An overview of early Multiple Sclerosis

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What is Multiple Sclerosis?

- Auto-immune disease
- Affects the central nervous system

What is an auto-immune disease?

What MS is not!

- Fatal
- Contagious
- Directly inherited
- Always severely disabling
- a reason to stop working
What is demyelination?

Nerve cell loss – the ultimate cause of disability...
How common is MS in Australia?

The most common debilitating neurological disease in young adults

prevalence in Australia (2009):
~21,200 patients (0.1%)

ABS Survey of Disability, Aging and Carers 2009

Costs

direct: $20,396
indirect: $15,085

Taylor et al., J Clin Neurosci 2007;14:532

overall:
$1.3 billion per annum

MS Australia

Why do we say it is debilitating, even early on?

A young person with chronic illness

• Relationship changes
• Financial
• Demands at work, employment opportunities
• Study
• Wanting children, fertility (medication SE), sexual dysfunction
• Young family
  Adjustment, grief, fear of unknown
• Loss of self esteem
• Independence vs care needs

Progressive illness, changing needs over time

Doctor of Medicine
What causes MS? Why me?

Genetics and MS

- genes are codes/messages that make a person different from another
- they work alone or in groups
- many gene codes are made into proteins by cells
  - some diseases happen because genes make faulty proteins
  - but NOT in MS
- people with MS has slight variations (called polymorphisms) in healthy genes, that by chance,
- fit together badly so that normal workings of cells, especially immune cells and brain cells are affected:
  - an abnormality in the “production line”...

MS in Focus: Genetics and hereditary aspects of MS. 2006
Genetics

• 1 in 5 people with MS has an affected family member
• but: actual risk of a direct relative of someone with MS to develop the disease is low:
  – child of pwMS: 3-5%
  – sibling of pwMS: 3-5%
  – if identical twin: 30%
  – if both parents and a sibling has MS: 20%

Why is MS genetics important?

• Can provide clues to which mechanisms affect the pattern of the disease in a person
• Can hopefully provide help with predicting how someone will do over their lifetime
• Developing new treatments and prevention
• What treatment would be best for a specific gene-type? And can we predict side-effects better?
• Are some people with some genes more susceptible to certain environmental factors like diet and sunlight and weight and smoking??
Environmental evidence…

• Smoking: increases risk of getting MS 1.4 to 1.9 times
  – Smoking cessation the first modifiable risk factor that can delay the onset of SPMS
• CONFIRMED seasonal variation in relapse risk: peak in spring, trough in autumn
• EBV: meta-analysis suggests increased risk after EBV (relative risk 2.3 (95% CI 1.7 to 3)
  • positive EBV serology in 83-90% of population
  • high EBNA and EBNA-2 titres develop months before presentations of MS
• Measles or mumps > 15 yrs of age
• Emotional trauma, stress: associated with increased risk of a MS relapse
• Obesity (BMI >27) before age 20 doubles the risk of MS
• Insufficient vit D intake


Less convincing environmental evidence…

• High salt/Western (inflammatory) diet
• Adolescent obesity
• Permissive gut microbiome
• Adolescent shift work
• Early life high hygiene environment/lack of parasitic exposures
• Confusing data on alcohol, caffeine (4-6 cups) being protective

Vit D and MS

MS SUSCEPTIBILITY

• Vit D deficiency in utero, early-life, late adolescence and young adulthood have a major effect in determining MS risk.
• Prospective study, 200000 women over 30 years, seen every 4 years (Munger, Neurology 2004)
  – incidence MS decreased with increased vit D intake (33% lower)
• MS increases with increasing latitude – inversely correlated with vit D concentration

Munger et al. Neurology 2004

Vitamin D and MS: A treatment for MS?

• Therapeutic effect of vitamin D unclear

• low Vitamin D levels at time of diagnosis with MS can indicate:
  – higher risk of a second attack after 1 year
  – higher risk of cerebral atrophy in year 1-5
  – higher risk of new MRI lesion in first 5 years
  – trend for worse disability

• So far, all the randomized controlled trials on the effect of vitamin D on relapses have been negative…but larger studies are awaited.

Ascherio et al. JAMA 2014
James, E., et al. Multiple Sclerosis 2013
Soilu-Hänninen et al. JNNP 2012
Løken-Amsrud et al Neurology 2012
Gut microbiome

- Consists of wide range of mainly bacterial species colonizing intestines
- Up to 1014 total bacteria, >1 million genes
  - esp. bacteroidetes and firmicutes (90%)
- Colonized starting at birth; unique 100-150 species per individual
- Influenced by diet, vit D, exercise, stress, smoking, alcohol

Gut microbiome

- GALT forms nearly 80% of immune compartment
- Microbiome gut-brain axis
  - microbiome affects BBB
  - changes microglia
- Microbiome affects inflammation, immune system
- Microbiome very influential in EAE; MS microbiome differs from controls
Hot TOPICS in MS pathogenesis:

1) **B cell dysfunction**: B cells function as antigen presenting cells and produce antibodies that damage myelin, oligodendrocytes and other neuronal structures.

1) **Mitochondrial damage**: d/t free radical reactive oxygen species and nitrous oxide (NO) activity (both a/w microglial activity) occurs.

1) **Iron deposition**: occurs too and contributes to OGD and myelin damage.

1) **KIR4.1 as a therapeutic target**: s-antibodies to KIR4.1 higher in MS than in other neurologic diseases and healthy donors. Antibodies bind to the first extracellular loop of KIR4.1, leading to a profound loss of KIR4.1 expression, altered expression of glial fibrillary acidic protein in astrocytes, and activation of the complement cascade at sites of KIR4.1 expression in the cerebellum.


Normal appearing white matter is not disease free!

- Evidence of nerve cell damage in brain areas away from the lesions seen in MS
- Evidence of immune cell infiltration in these “normal” appearing tissues
- **Microglial activation**
- Evidence of decreased N-acetyl aspartate levels on MR spectroscopy, indicating axonal loss

Types of MS

Clinically Definite MS (CDMS) Subtypes

Relapsing-Remitting MS (RRMS)
- most common, 90%
- more females: 2:1 to 3:1
- Relapses with (complete/incomplete) recovery and stable phase between relapses
- Relapses decrease after 1st 5 years

Secondary Progressive MS (SPMS)
- 50%-75% RR become SP w/in median 15 years
- Gradual neurological deterioration
- Without relapses 2/3
- With relapses 1/3
Primary progressive MS (PPMS)
- 10% overall
- 20% of males
- On average, behaves exactly like SPMS
- Gradual but continuous neurological deterioration

Progressive - Relapsing MS
- <5%
- Gradual but continuous neurological deterioration with superimposed relapses

MS Is a Complex Neurological Disease Characterized by Inflammation and nerve loss

Frequent inflammation, demyelination, axonal transection, plasticity, and remyelination

Continuing inflammation, persistent demyelination

Infrequent inflammation, chronic axonal degeneration, gliosis

First symptoms in MS

What are the first symptoms of MS? Clinically isolated syndromes (CIS) or First demyelinating events (FDE)

- Paroxysmal (stiffness, limb spasm)
- Bladder
- Cognitive
- Pain radiating from the spine – mimics a pinched nerve
- Facial pain
- Episodic Fatigue
- L’Hermitte’s (shock-like sensation when neck is flexed)
- Sexual dysfunction
Uhtoff’s phenomenon

- Reversible and usually predictable decrements in physical (running, walking, reading, etc) and cognitive (memory, thinking speed)
- Due to increased ambient body temperature and exercise
- Nerve conduction slowing and perhaps conduction block due to small (~0.5°C) increases in core temp

Clinically isolated syndromes of MS

- A single event in one part of the central nervous system
- Compatible with a possible future diagnosis of MS
- We need additional information before we can make a certain diagnosis of MS
Can we predict someone’s risk of developing MS?

On average:

• 30% of people with MS have another relapse after 1 year
• 45% within 2 years
• The majority of further attacks happen in the first 5 years.
Predictors of further relapses/attacks:

- Female patients, Younger age
- Non-white race
- More than one symptom at first episode
- If you do a lumbar puncture and it is positive for immune proteins (oligoclonal bands)
  - usually only done if MRI negative or atypical presentations

The MRI Scan at baseline...

<table>
<thead>
<tr>
<th>Risk of having a second attack</th>
<th>MRI lesions positive</th>
<th>MRI normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 7 years...</td>
<td>65%</td>
<td>8%</td>
</tr>
<tr>
<td>After 15 years...</td>
<td>72%</td>
<td>25%</td>
</tr>
<tr>
<td>After 20 years...</td>
<td>81%</td>
<td>21%</td>
</tr>
</tbody>
</table>

- If more than 3 lesions: risk >80% to develop MS
- Location of the lesion: higher risk if lesions are in back of the brain or in the spinal cord
- Size and number of lesions AND how quickly they develop early on can predict how disabled someone can potentially be after 20 years

Fisniku, L. K. et al. (2008). Brain, 131(Pt 3), 808–817
Should I start treatment now?

Reasons in favour of early treatment

• Delay onset of more clinical relapses
• Delay long-term disability

Evidence for this:
• Radiological
• Pathological (microscopic abnormalities in and out of the lesions)
• Clinical
Radiological reasons to treat early

• More lesions in first 5 years correlate moderately with disability long-term
• Brain volume loss occurs after just one attack/relapse
• Brain atrophy is very predictive of ultimate disability – much more so than lesion number
• The speed/rate that brain atrophy develops and changes also predicts long-term outcomes

What is happening in the brain tissues?

Early on when person is feeling and looking well:
• Nerve cell damage is happening and is the main reason for ultimate permanent disability
• Most prominent in the first year...
• Early on, the brain can recover by “firing” or conducting through the damaged nerves

Later on, when person gets worse:
• no compensation takes place anymore, enough damage is done that the person deteriorates clinically
• there is less inflammation for drugs to target

SO
• EARLY treatment may prevent nerve cell damage and delay the point where disability starts
Clinical reasons: does more relapses and MRI lesions early on have an impact long-term disability?

- People with CIS AND MRI findings consistent with MS have HIGH chance of further disease activity if not treated

- Disability can develop because of 1) relapses that does not fully recover OR 2) earlier onset of secondary progressive MS

- Lots of relapses in the first 2 years can lead to more early progression but the effect diminishes later in the disease


Clinical reasons to treat early

- 16-years of follow-up of people who were in untreated group in the first drug trials of Betaferon (interferon 1-b):
  - that physical and cognitive outcomes are determined early in the disease
  - placebo treated patients had 80% chance of further attacks
  - 50% of these people converted to SPMS and increased disability

- 21 years of follow-up of this group of people – most stayed in the study
  - Treatment with Interferon-beta reduced the hazard rate of death by 46.8% compared to placebo

Goodin et al. Neurology 2012
Do the MS medications we have available help to treat people who have had only one relapse?

- Treatment with Interferons (Betaferon or Rebif or Avonex) or with Glatiramer acetate (Copaxone) or teriflunomide (Aubagio)
  - Delays onset of having another attack by approx 45% at 2-3 years
  - Reduces new lesions on MRI markedly (80-90%)
  - Reduces cerebral atrophy (ETOMS study) by 30%
  - Better cognitive outcomes (~30%) after 5 years
  - Better outcomes in early treatment rather than delayed treatment groups: the delay treatment group never catches up...
- BUT: we don't know what the actual size of the benefit will be after say 10 or 20 years...
- NOT PBS approved in Australia, but available through compassionate use schemes

Reasons against treating early...

- Some patients (about 1 to 2 in 10) even with a positive first MRI do not get a second clinical attack even 20 years after onset...
- Significant cost to society
- Could I have “benign MS”...
  - **BUT So called BENIGN MS is MOSTLY NOT!!**
    - Definition weighted to motor disabilities at 10 yrs
    - Cognitive, psychological and social challenges still significant
    - “Benign MS” at 20 years
      - 50 percent remained benign
      - 21% needed a walking stick and 23% had SPMS
    - TRULY BENIGN MS can only be diagnosed after 20 years and in retrospect
- It is difficult to stop treatment once it has been started
- side-effects of the medications and impact on quality of life
So, how do we decide what to do?

• Does the person actually already have MS?
• Are there any factors present that predict a worse outcome?
  – low MRI lesion load vs more severe lesion-load
  – female vs male
  – younger vs older
  – brain involvement only vs spinal cord
  – infrequent relapses or short time from 1st to second relaps

• Estimate the risk of waiting
  – how severe was the first attack and what was the recovery like?

• What is the individual (and also the neurologist!) attitude towards this risk....

Conclusions

• The optimal window for impacting long-term disability is during EARLY RELAPSING PHASE of the disease

  GOAL:

• **SLOW** accumulation of lesion volume, **DECREASE** number of relapses and **PREVENT DISABILITY** from unresolved relapses AND disease progression
Diagnosis of MS

MS is a clinical diagnosis, but several supportive tests are usually done

- History
- Examination
- MRI – brain AND spinal cord
- Visual evoked responses
- Lumbar puncture – CSF immunoglobulins
EXTRA information needed for a diagnosis:

- **Dissemination in “**space**” in the CNS**
  - WAIT for a second attack or evidence that there has been a typical attack in the past
  - eg. evidence of optic neuritis (vision or pupil or nerve itself abnormal) AND spinal cord inflammation (numbness, abnormal reflexes etc.)
  - OR: evidence of more than 2 typical lesions on a MRI scan of the Brain

- **Dissemination in “**time**”**
  - WAIT for another attack
  - **OR:** lesions on the first MRI scan that do and do not show up after contrast
  - **OR:** a new lesion on a follow-up MRI scan

McDonald criteria, 2010

**Dissemination in space**

- **Clinical:** ≥2 areas of the brain/spinal cord involved in attacks

- **Radiological:** at least 2 lesions in at least 2 typical areas of CNS
  - periventricular
  - juxtacortical
  - infratentorial
  - spinal cord
**Dissemination in time**

- **Clinical:** at least 2 relapses that are at least 1 month apart
- **Radiological:**
  1. a new lesion on follow-up MRI Brian
    OR
  2. simultaneous non-enhancing AND contrast enhancing lesions

**There has to be no other explanation for the symptoms or MRI features**

1. Other primary demyelinating diseases of the CNS
   a. Devic’s disease or neuromyelitis optica
      • Refers to relapsing-remitting involvement of optic nerves and/or spinal cord spinal cord
   b. ADEM or acute disseminated encephalomyelitis
      • *Encephalopathy* with behavioural changes: irritability confusion or lethargy, drowsiness
      • Multifocal, polysymptomatic neurological deficit

2. Secondary demyelinating conditions
   a. Other systemic auto-immune diseases: SLE, Sjogren’s disease, poly-arteritis nodosa, Bechets disease
   b. Sarcoidosis

3. Infections
   a. Mycoplasma, EBV, CMV, HIV, HTLV, Ricketsia, Lyme disease (Borrelia)

4. Tumours

5. Psychiatric disorders – conversion disorder, somatisation

Doctor of Medicine
What is a relapse?

MS relapse

• an episode of neurological disturbance consistent with MS

• ≥48 hours; duration: usually 2-4 weeks

• not preceded by viral-like illness

• ≥30 days from the onset of the previous attack

• usually good recovery, but residual disability may persist
Pseudo-relapse – Uhthoff’s phenomenon

- Reversible worsening of symptoms associated with increased body core temperature:
  - Fever
  - Vigorous exercise
  - Hot water baths / showers
  - Environmental heating

What is my prognosis??
Prognosis

highly variable

MS Prognosis

Better prognosis if:

- female, young (onset before 35)
- initial sensory symptoms and optic neuritis (as opposed to motor or cerebellar dysfunction)
- initial presentation with one symptom rather than many
- good recovery after a relapse
- lower attack rates
- longer times between attacks (and between development of new MRI lesions)

Rolak, Neurology Secrets, 2011
Medical management of MS

- Relapse management
- Disease modifying treatments
- Symptomatic treatments
**Relapse Management**

- 3-5 days of IV methylprednisolone, 1g/day
  - Reduces severity of attack
  - Shortens recovery time
  - Effect on ultimate recovery uncertain

- Side effects/ precautions
  - Agitation (sleep disturbance - psychosis/ mania)
  - Hypokalemia (prophylactic slow K)
    - NB: combination with diuretics

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**Disease Modifying Treatments for RRMS**

- DMT goals:
  - relapse prevention, prevention of new MRI lesions
  - preventing disability progression
    
    *There is no ‘cure’ for MS*

- All available drugs have immuno-modulatory and/or immunosuppressive effects

- Rapid development of new treatments over the last 10-15 years
Currently Available Treatments
Disease Modifying Therapies (DMTs)

- **Interferons** 2nd daily, 3 x weekly S/C injections, weekly I/M injection, twice monthly injection
  - beta-1b (Betaferon®) or beta-1a (Avonex® & Rebif®& Plegridy®)
    Side-effects: Flu-like symptoms, depression, injection site reactions

- **Glatiramer acetate** (Copaxone®) daily S/C injections
  Side-effects: Joint pain, injection site reactions, post injection idiosyncratic reactions

- **Fingolimod** (Gilenya®) daily tablet
  Side-effects: Bradycardia, infections, macular oedema, hepatopathy, shingles, PML (extremely rare)

- **Natalizumab** (Tysabri®) monthly infusion
  Side-effects: PML (progressive multi-focal leukoencephalopathy), hypersensitivity reactions

- **Teriflunomide** (Aubagio) daily tablet
  Side-effects: hepatopathy, lymphopenia, hair loss, GI upset

- **Fumaric Acid** (Tecfidera) twice daily tablet
  Side-effects: GI upset, flushing, PML (extremely rare)

- **Alemtuzumab** (Lemtrada) – yearly infusions for 2 years
  Side-effects: infections, other auto-immune disease – thyroid disease in particular

What factors do we consider when choosing a therapy?

1) How effective is the specific treatment?
2) direct head-to-head studies of the different drugs in properly designed studies are generally not available
3) What are the expected side-effects
4) What is the person’s preference: injectable (daily vs once vs 3x per week) OR oral
5) specific factors like planning pregnancies, travel, work, certain past infections and medical problems..
How effective are the different therapies compared to untreated patients?

<table>
<thead>
<tr>
<th>Reduction in</th>
<th>Injectables (Avonex, Betaferon, Rebif, Copaxone)</th>
<th>Teriflunomide (Aubagio)</th>
<th>Fingolimod (Gilenya)</th>
<th>BG-12 (Tecfidera)</th>
<th>Tysabri (Natalizumab)</th>
<th>Lemtrada (alemtuzumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual relapse rate</td>
<td>30%</td>
<td>33%</td>
<td>51%</td>
<td>49%</td>
<td>66%</td>
<td>75%</td>
</tr>
<tr>
<td>Disability slowing over 2 years</td>
<td>20-25%</td>
<td>29%</td>
<td>24%</td>
<td>30%</td>
<td>35%</td>
<td>65%</td>
</tr>
<tr>
<td>New MRI lesions</td>
<td>50-75%</td>
<td>n/a</td>
<td>74%</td>
<td>78%</td>
<td>&gt;90%</td>
<td>68% compared to Rebif</td>
</tr>
<tr>
<td>New contrast-enhancing MRI lesions</td>
<td>n/a</td>
<td>80%</td>
<td>76%</td>
<td>82%</td>
<td>&gt;90%</td>
<td></td>
</tr>
</tbody>
</table>

Risk of side-effects

- Risk is present in all human activities
- Risk of side-effects versus risk of injury from the disease
Treatment choice considerations...

What is the Neurologists’ treatment paradigm?

<table>
<thead>
<tr>
<th>Maintenance and Escalation</th>
<th>Induction therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous treatment</td>
<td>Short courses/ pulsed treatment</td>
</tr>
<tr>
<td>Low to very high efficacy</td>
<td>Very high efficacy</td>
</tr>
<tr>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Perceived to be lower risk</td>
<td>Perceived to be higher risk</td>
</tr>
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</tbody>
</table>

GA, IFN-Beta, teriflunomide, Dimethylfumarate, fingolimod, natalizumab

Breakthrough disease
- Suboptimal or failure to respond
- NEDA reliable metric for efficacy
- Marker for retreatment
- NEDA unreliable to assess efficacy

Rebound Activity
- Highly likely
- Can be life-threatening
- Less likely
- Unlikely to be life threatening

No potential for a cure
- Rebound
- SPMS and progressive brain atrophy
- Potentially curative
- 15-20 year experiment

Tolerability: best to worst

- Tysabri
- Gilenya
- Lemtrada
- Copaxone/Aubagio
- Interferons

- Tecfidera

Data from the MSBase Australian MS immunotherapy study: fingolimod and natalizumab show higher adherence vs other DMTs

- MSBase registry (N>1600)
- Annualised switch / cessation rates were:
  - IFNβs: 16.3-20.4%
  - GA: 17.2%
  - Natalizumab: 12.1%
  - Fingolimod: 6.8%

Jokubaitis VG, et al. accepted for oral presentation at ANZAN May 2013
The biggest issues

• Tysabri – PML
• Gilenya – GP’s sending your patients to hematologists because of “lymphopenia”, Blood pressure
• Lemtrada – Graves’ disease, “turning up”
• Copaxone – local site reactions
• Aubagio – hair loss
• Interferons – flu-like symptoms
• Tecfidera – the gut – diarrhoea, nausea

If you want to get pregnant- best to worst

• Copaxone
• Tecfidera
• Lemtrada
• Tysabri

• Interferons
• Gilenya
• Aubagio
Interferons (Avonex, Betaferon, Rebif)

- Available for ~20 years, long-term safety
- Flu-like side-effects in first few months
- Headache (1 in 10)
- Depression (1 to 3 in 10)
- Injection-site reactions
- Monitor liver function and blood count over the first 6 months and then probably yearly

Glatiramer acetate (Copaxone)

- Available for ~20 years, long-term safety

- Adverse reactions:
  - Daily injection – more injection site reactions – 50%
  - Rare post-injection reaction can occur with palpitations, chest pain, dyspnoea (38%)
    - Usually safe to continue – recurrences are very rare
  - Pregnancy Category B (interferons Category C)
Teriflunomide (Aubagio)

- Not safe in pregnancy (male and female)
- Effects on liver
- Reactivation of tuberculosis
- Hair loss

Fingolimod (Gilenya)

- Cardiac events with first dose
- Herpes infections – Shingles
- Swelling of the macula (1 in 200 in first 3-4 months)
- Liver enzyme changes (14%)
- Drop in white blood cell counts
- PML- risk estimated to be 3:125000 = 1:42000
Dimethylfumarate (Tecfidera)

• Flushing – 30%, not harmful
• Stomach upset – 30-40%
• Drop in white blood cell counts (about 30% after 12 months)
• Twice a day dose
• PML: risk estimated 4:135000 = 1:34000

Natalizumab (Tysabri)

• PML – infection of the brain due to JC-virus reactivation
  – testing for virus prior to starting
  – risk of infection influenced by the duration of the treatment: very low risk in first 12-24 months
• Allergic reaction
• Increase in liver enzymes
Summary

- Balance between disease control and minimization of side-effects
- Personal for each person
- Frequent monitoring of side-effects
- There are strategies to minimize and manage side-effects and risk
- Permanent side-effects are very rare
- Risk/benefit trade-off can shift over time...

What’s on the horizon?

- More new treatments
  - B-cell therapies: Ocrelizumab – infusions twice a year
- Neuroprotective therapies
  - Remyelination
  - Axonal Protection
- Better ways to choose drugs for a specific person
  - Pharmacogenomics
Thank you for listening