


THE UNIVERSITY OF NEW MEXICO
HEALTH SCIENCES CENTER
Department of Neurology




Rare Presentations of Multiple Sclerosis

Corey C. Ford, MD, PhD
MS Specialty Clinic

*Southwest Neuroimmunologic Symposium
April 26-28, 2007*

Objectives


- Review the differential diagnosis of MS
- Consider the dilemma and value of common disorders with unusual or rare presentations
- Review some of the atypical presentations of multiple sclerosis



UNM Health Sciences Center

Differential considerations for MS


- Infections Lyme, syphilis, HIV, PML, HTLV-1
- Inflammatory SLE, Sjogren's, vasculitis, sarcoidosis
- Metabolic B12 deficiency
- Neoplastic CNS lymphoma, paraneoplastic
- Spinal disease Vascular malformations, spinal stenosis, Chiari, syrinx



UNM Health Sciences Center

The diagnosis of MS


- Schumacher and Poser criteria used "multiple" clinical events to define clinically definite MS (CDMS)
 - Two events separated in space and time
- Recent International Panel criteria allow changes on MRI to substitute for dissemination in space and time
- MRI findings are suggestive or confirmatory otherwise
- CSF findings are sensitive but not specific
 - Oligoclonal bands, IgG index or synthesis rate



UNM Health Sciences Center


Some unusual and rare presentations of MS

- Early onset, MS appearing in childhood
- Transverse myelopathy in children (MS v ADEM)
- Onset with prominent cognitive dysfunction
- Onset with distinct language abnormalities
- Psychosis and depression
- Late onset MS
- Onset with anti-TNF-alpha therapy (rheumatoid arthritis)



UNM Health Sciences Center

Early onset MS (EOMS)



UNM Health Sciences Center

Early onset MS (EOMS)

- Typical MS usually presents between age 20 and 40
- Childhood onset MS is rare
 - 3-5% present less than 16 y
 - <1% earlier than 10 y
- With MRI it is easier to evaluate very young patients for MS and there is heightened interest because potential treatments exist
- Most common presenting symptoms:

	Childhood(116)*	Adult(1721)**
– Sensory	26%	30%
– Optic neuritis	15-20%	16%
– Brainstem signs	12%	11%
– Gait disorder	8%	5%

* Paty, et al. 1994 and ** Boiko, et al. 2002, from Canadian MS-COSTAR database

UNM Health Sciences Center

Characteristics of EOMS patients

(MS-COSTAR database in 2002, n=116)

- Mean age at onset 12.7 years
- Female preponderance was 2.9:1 overall from
- At age 13 (n=18) ratio was 3.5:1
- At age 14 (n=26) ratio was 7.7:1
- Most had good recovery from initial relapse
- Progression endpoints:
 - 50% secondary progressive 23 years after onset
 - EDSS 3 (mild objective disability) mean age 28.5y
 - EDSS 6 (cane to walk 100 meters) mean age 32.3y

UNM Health Sciences Center

MS or ADEM?

UNM Health Sciences Center

Childhood MS or ADEM?

- Childhood MS is infrequent relative to adults, ADEM is believed to be more common
- ADEM characteristics
 - Disseminated CNS inflammation
 - Multifocal neurological symptoms
 - Mental status changes, headache, fever
 - MRI: poorly limited lesions associated with thalamus and BG
 - Typically monophasic but with relapses can become indistinguishable from MS
- Isolated CNS inflammation can be monophasic or herald MS

UNM Health Sciences Center

First episode demyelination in childhood: prognosis and outcome

- French data base, 296 children, survival analysis, mean follow up 2.9 years*
- Age at onset

– MS	12 y
– ADEM	7.1 y
– Single focal	8.8 y
- Transverse myelitis

– MS	8%
– ADEM	2%
– Single focal	63%



* Mikaeloff, et al. J Pediatr. 2004;144:246-252

UNM Health Sciences Center

First episode demyelination in childhood: Prognostic factors for MS

- 168/296 (57%) met criteria for MS at end of follow up
- 34/168 (20%) were initially diagnosed ADEM
- Prognostic factors for second attack and Dx of MS

	Hazard ratio	N
– Age >10 y	1.67	171
– MRI c/w MS	1.54	96
– Optic nerve lesion onset	2.59	12
– Myelitis at onset	0.23	42
- Relationship between MS and ADEM in controversial
- MS in childhood is rare at <5% and myelitis is not predictive of second, disease defining relapse

* Mikaeloff, et al. J Pediatr. 2004;144:246-252

UNM Health Sciences Center

Presentation with Cognitive Dysfunction

UNM Health Sciences Center

MS presentation with cognitive dysfunction

- Over 50% of MS patients have detectable cognitive impairment
- Impairments can occur early. Up to 85% in patients with CDMS less than 2 years, 66% with only optic neuritis
- Presentation with pure cognitive symptoms is rare
- Surprising given frequency in all stages of MS
- Physicians depend on physical symptoms
- Amnesic syndromes are most common often with depression

UNM Health Sciences Center

Cognitive deficits in MS

- Studies have shown relatively consistent patterns in neurocognitive deficits:
 - Amnesia
 - Aphasia
 - Dyscalculia
 - Dyslexia
 - Dysgraphia
 - Dyspraxia
 - Visuospatial disability
- Seizures, cortical sensory loss support "cortical MS"
- Most symptoms explained by cortical dysfunction rather than widespread idea of subcortical dementia

UNM Health Sciences Center

Brain studies with MS cognitive dysfunction

- Cortical involvement by MS was seen in 93% of patients (Lumsden, 1970)
- Most lesions at the gray-white junction
- Recent advances in MR imaging show extensive cortical lesions in MS
- Cortical burden of disease correlates better with cognitive dysfunction and disability than subcortical lesion load
- MS is in differential of unusual, intractable depression or dementia, even without neurological signs

UNM Health Sciences Center

MS Presentation with Language Dysfunction

UNM Health Sciences Center

MS onset with distinct language abnormalities

- Acute aphasia in MS is rare as initial presentation
- MRI typically shows enhancing lesions in left hemisphere
- Recovery is usually good after steroid pulses
- MS presenting with language deficits is very unusual and in adults must be distinguished from stroke or tumor
 - Only a few cases are reported in the literature
- Most language problems occur in established MS
 - Lesions often large, acute, with edema
 - Can associated with repeated focal seizures
 - MRI and EEG recommended as evaluation, treatment with steroids, antiepileptic drugs or both

UNM Health Sciences Center

MS with Psychiatric Onset

UNM Health Sciences Center

MS psychiatric onset

- Psychosis in MS is a rare occurrence, depression is common
 - Up to 50% of MS patients have depression, lifetime prevalence
 - Almost always diagnosed after MS diagnosis is established
- Psychiatric disorders include bipolar illness and schizophrenia-like symptoms
- Mean duration of psychosis is about 6 weeks, preceded by MS diagnosis at mean 8.5 years
- Later age at onset of psychosis in MS patients, correlates with white matter disease in frontal areas

UNM Health Sciences Center

MS with psychiatric symptoms

- Survey of 108 MS patients*
 - Abnormal mood 53%
 - Personality change 40%
 - Psychosis 4%
- MRI abnormalities in 2783 psychiatric inpatients**
 - 1.9% had MRI findings suggestive of MS (53 patients)
 - 0.83% met MRI criteria for MS, 15X expected MS prevalence
- Evaluation of acute psychiatric symptoms with any neurological findings should result in MRI

*SurrIDGE, 1969. Br J Psych. 115:749. **LyoO, etal. J NPsych Clin NSci. 1996. 8:54

UNM Health Sciences Center

Iatrogenic psychosis in MS

- Many relapses of MS treated with short bursts of high dose steroids
- Some patients react negatively with depression or more rarely, psychosis
- Phenomenon studied in ONTT cohort*
 - 457 ON patients received steroid treatment, high dose methylprednisolone, oral prednisone, or placebo
 - Two patients had serious side effects, one psychotic depression
- Short term steroid therapy in young MS patients is relatively safe

UNM Health Sciences Center

Late onset MS

UNM Health Sciences Center

Late onset MS

- Onset of MS after age 50 is infrequent but not rare*
- Studied 640 patients with clinically definite MS
- 4.6% had late onset, mean age 53.5 years
- 50% relapsing-remitting; 50% primary progressive
- All patients over age 54 y had PPMS
- 20% presented with major depression
- Differential diagnosis after age 50 is wider
 - Stroke and subcortical ischemia
 - Collagen vascular diseases
 - B12 deficiency
- Disability progression seems to be faster

*Polliack, etal. 2001. J Am Geriatr Soc. 49:168.

UNM Health Sciences Center

MS Associated with Anti-TNF-alpha therapy

UNM Health Sciences Center

Initial MS relapse with anti-TNF-alpha therapy

- TNF alpha blockers are prevalent treatments for rheumatoid arthritis
 - Etanercept (fusion protein), Infliximab, Adalimumab (mab's)
 - Increased risk of infection, usually minor
- TNF-alpha is elevated in serum and CSF of MS patients, especially during relapse
 - Found in active MS lesions
 - Toxic to oligodendrocytes
 - Worsens EAE
- Treatment trials of anti-TNF alpha in MS (lenercept and infliximab)
 - Both led to worsening MS symptoms and relapses
- Numerous literature reports of initial MS relapses in patient taking anti-TNF alpha treatments

UNM Health Sciences Center

TNF-alpha in MS

- The lenercept trial (n=168) was terminated because of MS worsening
 - Recombinant TNF receptor-p55 Ig fusion protein
 - More relapses (p=.007) occurring earlier (p=.006) than placebo
 - Neurological deficits more severe in those relapses
- MS patients on anti-TNF therapy have had increasing gadolinium enhancing activity on MRI
- Discontinuing drug associated with improvement, some patients have ongoing activity and relapses (trigger?)
- Unknown if patients on anti TNF who develop demyelinating symptoms are genetically predisposed

UNM Health Sciences Center

Summary

- Rare variations of MS (and other diseases) offer important insights
- Early onset, childhood variants and ADEM may reveal genetic predispositions to demyelinating illness or point to potential triggers such as viral illnesses at certain phases of development
- Studies of cognitive dysfunction reveal lesion locations and connectivity changes associated with deficits and sparked the recent focus on cortical involvement in MS
- Correlations with white matter damage may help us understand the origins and substrates of some patterns of depression and psychosis
- The TNF-alpha story and other treatment failures (eg. gamma INF) tell us much about the immunopathology of MS and are nearly as important as treatment successes in forcing revision of mechanistic assumptions

UNM Health Sciences Center