

Transverse Myelitis - The MS Connection

Joanne Lynn MD

Why look at MS?

“There is very little information about the immunologic aspects of ATM. Although this neglect may reflect the rarity of the disease, it more likely reflects a common belief, rightly or wrongly, that ATM is part of a spectrum of CNS demyelination, the cause of which can be unraveled through study of other more common diseases, such as MS.” - Dr. Lael Stone, 1997

Why discuss MS?

- 1) TM falls within the clinical category of neuroimmunology, so the specialists most interested in investigation will be those who specialize in MS.
- 2) Possible similarities of etiology, pathophysiology and clinical features between TM and MS
- 3) TM may be a first attack of MS

TM - The MS Connection

“MS is almost certainly not a single disease but a series of IIDD [idiopathic inflammatory demyelinating diseases].”

- Syndromes such as TM may be viewed as a monosymptomatic IIDD and have a poorly defined relationship to MS

TM and MS - Relative Incidence

- The incidence of MS varies with geography and, in particular, latitude. In the US, the incidence varies from 10 per 100,000 to above 100 per 100,000.
- There are fewer epidemiologic studies of TM but estimates are 1 to 5 per million.

TM as first attack of MS

- 40 to 50% of first attacks of MS are monosymptomatic
- Spinal cord attacks are common in MS but the syndrome of complete acute TM is unusual as first attack of MS
- Only 0.7% of a Canadian MS population had acute TM as their first attack (Paty and Ebers).

Optic Neuritis - Monosymptomatic MS

- Acute inflammation/demyelination of optic nerve
- Varies from mild visual blurring or decreased color vision to total blindness
- Prognosis is very good -recovery within weeks to months
- High dose IV steroids hasten recovery

Development of MS in ON: Studies of Cerebral MRI

<u>Study</u>	<u>Abnml Brain MRI</u>		<u>Nml MRI</u>	
Jacobs	6/23	26%	3/25	12%
Martinelli	7/23	33%	0/16	0%
Frederiksen	7/30	23%	0/20	0%
Miller	12/34	35%	0/19	0%
Morrissey	23/28	82%	1/16	6%
Beck	55/150	37%	19/202	9%

TM: MS Prognostic Factors

- Complete vs partial myelopathy
- Symmetry vs asymmetry of motor and sensory abnormalities
- Cerebrospinal fluid abnormalities
- Features of magnetic resonance imaging of brain and spinal cord

TM: MS Prognosticators Complete vs Incomplete

- Complete transverse myelopathy means total loss of movement and sensation below the level of the lesion
- Lipton and Teasdale (1973) reported that only 2.9% of patients with complete ATM converted to MS in period of 5 to 42 years
- Ford (1992): 12 of 15 (80%) of patients with partial TM converted in 3.2 years

TM: MS Prognosticators Symmetry vs Asymmetry

- Scott (1998) followed patients with acute TM and noted that 15/16 patients with acute myelopathic MS had asymmetric findings while 20/20 acute TM patients exhibited symmetric motor loss and 19/20 symmetric sensory loss
- They concluded that symmetry vs asymmetry was a more important factor than complete vs partial

TM: MS Prognosticators Cerebrospinal Fluid

- In one study of 183 patients with monosymptomatic suspected MS: 24 % with CSF OCBs versus only 9% without OCBs developed definite MS
- However, patients with monosymptomatic MS without CSF OCBs have been reported to develop MS so their absence does not rule out subsequent development of MS

TM: MS Prognosticators Spinal MRI

- No specific findings that distinguish MS from acute TM
- Swelling of the cord is more common in acute TM but may be seen in MS
- Multifocal lesions are more common in MS compared with acute TM

Development of MS in TM: Studies of Cerebral MRI

Patients with Monosymptomatic TM
converting to MS

<u>Study</u>	<u>Abnml Brain MRI</u>	<u>Nml MRI</u>
Ford	12/15 80%	1/3 33%
Morrisey	10/17 59%	1/11 9%

Cerebral MRI findings strongly suggestive of MS - UBC criteria

- Four white matter lesions
- Three white matter lesions, one of which is periventricular
- Diameter of all lesions > 3 mm and predominantly in the white matter

Other Cerebral MRI findings that add specificity for MS

- Diameter > 6 mm
- Ovoid shape of long axis of lesion usually 90 degrees to the plane of the lateral ventricle
- White matter lesions in the brainstem
- Lesions along the corpus callosum
- An open ring appearance on enhanced MRI

Controlled High-Risk Avonex Multiple Sclerosis Prevention Study a.k.a. CHAMPS

Intramuscular Interferon Beta-1a Therapy Initiated during a First Demyelinating Event in Multiple Sclerosis

Jacobs LD et al and the CHAMPS Study
Group. NEJM 2000;343:898-904

CHAMPS

Specific Aims:

In patients with nonsymptomatic:

1. Optic neuritis
2. Brainstem / cerebellar or
3. Spinal cord

AND

At least 2 T2 MRI lesions > 3 mm with at least 1 ovoid or periventricular

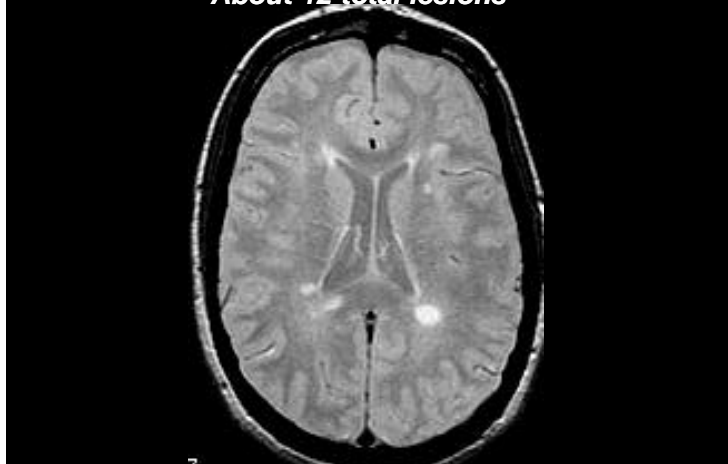
Does Avonex significantly delay the time to a second clinical attack?

CHAMPS

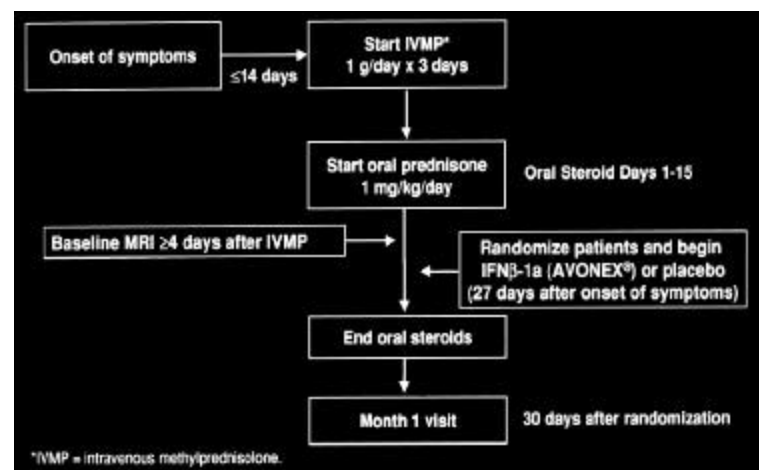
Methods:

- 383 patients (incidence study)
- 50 Centers in U.S and Canada
- A priori termination: $p < .029$

Qualifying:
About 12 total lesions



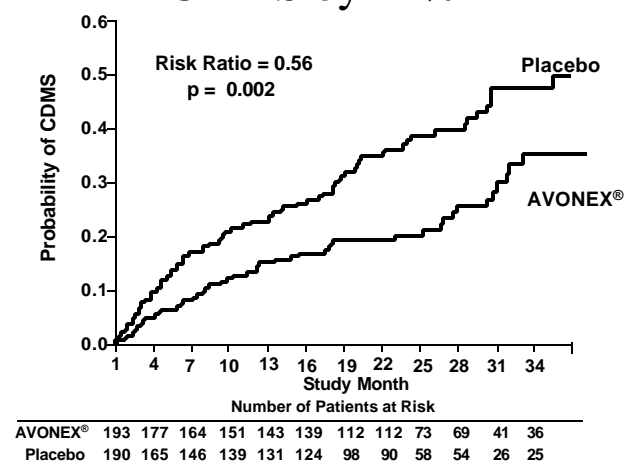
Conduct of Trial: CHAMPS



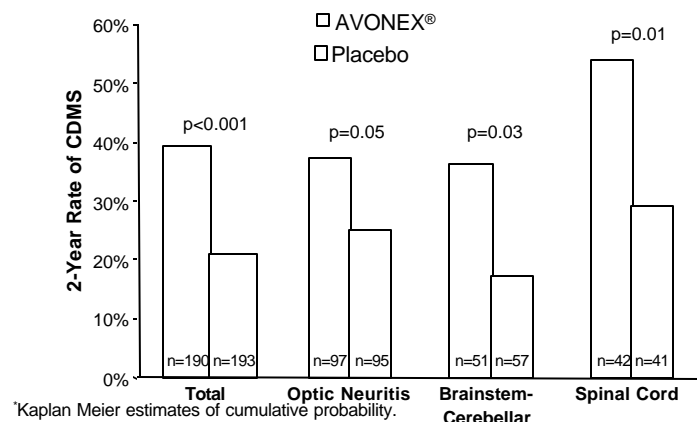
CHAMPS BASELINE

Syndrome	%
• Optic Neuritis	52%
• Brainstem / Cerebellum	27%
• Spinal cord	21%

IFNβ-1a (AVONEX®) Reduced CDMS by 44%



IFNbeta-1a Reduced the Rate of CDMS in All Subgroups



Relative Risk of Clinically Definite MS (CDMS)

Presenting Syndrome	AVONEX®		Placebo		Relative Risk†	p Value
	n	% CDMS*	n	% CDMS*		
Optic Neuritis	95	25%	97	37%	0.58	0.05
Brainstem-Cerebellar	57	17%	51	36%	0.40	0.03
Spinal Cord	41	29%	42	54%	0.30	0.01

*Kaplan-Meier estimates. †From proportional hazards model; adjusted model includes age, log T2 lesion volume, and presence of ≥ 1 gadolinium-enhanced lesion.

$$\text{group RR} = \frac{\text{Cumulative probability of CDMS in AVONEX}^{\circledR}}{\text{Cumulative probability of CDMS in Placebo group}}$$

CHAMPS MRI Summary

- AVONEX® had significant beneficial effects in Optic Neuritis and Brainstem-Cerebellar subgroups on the following MRI measures at Month 18:
 - T2 lesion volume (p=0.002 and p=0.02)
 - Number of new or enlarging T2 lesions (p=0.004 and p=0.001)
 - Percentage of patients with Gd-enhancing lesions (p=0.001 and p=0.008)

CHAMPS MRI Summary (cont)

In the Spinal Cord Syndrome subgroup:

- Differences were not significant; however, the AVONEX® group showed favorable trends for all MRI outcomes
- Lack of significant effects may be due to
 - The low number of patients in this subgroup
 - Active placebo patients reached CDMS early, and were not studied by MRI by study design

CHAMPS Conclusions

- Supports the recommendation to obtain a cranial MRI scan in people with TM to assess risk of subsequent MS
- Supports early intervention in people with TM and MRI findings that suggest high risk for the future development of MS.

Transverse Myelitis and the Multiple Sclerosis Connection

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Whether you are a person with TM or a health care professional involved in treatment or research in the area of TM, there are several reasons why it is appropriate to discuss the relationship between Transverse Myelitis and Multiple Sclerosis.

One reason is that people with TM tend to end up seeing MS specialists as neurologists. MS is a common inflammatory disease of the central nervous system (variable incidence 1-100 per 100,000 population depending on location) whereas the incidence of TM is much less in the range of 1 to 5 per million. Most departments of neurology at academic medical centers have one or more specialists in MS and these physicians also see people with other inflammatory or immunologic disorders of the spinal cord. I am aware of only one clinic with its primary focus on TM and this is the relatively newly formed TM clinic headed by Dr. Kerr. MS specialists have experience with treatment of the problems associated with spinal cord disease. Therefore, the clinicians who see and treat people with TM cannot help but view TM through a looking glass that is colored by what knowledge we have about the causes and pathology of MS.

The second reason is the fact that many people view ATM as one manifestation of a larger group of demyelinating illnesses. Dr. Lael Stone (1997) has written:

“There is very little information about the immunologic aspects of ATM. Although this neglect may reflect the rarity of the disease, it more likely reflects a common belief, rightly or wrongly, that ATM is part of a spectrum of CNS demyelination, the cause of which can be unraveled through study of other more common diseases, such as MS.”

Dr. Weinshenker (1998) has written that “MS is almost certainly not a single disease but a series of IIDD [idiopathic inflammatory demyelinating diseases].” Syndromes such as TM may be viewed as a monosymptomatic idiopathic inflammatory demyelinating disease and have a poorly defined relationship to MS.

The third reason is that a small number of people with ATM are actually experiencing their first attack of MS.

For these three reasons, I want to review some of what the medical literature says about the relationship between ATM and MS.

MS is a chronic inflammatory demyelinating disease of the central nervous system that affects over 200,000 persons in the United States. The etiology remains unknown, but evidence suggests that MS is an autoimmune disease likely directed against the protein components of myelin. Pathology of the MS lesion shows many features of a delayed type hypersensitivity reaction. Despite investigation of 16 bacterial and viral agents, none yet have been convincingly linked to MS. (The latest contenders are the Human Herpes 6 virus and *Chlamydia pneumoniae*).

It has been estimated that 40 to 50% of first attacks of MS are monosymptomatic or consist of neurologic symptoms, which can be caused by a single lesion in the central nervous system. Spinal cord attacks are characteristic of MS but the syndrome of complete acute TM is unusual as an initial symptom of MS. Only 0.7% of a Canadian population of 3500 people with MS had acute TM as their first attack (Paty and Ebers, 1998). Because of the low frequency of TM as the initial onset of MS, the literature is limited. Optic neuritis (ON) is one of the best studied of the monosymptomatic syndromes in MS and it is worth looking at what is known about optic neuritis and its relationship with MS to determine what might be relevant to the topic of TM and MS.

ON is an acute inflammation of one or both of the optic nerves (usually unilateral). Its manifestation varies from mild visual blurring or subtle alterations in color perception to total blindness. The prognosis is very good with significant recovery of vision over weeks to months. This recovery is hastened by administration of high dose intravenous corticosteroids. The reported risk of development of MS after ON varies widely from report to report – from 13% to 88%. The risk seems to be greatest in the first two years after ON (about 20%) and rises by an additional 20% by 5 years. Studies have reported life table estimates of risk within 15 years to be in the range of 45 to 80%.

Brain MRI has been demonstrated to predict those patients with optic neuritis who are at higher risk to develop MS. Six studies of optic neuritis demonstrate that patients with “clinically silent” cerebral white matter lesions on brain MRI have a risk of subsequent development of MS that is 4 to 5 times higher than that of patients with a normal brain MRI at the time of presentation with ON (38% vs. 8% on average). Various suggestions have been made about the type of MRI lesions that are strongly suggestive of MS. The University of British Columbia criteria for such lesions are: 1) 4 white

matter lesions; 2) 3 white matter lesions , one periventricular in location; or 3) all lesions > 3mm in diameter and predominantly in the white matter.

Results from six studies of patients with ON and cerebral MRI: percentage developing MS:

Study	Abnormal Brain MRI:	Normal Brain MRI:
Jacobs	6/23 (26%)	3/25 (12%)
Martinelli	7/21 (33%)	0/16 (0%)
Frederiksen	7/30 (23%)	0/20 (0%)
Miller	12/34 (35%)	0/19 (0%)
Morrissey	23/28 (82%)	1/16 (6%)
Beck	55/150 (37%)	19/202 (9%)

These rates of conversion vary with criteria used for MRI abnormalities and length of follow-up. The Morrissey study is the longest follow-up with 5.5 years average and allows a longer time for conversion. The higher rate obtained of 82% in that study does suggest that most patients with ON accompanied by MRI brain abnormalities suggestive of MS on presentation will eventually develop clinically definite MS.

The syndrome of acute TM can be caused by many different illnesses: infectious, autoimmune, etc. The neurologist searches for clues that the TM is due to any of the known causes. If none of those clues are present, then a diagnosis of idiopathic TM is made. Various clinicians have reported on long term follow-up of their own personal patients with TM, trying to see how many develop MS and if there are characteristics or laboratory studies at the time of the acute attack that might predict whether a particular patient with TM will develop MS.

The risk of developing TM is quite low in most studies ranging from 0 to 36% with one outlying study that cited a rate of 80%. These studies show the following:

- 1) One of the strongest variables predictive of whether TM will convert to CDMS is whether the lesion was *complete vs incomplete or partial* TM. The syndrome of complete TM is very unlikely to develop into MS. Complete means that there is total loss of movement and sensation below the level of the spinal cord affected by inflammation. In the study by Lipton and Teasdale in 1973, the risk of conversion to CDMS following an episode of complete transverse myelitis was very low – 2.9% after a variable follow-up period of 5 to 42 years. Most long-term follow-up

studies yield rates of conversion of less than 25%. However, a more recent study by Ford et al in 1992 showed that 12 of 15 (80%) of patients with the more common partial myelopathy converted to CDMS within a mean follow-up time of 3.2 years.

2) Symmetry vs Asymmetry of motor or sensory loss

It is a general observation that patients with MS frequently present with asymmetry of level or severity of weakness or sensory loss from one side to the other. People with acute TM are more likely to present with symmetric weakness. Scott et al (1998) reported that the degree of symmetry of motor and sensory neurology dysfunction in patients presenting with acute transverse myelopathy was a reliable discriminator of which patients would eventually develop MS and which appeared to have idiopathic TM. They reported that 15/16 patients with acute myelopathic MS had asymmetric motor or sensory findings and all ATM patients exhibited symmetric weakness and all but one (19/20) exhibited symmetric sensory loss. They concluded that symmetry is a much better distinguishing factor than severity of the motor or sensory loss in their study.

3) Cerebrospinal fluid studies – Various abnormal findings in the spinal fluid have prognostic value for predicting the development of MS in people presenting with monosymptomatic demyelination. In one prospective study of 183 people with monosymptomatic suspected MS, the presence of oligoclonal bands in the CSF was associated with a 24% conversion rate to MS within the follow-up period of 34 months, while only 9% of patients without oligoclonal bands in the CSF developed MS during the same period (Moulin et al, 1983).

4) MRI findings of cord and brain:

Cord: There is a tendency for spinal cord lesions to be smaller or multifocal in MS compared with ATM, but the MRI appearance often does not help distinguish between these entities. Swelling of the cord is more common in ATM than in MS but can be seen in MS.

Brain: The most important laboratory finding which will predict the chance that a patient with ATM will develop CDMS is the presence of asymptomatic lesions on the brain MRI.

Patients with Transverse Myelitis converting to Multiple Sclerosis:

Study	Abnormal brain MRI	Normal brain MRI
Ford	12/15 (80%)	1/3 (33%)
Morrisey	10/17 (59%)	1/11 (9%)

CHAMPS Study – Controlled Trial of High-Risk Subjects in A Multiple Sclerosis Prevention Study

Clearly brain MRI can help to identify a subset of patients with monosymptomatic demyelination who are at high risk to go on and develop MS. Treatment with interferon beta or glatiramer acetate has been the standard of care for patients with clinically definite relapsing MS for several years as each of these agents has been shown to reduce exacerbations by approximately one third. Certain observations suggest that the currently available interventions may be more efficacious if given early in the disease course. However, prior to the CHAMPS trial, there was no data available about treatment of patients with a monosymptomatic presentation. These observations formed the impetus for the organization of the CHAMPS trial to determine if treatment of patients with monosymptomatic demyelination would have beneficial effects on the rate of conversion to clinically definite MS and on the clinical course that follows.

The study enrolled 383 subjects with monosymptomatic presentations of MS: optic neuritis, brainstem, and spinal cord and abnormal cerebral MRIs, putting them into a high risk category for the subsequent development of MS. Each subject was treated with 3 days of high dose intravenous steroids followed by an oral taper of prednisone. Subjects were then randomized into two groups: one to receive interferon beta 1a IM q week (193) and the other to receive placebo (190). Each subject was followed with serial examinations until the study was completed or they reached the primary endpoint which is the development of a second clinical attack of demyelination which would warrant the diagnosis of clinically definite MS. The planned period of followup was to be 3 years.

The results of this study were published in the NEJM in September of 2000. The breakdown of enrollees by site of their monosymptomatic presentation was:

Optic neuritis	50%	192 patients
Brainstem/Cerebellar	28%	108 patients
Spinal cord	22%	83 patients

The published article only reports on the pooled group as a whole. During the period of the study a statistically significant difference was seen in the number of subjects treated with interferon who went on to have a second attack of demyelination compared with those treated with placebo. ($p=0.002$, Kaplan-Meier Estimates of cumulative probability of the development of clinically definite MS). For the group as a whole, the cumulative probability of developing CDMS was 35% in the IFN beta-treated group and 50% in the placebo group.

In addition, accumulation of new lesions on brain T2-weighted MRI scans differed significantly between the IFN and placebo groups. At 18 months follow-up, the IFN group had a 1% median increase in T2 lesion volume compared to the 16% increase in the placebo group. At all measurement times (6, 12 and 18 months), there were fewer new or gadolinium-enhancing lesions in the IFN treatment group.

This is an exciting clinical study which sheds new light on the value of intervention with immunomodulatory agents at the earliest point for patients with transverse myelitis and other monosymptomatic presentations of demyelination whose MRI studies give evidence of a high risk to develop MS. This study also supports the importance of obtaining a cranial MRI for patients who present with TM to determine if there is a high risk of the development of MS and whether there is benefit to be obtained from early initiation of interferon therapy.

This is a brief review into some areas of overlap between TM and MS. As Dr. Stone mused, there is a belief and a hope by many that the study of MS may contribute some understanding into the pathology and eventual treatment of transverse myelitis. Certainly, it is a fertile ground from which more focused research and understanding specific to transverse myelitis may grow.

References

Beck RW, Cleary PA, Trobe JD, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *New Engl J Med* 1993;329:1764-1769.

Ford B, Tampieri D, Francis G. Long-term follow-up of acute partial transverse myelopathy. *Neurology* 1992;42:250.

Frederiksen JL, Larsson HBW, Henriksen O, Olesen J. Magnetic resonance imaging of the brain in patients with acute monosymptomatic optic neuritis. *Acta Neurol Scand* 1989;80:512-517.

Jacobs L, Munschauer FE, Kaba SE. Clinical and magnetic resonance imaging in optic neuritis. *Neurology* 1991;41:15-19.

Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW, and the CHAMPS Study Group. Intramuscular Interferon beta-1a Therapy initiated during the first demyelinating event in multiple sclerosis. *N Engl J Med* 2000; 343:898-904.

Lipton HL, Teasdale RD. Acute Transverse myelopathy in adults. *Arch Neurol* 1993;50:532.

Martinelli V, Como G, Filippi M, et al. Paraclinical tests in acute-onset optic neuritis, basal data and results of a short follow up. *Acta Neurol Scand* 1991;84:231-236.

Miller DH, Ormerod IEC, McDonald WI, et al. The early risk of multiple sclerosis after optic neuritis. *J Neurol Neurosurg Psychiat* 1988;116:135-146.

Morrissey SP, Miller DH, Kendall BE, et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. *Brain* 1993;116:135-146.

Moulin D, Paty DW, and Ebers GC: The predictive value of cerebrospinal fluid electrophoresis in 'possible' multiple sclerosis. *Brain* 106:809-816,1983

Paty DW and Ebers GC. *Multiple Sclerosis*. F.A. Davis, Philadelphia, 1998.

Scott TF, Bhagavatula K, Snyder PJ, Chieffe C. Transverse myelitis – Comparison with spinal cord presentations of multiple sclerosis. *Neurology* 1998;50:429-433.

Stone LA. Transverse Myelitis in *Neuroimmunology for the Clinician*. Rolak LA and Harati Yadollah (eds), Boston, Butterworth-Heinemann, 1997; pp155-165.

Weinshenker BG. The Natural History of Multiple Sclerosis: Update 1998. *Seminars in Neurology* 1998;18(3):301-307.