Multiple Sclerosis & Peripheral Neuropathy

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MS Epidemiology

- Annual incidence UK and US 1-2/100,000 per year
- Prevalence: 1 in 800 of population
- Relapsing Remitting 80-90%
  - Most common women age 30
  - F:M ratio 3:1
- Primary Progresssive 10-20%
  - Most common age 40 at diagnosis
  - Equal gender ratio

MS Epidemiology

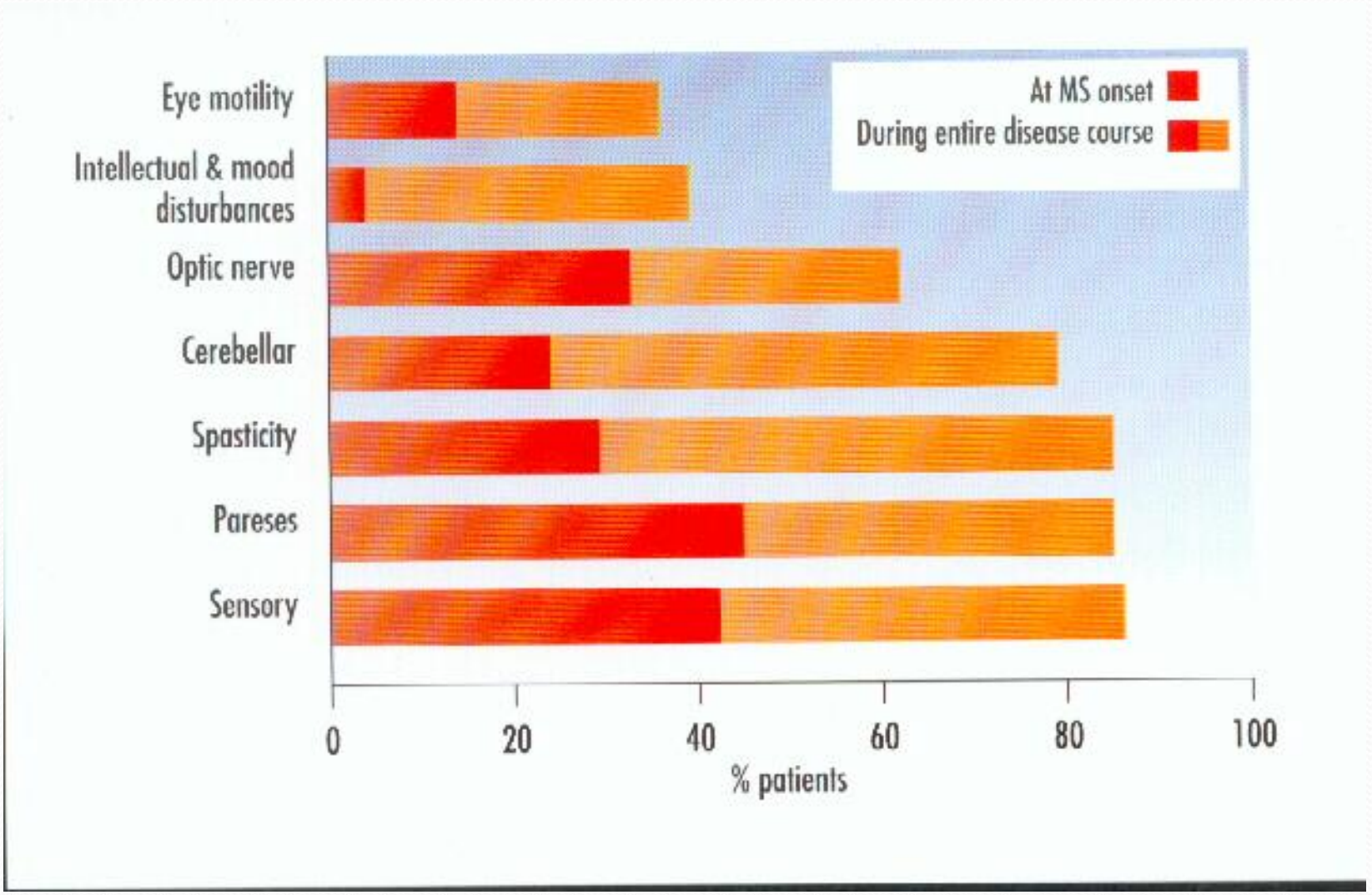
- Geographical variation: distance from equator
- Increasing incidence or just better diagnosis?
- Vitamin D and UV exposure? (not in Alaska!)
- Viruses? EBV/ HHV 6/ measles/ mumps
- HLA subtype: there is a genetic link (Vikings!)
- MZ twins 25% vs 3-5% DZ twins
- Smoking: increased risk? Just more severe?

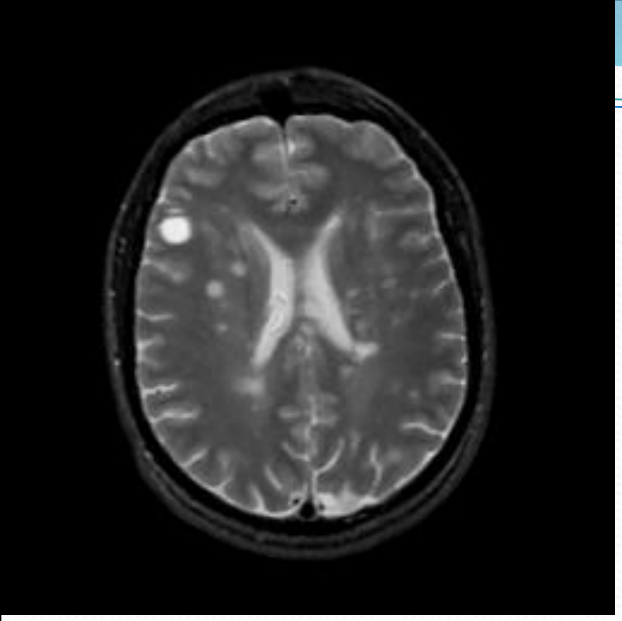
RR MS Diagnosis

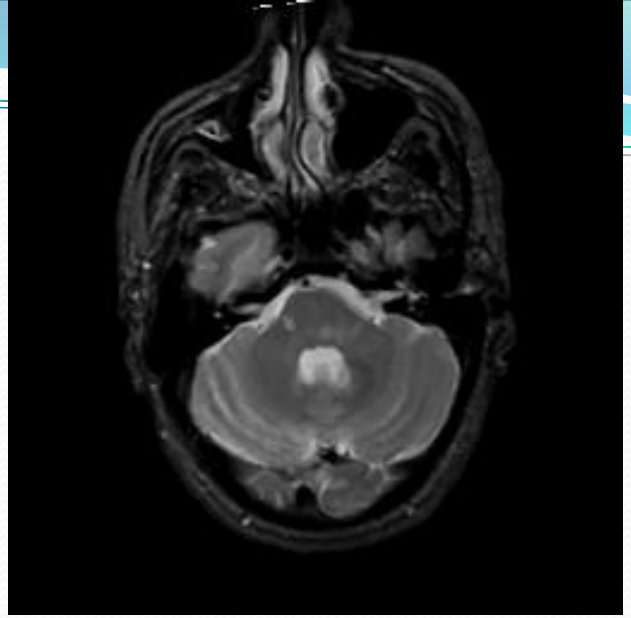
- Still clinical: “dissemination in time and place”
- Course of illness:
  - Subacute over hours to days
  - Symptoms maximum severity at 4 weeks
  - spontaneous remissions
- Investigations to confirm:
  - MRI Scans: brain with enhancement and cord
  - Lumbar Puncture: Oligoclonal bands (less infra-tentorial lesions in those negative)
  - Evoked potentials (single test only provide evidence of dissemination in space)

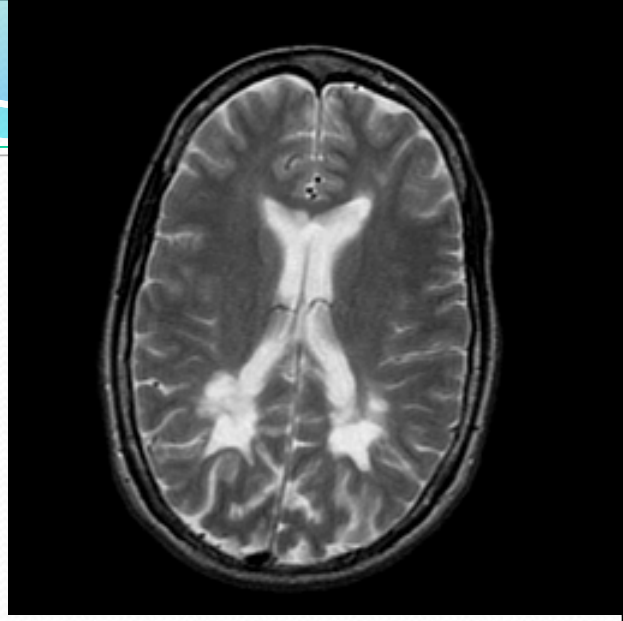
RR MS Diagnosis

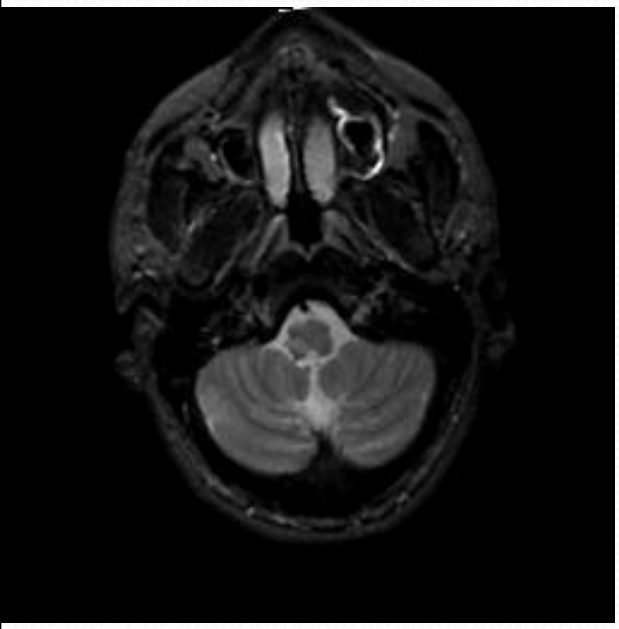
- Difficult:
  - Varied symptoms at onset and subsequently
  - Years before a definite diagnosis is made
- Common Presentations:
  - Optic neuritis : more common in those presenting below 30 yrs
  - Brainstem and cerebellar syndromes including TN
  - Spinal cord: bladder dysfunction and spasticity
  - Non-specific: cognitive decline and fatigue
- “Radiological” RRMS
  - Enhancement of some lesions

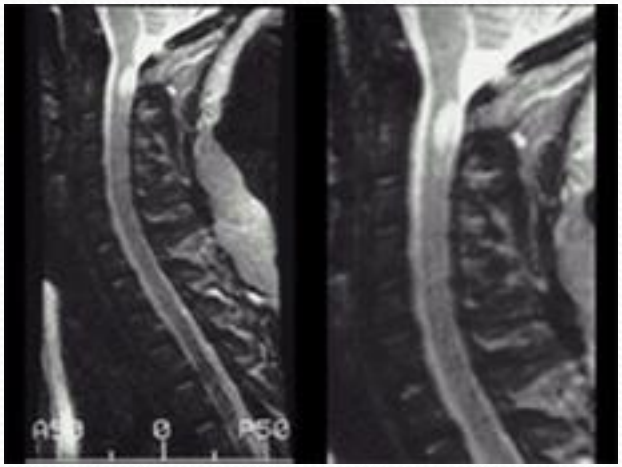

Eye motility
Intellectual & mood disturbances
Optic nerve
Cerebellar
Spasticity
Pareses
Sensory
At MS onset
During entire disease course
0
20
40
60
80
100
% patients

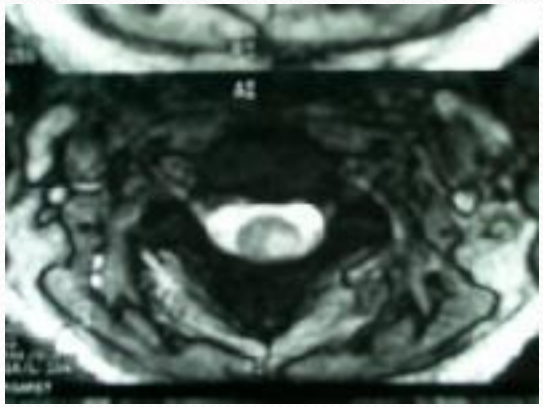












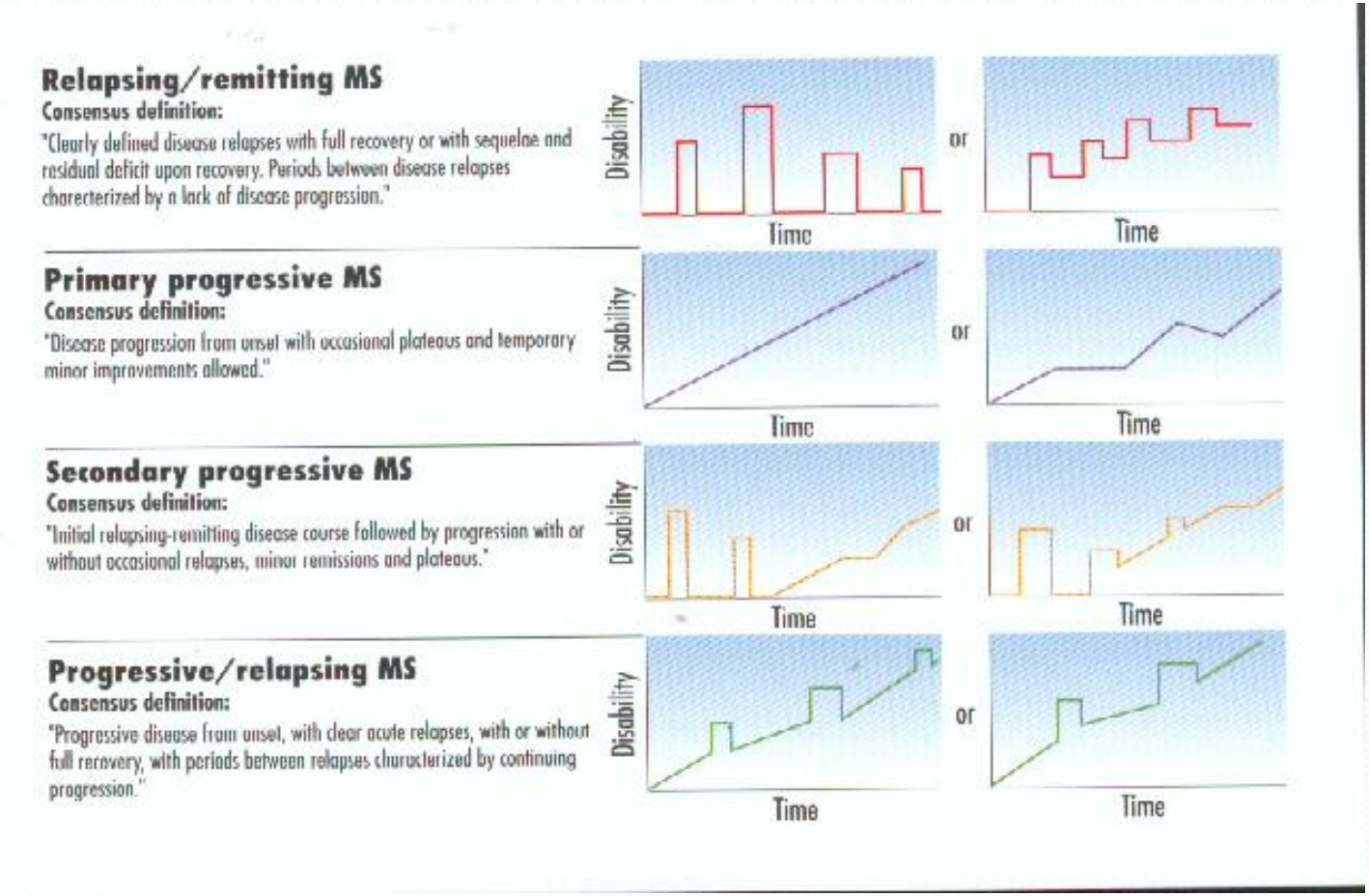
Atypical RR MS

- Atypical lesions
  - Balo's concentric sclerosis
  - Large enhancing lesions mimicking lymphoma or gliomas
- Children
  - Encephalopathy
  - Seizures

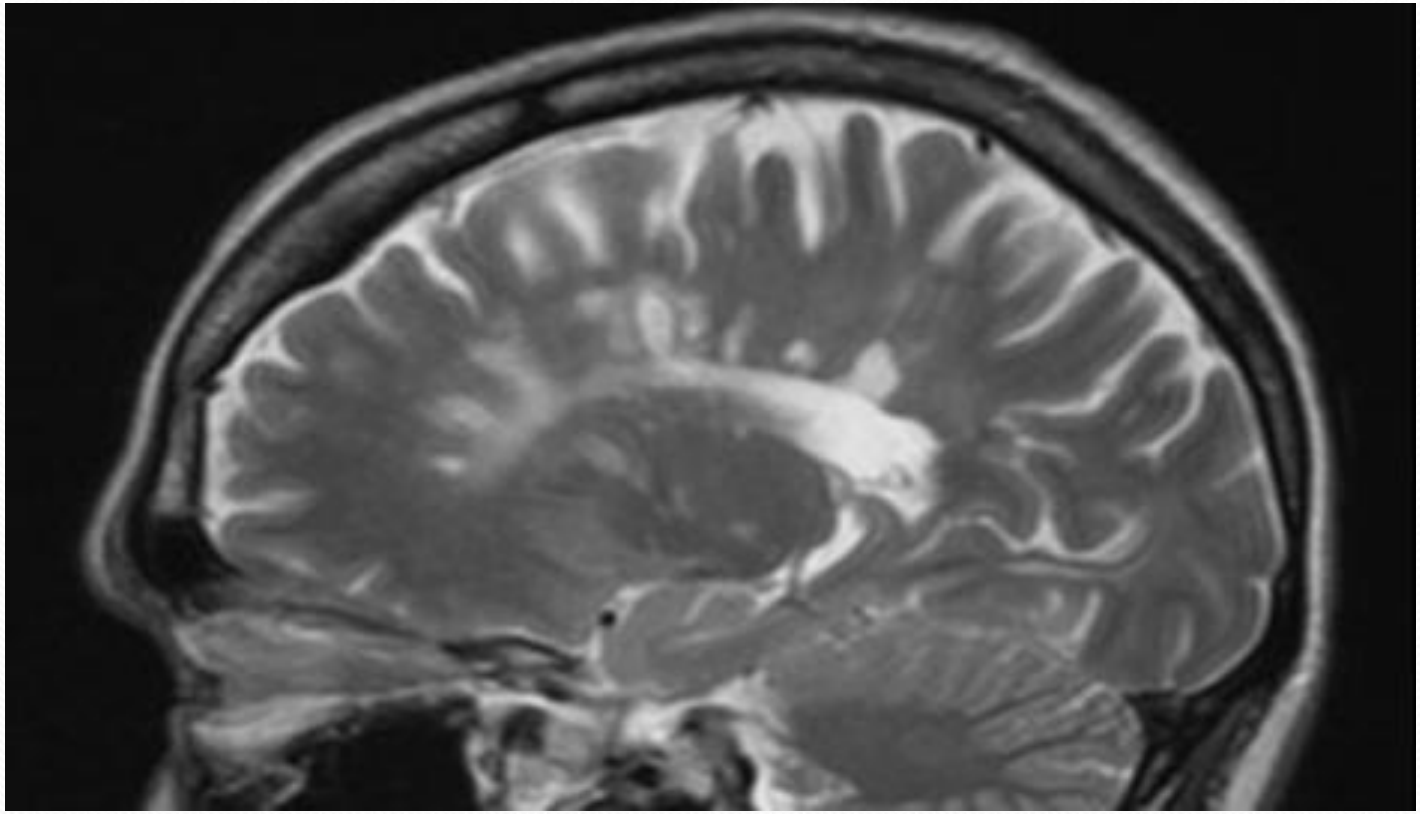
PP MS Diagnosis

- More insidious symptom onset over months to years
- Common presentation:
  - Spastic paraparesis
  - Hemiparesis less common
  - Progressive cerebellar syndrome
  - Progressive visual loss
  - Dementia
- Less MRI brain lesions
- Oligoclonal bands less common in CSF

MS: different course of illness



Typical MRI images of MS



Neuromyelitis Optica (Devic's)

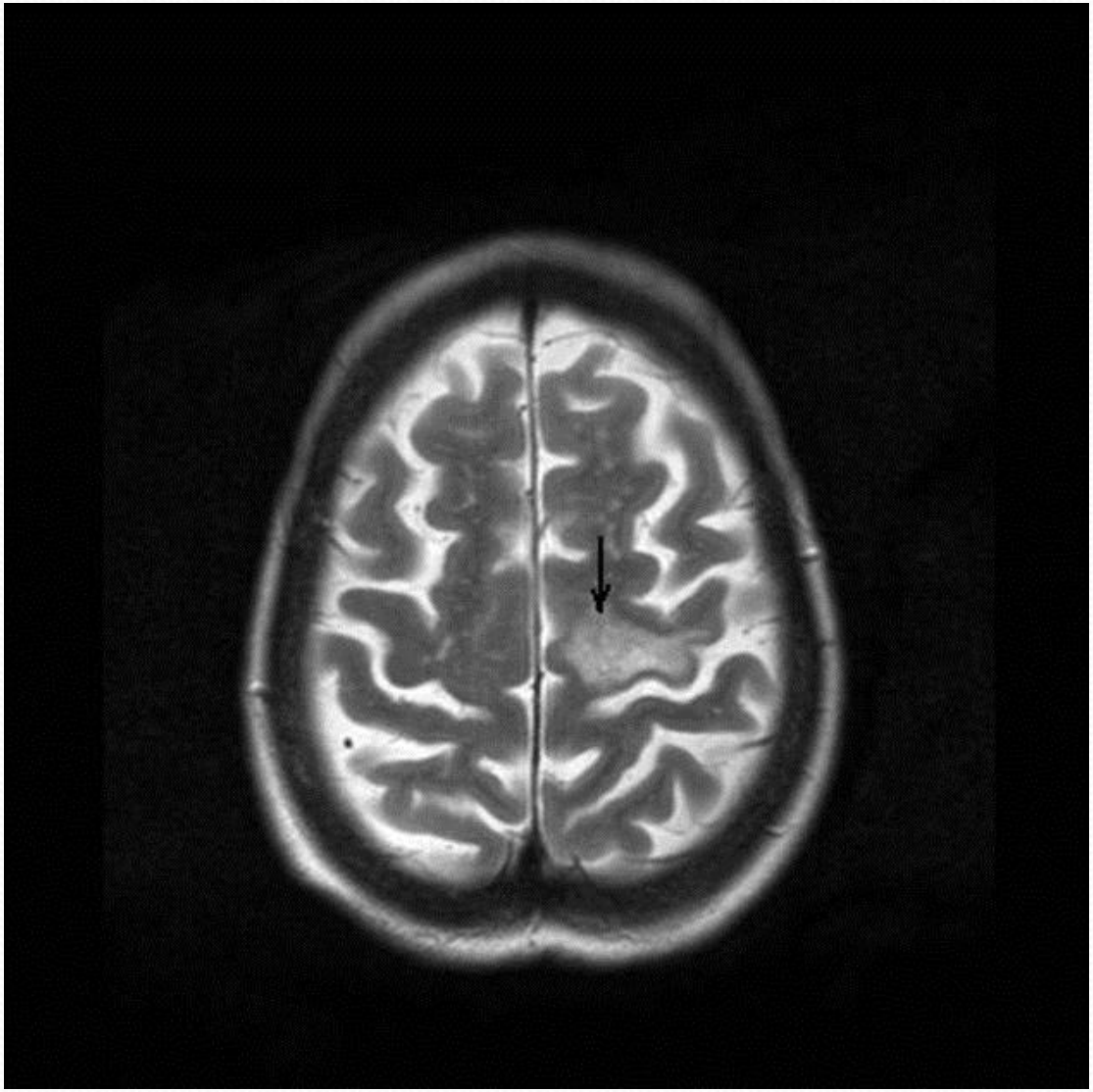
- More common Asians and Africans
- Affects:
  - Visual pathway- long lesions, less improvement
  - Spinal cord- more than 3 vertebral lesions, central
  - Brainstem- around III and IV ventricles
- Disability from multiple relapses-no 2° progression
- Aquaporin 4 (70%) or MOG
- Other auto-immune disorders: SLE, Sjogren's
- Different treatment strategies

ADEM

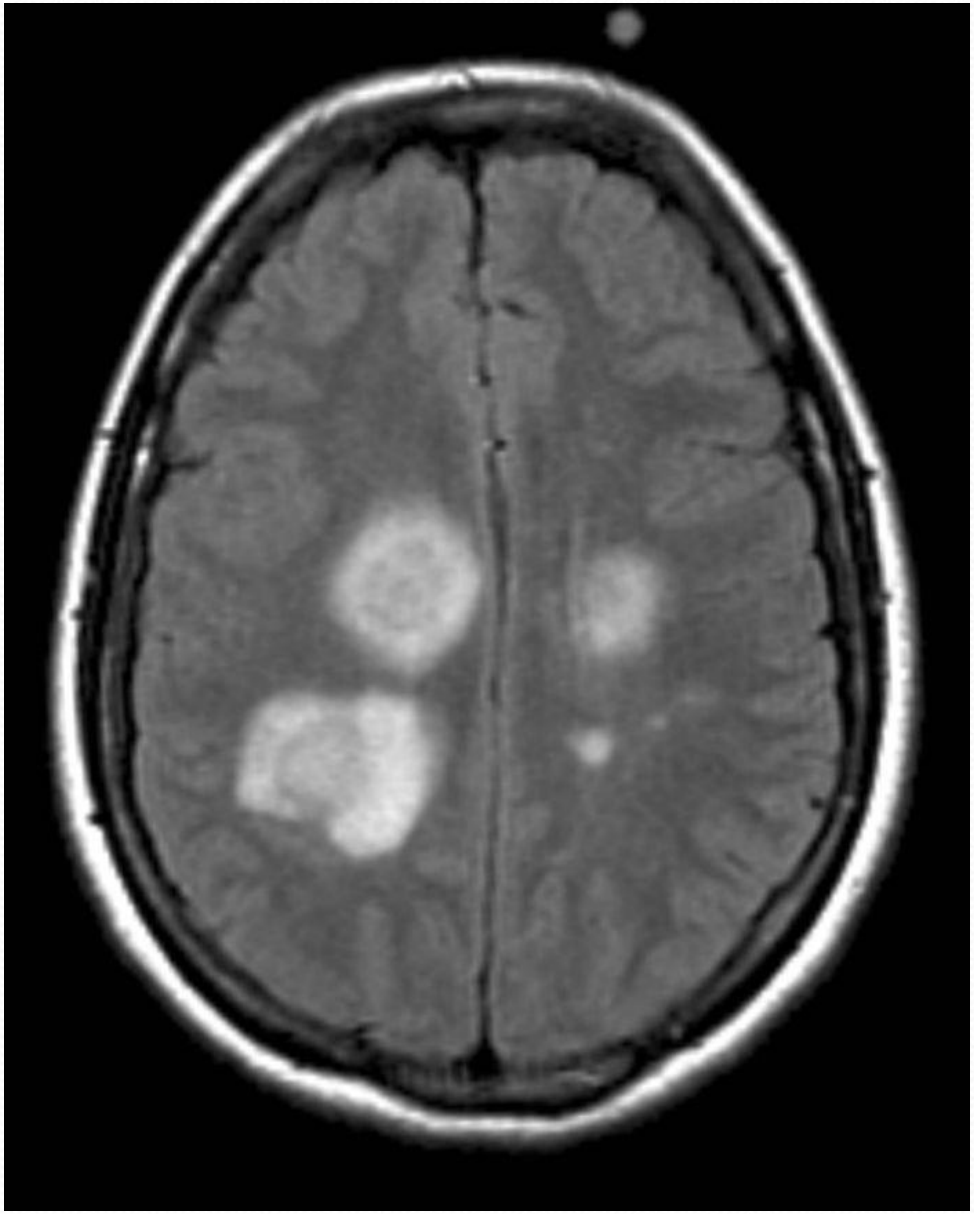
- Monophasic illness
- May precede an illness
- Encephalopathy strict diagnostic criteria:
  - Cognitive
  - Behavioural
  - Seizures
- Prognosis different

MS Differential Diagnosis

- Congenital:
  - Leucodystrophies, mitochondrial, Fabry's
- Acquired:
  - Infective: cystercercosis, Whipples', toxoplasmosis, Lyme, PML, TB
  - Inflammatory: SLE, sarcoid, Behcet's CNS vasculitis, anti-Phospholipid syndrome, Susac's
  - Neoplastic: lymphoma, glioma, secondaries
  - Vascular: Moya-Moya, CADASIL,
  - Metabolic: B12, Copper

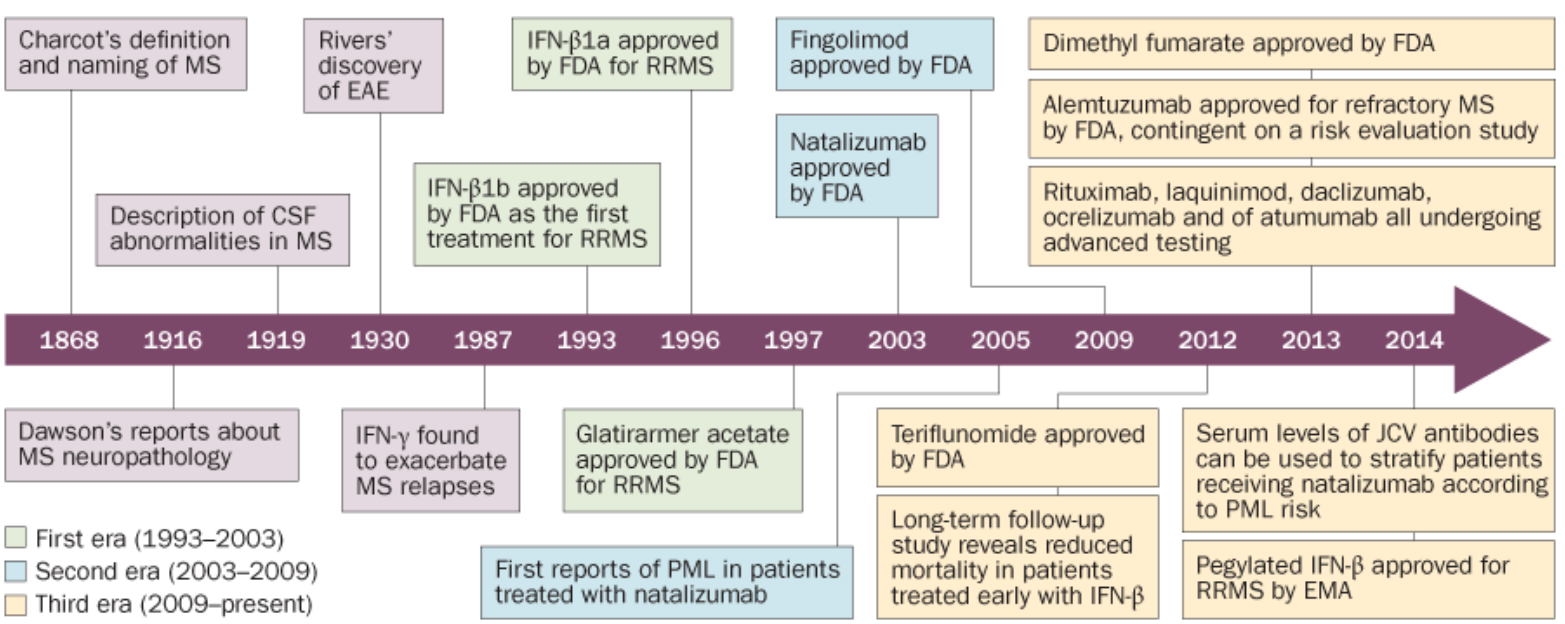


Progressive Multifocal Leucoencephalopathy



Acute Disseminated Encephalomyelitis (ADEM)

MS time line


Charcot's definition and naming of MS
Rivers' discovery of EAE
IFN-β1a approved by FDA for RRMS
Fingolimod approved by FDA
Dimethyl fumarate approved by FDA
Alemtuzumab approved for refractory MS by FDA, contingent on a risk evaluation study
Natalizumab approved by FDA
Description of CSF abnormalities in MS
IFN-β1b approved by FDA as the first treatment for RRMS
Rituximab, laquinimod, daclizumab, ocrelizumab and of atumumab all undergoing advanced testing
1868
1916
1919
1930
1987
1993
1996
1997
2003
2005
2009
2012
2013
2014
Dawson's reports about MS neuropathology
IFN-γ found to exacerbate MS relapses
Glatirarmer acetate approved by FDA for RRMS
Teriflunomide approved by FDA
Serum levels of JCV antibodies can be used to stratify patients receiving natalizumab according to PML risk
Long-term follow-up study reveals reduced mortality in patients treated early with IFN-β
First reports of PML in patients treated with natalizumab
Pegylated IFN-β approved for RRMS by EMA
First era (1993–2003)
Second era (2003–2009)
Third era (2009–present)

Vitamin D and MS

- Vit D deficiency is a risk factor ?early
- Possible mechanisms:
  - Vitamin D receptors on lymphocytes
  - Vitamin shifts from Th1 to Th2 cytokines
- Vit D levels measured at baseline, 6, 12, 24 months
  - 468 patients
  - **20ng/mL increment in average serum vitamin D level predicted:**
    - **57% reduction in new active lesions**
    - **25% lower yearly increase in T2 lesion volume**
    - **57% lower relapse rate**

Ascherio et al. JAMA Neurol. 2014 Mar;71(3)306-14.

Disease Modification

- Arrest the disease process
  - Slow down progression
  - Alter Outcome
- Aim to reduce:
  - Relapse rate
  - Disability

80% will be severely disabled within 10 years
Average life expectancy reduced by 10 years

Achieve NEDA (No Evident Disease Activity)

Disease Modifying Therapy

- Interferon beta-1b, subcutaneous (Betaseron)-1993
- •Interferon beta-1a , intramuscular (Avonex)--1996
- •Glatiramer acetate, sq (Copaxone)--1996
- •Mitoxantrone IV (Novantrone)--2000
- •Interferon beta-1a, subcutaneous (Rebif)--2002
- •Natalizumab IV (Tysabri)--2006
- •Interferon beta-1b (Extavia)--2009
- •Fingolimod (Gilenya)--2010
- •Teriflunomide (Aubagio)--2012
- •Dimethyl Fumarate (Tecfidera)--2013
- •Peginterferon beta-1a (Plegridy)--2014
- •Alemtuzumab (Lemtrada)--2014

Disease stratification?

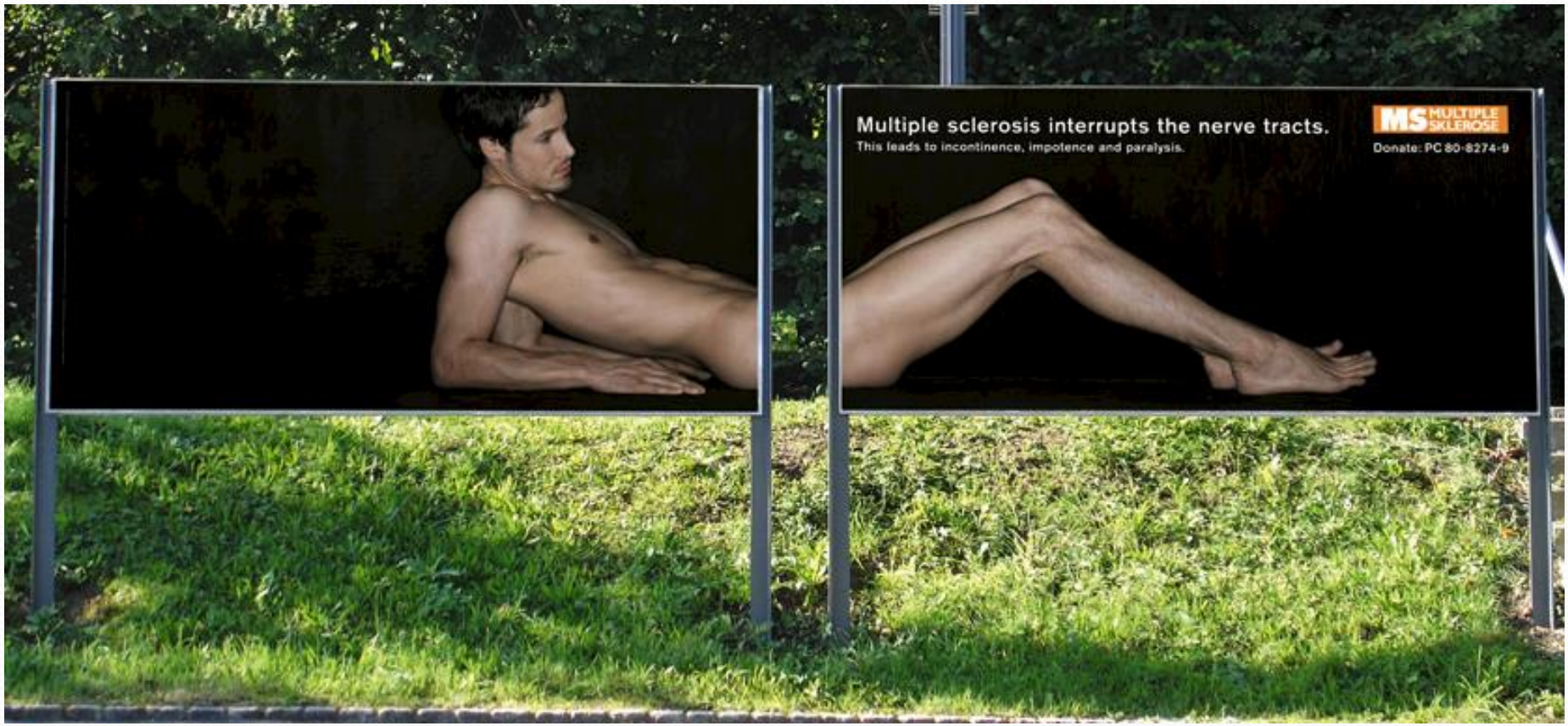
- Multiple relapses (2 in 1 year) /incomplete recovery
- MRI showed new lesions
- Poor prognosis:
  - Male
  - Older age onset
  - Multifocal relapses
  - Motor, cerebellar or bladder dysfunction
  - More than 2 enhancing or 9 T2 lesions on MRI
  - Evoked potentials
  - Thin peri-papillary retinal layer
  - Positive OCB

Symptomatic Relieve

- Corticosteroids improve symptoms during relapse of RRMS
- Fatigue: efficacy of amantadine, modafinil, behaviour modification, exercise unclear
- Spasticity: Botulinum toxin plus physiotherapy

  Role of oral anti-spasmodics?
- In-patient rehabilitation improves function

  ? Outpatient Physiotherapy


Multiple sclerosis interrupts the nerve tracts.
This leads to incontinence, impotence and paralysis.
MS MULTIPLE SKLEROSE
Donate: PC 80-8274-9

Peripheral Neuropathy

- It is very common
  - Diabetes: 3% within 5 yrs diagnosis but 15% at 20 yrs
  - Carpal Tunnel Syndrome 6% of all women
  - Toxic-
    - Alcohol: 25% alcoholics
    - HIV and cancer chemotherapy: virtually all?
- Can be confusing to the non-specialist
- May hide underlying problems:
  - Systemic disorder: diabetes, Vitamin deficiency
  - Paaraneoplastic: MGUS and underlying cancer

Types of Neuropathy

- Die back:
  - Length dependent
  - Glove and stocking sensory loss
  - Most distal muscles weak
- Multiple Mononeuropathies:
  - Nerve Specific
  - Discreet areas of sensory loss
  - Only muscles innervated by nerve is weak

Approach to Neuropathy

1. Which system affected?
   - Sensory, motor, autonomic or combinations
2. What distribution?
   - Distal, proximal, nerve pattern
3. What type of loss
   - Negative as well as positive symptoms
4. Any other systems affected?
   - Upper motorneurone/movement disorder
5. What course?
   - Acute, subacute, chronic
6. Family History?

Overell 2011 Practical Neurology 11: 62-70

Which system?

- Pure Motor
  - Motorneuron disease or multifocal motorneuropathies
- Sensory plus autonomic
  - Diabetes or amyloidosis
  - Acutely AIDP
- Sensory
  - Depends on pattern

Distribution

- Distal
  - Mainly die back neuropathy
  - Rarely with sensory forms of inflammatory neuropathies
- Proximal
  - Axial involvement: MND and CIDP
- Distal and proximal
  - AIDP and CIDP
- Nerve pattern
  - Radiculopathy, plexopathy or Multiple Mononeuropathies

Type of sensory change

- Pain and temperature loss
  - Small fibre neuropathies: diabetes, amyloid, toxic
- Painful
  - Diabetes, toxic, amyloid, Fabry's, AIDP
- Joint position sense (sensory ataxia)
  - Sjogren's, cisplatin toxicity, anti-Hu paraneoplastic syndrome
  - IgM paraproteinaemia and AIDP causing sensory ataxia

Other systems?

- Upper motorneurone:
  - Multiple radiculopathies and myelopathy
  - Infection: HIV and Syphyllis
  - Vitamin E and B12 deficiency
  - Copper
  - Frederich's ataxia
- Movement disorders:
  - Painful feet moving toes, IgM paraproteinaemia

Tempo of onset

- Acute:
  - AIDP, vasculitic neuropathies
- Sub-acute:
  - Paraneoplastic
  - Some toxic: arsenic, thallium
  - Compressive
- Chronic:
  - Majority of metabolic neuropathies
  - CIDP

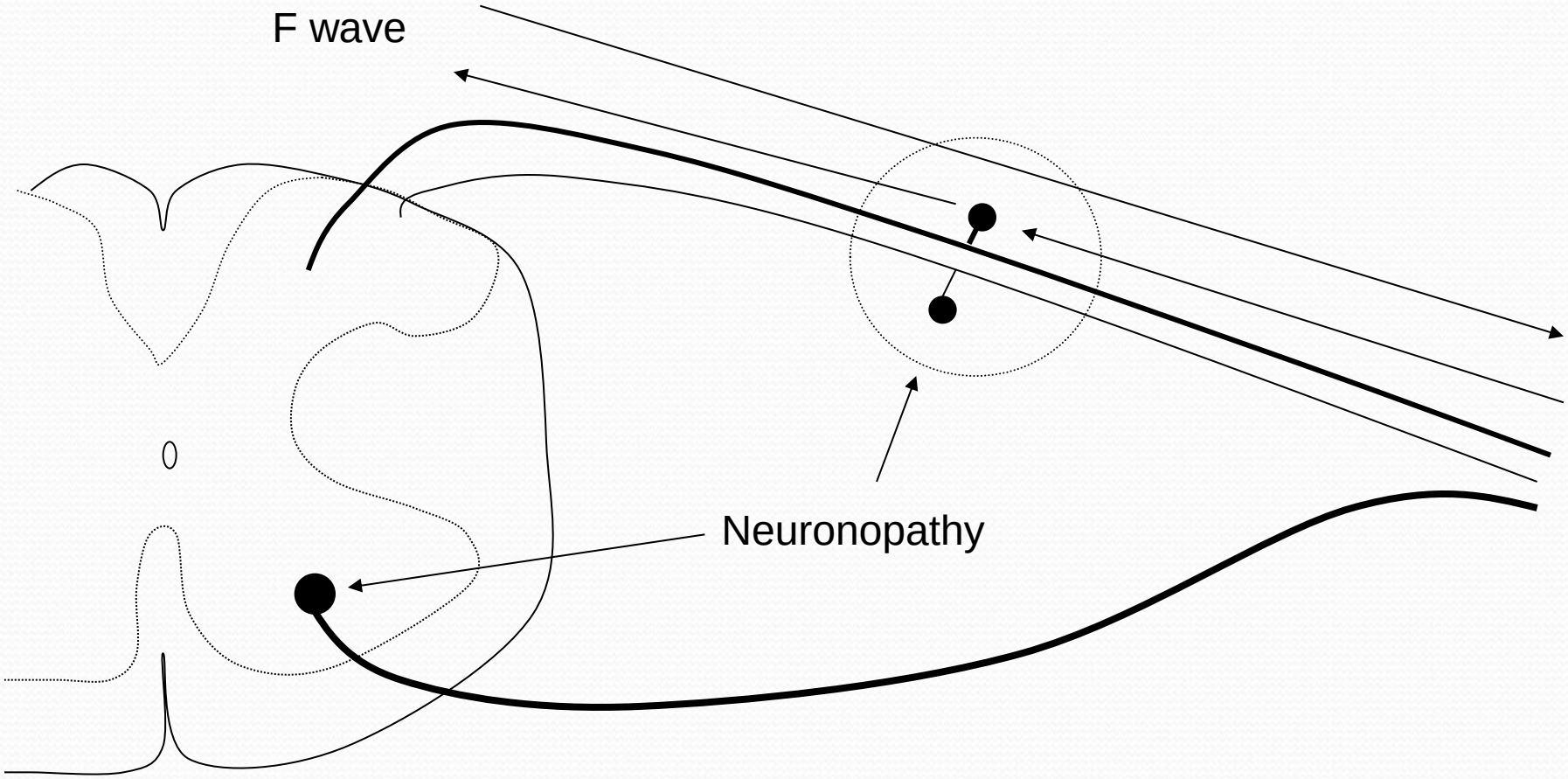
Family History

- Can be very difficult to determine
- Examination better than symptoms:
  - Pes cavus, wasting
  - Weakness: often put down to “arthritis”
  - Sensory loss: often not noticeable because gradual onset
    - Amyloid neuropathy
    - HSAN

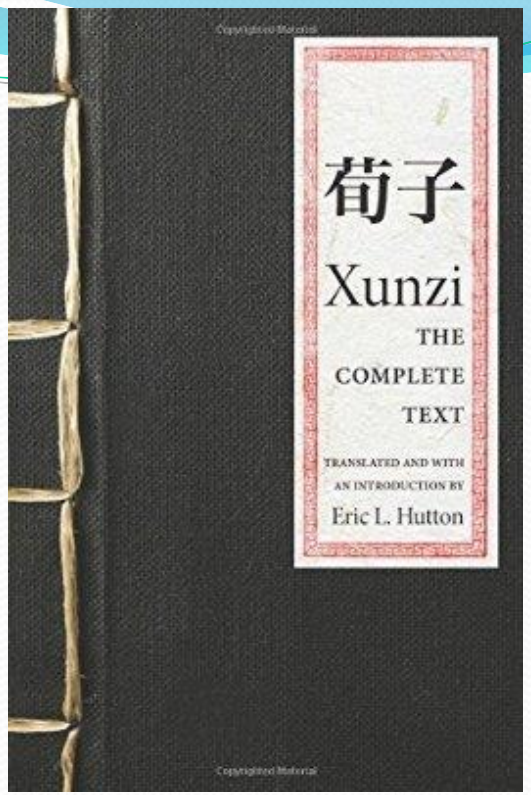
Investigations

- First line:
  - FBC, U+E's, LFT, TFT, B12/folate, sugar, protein electroporesis
- Additional:
  - Other Bloods
  - EMG/NCS
  - Autonomic function tests
  - Nerve Biopsy
  - Genetic testing

Neurophysiology limitations



不闻不若闻之，
闻之不若见之，
见之不若知之，
知之不若行之



Not having heard something is not as good as having heard it;
having heard it is not as good as having seen it;
having seen it is not as good as knowing it;
knowing it is not as good as putting it into practice.

Xunzi by
Xun Kuang BC 312-280