical training programmes		
Fatigue	Energy conservation management	Amantadine	
Spasticity	Physical therapy Physical modalities Splints & orthotic devices	Oral (baclofen, tizanidine, benzodiazepine, cannabinoids) Injection (botulinum toxin type A)	Orthopaedic procedures Neurosurgical procedures Intrathecal baclofen
Paralysis	Physical therapy Mobility & gait aids	Fampridine (improve walking speed)	
Visual problem	Low-vision rehabilitation		
Swallowing difficulty	Dysphagia therapy		
Speech difficulty	Speech therapy		
Bladder dysfunction	Behavioural therapy Intermittent catheterisation if post-void residual volume >100 ml Indwelling catheterisation in severe refractory symptoms (suprapubic preferred)	Oral (anti-cholinergics, alpha-blockers) Oral or intranasal desmopressin Injection (botulinum toxin type A)	Neuromodulation Major surgery
Bowel problem	Bowel management programmes		
Pain	Transcutaneous electrical nerve stimulation (chronic low back pain)	Anticonvulsants (gabapentin, lamotrigine, levetiracetam) & antidepressants (nortriptyline, duloxetine) for central neuropathic pain Nonsteroidal anti-inflammatory drugs or opioids for somatic nociceptive pain	
Paroxysmal symptoms		Carbamazepine Gabapentin Pregabalin	
Sexual dysfunction	Counselling Stimulation therapy Physical intervention	Female - Oral or topical oestrogen - Methyl-testosterone Male - Oral sildenafil citrate - Intra-urethral or intra-cavernosal prostaglandin E1	Inflatable, semi-rigid or rigid penile prosthesis
Cognitive impairment	Cognitive training		
Depression	Cognitive behavioural therapy, mindfulness-based intervention or stress management	Antidepressants	

TREATMENT OF ACUTE RELAPSES AND PREVENTIVE DISEASE MODIFYING THERAPIES FOR MS

Level of therapy	Level of pharmacological agent	Relapsing-remitting active MS*	Highly active relapsing-remitting MS*	Rapidly evolving/ aggressive relapsing-remitting MS*	Secondary progressive MS with relapses
Initial Therapy	First-line	Interferon beta/ Glatiramer acetate**/ Teriflunomide/ Dimethylfumarate	NA	Fingolimod/ Natalizumab***/ Alemtuzumab	Interferon beta
Escalation Therapy	Second-line	Refer to section on highly active relapsing remitting MS	Fingolimod/ Natalizumab***/ Alemtuzumab		Mitoxantrone/ Cyclophosphamide
	Third-line		Mitoxantrone/ Rituximab/ Cyclophosphamide	Mitoxantrone/ Rituximab/ Cyclophosphamide	
Relapse Therapy	First-line	Methylprednisolone			
	Second-line	Plasmapheresis			

NA = not applicable

*Refer to text for definitions of active MS, highly active MS & rapidly evolving or aggressive MS in CPG
**Currently not available in Malaysia
***John Cunningham virus (JCV) testing for risk stratification

TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS)