How does Progressive MS differ from Relapsing MS?

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Types of MS

- Progressive relapsing
- Progressive MS – secondary progressive (SPMS) and primary progressive (PPMS)
- SPMS: progression follows initial relapsing remitting phase
- PPMS: gradual steady and relentless functional decline from onset
- Relapsing remitting (RRMS)
- Most patients will be affected by progressive disease course at some stage

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Relapsing and Progressive MS

- Unknown
  - Primary trigger(s)
  - Specificity of pathogenic immune cells
  - Mechanism underlying progressive disability
  - Genetic contributors to progression
  - Does progressive MS result from primary neurodegenerative process involving loss of oligos or axons where inflammation is secondary process?

“Inside Out” or “Outside In”?
Primary Progressive MS

- More likely to affect men than other forms of the disease
- Typically begins a decade later than RRMS onset – age is important
- Shares similar genetic susceptibility and similar pathology with other forms of MS (variant of the same problem)
- Characterized by underlying neurodegenerative problem
- Meningeal infiltrates of B and T cells particularly prominent in progressive MS and lymphoid follicles associated with underlying microglia activation and cortical plaques
- White matter plaques often neuroinflammatory at the center but microglia and macrophages as well as evidence of ongoing axonal injury can be found (simmering and possibly concentrically expanding axonopathy)
- Diffuse low grade parenchymal inflammation with B cells, T cells, and microglia reported
- Perivascular inflammation often evident without associated disruption of blood-brain barrier – may explain failure of current therapies
- Axonal and neuronal death may result from glutamate-mediated excitotoxicity, oxidative injury, iron accumulation, and/or mitochondrial failure

Challenges of Progressive MS

- Current inability to develop effective therapies due to lack of understanding of underlying biology of this form of disease
  - Disease mechanisms driving progressive disease remain unknown
  - Therapeutic options currently limited to symptomatic treatments and physiotherapy
  - Currently no animal model available that accurately models this stage of disease
- Definition: gradual worsening of motor/cognitive function over time with or without superimposed attacks?
- Is evolution from relapsing to progressive MS different than PPMS?
Proposed theories to explain pathogenesis of progressive MS

- Brain damage driven by inflammation similar to what is seen in RRMS, but behind intact BBB
- Starts as an inflammatory disease but chronic inflammation leads to neurodegeneration /disease progression independent of inflammation
  - Microglial activation under control of intact neurons – control might be lost as consequence of neurodegeneration
- Primarily neuro-degenerative disease with progression amplified by inflammation in early disease

Relapsing vs. Progressive Disease
Differences in Pathophysiology

- Pathological hallmarks of RRMS: inflammatory demyelinating lesions in brain and spinal cord visualized by MRI – axonal damage and loss related to foci of inflammation
- PPMS: diffuse rather than focal inflammation; involves more prominent cortical demyelination (may contribute to progression of disease); diffuse axonal injury; frequent presence of microglial nodules in the brain
Pathological Differences between RRMS and PMS

Inflammation

- Present at all stages of MS
- Consists of perivascular and parenchymal infiltrates of lymphocytes and macrophages
  - **Active lesions**: dominate RRMS – initial response consists mainly of CD8+ T cells, abundant macrophage recruitment/activation; secondary response includes recruitment of T cells, B cells and macrophages as consequence of myelin destruction; infiltration of inflammatory cells into CNS results in profound damage to BBB as seen by gad-enhancing lesions on MRI
  - **Chronic lesions**: seen in SPMS and PPMS - relationship between inflammation and BBB damage less obvious (impairment can occur in presence or absence of inflammatory infiltrates); large aggregates of inflammatory cells observed in meninges display features of lymphoid follicles (T and B cell germinal centers and presence of follicular DCs); as disease progresses inflammation becomes compartmentalized behind intact BBB
Characterization of ectopic B-cell follicles and inflammatory cell infiltrates in SPMS and PPMS

Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology.

Characterization of ectopic B-cell follicles and inflammatory cell infiltrates in SPMS and PPMS

Focal Plaques of Demyelination

- Plaques present in grey and white matter at all stages of disease
- Slow expansion of pre-existing lesions leads to pronounced cortical demyelination associated with extensive diffuse injury throughout normal appearing white and grey matter in Progressive MS
- Cortical lesions most abundant in progressive stage of disease – most prominent in subpial cortical layers and can be linked to local inflammation in the meninges
- Activated microglia associated with active lesions
Focal inflammatory demyelinated plaques in the white matter dominate the pathology in acute and relapsing multiple sclerosis, while cortical demyelination and diffuse white matter inflammation are characteristic hallmarks of PPMS and SPMS.
**Diffuse global tissue injury**

- Brains of MS patients show widespread inflammation, microglial activation, astrogliosis, and mild demyelination and axonal loss in NAWM – loss of tissue volume also seen in cortex = brain atrophy
- Extent and severity increases with disease duration and most closely linked with PMS
- Small calibre axons most predominantly affected
- Extent of diffuse injury not correlative with number, size, or destructiveness of focal lesions but correlates moderately with extent of cortical demyelination

**Evolution of structural pathology and disease mechanisms in MS**

Mechanisms of MS Pathology

- Distinct patterns of demyelination and tissue injury present in RRMS – likely due to distinct immune processes in inflammatory lesions
- Patterns of tissue injury are largely homogeneous in SPMS and PPMS – likely the result of slow expansion of existing lesions with sparse remyelination
  - Age-dependent loss of trophic support from microglia or local environment in demyelinated plaques

Microglial Activation

- Active tissue injury associated with microglial activation in RRMS and PMS
- Microglial nodules seen in PMS
- Oxidative burst by activated microglia may have a major role in induction of demyelination and progressive axonal injury
- Microglia may also have neuroprotective functions and could promote remyelination following removal of debris and secretion of neurotrophic molecules

Altered axonal ion homeostasis

• Aberrant expression of Na⁺ channels, acid sensing Na⁺ channels, glutamate receptors, and voltage-gated calcium channels detected in demyelinated axons
• Alterations in expression or activity could result in intra-axonal Ca²⁺ accumulation and degeneration
• Ion channels could be targets for neuroprotective therapies in PMS

Mitochondrial Injury

• Energy deficiency or “virtual hypoxia” may have a pathogenic role in MS
• Impaired NADH dehydrogenase activity and increased complex IV activity in mitochondria in MS lesions
• Mitochondrial injury may reflect oxidative damage in areas of initial tissue injury
• Accumulation of mitochondrial DNA deletions in progressive MS could partly explain increased susceptibility to neurodegeneration in SPMS and PPMS

Oxidative Stress

- Oxidative stress drives mitochondrial dysfunction via several different mechanisms..
- Free radicals disrupt mitochondrial enzyme function
- Modify mitochondrial proteins and accelerate their degeneration
- Interfere with de novo synthesis of respiratory chain components and induce mitochondrial DNA damage
- Oxidative injury pronounced in progressive MS lesions despite low levels of inflammation and may be driven by factors other than inflammatory process in PMS
Iron Accumulation

- Iron accumulates in aging brain where it is predominantly stored in oligodendrocytes and detoxified by binding to ferritin
- Intracytoplasmic accumulation of iron in oligos may explain high susceptibility of these cells to degeneration under conditions of oxidative stress
- In MS lesions, iron is taken up by activated macrophages and microglia – which become dystrophic and undergo fragmentation and cellular degeneration
- Process is age-dependent and likely to be more pronounced in PMS patients
Conclusions

• Absence of definitive disease mechanism in both RRMS and PMS
• Current evidence indicates a number of interlinking pathways which contribute to disease pathogenesis
• Inflammation mediated by T cells, B cells, and macrophages drives demyelination and degeneration in all forms of the disease
• In progressive MS, inflammation, characterized by lymphoid follicles in meninges, becomes trapped behind intact BBB making anti-inflammatory treatment unsuccessful
• Tissue injury may be affected by microglia activation, oxidative injury and mitochondrial damage
• In PMS, liberation of iron may amplify oxidative damage resulting in increased neurodegeneration
• Accumulation of tissue damage leads to exhaustion of functional reserve capacity of the brain, which may accelerate clinical deterioration with slow progressive tissue injury
• A great need exists for better models of PMS to aid the development of effective disease-modifying therapies for this devastating form of the disease