Multiple sclerosis: initial presentation and relapse – what to look out for

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Introduction

• What is known about MS?

• MS is a chronic demyelinating neurological disease with both inflammatory and neurodegenerative components.
• Aetiology unclear.
• Pathological mechanisms are increasingly understood but how do they interact given the phenotypic heterogeneity of MS?
• Variable prognosis in which surrogate markers eg. MRI-visible white matter lesions poorly correlate with disability and in which clinical makers e.g. relapses are unpredictable and can be infrequent.
• Makes determining drug efficacy and patient selection challenging.
Introduction

• Recent opportunities/challenges in MS:
  • Understanding of pathogenesis (at least of inflammatory aspects) has improved.
  • Increasing number of potential targets identified for therapies.
  • Technological advances has opened doors to improved compounds.
  • Increasing experience with other autoimmune/malignant conditions has identified potential compounds that may cross over to MS.
  • Net effect is that status quo of last 10 years is about to be changed/already changing regarding our options to immunomodulate and immunosuppress patients with MS.
Cases

- 44 year old woman referred by GP
  - History over at least 5 years of pain (diagnosed fibromyalgia), fatigue (‘ME’), numbness everywhere and tingles.
  - Tinnitus, blurry vision, ‘thick-headed’, slurring speech, can’t think of the wards.
  - Balance less good, can veer and has fallen.
  - Hands can shake and gets ‘spasms’ in legs.
  - Symptoms can be episodic but something always there
  - Seen by rheum and ortho and ENT – finally gets to neurology clinic.
Cases

- On multiple analgesics, diazepam and pregabalin.
- Family history of cancer
- Smoker and drinks no alcohol
- Thinks she has MS....

- Does she??

- Any questions you would like to ask?
Cases

• It's a mess – with multiple co-morbidity and usually awful social situation, illness behaviour etc.
• Can be almost certain though it isn't MS

• Modern life – package of fibromyalgia, IBS, CFS and migraine

• Migraine aura can do just about anything

• Lots of people out there with migraine who have never had it diagnosed.
Cases

• 32 year old woman

• Fit and well – develops over 24-48 hours initially R foot sensory loss which then evolves proximally to involve whole R leg up to belly button and then after 24 hours L leg.

• Sensory loss and tingling with weakness evolving and reduction of perianal sensation.

• Diagnosis?

• Differential?
Cases

- Transverse myelitis
- There is a differential and imaging and CSF is needed to confirm if inflammatory and if MS or other inflammatory cause possible
- Inflammatory – MS, MS-variants, Connective tissue
- Infective
- Compressive
- Vascular
- Rule out malignancy

- Consider radicular – e.g. GBS
Cases

- 26 year old male
- Develops pain L retro-orbitally on moving his eye
- Following day notes that vision in centre of eye appears ‘misty’ and less defined – progresses over next 24 hours to almost complete central visual loss.
- Starts to recover after just under a week to almost complete recovery but bright colours appear desaturated
- After further questioning recalls an event 12 months ago of a ‘trapped nerve’ in his L arm and funny feeling down his back when he flexed his neck which resolved.
- Diagnosis?
- Differential?
Cases

- Optic neuritis
- Could consider migranous aura, other infiltrative disorders of eye, glaucoma – but all atypical
- Recovery is typical and good but often residual colour fading which can be picked up on Ichihara testing/other sensitive eye tests rather than Snellen chart.

- Lhermitte’s phenomenon – high cervical lesion
- Suggestive of inflammation but can also be seen in compressive lesions.
Cases

• 40 year old woman

• Presents with sensory disturbance on L arm – like a cold water tap running on it

• Power normal but difficulty with fine movement in hand and drops objects

• Otherwise well

• By the time she gets to clinic symptoms have resolved almost completely after about 4 weeks but notices some recurrence on exercise or when she has a shower

• On no medication, no PMH except for an episode of viral labyrinthitis 2 years ago.

• On examination: R internuclear ophthalmoplegia, reflexes L side ?brisker
Cases

• Sensory disturbance is concerning – it is hard to characterise, non-dermatomal and possible reflex change

• Recovery is in keeping with inflammatory disorders

• Exacerbation with heat/exertion – suggestive of Uhtoff’s phenomenon.

• The labyrinthitis takes on a different meaning now especially with the finding of eye signs on examination.
Diagnosis

• Relapsing-remitting form (80-85%): Can appear at times to be convoluted – basic principle is dissemination of clinical events in space (different parts of CNS) and time (at least 30 days between new symptoms).

• Requires two clinical events (dissemination in time) therefore one event termed clinically isolated syndrome (CIS) rather than MS.

• Newer MS diagnostic criteria (McDonald) can allow earlier diagnosis (new MRI activity can confirm dissemination in time rather than awaiting for a further clinical event – may have impact on treatment in future.
Diagnosis

- Relapsing-remitting form:
- Tends to be younger people (20-40) females (2:1).
- Relapses - varied symptoms: sensory (non-dermatomal, often positive), visual (optic neuritis), brainstem, spinal cord (sensory level, weakness) most frequent.
- Hemiplegic weakness and headache rare.
- Evolution over hours (at least) or days sudden less common (think vascular).
- Last over 24hrs (often weeks) then recovery to varying degrees.
- Approx 65% risk of progression over time – mean 15-20 years.
Diagnosis

- Primary progressive form (15-20%):
- Tends to occur in older people (40+) males=female.
- Slow progressive worsening – often mobility and spasticity and balance worsening.
- Sphincter almost always involved.
- Brainstem and visual less common.
- Small proportion of people (approx 5%) may still have relapses.
- Diagnosis requires appropriate symptoms, exclusion of mimics and appropriate MRI changes (ideally with abnormal lumbar puncture).
Diagnosis

- **Symptoms**
  - Most common presentations as described and also brainstem/cerebellar
  - Pain and fatigue with nothing else is unusual
  - Hemiplegic sensory or motor unusual
  - Headache controversial
  - Cognitive controversial early
  - Sphincter can be early but unusual to have urinary retention without definite cord lesion and unusual to have significant bowel symptoms early
  - Pattern recognition
Aetiological Factors

- So what causes MS??
Lots of theories from various places......

"I'M SORRY DOCTOR, BUT AGAIN I HAVE TO DISAGREE."
Aetiological Factors

• Most interest in genetics and environment

• Recent further interest especially in:

1. Sunlight exposure / vitamin D
2. EBV
3. Smoking
World Distribution of Multiple Sclerosis

Key:
- High risk
- Probable high risk
- Low risk
- Probable low risk
- North-South gradient risk
- Other risk

Aetiological Factors

• Evidence for genetic influences:

• Predilection for populations of northern European origin relative to indigenous peoples in same geographical location e.g. Australia, Eskimos.

• Increased incidence in first degree relatives (20-40x more common) and MZ twins 25-30% DZ twins 3-5%

• Absence of increased incidence in adopted relatives to patients with MS despite shared environment.

• Reported family clusters.
Aetiological Factors

• Evidence for environmental factors:

• Within temperate climate regions MS prevalence and incidence increases with latitude.
• Age of onset follows relatively constant pattern across different regions.
• Change of risk in migrants from high to low risk areas and vice-versa e.g. Migrants to Israel, UK and US. Change seems to be particularly marked if migration occurs during childhood.
• Different incidence in populations with similar genetic characteristics and location e.g. Malta and Sicily.
Aetiological Factors

• Family history:
  • MS approx 1 in 600 females more commonly affected.
  • Definite evidence of a genetic contribution with most evidence for HLA-DRB-1*1501 locus.
  • But even in monozygotic twins rates of only between 25-35% concordance for MS seen and in dizygotic twins only approx 5%.
  • Family studies done have limitations and wide ranges.
  • Age adjusted risk for siblings 3% (less for half-sibs)
  • One parent MS: 2%
  • Both parents MS up to 20%
Aetiological Factors

- Sunlight / Vitamin D:
  - Duration of sunlight correlates with latitude.
  - Decreased incidence of MS in populations with high fish consumption (vit D) and similar sunlight e.g.. Norway.
  - Suggestion in northern latitudes that being born in May is a risk factor compared with Nov (?in utero low sunlight exposure).
  - Evidence is increasingly promising.
  - Some evidence that Vit D may be involved in HLA DRB-1 expression and may play a role in deletion of auto-reactive T cells.
  - Link between environment and genetics.
  - Low levels of Vit D may predispose patients with MS to osteoporosis – increasingly recognised issue outside of co-prescribing of steroids in the condition.
  - Not recommending routine vit D supplementation to patients currently (not sufficient evidence) but unlikely to be harmful.
Aetiological Factors

• **EBV:**

  • Critical time for development of risk for MS appears to be adolescence.
  • EBV normally contracted much earlier in developing world, often in temperate climates not contracted until adolescence if at all.
  • Seropositivity for EBV displays a latitudinal gradient whilst early age of EBV observed at all latitudes in those populations who have a low risk of MS e.g.. Eskimos.
  • ?EBV just a marker for hygiene or is it directly pathological. Evidence that MS incidence increases following developing infectious mononucleosis at late age.
  • Higher rate of EBV seropositivity in MS but not 100%.
  • Attempts to isolate/prove autoimmunity from CSF have been contradictory.
  • Interesting but further study needed.
Aetiological Factors

• Smoking:

• Risk of MS increased in smokers with dose response of 25 or more pack years.
• Unclear if direct effect or coincidental marker.
• Possible mechanisms: (i) vascular effects; (ii) nitric oxide; (iii) increased respiratory tract infections; (iv) neurotoxic effects of cyanide; (v) nicotine effects on blood brain barrier and cerebral perfusion.
• Evidence smoking may adversely affect progression of MS and conversion from RR to SP MS.
• One factor only - would not explain geographical variations of MS or many other features.
Therapeutics

• What is a relapse?
  • Good question
  • Hugely subjective quite often – MRI can give some objective help
  • More I practice the less clinically meaningful I think they are
  • Disease modifying drugs will modify them
  • Research definition is hugely ambiguous
  • Everyone with MS will get bad days-weeks – is this a relapse?
  • But qualification for disease modifying drugs is dependent on them
Therapeutics

- Relapse management:
  - Evidence particularly from studies of recovery in optic neuritis that steroids do not appear to alter long term recovery but can hasten rate of recovery.
  - Hence tend to be reserved for ‘significant’ disabling relapses only.
  - No absolute evidence for steroid protocols – 500mg od for 5 days oral methylprednisolone most common with no steroid tail (make sure infection ruled out first).
  - Co-prescribe PPI and screen for infection.
  - Please inform local MS nurse of relapse occurrence – may influence choice of disease modifying therapy as options are increasing.
Therapeutics

- The conventional treatments...

- In the past...
  - Would only treat after two relapses (unlike most of Europe and USA) although new guidelines may change this.
  - Nothing for people with the progressive form.
  - Partially effective and need injecting.
  - This thankfully is changing....
When to treat in MS?

- **Known evidence:**
  - Certain relapses (optic neuritis, sensory) may have better outcomes than others (cord, brainstem) and longer the gap between first and second event the better the prognosis.
  - Increase in lesion load in first 5yrs is loosely predictive of disability at 20yrs.
  - EDSS 4 argument – evidence that once patients reach this level of disability (some degree of walking impairment) progressive decline is almost inevitable hence aim to prevent this.
  - Ongoing debate amongst neurologists treating MS in UK – should we treat early and aggressively even if clinical picture is mild for a hoped for ‘pay off’ in functional improvement later??
Current management

• Current therapeutic options:
• Currently licensed disease modifying drugs (DMDs) for relapsing-remitting MS:
  • Beta-interferon
  • Glatiramer acetate
  • Dimethyl fumarate
  • Teriflunomide
  • Alemtuzumab
  • Natalizumab
  • Fingolimod
Current management

- Significant unmet need in terms of modulating/slowing progression of neurological disability in MS.
- No proven role for steroids except in small number of selected cases (neurologist advice).
- Promising outcomes from clinical trials but much still to be understood.
- Balancing risk vs. benefit.
- Role of vitamin D
- Statins
Summary

- Considerable number of questions remain however progress has been made and is accelerating.
- The range of therapeutic options is already increasing but is likely to increase further even in the relative short-term.
- Challenges are accuracy of prognostication to identify patients risk stratify early.
- Will need considerable cooperation between neurologist and patient in deciding and the vital input of specialist nurses, GPs, community multidisciplinary teams.
- How we can help:
  - Shared care pathway/management protocols (recently introduced locally)
  - Specialist Neuroinflammatory clinics
  - Clinical trials ongoing to increase options for patients who we couldn't treat previously.
  - Aim to reassure people with MS that they are ‘not forgotten’ and that we can be increasingly proactive in the management of their disease.
“No doubt about it, Bob ... You’re infected with tiny fighter planes. What’s worse ... you’re a carrier.”