

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



P K Coyle, M.D.

**Professor and Vice Chair (Clinical Affairs)
Director, MS Comprehensive Care Center
Stony Brook University Medical Center, Stony Brook, NY**

Disclosures

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Controversies/Critical Issues

- Are there risk factors for PPMS?
- Is progression identical for PPMS and SPMS?
- What factor(s) cause progression?
- Why is it age locked?
- Is PPMS heterogeneous?
- How should we be treating progressive MS?

Case 1. Ted

Ted is a 58 year old WM with an 18 month history of progressive cerebellar syndrome. Examination shows mild dysarthria and bilateral intention tremor, wide based gait with inability to tandem, and slight increased tone in all 4 extremities. Blood studies indicate low vitamin D (18), and low normal B12. Brain MRI shows patchy T2 hyperintensities in periventricular and subcortical WM, and middle cerebellar peduncles in the posterior fossa.

A diagnosis of PPMS is made.

- Do you agree with this diagnosis?
- Would you do additional tests?

Case 1. Ted

- Spine MRI and CSF examination are normal
- Issues
 - somewhat old
 - cerebellar presentation is unusual
 - lab support lacking; brain MRI atypical

Fragile X Associated Tremor/Ataxia Syndrome (FXTAS)*

- Inherited degenerative disorder due to CGG repeat expansion in permutation range (55-200) in fragile X mental retardation 1 (FMR1) gene on the X chromosome
 - FXTAS/FXS DNA test
- Affects men>women, age at onset 61.6 ± 7.9 years, involves progressive intention tremor, cerebellar ataxia (\pm parkinsonian features, cognitive loss, dysautonomia, psychiatric, neuropathic features)

*Movement Dis 2007; 22:2018; J Invest Med 2009; 57:830

Fragile X Associated Tremor/Ataxia Syndrome (FXTAS)*

- Middle cerebellar peduncle sign relatively specific (60% men, 13% women); may see diffuse atrophy
- Involves overexpression and toxicity of FMR1 mRNA (intranuclear neuronal and astrocyte inclusions)

*Movement Dis 2007; 22:2018; J Invest Med 2009; 57:830

PPMS: Definition*

- Insidious onset of symptoms with gradual deterioration
 - occasional plateaus and minor improvements acceptable
 - worsening is independent of relapses
- 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 2013; 123:627

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/ \uparrow IgG index)
- Any brainstem or cord lesions counted must be asymptomatic

*Ann Neurol 2011; 69:292

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 \pm contrast, cervical and thoracic MRI
- CSF: OCBs, IgG index; cell count, protein; MBP; paired ACE; EBV, 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

Cervical Cord in PPMS*

- Evaluated PPMS (N=29), SPMS (N=29), RRMS (N=34), controls (N=28)
- Cervical cord lesion load ↑ in PPMS vs. RRMS (p=0.02), SPMS vs. RRMS (p=0.008)
 - involved 20%, 30%, 10% of cord
- Cervical cord volume loss ↑ in PPMS vs. RRMS (p=0.009), SPMS vs. RRMS (p<0.001)
- Cord lesion load (p<0.001), cord area (p=0.003), age (p<0.001), sex (p=0.001) independently correlate with disability

*Neurology 2015; 367

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

CSF Studies in PPMS*

- Evaluation of CSF biomarkers of intrathecal inflammation (sCD27, sCD21, sCD14) showed equal expression of activated T and B cells in progressive (PP, SP) MS as relapsing MS
 - about 10% in each MS subgroup lack intrathecal inflammation
 - activated T and B cells are preferentially imbedded in CNS tissue in progressive vs. relapsing MS
 - ?DMT efficacy dependent on CNS penetration
- Oligoclonal IgM bands identified PPMS cohort with more aggressive clinical course, ↑ CSF B cells, ↑ contrast enhancing lesions

*Ann Neurol 2015; 2014; 76:231

PPMS Differential Diagnosis*

- Spinal cord structural lesion (cervical spondylosis, Arnold Chiari, tumor)
- Genetic (hereditary spastic paraparesis, spinocerebellar/Friedreich's; adrenomyeloneuropathy, Krabbe)

*Lancet Neurol 2007; 6:903

PPMS Differential Diagnosis*

- Metabolic (vitamin B12, vitamin E, PKU, copper deficiency: bariatric surgery)
- Inflammatory (neurosarcoidosis, CNS vasculitis, Sjögren syndrome)
- Infection (HTLV, HIV, PML, syphilis, brucellosis, schistosomiasis, Lyme disease)

*Lancet Neurol 2007; 6:903

PPMS Differential Diagnosis*

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

*Lancet Neurol 2007; 6:903

Vanishing WM Disease*

- Inherited AR childhood leukoencephalopathy (childhood ataxia with central hypomyelination) ages 2-6
 - involves mutation in any of 5 genes of eukaryotic translation initiation factor eIF2B (initiation of protein translation)
 - targets oligodendrocytes, astrocytes
 - associated with (1°, 2°) ovarian failure

*Lancet Neurol 2006; 5:413; MSJ 2015; 21:666

Vanishing WM Disease*

- Wide phenotype variations include adult onset (up to age 60) slowly progressive syndrome
 - slowly worsening cerebellar syndrome, spastic paraparesis
 - extensive MRI WM changes/cystic degeneration, restricted diffusion on MRI

*Lancet Neurol 2006; 5:413; MSJ 2015; 21:666

Hereditary Diffuse Leukoencephalopathy with Spheroids*

- Onset age 40 (18-72) years
- AD plus de novo mutations; involves >30 mutations in colony stimulating factor 1 receptor (CSF1R) gene
- Wide clinical spectrum; can mimic PPMS
- May see early cognitive decline, severe WM changes without enhancement, parkinsonian features

**Europ J Neurol* 2015; 22:328

MS 2013 Phenotypes*

- PPMS: progressive accumulation of disability from onset
 - part of a spectrum of progressive disease; differences from SPMS relative rather than absolute
 - fluctuations, periods of stability and even improvement can occur
- Progressive relapsing collapsed into PPMS (active PPMS)

**Neurology* 2014; 83:278

MS 2013 Phenotypes*

- PPMS categorized as active or not active
 - based on clinical relapse, or MRI lesion (new/enlarging T2, or contrast lesion) over defined time period
- PPMS categorized as with or without progression (by clinical evaluation) over defined time period

*Neurology 2014; 83:278

PPMS: Genetic Analysis*

- No clearcut gene associations to date
- Two functional polymorphisms of neuroregulin-1 gene (growth factor for neurons, glia, other cells) associated with progressive vs. relapsing MS, esp males with PPMS, in Iranian population
- HLA-DRB1*15 positive early PPMS (vs. negative) showed ↑ brain GM/WM pathology (↓ MTR), ↑ T2 lesion volume, trend for faster T2 lesion load over 5 years
 - no difference in disability (suggesting >5 years necessary to see clinical sequelae)

*MSJ 2015; Neurology 2014; 83:1712; J Neurol Sci 2015; 351:154; Handb Clin Neurol 2014; 122:211

PPMS: Genetic Analysis*

- Using 107 susceptibility genes, higher weighted risk score associated with earlier age onset for relapsing MS, later age onset for PPMS (largely inflammatory genes)
- In 470 Italian PPMS patients, no major genome wide associations; pathways and networks associated with age at onset/MSSS involved oxidative stress and immune dysfunction

*MSJ 2015; Neurology 2014; 83:1712; J Neurol Sci 2015; 351:154; Handb Clin Neurol 2014; 122:211

Impact of Relapses on PPMS*

- Mayo Clinic database of PPMS (N=322), bout onset progressive MS (N=112), SPMS (N=421)
- Age at progression 45.7, 45.5, 44.8 years
 - mean EDSS 1.5 to 2, 2.2, 3.4
- Post progression relapses in 3.1%, 10.7%, 29.5%
 - most within 5 years of onset (91.6%), ≤age 55 (95.4%)
- Only 2% reached EDSS 6 in relapsing stage

*Neurology 2015; 84:81

Impact of Relapses on PPMS*

- Time to EDSS 6 from progressive onset in 50% took 10 years, 7 years, 4 years
- Shorter time to EDSS 6 with post progression relapses, age >50 at progression, female sex
- Contradicts earlier studies that superimposed relapses have no impact on PPMS

*Neurology 2015; 84:81

Late Onset vs. Adult Onset MS*

- Retrospective British Columbia 1980-2004 database
- Late onset MS ≥ 50 years in 6% (N=358) vs. adult onset 18 to <50 years in 94% (N=5,627)
- Late onset more likely to be male (36.9% vs. 27.5%, $p < 0.001$); PPMS (42.5% vs. 8.2%, $p < 0.001$); \uparrow motor onset (39.1% vs. 18.5%, $p < 0.001$) and posterior fossa onset (19.8% vs. 15.1%, $p = 0.016$); \downarrow sensory onset (29.9% vs. 45.6%, $p < 0.001$) and optic nerve onset (5.6% vs. 16.9%, $p < 0.001$)
- Late onset MS progressed more rapidly to EDSS 6

*Biomed Res Int 2015; ID 451912

Late Onset MS*

- Late onset MS defined as after age 50
 - 3.4% to 12%
- Very late onset MS \geq 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

*MSJ 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

Risk Factors for PPMS*

- Systemic review of literature indicated few studies evaluated for PP vs. relapsing MS, or had limited PPMS numbers
 - modifiable risk factors identified as gap
- MSBase registry of PPMS (N=881) vs. relapse onset MS (N=11,570)
 - F:M ratio 1.2:1 for PPMS (vs. 2.53:1)
 - relapses associated with female sex, (17.7% \uparrow) \downarrow with age $>$ disease duration

*Biomed Res Int 2015; ID 817238; Brain 2013; 136:3609; PLoS ONE 2014; 9:e90509

Risk Factors for PPMS*

- RIS cohort (N=451) in 5 year follow up
 - 34% clinical event within 5 years; PPMS in N=9 (9.6%) (entire f/u N=14); median age 43.8 years, 50% male
 - presymptomatic phase for PPMS

*Biomed Res Int 2015; ID 817238; Brain 2013; 136:3609; PLoS ONE 2014; 9:e90509

Pathophysiology of Progression Hypotheses*

- 1° neurodegeneration (disturbed axon-glial unit) with 2° inflammation (response to tissue degeneration)
- Compartmentalized inflammation drives disease progress
 - axonal injury markers in lesions correlate with immune cell infiltration
 - meningeal B cell inflammatory aggregates (associated with more severe pathology/clinical disease)
 - proinflammatory cytokines in meninges, CSF; may be connected to subpial demyelination

*Lancet Neurol 2015; 14:406

Pathophysiology of Progression Hypotheses*

- Compartmentalized CNS inflammation is constant low grade insult, worsened by \uparrow susceptibility/ \downarrow repair capacity of damaged axon-glial unit
 - disrupted iron metabolism and \uparrow oxidative stress; changed glutamate homeostasis/impaired glial scavenging to \uparrow glutamate
 - chronically demyelinated axons need additional energy, but neuronal ATP production impaired due to increasing mitochondrial injury; energy supply and demand discrepancy

*Lancet Neurol 2015; 14:406

Phenotype Immune Differences*

- Progressive MS involves persistent subarachnoid inflammation behind intact/repared BBB
 - leukocyte surface expression of adhesion molecules, soluble serum adhesion molecules are \uparrow in relapsing and SPMS, but not PPMS
 - fewer, smaller contrast cerebral lesions
 - widespread demyelination, diffuse degenerative changes in entire WM and GM
 - \downarrow reactivity to HSP (vs. relapsing MS)

*J Neurol Sci 2015; 349:10

Phenotype Immune Differences*

- ↑ Autoantibodies to gangliosides in serum and CSF of progressive (esp PP) MS; ↑ T cell reactivity in PPMS

**J Neurol Sci* 2015; 349:10

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 \leq 3 after 10 years

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

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

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

Age-Related Factors

- 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

Progressive MS Damage Mechanisms

- Microglial activation
- Oxidative injury
- Progressive mitochondrial injury
- Age dependent iron accumulation
- Glutamate excitotoxicity

PPMS Neuropathology*

- Global inflammatory process
- Marked microglial activation
- Extensive cortical demyelination
- Diffuse axonal injury
- Less prominent focal inflammatory lesions
- Oxidative injury with mitochondrial damage

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

PPMS Neuropathology*

- 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

Case 2. Ellen

Ellen is a 43 year old WF, mother of two children ages 4 and 6. She has just been diagnosed with PPMS.

She asks about treatments for her MS, what the data is, what is available to her, and what she should do. She wants to remain able to care for her children.

- What do you tell her?

PPMS Therapy

- Explain the course is not inexorable
- Healthy maintenance/wellness/vascular risk factor control program
- Optimal symptomatic therapy
- No proven DMT, but a number are under study
- If the decision is to go on a DMT, choose a logical one and follow closely

Biotin (Vitamin H)*

- Ubiquitous water soluble vitamin
- Essential coenzyme for carboxylases (energy metabolism, FA synthesis)
- High biotin doses could
 - activate Krebs cycle in axons (\uparrow ATP)
 - activate Krebs cycle in oligos (\uparrow citrate for lipid synthesis)
 - activate ACC1, ACC2 (rate limiting enzymes in LCFA synthesis for myelin)

*MS Rel Dis 2015; 4:159

High Dose Biotin in Progressive MS*

- Phase III trial of MD1003 (high grade/concentration of biotin 300 mg QD; equivalent of 30 tabs)
 - N=154 patients with progressive (PP, SP) MS
 - EDSS 4.5 to 7
 - randomized to biotin (N=103) or placebo (N=51)
- 1° outcome improvement at 9 months, confirmed at 12 months (EDSS improved, or 25 FTW improved 20%)
 - ITT 12.62% vs. 0% ($p=0.0051$)
 - per protocol 14.9% vs. 0% ($p=0.0093$)

*MS Rel Dis 2015; 4:159; AAN 2016

High Dose Biotin in Progressive MS*

- Mean EDSS change -0.03 vs. +0.13 (p=0.015)
- EDSS progression in months 9 to 12 in 4% vs. 13% (p=0.07); 67% risk reduction
- Ongoing phase III placebo trial in optic neuritis permanent vision loss
- Pilot study of 23 consecutive progressive MS (14 PPMS, 9 SPMS) treated (100-300 mg QD) for 2-36 (mean 9.2) months
 - improvement after 2 to 8 months in vision (N=4), MRS (N=1), field cut (N=1), spinal cord features (N=16)

*MS Rel Dis 2015; 4:159; AAN 2016

Progressive MS Trials

- Phase III INFORMS (fingolimod 0.5 mg daily vs. placebo) failed to show benefit on progression or brain volume loss (did see ↓ in MRI lesions)
- Phase III ORATORIO (ocrelizumab IV vs. placebo) will be reporting data this year
 - ? for younger PPMS with +contrast lesions

Progressive MS Trials

- Other studies
 - oral masitinab (mast cell inhibitor)
 - oral idebenone (CoQ10 analog)
 - oral sunphenon epigallocatechin-gallate (green tea extract)
 - oral ibudilast (phosphodiesterase-4 inhibitor)
 - oral laquinimod
 - oral andrographolides (medicinal herb)

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

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