

## **Transverse Myelitis – The Multiple Sclerosis Connection**

Joanne Lynn MD

Dr. Bowen has spoken to us about the relationship between MS and TM. At least some of you must be wondering why there are two talks on TM and MS. There are several reasons for this:

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) where as 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 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 IIDDD [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 followup 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%)

**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. These observations formed the impetus to 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 current standard of care is to consider treatment with interferon beta or glatiramer acetate in patients with clinically definite relapsing MS as each of these agents has been shown to reduce exacerbations by approximately one third. However there is no data available about treatment of patients with a monosymptomatic presentation. Certain observations suggest that currently available interventions may be more efficacious if given early in the disease course.

The study is underway and enrolled 380 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 and the other to receive placebo. Each subject will be followed with serial examinations until they reach the primary endpoint which is the development of a second clinical attack of demyelination which will warrant the diagnosis of clinically definite MS. The period of followup will be 3 years.

This is an exciting clinical study that will shed 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 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**

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

***Curriculum Vita***  
***Deborah Joanne Lynn M.D.***

**Address:** 2007 Hythe Road  
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**Date & Place of Birth:** April 30, 1958; Columbus, Ohio

**Personal Data :** Married, 2 daughters

**Education & Degree**

1972-1976	Columbus School for Girls, Columbus, Ohio
1976-1980	Amherst College, Amherst, Massachusetts (Bachelor of Science)
1980-1984	Ohio State University College of Medicine, Columbus, OH, (MD)

**Post-MD Training**

1984-1987	Resident, Internal Medicine, University of Rochester, Rochester, NY
1987-1990	Resident in Neurology, University of Rochester, Rochester, NY
1990-1992	Neuromuscular Fellow, The Ohio State University, Columbus, OH

**Academic Appointments**

1992 -	Assistant Professor, The Ohio State University Department of Neurology, Columbus, OH
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**Hospital or Clinical Appointments**

1992 -	Staff Neurologist, The Ohio State University Medical Center
1992 -	Staff Neurologist, The Arthur James Cancer Hospital and Research Institute
1992 -	Consulting Neurologist, Twin Valley Psychiatric Systems, Columbus Campus

**Certification & Licensure**

Diplomate, National Board of Medical Examiners, March, 1985  
Diplomate, American Board of Internal Medicine, September, 1987 #114423  
Diplomate, American Board of Psychiatry & Neurology, October, 1991 #35017  
Certified, State Medical Board of New York, February, 1986 #165379 (inactive)  
Certified, State Medical Board of Ohio, April, 1992 #59740

## **Awards & Honors**

Alpha Omega Alpha

## **Professional Society Memberships**

American College of Physicians  
American Academy of Neurology  
AAN Education Section  
AAN Multiple Sclerosis Section  
Consortium of Neurology Clerkship Directors

## **Service**

Member, Professional Advisory Committee, National Multiple Sclerosis Society,  
Mid-Ohio Chapter, 1994 -

Physician Advisor, Transverse Myelitis Association, 1997 -

## **Presentations**

- 1992 Eosinophilia Myalgia Syndrome, Ohio State University Neuroscience Grand Rounds
- 1993 Neuroleptic Malignant Syndrome, Central Ohio Psychiatric Hospital, Columbus OH
- Guillian Barre Syndrome, Ohio State University Physical Medicine Department Grand Rounds
- Adrenoleukodystrophy, Ohio State University Neuroscience Grand Rounds  
Insomnia, lecture for primary care physicians, Columbus, OH
- 1994 Multiple Sclerosis, Ohio State Medical Education Network (OMEN)
- Acute Weakness, Ohio State University College of Medicine CME Course  
"Neurology for the Non-Neurologist"
- 1995 Multiple Sclerosis Update, The Ohio State University CME Course "Bread and Butter Ophthalmology", Columbus, OH
- 1996 Multiple Sclerosis Update, The Ohio State University Department of Physical Medicine and Rehabilitation Grand Rounds



Multiple Sclerosis and Urologic Issues, The Ohio State University Department of Urology

Multiple Sclerosis – Research and Drug Update, CME Conference for Allied Medical Professionals, Columbus, OH

1997 New Treatments for Multiple Sclerosis, Mansfield Neurology Group, Mansfield, OH

“Overview of the CHAMPS Trial”, The Ohio State University Department of Ophthalmology Grand Rounds

“Multiple Sclerosis Update”, The Ohio Medical Education Network

1998 “MS Update - The ABC Drugs”, The Ohio State University Neuroscience Grand Rounds

“The Rationale for Early Treatment of Multiple Sclerosis” Grandview Hospital Section of Neurology, Psychiatry, and PM&R Department Meeting, Dayton, OH

“Sexual Dysfunction in Women with MS” at “A Patient Centered Therapeutic Framework for MS – An International Conference on Models of Care”, Dallas, TX

“Rationale for Early Treatment of Multiple Sclerosis” at Neurology Grand Rounds, Medical College of Toledo, Toledo, OH (2/26/99)

“Recent Advances in the Treatment of Multiple Sclerosis” and “Paraneoplastic Neurological Disorders” at Neurology Update 1999, CME program sponsored by Ohio State University CCME, May 8, 1999, Columbus, OH

“Multiple Sclerosis – Rationale for Early Treatment and treatment options for MS” at Neurology Update for Primary Care, New Harmony, Indiana – sponsored by St. Mary’s Medical Center in Evansville, IN, June 12, 1999

**Journal Reviewer**    Neurology, Archives of Neurology, Muscle & Nerve

**Grant Funding (Listed in reverse chronologic order with most recent grants first)**

**A) Funded Grants with Candidate as Principal Investigator**

- 1)     Role:           Site Principal Investigator  
       Source:        ICOS Corporation  
       Title:          Phase 2 Study of Hu23F2G in Acute Exacerbations of Multiple Sclerosis  
       Period:        9/30/97 - 9/30/99  
       Direct Costs:  \$75,000
  
- 2)     Role:           Site Co-PI with Dr. Kottil Rammohan  
       Source:        Berlex Laboratories  
       Title:          Phase III, Double-Masked, placebo-controlled study to evaluate the safety and efficacy of two doses of Betaseron in patients with secondary progressive multiple sclerosis  
       Period:        10/1/95 – 10/1/98  
       Amount:        \$27,020 per/pt, est. total of \$783,580 if 29 pts complete study
  
- Role:           Site PI  
       Source:        National Medical Research Corporation (Berlex Laboratories)  
       Title:          Betaseron Patient Experience Study  
       Period:        8/1/94 – 2/1/97  
       Amount:        \$2,250
  
- Role:           PI  
       Source:        The Ohio State University, Bremer Grant  
       Title:          Immune Effects of Glucocorticoid Therapy in Multiple Sclerosis  
       Period:        12/1/92 – 12/1/93  
       Amount:        \$4,960
  
- Role:           PI  
       Source:        The Ohio State University Seed Grant  
       Title:          Immune Effects of Glucocorticoid Therapy in Multiple Sclerosis  
       Period:        12/31/92 – 12/31/93  
       Amount:        \$19,137.60

**B) Funded Grants with Candidate as Co-Investigator**

PI: Kottil Rammohan MD  
Source: Biogen Corporation  
Title: Autoimmunity to Axonal Ion Channel Proteins in Multiple Sclerosis  
Period: 10/1/98 – 10/1/99  
Amount: \$50,000

PI: Kottil Rammohan MD  
Source: Biogen Corporation  
Title: IMPACT: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Avonex in the Treatment of Secondary Progressive Multiple Sclerosis  
Period: 4/14/98 – 12/31/00  
Amount: \$10,820/pt

PI: Kottil Rammohan MD  
Source: Biogen Corporation  
Title: Randomized, double-blind comparison, immunologic study of Avonex (interferon beta-1a) in the treatment of subjects at risk for development of multiple sclerosis following the first onset of an isolated demyelinating event  
Period: 7/01/98 – 3/31/99  
Amount: \$3,525

PI: Kottil Rammohan MD  
Source: Biogen Corporation  
Title: Randomized, double-blind, placebo-comparison study of Avonex (interferon beta-1a) in the treatment of subjects at risk for development of multiple sclerosis following the first onset of an isolated demyelinating event  
Period: 7/01/97 – 3/1/01  
Amount: \$13,482

PI: Kottil W. Rammohan MD  
Source: Biogen Inc. – RF 737060  
Title: Autoimmunity to Axonal Ion Channel Proteins in Multiple Sclerosis  
Period: 1/1/99 – 12/31/99  
Amount: \$32,400

PI: Kottil Rammohan MD  
Source: Teva Marion Partners  
Title: Study to evaluate the efficacy, tolerability and safety of glatiramer acetate for injection in primary progressive multiple sclerosis

Period: presents.  
\$ 99 – 1/1/04  
Amount: \$ 000 per patient

**C) Grants Submitted but Not Funded**

PI: Glen Apseloff MD  
Others: Kottil Rammohan MD, Daniel Mullet Ph.D., Nicholas Gerber  
Ph.D., D. Joanne Lynn MD, Donald Chakeres MD  
Submitted to: FDA  
Title: Treatment of Relapsing-remitting Multiple Sclerosis with Gallium  
Date: 1/13/95

## **Publications**

### **Journals (peer-reviewed)**

Lynn DJ, Mirkin IR, Lanese DM, Schmidt HS, Arnold LE. Correspondence between DSM-II Hyperkinetic Reaction and DSM-III Attention Deficit Disorder. *J Amer Academy Child Psych* 1983;22:349-350.

Lynn DJ, Rammohan KW, Bornstein RA, Kissel JT. Central Nervous System Involvement in the Eosinophilia-Myalgia Syndrome. *Arch Neurol* 1992;49:1082-1085.

Kissel JT, Lynn DJ, Rammohan KW, Klein JP, Griggs RC, Moxley RT, Cwik V, Brooke MH, Mendell JR. Mononuclear Cell Analysis of Muscle Biopsies in Prednisone- and Azathioprine-Treated Duchenne Muscular Dystrophy. *Neurology* 1993;43:532-536.

Tan E, Lynn DJ, Amato AA, Kissel JT, Rammohan KR, Sahenk Z, Warmolts JR, Jackson CE, Barohn RJ, Mendell JR. Immunosuppressive Treatment of Motor Neuron Syndromes: Attempts to Distinguish a Treatable Disorder. *Arch Neurol* 1994;51:194-200.

Basso MR, Beason-Hazen S, Lynn J, Rammohan K, Bornstein RA. Screening for Cognitive Dysfunction in Multiple Sclerosis. *Arch Neurol* 1996;53:980-984.

Pfeil S, Lynn DJ. Wilson's disease: Copper unfettered. *J Clin Gastroenterol* 1999;29(1):22-31.

### **Abstracts:**

Kissel JT, Rammohan KW, Halterman R, Lynn DJ, Mendell JR. Circulating Complement Membrane Attack Complex in Dermatomyositis. *Neurology* 41 (Suppl 1):419, 1991.

Lynn DJ, Kissel JT, Rammohan KW. Cerebrospinal Fluid Terminal Complement Complex in Multiple Sclerosis. *Neurology* 42 (Suppl 3):248, 1992.

Kissel JT, Lynn DJ, Rammohan KW, Griggs RC, Moxley RT, Brooke MN, Cwik V,

Mendell JR. Mononuclear Cell Analysis of Muscle Biopsies in Azathioprine - Treated Duchenne Dystrophy. *Neurology* 42 (Suppl 3):227, 1992.

Rammohan KW, Beason-Hazen S, Lynn DJ, Bornstein RA. Dysfunction in Multiple Sclerosis. *Neurology* 43(Suppl 2):204,1993.

Sahenk Z, Tan E, Kissel JT, Lynn J, Barohn RJ, Mendell JR. Immunosuppressive Treatment in Motor Neuron Syndromes: Sural Nerve Biopsy Findings. *Neurology* 43 (Suppl 2):258,1993.

Tan E, Lynn DJ, Barohn RJ, Kissel JT, Rammohan KW, Sahenk ZS, Jackson CE, Warmolts JR, Amato AA, Mendell JR. Immunosuppressive Treatment of Motor Neuron Syndromes: Attempts to Distinguish a Treatable Disorder. *Neurology* 43 (Suppl 2):416,1993.

Beason-Hazen S, Lynn DJ, Rammohan KW, Bornstein RA. Stereognosis and Neuropsychological Function in Multiple Sclerosis. *Ann Neurol* 34(2):285,1993.

Lynn DJ, Rammohan KW, Kissel JT. Humoral Immunity to Bovine type I Collagen in Inflammatory Myopathies. *Ann Neurol* 32(2):307,1993.

Rammohan KW, Lynn DJ, Vaglienti PA, Kennard EA, Miller LA, Simeo ME, Hale KN, Friedman CI. Efficacy of Leuprolide in Treatment of multiple sclerosis. *Neurology* 45(Suppl 4):234,1995

#### **Book Chapters:**

Lynn DJ, Mendell JR. Peripheral Neuropathy. (book chapter) In: Rakel RE (ed.). *Conn's Current Therapy*, 1993. W.B. Saunders Co., Philadelphia, PA.

Lynn DJ, Woda RP, Mendell JR. Respiratory Dysfunction in Muscular Dystrophy and other Myopathies. (book chapter) *Clin Chest Med*. 1994;15:661-674.

Lynn DJ, Mendell JR. Peripheral Neuropathy. (book chapter) In: Koller WC (ed.), *Current Practice of Medicine*, 1996, Current Medicine, Philadelphia, PA.