Welcome to today’s webinar: Learn about MS

Your Presenter is Dr Todd Hardy

Your Facilitator is Belinda Saunders

Housekeeping

Thanks for joining us for this webinar – welcome!

You will be able to:
• hear the presenter
• see the slides
• see the presenter

You do not need to have camera or microphone.

We cannot see you or hear you today, but our system tells us that you are online.
Control Panel

Control panel appears on the right of screen

If you are using a Mac, a tablet or an iPad, you need to look for the control icons across the top, side or bottom of your screen;

Click the down arrow on the Questions pane to open

Type in your question and click send

Handouts

Handouts have been sent separately. This contains a copy of the slides presented today and possibly other relevant reading material depending on the topic.

The webinar will be recorded and will be available on our website: www.ms.org.au via the Webinar library.
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Acknowledgement

We acknowledge and pay respect to the traditional custodians past and present on whose lands we meet today.

We acknowledge the deep feelings of attachment and the relationship of Aboriginal people to country and respect the cultural authority of the elders in each community.
Introduction to Presenter

Dr Todd Hardy is Staff Specialist Neurologist at Concord Hospital, Clinical Senior Lecturer in Medicine at the University of Sydney and Co-Director of the MS Clinic at the Brain & Mind Centre. Dr Hardy’s clinical and research interests are in the field of neuroimmunology. His main focus is on multiple sclerosis, including atypical forms of demyelination, and other neuroinflammatory diseases of the central nervous system. He Co-Chairs the NSW MS Clinical Trials Network and is Co-Editor of Advances in Clinical Neuroscience and Rehabilitation.

Informed Choice

This presentation has been prepared and is presented by an independent expert.

The views presented are not necessarily the views of Multiple Sclerosis Limited.

Individuals are encouraged to seek further advice regarding the relevance of the information presented for their situation.
Learn about MS

Dr Todd Hardy

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2. Neuroimmunology Clinic, Concord Hospital
3. Clinical Senior Lecturer, University of Sydney

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Multiple Sclerosis

• What is MS?
• What causes MS?
• How does damage occur?
• How do symptoms occur?
• What types of MS are there?
• How is MS diagnosed?
• What can be done to help?
What is MS? - people

25,600 people in Australia

Commonest cause of disability in young adults

Nervous system

Central nervous system
- Brain
- Spinal cord

Peripheral nervous system
- Somatic
- Autonomic
  - Sympathetic
  - Parasympathetic

Multiple sclerosis
**MS – Radiological Features**

Dawson’s fingers

**What is MS?**

- *Autoimmune* inflammatory disorder of the CNS
- CNS plaque = discrete region of *demyelination* of neurons
- Active plaques i.e perivascular infiltration of lymphocytes (predominantly T cells), macrophages and occasional plasma cells
How Does Damage Occur?

- Activation of the immune system in the periphery - molecular mimicry
- Activated immune cells cross the blood-brain barrier
- Cascade reaction within the CNS
- Attack on myelin i.e demyelination

The electrical cabling is going down

Axons can also become damaged in MS
Axonal neurodegeneration is the hallmark of the later stages of the disease
Dutta & Trapp, 2007, Neurology

Axons = Green
Myelin = Red

MRI Tractography
Telephone cabling analogy

How do symptoms occur?

• Fluid (oedema) blocks nerve conduction
  - Stops messages getting through

• Damage to myelin
  - Stops or slows electrical conduction

• Loss of axons
  - Causes permanent damage once a critical number are damaged
Symptoms

- Visual blurring
- Double vision
- Fatigue
- Weakness
- Bladder
- Balance
- Sensory disturbance

What is the clinical picture?

- Variable
- Unpredictable
- Multiple symptoms
- Characterised by relapses and remissions
- Some patients enter progressive phase
Course of MS

- Clinically isolated syndrome
- Clinically definite MS
- Secondary progressive (60%)
- Primary progressive (15%)
- Progressive relapsing (rare)

What causes MS?

Unknown!

- Genetic Influence
- Environmental Influence
We know quite a lot about it

- Peak age 35-45
- F>M
- Prevalence varies around the world

Prevalence of MS in Australia by latitude

Hollingworth et al. 2013
Risk factors

- Risk of MS largely determined before age 15 years

![Graph showing prevalence of MS in migrants and non-migrants](image)

Cabre et al 2005

Risk factors for MS

- Latitude
- UV light/Vitamin D
- Caucasian
- Obesity
- Epstein-Barr Virus
- Smoking
- Parasites
How is MS Diagnosed?

**CLINICAL DIAGNOSIS!**

- Two or more attacks
  - Involving different parts of the central nervous system
  - Occurring at different times
  - In some circumstance can diagnose after a single attack

Tests performed to find supportive evidence of MS and to rule out other conditions which mimic MS

Tests in Multiple Sclerosis

- MRI – Magnetic resonance imaging
- VEPs – Visual evoked potentials
- SSEPs – Somatosensory evoked potentials
- LP – Lumbar puncture
  - oligoclonal bands
Management

• Information, information, information
• Healthy lifestyle
• Diet
• Exercise

=> SELF MANAGEMENT

Disease Modifying Treatments and Future Research
Aims of disease modifying treatments in MS

• Reduce relapse frequency
• Reduce disability from relapse
• Prevent progressive disability
• Reverse persistent disability

How are potential disease modifying treatments assessed?

• Gold standard = randomised, double-blind, placebo-controlled trial

• Overcomes:
  – placebo effect (30-50%)
  – biases e.g. selection bias
Clinical outcomes

- Relapse rate
- Disability
- MRI appearance

- Challenges:
  - Subjective relapses
  - Insensitive: need long and large trials
  - Hard to measure all symptoms
e.g. bladder, cognition, fatigue

Disease modifying treatment in MS

- Assessment
  - History
  - Examination
  - MRI
- Shared decision making
- Websites to assist treatment choice
  (https://www.msaustralia.org.au/about-ms/medications-treatments)
Current disease modifying treatments are for relapsing remitting MS

PBS criteria for disease modifying therapies in Australia

- Definite relapsing remitting MS
- At least two clinical relapses in two years
- Ambulant
### Licensed treatments for preventing relapses and related disability

#### Injectable therapies
- **β-(beta)-interferons**
  - **Avonex** Intramuscular β-interferon-1a 30ug once/week
  - **Rebif** Subcutaneous β-interferon-1a 22 or 44ug 3 times/week
  - **Betaferon** Subcutaneous β-beta interferon-1b 250ug alternate days
  - **Extavia** Subcutaneous β-beta interferon-1b 250ug alternate days
  - **Plegridy** Subcutaneous β-beta interferon-1a 250ug/ml every 2 weeks
- **Glatiramer acetate**
  - **Copaxone** Subcutaneous 20mg daily

#### Oral therapies
- **Teriflunomide**
- **Aubagio** Orally 14mg daily
- **Dimethyl fumarate**
- **Tecfidera** Orally 240mg twice daily
- **Fingolimod**
- **Gilenya** Orally 0.5mg daily
- **Cladribine**
- **Mavenclad** Orally - dose depends on body weight - given over 4-5 days and then repeated one month later with dosing repeated again 12 months later

#### Intravenous therapies
- **Natalizumab**
- **Tysabri** Intravenous 300mg/4 weekly
- **Ocrelizumab**
- **Ocrevus** Intravenous 300mg 2 weeks apart then 6 monthly
- **Alemtuzumab**
- **Lemtrada** Intravenous 12mg given daily for 5 days and then 3 further doses 12 months later (with further “top-up” doses as needed)
Glatiramer (Copaxone) vs β-interferons

- Randomised head-to-head trial (BEYOND, 2009)
- Similar results seen in REGARD and BECOME trials
- No difference in relapse rate (reduced by ~33% compared to placebo), disease progression, lesion load at 2 years
- Both classes of injectable therapy have a good long term safety profile

Teriflunomide (Aubagio)

- Inhibitor of pyrimidine synthesis leading to reduction in inflammation
- Reduces relapses by 30-33%
- Reduces new MRI lesions

- Adverse effects
  - nausea, diarrhoea within the first few months
  - hair thinning
  - Asymptomatic, transient elevation of ALT levels
  - Category X in pregnancy
Dimethyl fumarate (Tecfidera)

- Small molecule immuno-modulator (Kreb’s cycle)
- Reduces relapses by about **50%**
- Reduces new MRI lesions

- Adverse effects:
  - GI upset
  - Flushing
  - Microalbuminuria (protein in urine)
  - Low lymphocyte counts and deranged liver tests
  - 5 cases of PML

Fingolimod (Gilenya)

- Blocks white blood cells from leaving lymph nodes
- Reduces relapse rate in patients with RRMS by **50-55%**
- Reduces new MRI lesions
Adverse effects of Fingolimod (Gilenya)

- Herpes virus infections (2 deaths in trials)
- First dose heart block
- Hypertension
- Macular oedema
- Cryptococcal meningitis
- Decreased white cell count, liver dysfunction
- Tumour development e.g. melanoma
- PML – 19 cases

Cladribine (Mavenclad)

- A purine nucleoside analogue that interferes with DNA synthesis and repair resulting in cell death
- CLARITY and ORACLE trials showed cladribine effective for reducing relapse rate by 55% and 58%
- Oral therapy
- Prolonged low white blood cells with risk of URTI, herpes virus infections and headaches
Natalizumab (Tysabri)

• Blocks white blood cells entering the brain
• Reduces relapse rate by 68%
• 80-90% reduction in new MRI lesions
• Side effect (rare):
  – Progressive multifocal leukoencephalopathy (PML)
  – PML is viral brain infection that is often fatal

Risk factors for PML

• Previous or current immunosuppression
• JC virus positive serum
• ?duration of treatment with Natalizumab
Ocrelizumab (Ocrevus)

- Humanised anti-CD20 monoclonal antibody
- OPERA 1 AND OPERA 2 trials showed \(~46-47\%\) reduction in relapses compared to interferon beta
- Intravenous therapy – every 6 months after initial dosing 2 weeks apart
- Infections including URTIs, herpes virus infections, infusion reactions

Alemtuzumab (Lemtrada)

- A powerful antilymphocyte immunosuppressant
- Reduces relapse rate by 50-55% compared to interferon beta 1a
- 80-90% reduction in new MRI lesions
Adverse effects

• Alemtuzumab
  – Thyroid dysfunction (up to 40%)
  – Loss of platelets (bleeding)
  – Irreversible kidney damage
  – Other autoimmune disease
  – Infections

• **Long term risk unknown**

Autologous haemopoietic stem cell transplant (AHSCT)

• Promising treatment option in relapsing MS
• Good outcomes in small, uncontrolled, unblinded studies (similar to alemtuzumab)
• Mortality as high as 5% in first 12 months
• Risk of infertility due to cyclophosphamide induction
• Consider for patients with early, highly active MS who have failed existing therapies
• RCTs are needed
Progressive MS

Relapsing remitting
(onset: 85% remains: 30%)

Secondary progressive (60%)

Primary progressive (15%)

Progressive relapsing (rare)

Time in years

Trials in progressive MS

Progressive MS trials focus on neuroprotection

- Lamotrigine - secondary progressive MS (negative)
- Cannabinoids – progressive MS (negative)
- Fingolimod – primary progressive MS (negative)
- Natalizumab – progressive MS (negative)
Progressive MS

- No currently licensed treatments
- Supportive care

- Adverse effects prohibitive:
  - Mitoxantrone
  - Cyclophosphamide

- Watch this space:
  - Ocrelizumab (PPMS)
  - Siponimod (SPMS)

Primary progressive MS

- Phase III trial of ocrelizumab in PPMS - ORATORIO
Secondary progressive MS

- Phase III trial of siponimod in SPMS - EXPAND

MRI used to detect neuroprotection

- Simvastatin
  - Phase II trial of Simvastatin in secondary progressive MS promising (Chataway et al., 2014)
  - Reduction in brain atrophy
  - Reduction in disability progression
  - Phase III trial underway
Prospects for remyelination (repairing damage)

• Suppression of inflammation may facilitate natural repair processes

• Possible strategies
  – Stem cells
  – Growth factors

No reliable evidence!

• Stem cells

• Low dose naltrexone

• Stenting veins in the neck
Once upon a time

- Infusion of Gentian
- Ingestion of Strychnine
- Barium chloride
- Arsenic
- Silver
- Antimony
- Pyrexia therapy
- Histamine
- Vitamin B12
- Intra-thecal Tuberculin
- Heparin…..

2010-2020s

Effective & safe immunomodulation (relapsing remitting MS)

Remyelination

Neuroprotection & repair (progressive MS)
Questions

MS Connect
1800 042 138
msconnect@ms.org.au

Free E-books

Contact MS Connect to obtain login details
1800 042 138
Get Your Act Together

- Online Tool – designed to help you better manage your multiple sclerosis symptoms
- Focuses on some of the common symptoms of MS – emotions, fatigue, continence, cognition, pain and heat sensitivity
- Designed for people living in the ACT but includes useful information for all people living with MS
- Complete the tool to receive a personalized report (listing services, resources, tips etc)

Visit www.ms.org.au and search Get Your Act Together

The National Disability Insurance Scheme

A major change to the way disability supports and services are funded and delivered

- Available to people who are: under 65, satisfy residency requirements and are able to demonstrate that their disability substantially affects daily living
- Promoting choice, control and social and economic participation
- Providing a whole-of-life approach
- It is not means tested
- Providing reasonable and necessary supports and services
- Ensuring equity of access
We can help you to

- understand the eligibility requirements
- understand the pathways to access the NDIS
- prepare for a planning conversation
- understand your current supports and any unmet need
- develop your goals

We are a ‘Registered Provider’

MS is a registered NDIS provider in NSW, ACT, Vic and Tas. MS is approved to provide:

- Preplanning prior to your conversations (All areas)
- Support Coordination/Connection – assistance to help make your plan active (All areas)
- Short term accommodation (Vic)
- Community Participation (NSW)
- Exercise physiology and personal training (NSW)
- Specialist Continence Assessment (NSW and Vic)
- Physiotherapy and Occupational Therapy (NSW and Vic)

Want to learn more?
Please call MS Connect
1800 042 138
MS Financial Assistance program

MS Financial Assistance program provides one-off funds for those facing financial hardship. The funds can be used to purchase equipment or air conditioners to promote quality of life and help with health related matters.

Thank you

MS Connect
1800 042 138
msconnect@ms.org.au
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