Multiple Sclerosis
An Update for Primary Care Physicians

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Back to Basics
What is M.S.?

- Autoimmune disease whereby one’s immune system gains access to the CNS and causes inflammation and cell damage
- Inflammation results in
  - demyelination—stripping of the myelin from nerve fibres through inflammatory damage to oligodendrocytes
  - underlying neuronal injury
Back to Basics: who does MS affect?

- All ages including children can be affected
- Average age of onset is 30 years
- Median age of onset is 23.5 years
- Females:males approx.= 1.8 : 1
- Relapsing remitting disease averages an earlier onset than primary progressive
- 60 per 100 000 affected in high prevalence areas
Back to Basics: Who does MS affect?

- Caucasians more than Asians, Africans or first nations
- Higher latitude seems to play a role in prevalence
  - Has been the substrate for the Vitamin D hypothesis
- Genetics: four percent risk of developing MS if you have a first degree relative with MS
- Everyone who has MS also has had exposure to EBv
Clinical presentation and diagnosis of MS

- The criteria used to make a definite diagnosis of MS are continually evolving.
- The basic premise that diagnosis requires proof of dissemination in space and time still stands.
- Careful diagnosis is important.
  - Clinical trials
  - Misdiagnosis a problem both ways.
clinical presentation and diagnosis of MS

- strict criteria have evolved
- take into consideration
  - clinical attacks--requires 2 disseminated in time
  - mri--must have changes typical for MS
ms diagnosis

- clinical attacks
  - symptoms lasting over 24 hours
  - ideally correlate with an examination finding and/or imaging which corresponds to the clinical lesion
- examples
  - optic neuritis
  - diplopia
  - sensory dysfunction
  - vertigo
  - weakness
  - bowel/bladder dysfunction
  - ataxia
ms diagnosis

- MRI features
  - ovoid lesions
  - oriented perpendicular to the ventricles
  - involve the corpus callosum
  - subcortical “U” fibres--juxtacortical
  - brainstem lesions
  - spinal cord lesions
  - “black holes”
  - atrophy
ms diagnosis

- together the clinical and MRi features have been worked into recently revised MacDonald Criteria for the diagnosis of MS

- **Dissemination in time** determined by
  - two clinical attacks
  - mri showing serial development of lesions on serial MR’s
  - or, by the presence of a Gadolinium enhancing lesion while a non-gad enhancing lesion is also present
MS diagnosis

- Dissemination in space determined by
  - one or more lesions in at least 2 areas of the cns
    - juxta-cortical
    - periventricular
    - infratentorial
    - spinal cord
Clinical sub-types

- relapsing remitting
- primary progressive
  - has separate diagnostic criteria
- relapsing progressive
  - likely a transition diagnosis between relapsing and progressive disease
- secondary progressive
# clinical sub-types

- other important nomenclature
  - clinically isolated syndrome
  - benign ms
- neuromyelitis optica (nmo)
  - aquaporin 4 antibodies
    - specific to astrocytes
  - b-cell mediated disease
- overall poor prognosis
- different treatment strategy from ms
clinical course

- clinical course is variable and unpredictable
- two natural history studies
  - London On, 50% of people will need a cane at 16 years
  - UBC, 50% will need a cane after 29 years
- some differences in data acquisition between the two studies and also a 20 year time lag between studies
ms treatment

- disease modifying therapy
- symptomatic therapy
Disease modifying therapy (dmt)

- old DMt’s
  - Interferons
    - Betaseron
    - avonex
    - Rebif
    - extavia
  - glatiramir Acetate (copaxone)
DMT’s

- indications
  - relapsing remitting MS
    - for pharmacare there must be two relapses in two years
    - clinically isolated syndrome
      - not covered by pharmacare in bc
  - no efficacy in secondary progressive or primary progressive ms
DMT’s

- old dmt’s
  - reduce relapse rates by a third in clinical trials
  - decrease in new lesions on mri
  - ultimate reduction in disability is inferred but not proven
  - overall risk with these drugs is low but there are some tolerance issues
DMT’s

- the new era
- biologics
- oral agents
DMT’s--new agents

- biologics
  - nataluzimab (tysabri)
    - once a month infusion
    - prevents immune system access to the cns
    - well tolerated
    - very effective (50% reduction in relapses)
DMT’s new agents

- natazulimab has one major issue

- progressive multifocal leukoencephalopathy (PML)
  - viral infection of the brain caused by the JC virus
  - risk is probably around 1:700 but there are factors which increase risk
  - duration of treatment greater than 24 months
  - previous immunosuppressive use
  - known JC virus positive
  - symptoms of PML can include
    - rapid change in neurologic function
    - behaviour change
    - new focal neurologic symptoms
    - vigilance require
DMT’s: new agents

- oral agents
  - fingolimod (gilenya)
    - first approved oral treatment for MS
    - novel agent
    - reduces circulating lymphocytes
    - reduces relapse rates by ~50%
dmt’s: new agents

- fingolimod risks include
  - first dose bradycardia
  - macular edema
  - lymphopenia
  - immunosuppression
  - elevated LFT’s
  - ???long-term risks uncertain
new treatments

- New agents
  - indications
    - aggressive disease refractory to “older” treatment
    - intolerant of older treatment
    - severe needle phobic
  - access to coverage
    - tysabri
      - covered by pharmacare with significant restrictions
    - Gilenya
      - coverage through extended benefits only
Ms symptomatic treatment

- symptomatic treatments
  - relapse management
  - spasticity
  - fatigue
  - bladder
  - bowel
  - pain/ spasms
  - depression/anxiety
  - cognitive impairment/dementia
  - sexual dysfunction
symptomatic therapies
fatigue

- rule out other causes
- other contributors to manage
  - depression
  - sleep
  - pain
  - spasticity
- modafenil (alertec)
- Amantadine
- 4-aminopyridine
symptomatic therapy
spasticity

- spasiticity
  - baclofen
  - zanaflex
  - botox
  - (benzo’s)
symptomatic treatment relapses

- Relapse Management
  - to assist in a more rapid recovery
  - used for disabling relapses
    - one gram IV methylprednisilone for 3-5 days
    - 1250 mg per day of oral prednisone for 3-5 days
  - screen for infection prior to treatment
  - hs sedation often helpful
    - ativan
    - low dose seroquel
symptomatic treatment

bladder

- Most commonly an urgent bladder
- some get a mixed picture of urgency, hesitancy and incomplete emptying
- anti-cholinergics
- bladder scan for retention
- intermittent catheterization
- indwelling catheter
- monitor for infection
  - major cause for pseudo-relapse
- incontinence nurse
symptomatic treatment of bowel incontinence major impact on QOL. Patients become literal “shut ins”. Trial of bulking agents, loperamide when dire, routine bowel habit.
depression

- extremely common
- partly due to extraordinary loss experienced
- fatigue interplays
- pain contributes
- primary sleep disturbances exacerbate
- certain brain lesions are felt to directly contribute
- treatment is as with other patients
  - cymbalta, effexor
  - wellbutrin
- in our clinic we make use of Dr. chris blashko
- Other axis I diagnoses are seen
- remember the MS “belle indifferance”
  - this is seen but much less frequently than the individual who fully grasps their predicament
pain

many types

- ache
- burning
- tingling
- shooting
- “MS HUG”
- spasms

treat based on co-morbidities

- tca’s
- lyrica, gabapentin
- cymbalta
- cesamet
- tegretol
- baclofen
cognitive impairment/dementia

- disabling
- under-recognized
- comes in different forms
- both sub-cortical and cortical type of cognitive decline
- standardized testing ideal
- neuro-psychologic testing referral--dr. Claire sira
- can trial acetylcholinesterase inhibitors
- depression often confounds (so treat!)
- progress being made using imaging techniques to quantify brain atrophy
sexual dysfunction

- viagra/cialis/levitra
- depression management
- beware co-morbidities and medication effects which may be interfering with sexual function
- referral to sexual health program at Gf Strong
other treatments/interventions

- physiotherapy
- occupational therapy
- physiatry
- spasticity clinic
- exercise
- weight control
- general medical health
- (CCSVI)
Dr. Paulo Zamboni examined the veins of the head of 65 patients with MS and 235 controls.

- used trans-cranial and extra-cranial color Doppler
- the technician was not blinded
- the study reported that 100% and no controls had vein abnormalities

Based on this, Dr. Zambonie proposed that narrowing or blockage of the internal jugular veins or azygous veins were responsible for MS.
ccsvi--the theory

- veinous blockage leads to a break-down of the blood brain barrier
- blood-brain barrier breakdown causes an accumulation of iron in the brain
- this triggers ms
- hence “chronic cerebrospinal venous insufficiency”
Dr. Zamboni proceeded to an un-blinded pilot study where patient and investigator knew the treatment was being done:

- Patients remained on their DMT’s
- No benefit seen in progressive forms of MS
- 47% of the veins re-stenosed
- Even in this non-scientific method based trial—the reported outcome was no better than that found in standard DMT therapy MS trials
there are increasing numbers of groups outside of Italy who are publishing data which does not suggest that CCSVI plays a key role in the development of MS.

despite this, there remains extraordinary political pressure to proceed with clinical trials and they are underway (literally millions of taxpayers dollars is now being invested in CCSVI research)
patients are going on their own to be “liberated”

we have a list of 110 patients from Vancouver island who have travelled to clinics abroad

mixed results

no “miracles” (that i have seen)

several complications that I have seen

- groin hematoma requiring transfusion and repair
- stroke
- two patients i have seen literally crash en route home with complete deterioration in their ms--confirmed on MRI
- stent occlusion

cost varies $10 000-30 000

very very strong advocacy group here on Vancouver island
ccsvi

- my questions re CCSVI
  - why MS and not idiopathic intracranial hypertension?
  - what is normal venous flow from the brain?
  - is there a reproducible means to reliably measure and quantify it?
  - What is normal venous anatomy for the brain and spinal cord?
  - postural changes
  - many cancer and trauma patients have their jugulars tied off—why don’t they get m.s.?
ccsvi: is there any silver lining?

- not sure yet
- more awareness for ms
- patients feel empowered
- warmer feet
ccsvi: the disaster in its wake

- the real cost
- our patient’s limited financial resources consumed
- severe depression when patients return not cured
- the loss of trust in the doctor-patient relationship
- opportunistic physicians abroad making vast and incomprehensible amounts of money
- shunting of research dollars into ccsvi rather than other potential interventions
- patients discontinuing their potentially helpful DMT’s to pursue CCSVI
- medical complications and two canadian deaths so far (there will be more)
vancouver island multiple sclerosis clinic

- 1 full time nurse, 1 half time Nurse
- 1 full time clerk, 1 half time clerk
- social work help 1/2 day q 2 weeks
- Neurologists
  - Dr. olinka Hrebicek ms clinic Medical director
  - Dr. David Parton
  - Dr. Kristen Attwell-Pope clinical trials director
  - Dr. Viera Saly
  - Dr. stan hashimoto
- Psychiatry--dr. Chris blushko
- physiatry--dr. james filbey
- neuro-ophthalmology--dr. ray bell and dr. jason Barton
vancouver island ms clinic

- 1500 patients from the island
  - generally come with a known Ms diagnosis
  - most have seen a community neurologist first
- ~350 on disease modifying therapy
- visit frequency q 3-12 months depending on disease
- clinical trials
ms in the future

- MS will in 10 years be viewed as an interventional disease and we will look back on this decade with horror at what we will perceive to be relative inaction.
- We will be making an even greater difference to the future quality of life of our patients.
- It is a better time to be getting MS now than even 5 years ago.
- This shift to further raising treatment level will take resources but the results will be worth it.
  - Less disability
  - More MS patients in the work place
  - Better lives for our patients and their families
future directions
v.i. ms clinic

- relapse clinic
- iv methylprednisilone
- consultation and follow up for all clinically isolated syndromes
- increased clinical trials capacity
- telemedicine for upisland patients
- increased symptom specific care
- closer follow up of patients with using high risk dmd’s
M.S. the future is near

- in the future
  - acquired disability will be a cause for escalating therapy
  - more and more biologics to become available
    - and with this will come closer follow up
  - relapses will not be tolerated
  - MRI techniques will be able to differentiate patients who have more aggressive disease and warrant escalated treatment (imaging based prognostication)
  - more attention to the cognitive impact of this disease
- overall decrease in disability for patients with MS
  - enormous social and economic benefits
  - less suffering