

Distinguishing Pediatric Multiple Sclerosis from Transverse Myelitis and ADEM

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Overview

- What is Pediatric Multiple Sclerosis?
- Clinical Characteristics of Pediatric ADEM
- Clinical Characteristics of Pediatric TM
- How can we distinguish Pediatric MS vs TM vs ADEM?

How Frequent is CNS Demyelination in Children?

- Yann Mikaeloff MD et al in Journal of Pediatrics 2004
- Included Children under 16 yrs between 1985-1991 admitted to 12 Pediatric Neurology Centers in France
- Exclusion criteria include preceding neurologic abnormality, metabolic cause, infectious cause, systemic immunologic disorder

Journal of Pediatrics Article

- Follow up period 2.9 +/- 3 yrs with 20% < 5yrs
- 296 patients (>80% White)
- Age of Onset first attack 9.9 yrs
- MS 12 yrs
- Monophasic ADEM 7 yrs
- Single focal episode 9 yrs

Journal of Pediatrics Article

- Other distinguishing characteristics
- Infection during preceding month (ADEM/Focal episode 51-55% vs MS 16%)
- TM was high (63%) with a single focal episode (low in MS 8% or ADEM 2%)
- Optic Neuritis was more common in MS (35%) vs ADEM (7%)
- Brainstem dysfunction was common in ADEM (55%) vs MS (36%)
- Severe mental status changes are more common in ADEM (75%) vs MS (13%)

Journal of Pediatrics Article

- Initial MRI findings
- In group with final Dx-ADEM, 100% suggestive of ADEM and 15% suggestive of MS
- In group with final dx- MS, 57% suggestive of MS and 0% suggestive of ADEM

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- **Distribution of Initial MRI lesions**
- Subtentorial lesions – MS (72%) and ADEM (86%)
- Thalamus/BG- MS(8%) vs ADEM (40%)
- Optic Nerve lesion- MS (6%) vs ADEM (0%)
- Spinal Cord lesion- MS (19%) vs ADEM (11%)
- Tumor like lesion- MS (12%) vs ADEM (18%)
- Gadolinium enhancement- MS (28%) vs ADEM (11%)

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- **CSF Findings**
- >10 WBC cells- MS (37%) vs ADEM (51%)
- >0.5 gm/dl protein- MS (18%) vs ADEM (36%)
- Oligoclonal bands- MS (40%) vs ADEM (5%)

Message from This Article- Identified thru Multivariate Cox Analysis

- Predictive factors of second attack of demyelination
- Age at onset
- Presence of myelitis or optic nerve lesions
- MRI at onset suggestive of MS
- Protective factors of second attack of demyelination
- MRI at onset suggestive of ADEM

Pediatric Multiple Sclerosis

- 400,000 US patients with MS
- Up to 15% of these will have presentations before age 18.
- Incidence 1-2 per 100,000 kids
- As a teenager, Saint Ludwina of Schiedem (Holland) developed sensory symptoms and visual loss with a relapsing remitting course (14th century).
- Earliest documented autopsy case is 10 months of age.

Pediatric Multiple Sclerosis

- Diagnosis is exactly the same as adult patients. Two or more discrete neurologic events separated in time.
- Optic neuritis (50%), sensory disturbance (16%), or transverse myelitis (10-15%). Motor symptoms are low in primary presentations (8%).
- 71% of children have a rapid initial presentations (hrs to a few days).

Pediatric Multiple Sclerosis

- **Lab features**
- 60% of routine CSF analyses is normal in children with MS.
- Lymphocytosis (<50 cells/mm³)
- Increased CSF protein (<75 mg/dL)
- 80% of children with MS have increased CSF IgG synthesis
- Oligoclonal bands are present in 40-87% of Children with MS.
- Sometimes the OCB appear during the convalescence or relapse phase.

Pediatric Multiple Sclerosis

- Evoked Potentials (82% of children had one abnormal EP)
- VEP – 95% abnormal EP after first attack
- SSEP-57% abnormal EP after first attack
- BAEP-46% abnormal EP after first attack

Pediatric Multiple Sclerosis

- MRI criteria
- 50-67% of clinical definite pediatric MS patients fit the McDonald imaging criteria
- Smaller number of total lesions at presentation.
- High incidence of deep WM ring enhancing lesions (tumefactive lesion) in pediatric MS patients.
- Long axis callosal lesions plus other well defined focal lesions may define CD pediatric MS from ADEM.
- ADEM tends to have GM lesions and subcortical WM lesions as opposed to periventricular WM lesions typical more in pediatric MS patients

Pediatric Multiple Sclerosis

- Pathogenesis
- There are those much more eloquent on the program.
- Susceptibility loci- chromosome 6- MHC II alleles- DR15 and DQ6.
- Environmental factors- anti-viral titers, geographic distribution of MS, etc. which exploit the concept of “molecular mimicry”.

Pediatric Multiple Sclerosis-Tx

- Disease modifying therapy. We will highlight pediatric data if available.
- IV Solumedrol- 15-30 mg /kg/d x 3-5 days. Plasma exchange for acute exacerbations.
- Interferons (beta)
- Avonex 30 ug IM weekly
- Rebif 22-44 ug SC (3x/week)
- Betaseron 250 ug SC qod

Pediatric Multiple Sclerosis-Tx

- Interferons (beta) report in Pediatric MS patients- Banwell et al 2006)
- Avonex 30 ug IM weekly
- Rebif 22-44 ug SC (3x/week)
- Betaseron 250 ug SC qod
- Side effects were similar to adults-fever, headache, myalgia, flu like symptoms, etc. Transient in most cases.
- Pre-med- Tylenol, naproxen, Motrin
- Elevated LFTs- discontinued med, then re-started.

Pediatric Multiple Sclerosis-Tx

- Interferons (beta) report in Pediatric MS patients- Banwell et al 2006)
- 25 of 43 patients discontinued these meds after 111 weeks because of lack of efficacy, cost, lack of adherence, injection pain, or change in diagnosis.
- 38 of 43 patients with clinically definite MS, the annualized relapse rate was reduced by 50%.
- 2005 Ghezzi et al- showed a similar reduction with copaxone and interferons from 2.8 to 0.5 ARR.

Pediatric Multiple Sclerosis-Tx

- Natalizumab (Tysabri)- monoclonal antibody against alpha 4 integrin.
- Rituxan (Rituximab)- monoclonal antibody against CD20.
- Mitoxantrone (Novantrone) –anti-cancer agent.
- IVIG q monthly- 0.125-0.2 g/kg IV per month for two years resulted in a 49% reduction of clinical attack rate and a possible 60% reduction in total and enhancing lesions seen on MRI brain. (Fazekas et al, 1997; Sorenson et al, 1998).

Acute Disseminated Encephalomyelitis (ADEM)

- Inflammatory demyelinating disease of the CNS after viral infection or vaccine
- Typically monophasic illness 90%
- Multiphasic illness 10%
- A clear infectious event or vaccination precedes (1-4 weeks) the onset of neurologic symptoms in 75% of patients
- Typical interval between febrile prodrome and onset of neurologic symptoms is 12-14 days
- Age of onset 5.3 +/- 3.9 yrs

Labs

- CSF had abnormalities in 62%
- Most common elevated WBCs (mean 210 cells with range 0-1800)
- 3/24 had slightly elevated protein (up to 120 mg/dl)
- 5/24 patients (20%) had serologic evidence of recent viral infection (HSV, EBV, Varicella, Measles)
- None had oligoclonal bands
- MRI spine- with swelling and increased T2 signal in cervico-thoracic regions
- Increased T2 signal is located centrally in spinal cord

ADEM : Prodromal Events

- Tenenbaum et al, Neurology 2002
- 84 consecutive patients in Argentina
- Nonspecific URI 35%
- No defined prodrome 26%
- Vaccine 12%
- GI illness 11%
- Varicella 5%
- HSV encephalitis 2%, Mumps 1%, Rubella 1%

ADEM: Presenting Features

- Long tract signs 85%
- With acute hemiparesis 76%
- Changes in sensorium 69%
- Cerebellar ataxia 50%
- Seizures 35%
- CN palsy 44%
- Meningeal Involvement 43%
- Headache/vomiting 24%

ADEM: Presenting Features

- Visual loss 23%
- Aphasia 21%
- Extrapyraxidal syndrome 12%
- Hemiparasthesia 2%

Radiologic Features: 4 groups

- Small lesions (<5 mm) in GM and WM : scattered and asymmetric 62% (Group A)
- Confluent asymmetric and tumor like white matter lesions 24% (Group B)
- Bilateral symmetric basal ganglia or thalamic lesions with either small or large cerebral WM lesions 12% (Group C)
- Large demyelinating lesion with hemorrhage (acute hemorrhagic encephalomyelitis) 2% (Group D)

ADEM: CSF findings

- 28% patients <180 cells/mm³
- 38% patients >1gm/dl protein
- 96% patients negative for oligoclonal bands
- 13% patients elevated CSF IgG
- 17% patients antibody or PCR evidence of recent infection
- 11% patients elevated MBP

ADEM: Treatment

- 20 mg/kg solumedrol or steroids- 80%
- AEDs 35%
- Acyclovir 69%
- PICU patient 43%
- Ventilation 16%

ADEM: Outcome

- IV solumedrol or dexamethasone followed by PO steroid taper over 4-6 weeks
- Mean follow up 6.6 +/- 3.8 yrs
- Disability- ranked by MRIs scan
- Group A 96% normal or nearly normal
- Group B 80%
- Group C 80%
- Group D (AHM) 50%

Residual Deficits & Neurologic Syndromes

- Mild to severe hemiparesis 8%
- Symptomatic partial epilepsy 6%
- Visual acuity reduction 6%
- Mild paraparesis 4%
- Mental handicap 4%

Bi- or Multiphasic ADEM

- 2-10%
- Age of onset 4.6 +/-3.7 yrs
- 1-2 relapses
- Mean interval between relapses 2.9 yrs
- No patients with oligoclonal bands in CSF
- Follow up period mean 8 yrs

Pediatric Acute Transverse Myelitis

- Incidence: 1:100,000
- Defreense et al, Journal of Child Neurology 2003
- 24 patients
- Defined as acute onset of bilateral spinal cord dysfunction
- Exclusion criteria: Prior neurologic illness, evidence of trauma, irradiation, or spinal cord compression

Pediatric Acute Transverse Myelitis

- Mean age of onset- 8 years
- M:F- 1:1
- 58% had illness in setting of infection (URI)
- 50% of cases in the winter season
- Fever was present in 60% patients
- In the initial phase (5 days), severe symmetric pain was present in 88% patients over one or more spinal segments

Pediatric Acute Transverse Myelitis

- Sudden of severe motor dysfunction over 12 hours or respiratory insufficiency in 30% of patients
- Mean duration of plateau phase is 6 days
- 75% had back pain, most commonly in the neck
- 23/24 patients developed a symmetric flaccid paralysis of LE with sphincter dysfunction
- One or more DTRs were abolished in 83% patients
- 42% of patients had moderate UE weakness
- Abnormalities (82%) in sensation were present, being asymmetric (83%). The levels were thoracic in 88% and cervical in 12% of patients
- Sphincter dysfunction (83%) was severe in 50% of patients, requiring catheterization for a mean of 12 days

Pediatric Acute Transverse Myelitis

- All patients were treated with IV solumedrol
- Mean duration of follow up 7 yrs
- Mean time to independent walking 56 days
- 50% had a normal recovery
- 13% had mild motor sequelae
- 24% had moderate motor sequelae
- 13% had severe motor sequelae

Outcome Factors

- Unfavorable outcome: 1) complete paraplegia or 2) time to maximum deficit < 24 hrs
- Favorable outcome: 1) plateau < 8 days or 2) time to independent walking < 30 days
- No patients had a re-occurrence of their TM or other neurologic deficits
- None developed MS