Multiple Sclerosis Overview

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Content Overview

• Multiple Sclerosis Background
  • What is MS???
• MS Presentation
• MS Diagnosis
• MS Treatment Options & Management
• Approach to MS Management & Decision-Making
• Questions????
Multiple Sclerosis (MS) Definition

- MS involves an immune-mediated process in which an abnormal response of the body’s immune system is directed against the central nervous system (CNS), which is made up of the brain, spinal cord and optic nerves.

- The exact antigen or target that the immune cells are sensitised to attack, remains unknown, which is why MS is considered by many experts to be an "immune-mediated" rather than "autoimmune“ disease. [There remains debate over this.]

http://www.nationalmssociety.org/

Immune System in MS

- **Autoimmunity = Immune system attacks itself**

- Multiple Sclerosis is considered an autoimmune disease driven predominantly by T cells & mediated by macrophages

- But other immune system cells (B cells & regulatory T cells) & primary injury to the oligodendrocytes (that form myelin) are all thought to be contributory

MS is a Central Nervous System disease

Neuron = Nerve Cell
MS Background

- **MS** is classically characterised by **inflammation** & **destruction of myelin**

- **Demyelination** is an important & well known aspect of MS

- **Axon damage** has continued to gain attention recently and there is now substantial evidence that **axonal damage** plays an important role in MS

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**MS disease processes: Theory**

**Demyelination/Remyelination**

**Axonal Destruction/ Nerve Loss**

**Degeneration of Chronically Demyelinated**

Structures Involved in MS

- Known for being a white matter disease
- White matter plaques
  - Classic feature
  - Readily visible with conventional MRI
- Grey matter also involved
  - Cortical & deep grey matter structures
  - GM lesions not generally seen with standard MRI
- Normal appearing brain (on MRI)
  - Abnormalities can be detected at the cellular level

MS Fast Facts

- Prevalence
  - > 23,000 Australians living with MS
  - Female:Male ratio approximately 3:1 in Australia

- Cause
  - Exact Cause Unknown
  - Genetic & Environmental factors thought to play a role

MSRA 2014
MS Fast Facts

- Risk factors
  - Epstein-Barr Virus Infection
    - Almost all MS patients seropositive for EBV antibodies
    - Increased MS risk in those who suffer infectious mononucleosis ('glandular fever')
  - UV light
    - Higher sun exposure childhood/adolescence reduced MS risk
  - Vitamin D
    - Low vitamin D levels associated with higher rates of MS
  - Latitude
    - Higher latitudes generally associated with higher MS prevalence
  - Smoking
    - Increased risk of developing MS in ever smokers
    - Heavy smoking worse
  - Genetics
    - Multiple risk genes identified; complicated genetics multiple genes interacting
    - Increased risk in relatives – identical twin 30% risk, child or sibling of person with MS 3-5% risk

Types of MS

©Copyright, Children’s Hope for Understanding Multiple Sclerosis, 2002-2015
**MS: Inflammatory & Neurodegenerative**

![Diagram showing the natural history of MS with stages: Pre-clinical, Clinical Threshold, RRMS, SPMS, and associated changes in brain volume, axonal degeneration, and MRI lesion activity.](image)

**Natural History of MS**

- Pre-clinical: Brain Volume
- Clinical Threshold: CIS, RRMS, SPMS
- Axonal Degeneration
- Total lesion load (T2 lesion volume)
- MRI lesion activity
- Number of lesions

*Sydney Neuroimaging Analysis Centre 2013*
MS Presentation

• Clinical presentation is **highly variable** between patients & depends on the areas of the CNS (brain, spinal cord, optic nerves) involved

• Clinical presentations can be:
  • **Focal** OR **multifocal** (one or multiple lesions)
  • **Relapses/’attacks’** (relapsing MS) OR **gradually worsening** neurological symptoms (**progressive MS**)
MS Presentation: Notable Clinical Presentations Features

- Optic Neuritis
- Transverse Myelitis
- Sensory Symptoms
- Uhthoff’s Phenomenon
- Lhermitte’s Phenomenon

Optic Neuritis

- Inflammation of the optic nerve
- Classic & common presentation
- Not always caused by MS; does not always progress to MS
- Usually only one eye affected at a single point in time; rarely bilateral
- Blurred vision, part of visual field missing, reduced vision, reduced colour vision (especially red), painful eye movements
- Steroid treatment may be given to reduce duration of symptoms

Transverse Myelitis

• Myelitis = Spinal cord inflammation
• Transverse = Across the width of the cord
• Classic & common presentation
• Not always caused by MS; does not always progress to MS
• Symptoms & signs vary depending on part(s) of spinal cord involved
  • Both legs +/- arms – one side may be more affected
  • Weakness, sensory change or both
  • Abdominal/chest ‘band’ sensation
  • Bladder/bowel symptoms; sexual dysfunction
• Steroid treatment may be given to reduce duration of symptoms

https://en.wikipedia.org/wiki/Transverse_myelitis

Sensory Symptoms

• Sometimes the initial MS clinical presentation can be with sensory symptoms only
• Intermittent ‘tingling’ or ‘pins & needles’
• Numbness, ‘burning’, ‘odd feeling’, loss of sensation
• Especially notable if lasting over 24 hours in the same region

http://www.twyman.org.uk/copyright-photos/pins_and_needles.htm
Uhthoff’s Phenomenon

- Worsening of neurological symptoms in demyelinating conditions when the body gets overheated from:
  - Hot weather
  - Exercise
  - Fever
  - Saunas/spas

- Increased body temperature → nerve impulses blocked or slowed in the damaged nerve

- Once body temperature normalizes → symptoms improve/disappear

http://quotesgram.com/img/funny-quotes-about-hot-weather/5697325/

Lhermitte’s Phenomenon/Sign

- Electrical sensation that runs down the back & into the limbs brought on by bending the neck forward

- This sign suggests a lesion in the upper part of the spinal cord

- Classic MS sign but can occur in other conditions also

www.medscape.com
Is there a way of predicting what will happen???

Poor Prognostic Factors

- Age > 40 years at disease onset
- Male
- Asian or African–American ethnicity
- Initial presentation with motor, cerebellar or sphincter symptoms OR multifocal symptoms
- Incomplete recovery after initial attacks
- Frequent attacks during the early years of the disease
- Short interval between the first two attacks
- Rapid disability progression
- Progressive disease from disease onset
- Short interval from the time of disease onset to the start of the progressive phase
- Cognitive impairment at disease onset
- Presence of oligoclonal immunoglobulins in the CSF
- High disease burden or gadolinium lesion enhancement on initial MRI

Milo & Miller 2014
Is it a relapse or not???

‘Attack’/relapse criteria

<table>
<thead>
<tr>
<th>What Is An Attack?</th>
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<tbody>
<tr>
<td>• Neurological disturbance of kind seen in MS</td>
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<tr>
<td>• Subjective report or objective observation</td>
</tr>
<tr>
<td>• At least 24 hours duration in absence of fever or infection</td>
</tr>
<tr>
<td>• Excludes pseudoattacks, single paroxysmal symptoms (multiple episodes of paroxysmal symptoms occurring over 24 hours or more are acceptable as evidence)</td>
</tr>
<tr>
<td>• Some historical events with symptoms and pattern typical for MS can provide reasonable evidence of previous demyelinating event(s), even in the absence of objective findings</td>
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<table>
<thead>
<tr>
<th>Determining Time Between Attacks</th>
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<tr>
<td>• 30 days between onset of event 1 and onset of event 2</td>
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**MS Relapse??: Important Information**

**Relapse versus Pseudorelapse**
- Symptoms/signs
  - New/Old
  - Constant/Intermittent
  - Duration of symptoms
  - Residual symptoms/signs from a prior relapse
- Current illness/fever
  - UTI, viral illness, surgery etc.

**MS-related versus non-MS or treatment related**
- Other comorbidities/problems not related to MS
  - Eye disease, spinal canal stenosis
- Treatment complication
  - PML, macula oedema

**MS Relapses**
- Important to determine if true MS relapse or pseudorelapse
  - Treatment decision-making implications
- Important to determine if MS relapse or other comorbidity
  - Don’t want to miss a problem that requires treatment
  - Don’t want to miss a MS treatment complication – treatment may need to be ceased/changed
  - Sometimes people with MS get other problems incorrectly attributed to their MS
- Medical review by your GP +/- Neurologist is recommended with any new or concerning symptoms
- Sometimes even despite best efforts and MR imaging it can be difficult to establish whether symptoms represent a relapse or not
What is an MRI & why do I need to have them???

MRI in MS

- MRI = Magnetic Resonance Imaging
- High resolution images of the brain, spinal cord & optic nerves
- Uses a magnetic field & patients are not exposed to radiation
- Involves going through a noisy tunnel
- Gadolinium is often injected into the veins through a cannula during an MRI scan to help show whether there is any MS disease activity (inflammation) present
- Computed tomography (CT) scans are generally not useful in the diagnosis & management of MS as white matter plaques are usually not visible on CT

http://spinms.ca/?page_id=663
MRI in MS

• MRI safety & tolerability
  • Claustrophobia – sedation can be arranged
  • Safety questionnaire – metal foreign bodies, devices affected by magnetic fields etc.
  • Gadolinium – allergies can occur but are rare

• MRI provides important information for **MS diagnosis & treatment monitoring**
  • MRI features are included in the MS diagnostic criteria
  • Sometimes patients are stable clinically (no new symptoms) but there are changes (new lesions/plaques) on MRI suggestive of disease activity. MRI gives us additional information to help us better treat people with MS.

How is MS diagnosed???
MS Diagnosis

• There is no single test that allows us to diagnose MS
• Currently MS is diagnosed based on:

The 2010 McDonald Criteria for Diagnosis of MS

• Diagnosis can be made on clinical grounds alone
• MRI can support, supplement or even replace some clinical criteria
• This version utilises MRI findings more than previous criteria


The 2010 McDonald Criteria for Diagnosis of MS

Relapsing-Remitting MS Diagnosis

• Dissemination in Space
  • Separation in space = Lesions present in more than one region of the CNS
• Dissemination in Time
  • Separation in time= Lesions present at different times via MRI or clinical criteria
• Essentially diagnosis made if:
  • 2 clinical attacks OR
  • 1 clinical attack + MRI criteria met

Dissemination in Space (DIS)

**TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS**

DIS Can Be Demonstrated by \( \geq 1 \) T2 Lesion\(^a\) in at Least 2 of 4 Areas of the CNS:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord\(^b\)


Clinical DIS => e.g. Optic neuritis & spinal cord syndrome

Dissemination in Time (DIT)

**TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT**

DIT Can Be Demonstrated by:

1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time


Clinical DIT => e.g. Episode optic neuritis & then spinal cord syndrome 6 months later
The 2010 McDonald Criteria for Diagnosis of MS

### Primary Progressive MS Diagnosis

- One year of disease progression
**AND** 2 of the following 3
  - Dissemination in Space in the Brain
  - Dissemination in Space in the Spinal Cord
  - Positive Cerebrospinal Fluid

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**TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 attacks(^a), objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack(^b)</td>
<td>None(^c)</td>
</tr>
</tbody>
</table>
| ≥2 attacks\(^a\), objective clinical evidence of 1 lesion | Dissemination in space, demonstrated by:
  - ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)\(^d\), or
  - Await a further clinical attack\(^e\) implicating a different CNS site |
| 1 attack\(^a\), objective clinical evidence of ≥2 lesions | Dissemination in time, demonstrated by:
  - Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or
  - A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or
  - Await a second clinical attack\(^e\) |
| 1 attack\(^a\), objective clinical evidence of 1 lesion (clinically isolated syndrome) | Dissemination in space and time, demonstrated by:
  - For DIS:
    - ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)\(^d\), or
    - Await a second clinical attack\(^e\) implicating a different CNS site; and
  - For DIT:
    - Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or
    - A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or
    - Await a second clinical attack\(^e\) |

Primary Progressive MS Criteria

**TABLE 3: 2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset**

PPMS May Be Diagnosed in Subjects With:

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria:\[b\]
   A. Evidence for DIS in the brain based on $\geq 1 \ T_2$ lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
   B. Evidence for DIS in the spinal cord based on $\geq 2 \ T_2$ lesions in the cord
   C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)


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**Diagnostic Challenges**

- Because there is no single reliable test to diagnose MS, MS diagnosis can be very challenging in some cases
- Many MS mimics / differential diagnoses
  - Inflammatory, vascular, mass lesions etc.
- Careful work up needs to be performed to screen for MS mimics
  - Blood tests, MRI brain & spinal cord, +/- lumbar puncture (CSF), +/- evoked potentials
- It is important to diagnose correctly!
  - MS mimics require different or no treatment
  - MS treatments may be harmful if used in the wrong context
What treatments are available???

MS Treatment

- Disease modifying therapies (DMTs)
- Symptomatic therapies
- Management of lifestyle factors

- Therapies only available as part of clinical trials/research

- Neuroprotective or reparative therapies – not yet available
Disease modifying therapies (DMTs)

- Aim of therapy is to stop/minimise further relapses & reduce future disability
- DMTs do not reverse damage that has already occurred
- DMTs are believed to be most effective early in disease & on the inflammatory component of MS
- Approved & available medications are for use in relapsing MS only
  - Multiple are available & more are being developed
- No therapies are approved & available that favourably alter the disease course in progressive forms of MS
  - Ongoing research continues

**Some treatments do not have MS indication in Australia e.g. Mitoxantrone**

- Betaferon
- Rebif
- Copaxone [Glatiramer Acetate]
- Avonex
- Novantrone [Mitoxantrone]
- Tysabri [Natalizumab]
- Cladribine X
- Gilenya [Fingolimod]
- Aubagio [Teriflunomide]
- Tecfidera [Dimethyl Fumarate]
- Lemtrada [Alemtuzumab]
- Plegridy
- Copaxone (3x/week)
- Daclizumab?
- Cladribine?
- Laquinimod?
- Rituximab/Ocrelizumab?

MH Barnett 2013
Interferons

• Multiple types
  • Different administration & frequency
  • Injections

  • Betaferon (Interferon beta-1b) [1st therapy]
    • Subcutaneous (under the skin), alternate daily

  • Rebif (Interferon beta-1a)
    • Subcutaneous, 3x/week

  • Avonex (Interferon beta-1a)
    • Intramuscular (into the muscle), weekly

  • Plegridy (Pegylated Interferon beta-1a) [Newest]
    • Subcutaneous, fortnightly

Australian Product Information - Betaferon (Bayer, Aug 2015); Rebif (Merck Serono, Feb 2016); Avonex (Biogen, Jan 2016); Plegridy (Biogen, Feb 2015).

Interferons

Benefits
• Effective: Reduce relapse rates by approx. 32-36% versus placebo
• Safety: Rare problems (hepatitis, low WCC, allergy); long term safety data for most products

Practical Issues
• Injection site issues; lipoatrophy (loss of fat tissue)
• Flu-like symptoms – headache, muscle aching, fatigue etc.
• Depression history
• Compliance – support nurses helpful
• Remember to do monitoring blood tests (FBC, LFTs)

Australian Product Information - Betaferon (Bayer, Aug 2015); Rebif (Merck Serono, Feb 2016); Avonex (Biogen, Jan 2016); Plegridy (Biogen, Feb 2015).
Copaxone (Glatiramer Acetate)

- Two preparations
  - Subcutaneous, 20mg daily
  - Subcutaneous, 40mg 3x/week

**Benefits**
- Effective: Reduce relapse rates by approx. 29-34% versus placebo
- Safety: Rarely problems (allergy); long term safety data

**Practical Issues**
- Injection site issues; lipoatrophy
- Immediate post-injection reaction (rare)
  - Flushing, palpitations, throat constriction, urticarial (‘hives’ – red, itchy, raised rash)
- Compliance – support nurses helpful


Aubagio (Teriflunomide)

- Tablet 14mg daily

**Benefits**
- Effective: Reduce relapse rates by approx. 31-36% versus placebo
- Convenient – once daily tablet

**Practical Issues**
- Pre-screening blood tests
- ADRs: Hair thinning, GI sx, LFTs, peripheral neuropathy (rare)
- Monitoring: Monthly bloods for 1st 6 months (WCC, LFTs)
- Regular blood tests
- Washout: Charcoal, cholestyramine
- Safety: Pregnancy category X, lack of long term safety data

Tecfidera (Dimethyl fumarate)

- Capsule 240mg bd

**Benefits**
- Effective: Reduce relapse rates by approx. 44-53% versus placebo
- Capsule

**Practical Issues**
- Pre-screening blood tests (recent FBC inc. lymphocytes recommended)
- ADRs: GI sx, flushing, lymphopaenia, LFTs (rare)
- Monitoring: Blood (FBC including lymphocytes), Urine (protein)
- Rare progressive multifocal leukoencephalopathy (PML) cases with lymphopenia
- Regular blood tests
- Lack of long term safety data


Gilenya (Fingolimod)

- Tablet 0.5mg daily

**Benefits**
- Effective: Reduce relapse rates by approx. 54% versus placebo
- Convenient – once daily tablet

**Practical Issues**
- Pre-screening: Blood tests (TB, HIV, hepatitis, VZV), macula
- First dose monitoring: 6 hours (bradycardia, AV block)
- ADRs: LFTs elevated, lymphopaenia, infections (herpes, viruses, cryptococcal)
- Monitoring: Blood (WCC, LFTs), macula oedema (3-4 months post)
- Rare PML cases
- Regular blood tests
- Lack of long term safety data

Tysabri (Natalizumab)

- Intravenous infusion 300mg 4 weekly

**Benefits**
- Effective: Reduce relapse rates by approx. 68% versus placebo

**Practical Issues**
- JC virus screening!! – Increased PML risk with JCV positive & prior immunosuppression
- Pre-screening blood tests (TB, HIV, hepatitis, VZV)
- IV infusions at an infusion centre
- ADRs: LFTs elevated, infections (esp. herpes), infusion reactions, allergic reactions (rare)
- Monitoring: JCV serology 6 monthly, blood (WCC, LFTs), strict MRI monitoring

Australian Product Information - Tysabri; Polman, et al. NEJM 2006.

Lemtrada (Alemtuzumab)

- Intravenous infusion daily for 5 days then 12 months later daily for 3 days

**Benefits**
- Effective: Reduce relapse rates by approx. 49-55% versus S/C IFN beta-1a (Rebif)
- Depending on response – 2 cycles treatment 12 months apart

**Practical Issues**
- Extensive pre-screening blood tests (TB, HIV, hepatitis, VZV, TFTs/abs, Cr, urinalysis)
- IV infusions at an infusion centre
- ADRs: Thyroid disease, Idiopathic Thrombocytopenic Purpura (ITP), kidney disease (rare), autoimmunity diseases, infections (herpes, listeria meningitis), infusion reactions, allergic reactions
- Strict & frequent monitoring: Blood & urine monthly (platelets, TFTs, Cr, urine blood & protein)

What treatment(s) should I be having????

MS Treatment Decisions

**Treatment Groups**
- Injections
- Orals
- Infusions

**Treatment Decisions**
- Efficacy – how well the medication works
- Safety
- Disease severity
- Risk-benefit considerations
- Individual patient factors
- Other factors
Treatment Options

- **Natural history/No treatment**
  - Not Safe
  - Disability +++

- **Immunomodulator**
  - Safe
  - Less effective?

- **Immunosuppressive**
  - Cumulative risk
  - More effective

- **Immuoablative**
  - 6 month infection risk
  - 5 year autoimmune risk
  - Does it offer cure?

Treatment Decisions

- **Individual patient factors**
  - Disease severity – poor prognostic factors, evidence of disease activity
  - Risk-benefit – safety concerns versus long-term disability concerns
  - Co-morbidities – diabetes, IHD, chronic infections etc.
  - Other patient preferences – needle-phobia, monitoring requirements, travel, lifestyle, other factors
  - Pregnancy plans, breastfeeding

- **Other factors**
  - Access to therapies – geographical, expertise
  - Physician concerns, perceptions, expertise
Treatment Approach

• Confirm correct diagnosis of MS
• Using all available evidence make an assessment of disease severity (an imperfect science)
• Carefully discuss with patients their views on treatment
• Give patients options to think about taking into account their views
• Carefully explain the pros, cons & potential consequences of each option
• Start screening procedures for therapies being considered
• Follow up with the patient after a short period of time to make a final combined decision regarding treatment & future management
  • Short time frame if aggressive disease

Switching medications

• Once a treatment choice is made you don’t need to stick with it forever in most cases
• Switching between DMTs can be straight-forward or complex
• Best to avoid switching DMTs too often as medications take time to become effective each time
• Don’t persist too long with an ineffective drug either
MS Treatment Monitoring

• Clinical relapses
  AND
• Presence/absence of new lesions on MRI

Current Treatment Goals in MS

NEDA 3 (No Evidence of Disease Activity) concept fits with current aggressive MS treatment goals

NEDA 3 = No clinical activity +
  (clinical relapses)
No clinical progression +
  (disability progression)
No MRI activity
  (No new/enlarging T2 lesions & no new gadolinium enhancing T1 lesions)
Symptomatic Therapies

Depends on symptoms experienced:

• Spasms/cramps/stiffness
  • Stretches; Medication – oral, botox, intrathecal
• Fatigue
  • Treat other causes; Medication
• Pain
  • Neuropathic pain medications; Pain clinics
• Mobility issues
  • Physical therapy; Rehab; Mobility aids; Medication

Symptomatic Therapies

Depends on symptoms experienced:

• Bladder dysfunction
  • Assessment; Fluid management; Medication; Self-catheterisation; Botox; Surgical procedures
• Bowel & sexual dysfunction
  • Medication; Procedures; Psychological support
• Tremor
  • Medication – oral, botox; Hand weights; Thalamic deep brain stimulation (v. severe)
• Depression
  • Counselling; Cognitive behavioural therapy; Medication
Lifestyle factors

Recommendations for all people with MS

• Stop Smoking!
  • Delay onset of SPMS/disability progression
  • Reduce MRI disease activity (lesions, brain atrophy)

• Vitamin D supplementation
  • Aim for the higher end of normal range
  • Therapeutic effect of supplementing vitamin D unclear – ongoing research

• Exercise
  • Maintain condition & fitness

• Healthy, balanced diet

• Address other health issues

[Potential] Multidisciplinary Team

• Neurologist
• MS Nurse Specialist
• Neuroradiologist
• General Practioner
• MS Physiotherapist
• Continence Advisor
• Urologist
• Infusion Unit/Centre
• Clinical Psychology
• Neuropsychologist
• Ophthalmologist
• Dermatologist
• Occupational Therapist
• Other Specialists
Take Home Points

• This is an introductory & general overview only
• Some of this is personal opinion
  → There are many different approaches used to deliver good quality MS care
• Individual people with MS need individual attention
  → MS is extremely heterogenous & all cases of MS are different
• Liaise closely with your health care team to optimise your management

QUESTIONS