

# PVA Summit 2011+Expo

## Progressive MS



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# Disclosures

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- Participant in TYGRIS: Tysabri Global Observation Program in Safety and STRATIFY2: JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri, sponsored by Biogen, Idec
- Past participant in multicenter drug trials sponsored by Biogen, Serono, TEVA, Berlex, Pharmacia/Upjohn



# Learning Objectives

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At the conclusion of this activity the participant will be able to:

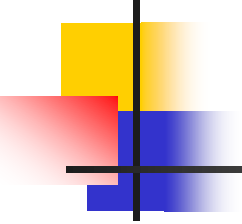
- Properly diagnose and classify progressive MS patients based on clinical presentation, imaging and ancillary testing
- Discuss the treatment of primary progressive and progressive relapsing MS patients
- Identify changes in clinical status that may warrant changes in disease modifying therapy (DMT)
- Describe the role of DMT in progressive Multiple Sclerosis



# Case Presentation

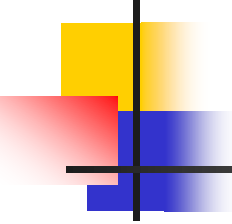
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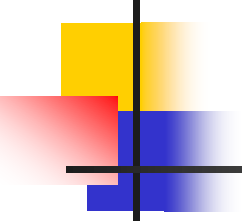
- This is a 63 year old left-handed white male with progressive right leg weakness beginning in 2001 with right foot drop and difficulty walking, also right leg stiffness. Starting in 2006 he noticed progressive weakness in the left leg. He had an MRI of the entire spine in 2005 which showed a T2 lesion in the cord at T8 with some cord atrophy, and subtle T2 lesions at T4-5 and C4 without enhancement. Examination in 2006 showed increased tone in both legs, weakness in both hip flexors, hyperreflexia in all limbs up to the pectoral region, bilateral Babinski sign, decreased vibration and position sense in the feet, and a spastic wide-based gait. CSF showed elevated IgG synthesis and 2 oligoclonal bands. MRI of the brain showed several small periventricular T2 lesions and one lesion in the left frontal pole without enhancement. Extensive serologic and CSF testing for MS mimics was negative.

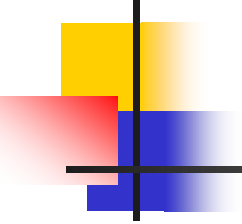
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- Is the diagnosis of multiple sclerosis established?
  - If so, what type?
  - What treatment should be offered for this patient?

# 2010 Revised McDonald PPMS Diagnostic Criteria

Clinical Attacks	Objective lesions on exam	Additional Requirements
0 (progression from onset)		<p>One year of disease progression (retrospective or prospective) AND at least 2 out of 3 criteria:</p> <ul style="list-style-type: none"><li>▪ Dissemination in space in the brain based on <input type="checkbox"/> 1 T2 lesion in periventricular, juxtacortical or infratentorial regions;</li><li>▪ Dissemination in space in the spinal cord based on <input type="checkbox"/> 2 T2 lesions;</li><li>▪ Positive CSF</li></ul>

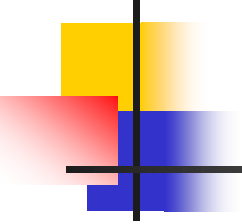
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- The patient was diagnosed with primary progressive multiple sclerosis and was started on interferon beta-1b. Seen later in 2006, he had increased right leg weakness and interferon was continued. Seen in 2007, his condition was slowly progressing, he C/O weakness in both legs now, had burning pain in his knees, and spasms in the legs were not controlled with either baclofen or tizanidine. Examination showed weakness of all muscle groups in the right leg. Gait showed a circumducted right leg and the patient was using a cane for assistance in walking. Repeat MRIs showed lesions in the thoracic spine at T3, T5, T8 and T10, which in retrospect may all have been there before, and a subtle new lesion at C5-6. Brain MRI was unchanged and there was no enhancement of any of the lesions. NMO antibody determination was negative. His examination in early 2008 showed some nystagmus on left gaze, ataxia of the right arm and both legs, mild trunkal ataxia, moderate spasticity of both legs, some vibration loss in the right arm, mild pinprick loss in both legs, and ambulation only with a cane (EDSS=6.0).

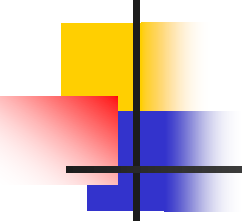
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- Should an change to his disease modifying treatment be made at this point?
  - If so, to what?

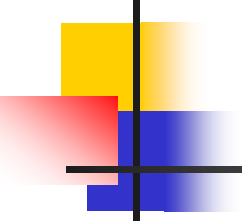


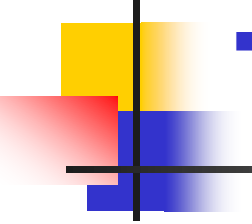
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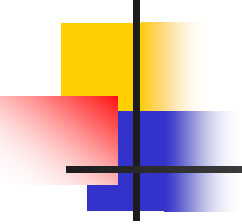
The patient was switched to glatiramer acetate (Copaxone). About one month later he had an acute worsening of his condition with increased weakness of his right leg, progressing to weakness of his left leg over the course of 10 days so that he could no longer walk. There was also severe pain in both legs, cramps and stiffness, constipation and more urinary frequency. No evidence for infection was found. He discontinued his glatiramer acetate. Two days later he started to get better and was on his feet at work for 5 hours. Seen 2 days later, his exam showed some right disk pallor not seen before, left arm ataxia, increased tone in the right leg, increased right hamstring and foot dorsiflexion weakness, a sensory level on his trunk not observed before, and gait unchanged (EDSS=6.0).

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- Was this a reaction to glatiramer acetate?
  - If not, should this patient be reclassified as progressive relapsing?
  - Is it possible to predict primary progressive patients who will go on to have relapses?

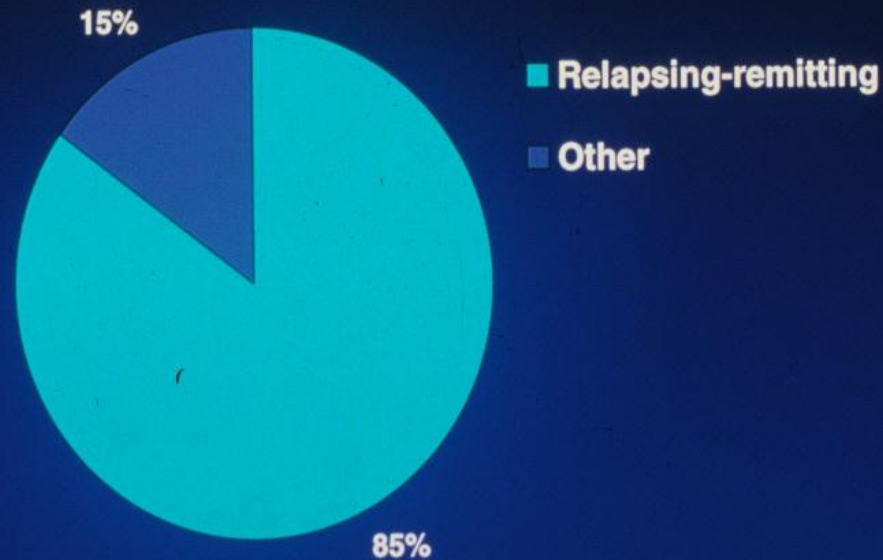
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- After some delay, the patient was restarted on glatiramer acetate. In early 2009 he again reported marginal worsening, not able to stay up as long on his cane and balance was worse. Examination was unchanged. In 5-09 he had another relapse with more right leg weakness and difficulty walking. He was given methylprednisolone for 5 days and partially recovered. He was seen in June, his exam was still worse although EDSS was still 6.0, and he was given a tapering course of qod prednisone. In 10-09 he reported further worsening and he had new weakness in his left leg, although EDSS was still 6.0. MRI of brain showed new T2 lesions in the right thalamus and left internal capsule.

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- Should his DMT be changed at this point?
  - If, so to what?

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- The patient was started on natalizumab (Tysabri) in Jan, 2010. In 2-10 he reported his right leg was getting weaker, cutting down on the distance he can walk. On exam his right hip flexion was weaker, although EDSS is still 6.0. Natalizumab was continued. In 10-10 he noted further worsening, right leg is weaker, and the right knee collapsed when he walked. Exam now showed moderate ataxia in right leg, bilateral hamstring weakness, and antigravity only for dorsiflexion of the right foot. Natalizumab neutralizing antibody was negative. He was seen again 1-11, his condition had further worsened, he was falling using one cane and now used a walker, tone in right leg was severely increased, he walked 100 meters, but only with a walker, EDSS=6.5. MRI brain showed no change in disease. Seen on 5-11 he reported continued progression, right leg was more spastic with severe pain, 8-10/10, which wakes him from sleep, he was now dependent entirely on a walker. Exam was stable.

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- Should his DMT be changed again at this point?
  - If so, to what?

## Percent of patients presenting with relapsing-remitting MS



- 50% of patients require walking aids within 15 years of diagnosis

Adapted from: Weinshenker BG et al. *Brain*. 1989;112(1):133-146.



# Treatment of Primary Progressive MS

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- One concept: No approved treatments available, so should not even try
- Patients should be enrolled in ongoing treatment trials
- Concentrate on symptomatic treatment and physical and occupational therapy
- However, several studies of DMT have suggested a trend towards a treatment effect in selected patient populations

# Phase III Randomized Controlled Trial of SC Glatiramer Acetate in PPMS (PROMiSe trial)

- 943 patients, randomized 2:1 to 20 mg subcutaneously or placebo daily for 3 years
- Primary endpoint: time to sustained EDSS progression for 3 months
- Secondary outcomes: MS functional composite (MSFC), MRI T1 and T2 lesion load, Gd-enhanced lesions, spinal cord and cerebral atrophy, MRS
- Progression of disease was much slower in the patients than planned. Study was prematurely discontinued by DSMB for futility
- Negative for primary endpoint, but treated group had significant reductions in Gd-enhanced lesions at year 1 and T2 lesion volume at year 2. Post hoc analysis showed treated male patients had a significant reduction in the primary endpoint.

# Phase II/III Randomized Controlled Trial of IV Rituximab in PPMS (OLYMPUS trial)



- 439 patients, randomized 2:1 to two 1000 mg infusions of rituximab or placebo every 24 weeks for 3 years
- Primary endpoint: time to sustained EDSS progression for 3 months
- Secondary outcomes: T2 lesion load, brain parenchymal fraction, MS functional composite (MSFC), sustained EDSS progression for 6 months
- Negative for primary endpoint, but significantly less T2 lesion volume increase and worsening on 25-foot walk test in treated patients
- Primary endpoint positive for patients < 51 years old or having Gd enhanced MRI lesions at baseline. Even greater benefit for patients with a combination of the two.
- Patients with a shorter disease duration, < 3 yrs also benefited



# PPMS patients who may respond to Available DMTs

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- Male patients
- Younger patients < 50 years old
- Patients with Gd-enhanced lesions on MRI
- Patients with increased intrathecal IgG synthesis or oligoclonal bands in CSF
- Patients with disease duration of < 3 years



# Obtaining CME Credit

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- If you would like to receive CME credit for this activity, please visit:

<http://www.pesgce.com/PVAsummit2011/>

- This information can also be found in the Summit 2011 Program on page 8.