Primary Progressive MS:
Diagnosis, Clinical Course, and
Long-Term Management

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Disclosures

Consultant: Accordant, Acorda, Bayer, Biogen,
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Primary Progressive (PP) MS

- Diagnosis
- Natural history and prognostic factors
- Etiology/pathogenesis/neuropathology
- Therapy/management

Major Take-Homes

- All progressive MS involves the same process
- This process is neurodegeneration, with neuroaxonal injury and diffuse inflammation
- Progression is linked to age
- The seeds of progression are present from the onset
- Wellness/health maintenance is a treatment for progressive MS (because it helps CNS reserve)
Case 1

A.L. is a 40 year old man with a 10 month history of progressive left leg weakness. He has no prior medical history, and is on no medications. Exam shows a weight of 250 pounds, BP 155/90, mild paraparesis (L>R), bilaterally upgoing toes, vibration sensation 9 seconds in the toes.

Blood shows vit D 25 hydroxy level 19, vit B12 347, HTLV and Lyme antibodies negative. Brain MRI shows 6 lesions (3-8 mm); 2 are periventricular and 1 juxtacortical. Spinal MRI shows 2 lesions at C4 and T10. CSF is + for OCBs.

Case 1

Does A.L. meet formal criteria for PPMS?
**PPMS: Definition**

- Insidious onset of symptoms with gradual deterioration
  - occasional plateaus and minor improvements acceptable
  - worsening is independent of relapses (they do not occur)
- Typically progressive myelopathy/spastic paraparesis in 83%; sometimes progressive cerebellar (8%), hemiplegia (6%), brainstem (1%), cognitive decline (1%)
- Generally gait, balance, spasticity, weakness, bladder/bowel; sensory much less common

*Continuum 2013; 19:922; Acta Neuropath 2012; 123:627

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**PPMS: Definition**

- Decade older age at onset (late 30s, early 40s)
- Equal gender ratio
- 10 to 15% of MS at onset
- Very unusual in pediatric MS (2.3-7%)
- Worse prognosis
- Macroscopic MRI lesions (T2, T1, contrast) typically fewer (than in relapsing MS)

*Continuum 2013; 19:922*
### 2010 McDonald Criteria: PPMS Diagnosis*

- One year of disease progression (retrospective or prospective)
- Two of the following
  - Brain MRI DIS: >1 T2 lesion in at least one area (periventricular, juxtacortical, infratentorial)
  - Spinal cord MRI DIS: >2 T2 lesions
  - Positive CSF (+OCB/↑ IgG index)
- Any brainstem or cord lesions counted must be asymptomatic

*Ann Neurol 2011; 69:292

### Proposed PPMS Modified Diagnostic Criteria*

- Retrospective review (from 1990-2011) of N=95 PPMS; 88 had MRI or CSF results
- CSF OCBs was more sensitive diagnostic criteria than spinal cord MRI lesions
- Single spinal cord lesion improved diagnostic sensitivity (vs. 2 lesions) and simplified diagnosis

*MSJ 2012; 19:1095
PPMS Variant*

N=7 patients over 6 years (Mayo Clinic)
  median age 43 (33-51)

Single ventral cervicomедullary junction (N=4), ventral cervical (N=2), pons (N=1) lesion

Progressive myelopathy without additional lesions

N=4 had CSF c/w MS

*Neurology 2012; 78:540

PPMS Workup

Bloods: CBC + diff; PT/PTT/platelets; metabolic panel; ESR, CRP; vitamin B12, D, E; ANA, RF, SSA/SSB, anticardiolipin antibodies; ACE; copper, zinc; HTLV-1,2 and HIV antibodies; Lyme ELISA and western blot; RPR

MRI: brain + contrast, cervical and thoracic MRI

CSF: OCBs, IgG index; cell count, protein; MBP; paired ACE; HSV, VZV PCR; paired Lyme antibodies; cytology; VDRL
MRI and PPMS*

- Low level of T2 and contrast lesion activity and lesion load
- Spinal cord may show diffuse mild T2 hyperintensity
- Atrophy occurs in both GM and WM; GM involves deep nuclei and cortex
- MTI abnormalities in NAWM and NAGM

*J Neurol 2012; 259:611

MRI and PPMS*

- DTI indicates injury to GM and WM, cervical cord
- MR spectroscopy indicates ↓NAA in NAWM, whole brain
- Functional MRI documents cortical reorganization, recruitment changes

*J Neurol 2012; 259:611
CSF and PPMS*

Retrospective British Columbia database review (N=1,120)

Higher proportion of OCB positivity seen with PPMS vs. relapsing MS

Total CSF IgG and protein levels were higher in PPMS

CSF findings not associated with progression

*MSJ 2012; 19:577

CSF and PPMS*

Evaluated IgM OCB in relapsing (N=69) and SPMS (N=35), vs. PPMS (N=45)

IgM OCB+ in 40% relapsing onset vs. 13% PPMS

Correlated with time to reach EDSS 4 only in relapsing onset

Some CSF biomarker studies found ↑ NF-H, ↑ antibodies to NF-L, in PPMS

*MSJ 2010; 17:303
PPMS Differential Diagnosis*

- Cord compression
- Genetic (hereditary spastic paraparesis, spinocerebellar/Friedreich’s; adrenomyeloneuropathy, Krabbe)
- Metabolic (B12, PKU, Copper deficiency: bariatric surgery)
- Inflammatory (neurosarcoidosis, CNS vasculitis)
- Infection (HTLV, HIV, syphilis, brucellosis, schistosomiasis)

*Lancet Neurol 2007; 6:903

PPMS Differential Diagnosis*

- Degenerative (MND)
- Toxic (lathyism, nitrous oxide)
- Vascular (CADASIL, spinal vascular malformations, dural AV fistula, spinal cord infarction)
- Paraneoplastic

*Lancet Neurol 2007; 6:903
Evaluated RRMS (N=60), PPMS (N=41), HC (N=415)

Matched by age, sex, education level

Assessed on cognitive battery

PPMS performed worse than HCs on almost all tests; worse scores, more impaired vs. RRMS

controlling for EDSS had no effect

Involved information processing speed, attention, working memory, executive function, verbal episodic memory (vs. information processing speed, working memory in RRMS)

In other studies, 33% showed cognitive decline over 2 years; cognitive loss has MRI correlates
PPMS and Pregnancy*

- Limited data on pregnancy
  - 87% to 97% of pregnant MS patients are relapsing
- In one Belgium database of N=973 MS women, pregnancy protected against reaching EDSS 6 in relapsing but not PPMS
- For PPMS later menarche ↓ risk to reach EDSS 6, while oral contraceptive use ↑ risk
- This was based on 298 PPMS patients

*J Neurol 2012; 259:855

PPMS Natural History*

- British Columbia database, N=352 (12.4%) PPMS patients
- Mean age at onset 40.1 years, 53% female, disease duration 17.2 years
- 25% reached EDSS 6 by 7.3 years, but 25% had not reached this after 25 years

*Neurology 2005; 65:1919
**Neurology 2009; 73:1996
**PPMS Natural History**

- Median time to EDSS 6 (based on N=552) was 14 years (median age 58.6)**
  - Sensory onset symptoms associated with longer time to, and older age at, EDSS 6
  - 50 (9%) PPMS patients had EDSS ≤ 3 after 10 years

*Neurology 2005; 65:1919
**Neurology 2009; 73:1996

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**Innate MS Improvement**

- British Columbia database from 1980-2009
- Looked for EDSS improvement based on yearly or biennial EDSS scores (independent of relapses)
- 82 of 344 PPMS (23.8%) showed EDSS improvement
- 29 of 344 (8.4%) showed sustained improvement
- Innate improvements do occur in MS (? link to endogenous repair)

*MSJ 2012; 18:1412
PPMS Prognosis Features*

Poorer prognosis
- multisystem involvement (> 3) at onset
- more rapid early deterioration

Better prognosis
- sensory symptoms at onset
- younger age at onset

*Neurology Research Intern 291; ID740505
*Neurology 2009; 73:1996

MRI Predictors of Long Term Disability*

Retrospective analysis of MS; MRI at baseline, and after 1-2 years; EDSS at baseline and year 10

PPMS (N=77), CIS (N=18), RRMS (N=97), SPMS (N=69)

Whole brain atrophy predicted 10 year EDSS in PPMS

Central atrophy predicted EDSS in RRMS/EDSS ≤ 3.5; lesion volume predicted in RRMS/EDSS 4-6

*JNNP 2013; 84:1082
Progressive MS
Etiology/Pathogenesis

- Neurodegenerative component of MS with axonal/neuronal injury
- Has a unique inflammatory component distinct from relapsing MS
- Microscopic injury to normal appearing brain tissue (NABT)
- Important link to aging (? loss of CNS reserve/recovery mechanisms)
- Yet relapsing and PPMS may exist in the same family

Late Onset MS*

- Late onset MS defined as after age 50
  - 3.4% to 12%
- Very late onset MS > age 60
  - 0.45% to 0.8%
- Higher rate of PPMS
- Boston cohort (N=4,273)
  - Adult onset 88.6%, late onset 7.96%, very late onset 1.33%

*MSJ 2012; 18:1472
Late Onset MS*

- Fewer women: 74%, 65%, 61.4%
- PPMS: 6.9%, 25.6%, 35.1%
- More likely to have motor, coordination issues

*NMSI 2012; 18:1472

Late Onset MS*

- N=18 (4.8% of cohort)
- 62% PPMS, 16% relapsing, 22% SPMS at ≥5 years
- At onset motor (33%) and multisystem deficits (33%) most common features
- Diagnosis was delayed >5 years in 67%; initial EDSS >4 in 33%
- Major differentials were cerebrovascular disease, spondyloarthritic cervical myelopathy

*Neurologia 2011; 26:291
Mayo Clinic study
Evaluated PPMS (N=322), single attack progressive MS (SAMS) (N=112), SPMS (N=421)
Age at progression onset did not differ: 45.7 years (PPMS), 45.5 years (SAMS), 44.9 years (SPMS)
Relapses after progression: 0.3% (PPMS), 12.3% (SAMS), 27.3% (SPMS)

98% of those reaching EDSS 6 were in progressive stage (only 2% of relapsing MS reached EDSS 6)
Conclusion: Onset of progression is age dependent

*MSJ 2012; 19:188*
Age-Related Factor

- Age dependent decrease in neuroprotective/repair mechanisms
- Age dependent iron accumulation
  - released by oligos
  - may amplify oxidative injury
- Compact WM myelination ends by fourth decade, followed by slow WM tract degeneration

*MSJ 2012; 19:188

PPMS Genetics*

- PPMS and relapsing MS can occur in same family
- Genetic variants associated with MS make only weak contributions to susceptibility
- No distinct genes yet associated with PPMS
- May require very large data sets to determine associations
- Gene expression in PBMCs: PPMS showed as most prominent innate immune pathways, relapsing MS adaptive immune pathways, and SPMS a mix of both

*Handb Clin Neurol 2014; 122:211
*MSJ 2013; 19:1841
Familial vs. Sporadic PPMS*

- Comparison of familial (N=84) vs. sporadic (N=327) PPMS
- No difference in gender, onset symptoms
- Familial MS younger at onset (mean 37.6 vs. 42.7 years, p=0.007)
- Suggest: hereditary component to PPMS

*MSJ 2010; 16:694

Progressive MS Damage Mechanisms

- Microglial activation
- Oxidative injury
- Progressive mitochondrial injury
- Age dependent iron accumulation
- Glutamate excitotoxicity
Global inflammatory process
Marked microglial activation
Extensive cortical demyelination
Diffuse axonal injury
Less prominent focal inflammatory lesions
Oxidative injury with mitochondrial damage

Abnormal endothelial tight junctions in lesions and NABT
Higher brain remyelination in PPMS vs. relapsing MS (not seen in spinal cord)
Diffuse injury to NAWM, NAGM

myelin phospholipids affected much more than proteins (? 1° lipid abnormality)

*Lancet Neurol 2007; 6:903
*Brain 2010; 133:2983
*MSJ 2013; 19: 266
*J Neuropathol Exp Neurol 2013; 72: 42
Meningeal Inflammation in PPMS*

- N=26 PPMS postmortem brains
- Meningeal inflammation associated with more extensive demyelination/neurite loss in cortical GM
- No tertiary lymphoid follicles
- Profound microglial activation, ↓neuronal density in cortical lesions and NAGM

*Brain 2012; 135: 2925

Meningeal Inflammation in PPMS*

- More extensive meningeal enhancement associated with more severe clinical course (shorter disease duration, younger age at death)
- Widespread demyelinating pathology greater in cortical GM than underlying WM, predominantly subpial, associated with meningeal inflammation
- Wide range of inflammatory activity, similar to SPMS

*Brain 2012; 135: 2925
Case 1

A.L. is a 40 year old man with a 10 month history of progressive left leg weakness. He has no prior medical history, and is on no medications. Exam shows a weight of 250 pounds, BP 155/90, mild paraparesis (L>R), bilaterally upgoing toes, vibration sensation 9 seconds in the toes.

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Case 1

What therapeutic interventions would you recommend?
**Therapeutic Intervention**

- Weight loss
- Blood pressure control
- Replace vit D to level ~70
- Replace B12 to level >400
- Institute regular exercise, health maintenance, wellness program

**Current PPMS Therapy**

- No proven DMT
- Health maintenance/wellness program is critical
- Symptom management important
- If DMT is tried, there should be ongoing assessment and review
- Expectation is still gradual (but slowed) deterioration
**Prior PPMS Trials**

**PROMISE**
- failed phase III trial of GA vs. placebo
- post hoc analysis: significant treatment effect in male PPMS patients

**OLYMPUS**
- failed phase II trial of rituximab vs. placebo
- subset analysis: significant treatment effect in patients < age 51 and those with contrast lesions


**Prior PPMS Trials**

**IFNβs**
- Cochrane analysis found only 2 randomized studies (N= 123)
- 5 year F/U of IFNβ-1b study saw benefits on clinical and MRI parameters

Current PPMS Trials

Phase III
- Fingolimod
- Ocrelizumab
- Masitinib (oral protein kinase inhibitor) (phase IIb/III in PP and SPMS)
  - Trial is currently on hold

Current PPMS Trials

Phase II
- Epigallocatechin-gallate (oral green tea flavanoid/catechin)
- Fluoxetine (oral 40 mg)
- Ibudilast (oral phosphodiesterase inhibitor)
- Idebenone (oral coenzyme Q10-like agent)
MS Symptom Management

- Important in PPMS to optimize management
- Improves QOL, ADLs
- Determine bothersome symptoms (rank order list)
- Devise treatment program for each (order will be based on impact, and patient emphasis)
- Therapy is not just writing a drug script

Exercise and Progressive MS*

- Exercise promotes neuroregeneration, plasticity, improves learning/memory in rodents
- Aerobic exercise improves cognitive function in humans
- Exercise improves QOL, walking ability

*MSJ 2014; 20:382
**Exercise and Progressive MS**

- Randomized controlled pilot study in progressive MS (11 PPMS, 31 SPMS)
  - Randomized to 3 exercise interventions (arm ergometry, rowing, bicycle ergometry) or waitlist control
  - Exercise improved aerobic fitness, walking ability, depression, fatigue, several cognitive domains

*MSJ 2014; 20:382

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**Summary**

- Progressive MS is now a major focus
- Many trials ongoing and planned, looking at an array of distinct damage mechanisms
- CNS repair/restoration will be important (stem cells, remyelinating antibodies, microglial inhibitors, etc)
- Do not neglect symptom management, and health/wellness