Roadmap to Pediatric Demyelination: Clinical Features

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Acute central nervous system demyelination in children

• Monophasic Diseases
  – Acute disseminated encephalomyelitis (ADEM)
  – Clinically Isolated Syndrome (CIS)
    • Optic neuritis
    • Transverse myelitis

• Chronic Diseases
  – Multiple sclerosis (MS)
  – Neuromyelitis optica (NMO)

• Mimickers of demyelination

Acquired Demyelinating Syndrome (ADS) Incidence

• Canadian cohort
  – 0.9 per 100,000 Canadian children

• Californian cohort
  – 1.63 per 100,000 person-years

• Washington DC cohort
  – 11.79 cases per million children

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First, the basics
Consider the differential diagnosis
Look for red flags
Acknowledge the differences between adults and children

Location, location, location!
Consider genetic & environmental factors
Provide anticipatory guidance
Maintain a holistic approach

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Heterogenous Mechanisms

Clinically Isolated Syndromes (CIS)
Paradigm for evaluation: CIS

**CIS:** Optic Neuritis

- May be a presenting feature of MS, ADEM, NMO
- Clinical presentation:
  - Younger children may be more likely to have bilateral involvement
  - Clinically, only 40% report pain with eye movement
  - Mean age of onset 9-12 years, slightly increased
  Female: Male


CIS: Optic Neuritis

• Evaluation
  – Formal visual fields, low contrast sensitivity
  – VEP or OCT

• Differential Diagnosis
  – B12 deficiency, optic nerve glioma, Leber’s Hereditary Optic Neuropathy

• Outcome
  – Demyelination outside the optic nerve portends progression to multiple sclerosis


CIS: Transverse Myelitis

• May be an isolated occurrence (idiopathic or ADEM) or a manifestation of a relapsing disease, MS or NMO

• Clinically
  – Most cases are idiopathic, resulting from autoimmune process
    • 47% preceded by a febrile illness
    • 25% preceded by vaccination
  – Weakness, paresthesias and urinary dysfunction are common presenting features
  – Up to 58% with longitudinally extensive TM in one cohort


CIS: Transverse Myelitis

• Evaluation
  – MRI brain and spinal cord with contrast
  – Lumbar puncture

• Differential diagnosis
  – Compressive lesions, intramedullary tumors, spinal cord infarction, vascular malformations, infection, lupus
  – Guillain Barre Syndrome


CIS: Transverse Myelitis

• Outcome
  – Cervical lesions, length of lesion predict worse outcome
  – Focal acute TM carries greater risk of progression to MS
  – Among one cohort of children with complete TM (n=24), none progressed within 7 years

CIS: Polyfocal presentation

- More than one area of the CNS involved
- Without encephalopathy: polyfocal CIS
- With encephalopathy: ADEM

Acute Disseminated Encephalomyelitis
**ADEM Diagnostic Criteria**

*Pediatric ADEM (all are required)*

- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after the onset
- Brain MRI is abnormal during the acute (three-month) phase.
- Typically on brain MRI:
  - Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
  - T1 hypointense lesions in the white matter are rare
  - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

*Clarification of terminology:* ADEM is a heterogeneous entity and is best viewed as a 'syndrome' rather than a specific disorder.


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**ADEM**

- **Clinically**
  - Most children present before age 10
  - Acute or subacute onset
    - Viral infection or vaccination within one month
  - Multifocal neurologic deficits with encephalopathy
  - Additional clinical features: headache, fever, meningismus, seizures
  - Monophasic, with duration up to 3 months
- **Multiphasic:** 2 episodes consistent with ADEM separated by 3 months
ADEM

• Evaluation
  – MRI brain and spinal cord
  – Lumbar puncture
    • Pleocytosis, elevated protein, normal glucose, transient oligoclonal bands
  – Viral studies: HSV, enterovirus, cytomegalovirus, EBV, VZV and West Nile virus

• Outcomes
  – >50% patients experience full recovery over several weeks
  – Rubella and varicella infections are associated with a worse outcome
  – Neurobehavioral and cognitive sequelae common
  – A minority of patients will progress to MS (<20%)

Defining ADEM

- ADEM may follow a prodromal illness
- ADEM patients may have fever and meningismus
- ADEM patients are younger (mean age 7.4 years) than CIS patients (11.2 years for multifocal presentation)
- Myelopathy of ADEM is often complete
- Ataxia is a common presenting feature


Role of MRI in the differentiation of ADEM from MS in children

Retrospective analysis of MRI scans obtained at first attack:
- 28 children subsequently diagnosed with MS
- 20 children diagnosed with ADEM

Total number of lesions did not vary between groups.

>=2 of the following (sensitivity 85%, specificity 98%):
1. Absence of a diffuse, bilateral lesion pattern
2. Presence of black holes
3. Presence of two or more periventricular lesions

MRI in Peds MS

Appendix 3. Magnetic resonance imaging (MRI) characteristics for dissemination in space (DIS) that increase the likelihood of a pediatric multiple sclerosis (MS) diagnosis.

<table>
<thead>
<tr>
<th>Barkhof²²</th>
<th>KIDMUS²³</th>
<th>Callen MS vs ADEM²⁴</th>
<th>Callen Diagnostic MS²⁵</th>
<th>Verhey Differential²⁶</th>
<th>2010 Revised McDonald²⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 of 4:</td>
<td>1 of 2:</td>
<td>2 out of 3:</td>
<td>2 out of 3:</td>
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<tr>
<td>≥9 T2 lesions or 1 gadolinium enhancing</td>
<td>Lesions perpendicular to long axis of the corpus callosum</td>
<td>Absence of a diffuse bilateral lesion pattern</td>
<td>Presence of black holes</td>
<td>≥1 periventricular lesions</td>
<td>≥1 periventricular lesions</td>
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<tr>
<td>≥3 Periventricular</td>
<td></td>
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<td>≥2 periventricular lesions</td>
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<td>≥1 hypointense lesions on T1 images</td>
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<td>≥1 Infratentorial</td>
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<td>≥1 Juxtacortical</td>
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<td>≥1 spinal cord</td>
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ADEM: acute disseminated encephalomyelitis.
Pediatric Multiple Sclerosis

- ~5% of all patients with MS
- ~1% patients have onset before age of 10 years
- Acute and chronic inflammation in the brain, optic nerves or spinal cord
- >95% relapsing and remitting
- Female: Male of 2.8:1 in post-puberty


Clinical phenotype in children

- Little/ no progressive form from onset
- Higher relapse rate
- More frequent involvement of brainstem or cerebellum at disease onset
- Presence of “encephalopathy” at disease onset in children < 11 years: up to 20%
- Better recovery from early relapses than adults, yet disability is achieved at a younger age

2010 McDonald Criteria for Diagnosis of Pediatric MS

Dissemination in Time (DIT) and Space (DIS)


2010 McDonald Criteria for Diagnosis of Pediatric MS

- DIT and DIS require serial clinical & MRI observations if patient presents with encephalopathy
- For children presenting with non-ADEM demyelinating event:
  - Sensitivity 100%
  - Specificity 86%
  - Positive Predictive Value 76%
  - Negative Predictive Value 100%

Sedaka, et al. 2010 McDonald Criteria for Diagnosing Pediatric Multiple Sclerosis; 2012
IPMSSG criteria for pediatric MS

Any of the following:
- Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than one area of the CNS
- Single clinical event and MRI features rely on 2010 Revised McDonald criteria for DIS and DIT (but criteria relative for DIT for a single attack and single MRI only apply to children ≥12 years and only apply to cases without an ADEM onset)
- ADEM followed three months later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS

Neuromyelitis Optica
Neuromyelitis Optica

• Classically characterized by optic neuritis and longitudinally extensive transverse myelitis
• Core characteristics:
  – Optic neuritis,
  – Acute myelitis,
  – Area postrema syndrome (nausea, vomiting, hiccups),
  – Other brainstem syndromes,
  – Symptomatic narcolepsy or acute diencephalic syndrome with MR findings and
  – Symptomatic cerebral syndrome with MRI findings
• If antibody positive, only one core characteristic required
• If antibody negative, must have 2 or more core characteristics
• Clinical course may be fulminant and monophasic or relapsing and remitting

NMO IgG

• Selectively binds to aquaporin 4 water channel
• 93% seropositive patients had recurrent attacks
• Overlap with other autoimmune disorders, including systemic lupus erythematosis, anti-NMDAR encephalitis and Sjogren’s syndrome

NMO Images

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Incidence in children

- **Pediatric MS:** 0.51 per 100,000 person-years
- **Other ADS (ADEM, ON, TM, CIS):** 1.56 per 100,000 person-years
- **NMO (adult and child):** 0.05-0.4 per 100,000 patient-years
- **Primary vasculitis (adults):** 0.24 per 100,000 person-years
- **Neurosarcoidosis (adult and child):** 0.2 per 100,000 persons
- **Langerhans Cell Histiocytosis (CNS):** 0.2 per 100,000 persons
- **CNS Sjogren syndrome (adult and child):** unreported


Laboratory studies

Suspected autoimmune or inflammatory workup:

- CBC, LFTs, CRP/ESR, ACE if considering neurosarcoidosis
- NMO IgG (serum) if severe optic neuritis, longitudinally extensive transverse myelitis, atypical periventricular brain lesions
- ANA panel, dsDNA, anticardiolipin and antiphospholipid antibodies, ferritin, C3, C4
- TSH, T4, anti-TPO antibodies if Hashimoto encephalopathy is a consideration
- CSF: cell count, protein, glucose, cytology (if indicated), oligoclonal bands with IgG index; NMO IgG only if serum NMO IgG negative with a high index of suspicion

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Clinical History: Red Flags

IF: CONSIDER:

**Hyperacute onset**
- Cerebral sinus venous thrombosis (CSVT), infarction

**Presence of headache**
- Primary angiitis of the CNS (PACNS), CSVT, Susac syndrome

**Recurrent or Severe Optic Neuropathy**
- Neuromyelitis optica (NMO), Leber’s Hereditary Optic Neuropathy (LHON), chronic relapsing optic neuropathy (CRION), neurosarcoidosis, Sjogren Syndrome

**Seizures**
- Autoimmune encephalitis (anti-NMDA Receptor), PACNS, Neuro Behçet, CNS Lupus

**Psychosis**
- PACNS, autoimmune encephalitis, CNS Lupus, Susac syndrome

**Systemic disease**
- Neurosarcoidosis, vasculitis, CNS lupus, Susac syndrome, Langerhans cell histiocytosis, Sjogren Syndrome

**Family history of autoimmune disease**
- Neuro Behçet, CNS Lupus, NMO

Exam: Red Flags

IF: CONSIDER:

**Cranial nerve involvement**
- Neurosarcoidosis (50-75%), Neuro Behçet’s, infection

**Joint involvement**
- CNS Lupus

**Focal neurologic change with headache**
- Vasculitis

**Fever, constitutional symptoms**
- Infection, lymphoma
Red Flags: Laboratory Evaluation

CSF white blood cells greater than 50
– Think: Infection, HLH, AHLE, NMO

Elevated opening pressure
– Think: neurosarcoiics, PACNS, lymphoma, CSVT

Conditions associated with oligoclonal bands:
- Paraneoplastic disorders
- SLE
- Neurosarcoiics
- Neuro-Behçet’s
- Sjogren’s syndrome
- Anti-Glutamic acid decarboxylase antibody syndrome
- Steroid-responsive encephalopathy (Hashimoto encephalopathy)
- Vogt-Koyanagi-Harada (uveomeningoencephalitis)


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Clinical features specific to children

- **Optic neuritis**
  - Clinically, only 40% of children report pain with eye movement
  - Younger children may be more likely to have bilateral involvement

- **Transverse Myelitis**
  - May have hyperacute presentation, sometimes confused with Guillain-Barre Syndrome

- **Neuromyelitis Optica**
  - Time to severe residual vision loss is shorter
  - Brain lesions are common

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Clinical features specific to children

- **Pediatric MS**
  - Children commonly present with isolated optic neuritis, isolated brainstem syndrome or encephalopathy
  - Relapsing and remitting course
  - Annual relapse rate 2-3 times that of adults
  - Pediatric MS patients are more racially & ethnically diverse
  - Boys and girls are more evenly affected prior to puberty
Laboratory features specific to children with MS

- CSF Analysis
  - IgG index
    - Elevated in 68% patients with MS >11 yrs
    - Elevated in 35% patients with MS <11 yrs
  - Neutrophils
    - More common in younger children
    - Absence of neutrophils associated with 2nd neurological episode
  - Oligoclonal bands
    - Seen in up to 92% children with MS
    - Up to 29% of children with ADEM

MRI features specific to pre-pubertal children with MS

At onset

3 months later

Chabas 2008
At onset

MRI features specific to post-pubertal children with MS

3 months later

Chabas 2008

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Location, Location, Location

- Lesions that occur within a vascular territory should raise concern for infarction
- Symmetric, confluent lesions should raise concern for inherited and metabolic disorders

NMO lesions occur at the sites of greatest AQP4 concentration
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Risk Factors for Pediatric MS

• Genetic susceptibility
  – 5% lifetime risk of developing MS in first degree relatives
  – Monozygotic twins have 25% risk
  – Haplotypes DRB1*1501, DQA1*1501, DQB1*0602
  – Up to twice as common in African Americans
• Among patients with European ancestry, risk of MS was greater with + DRB1 status: 37% v. 15%, p=0.001
• Risk of MS in non-European children was not influenced by DRB status, 36% v. 22%, p=0.15
• Logistic regression: When accounting for age and sex, DRB1*15 status remained an independent predictor of MS diagnosis — OR=3.2, CI 1.7-6.1

Disanto, et al., 2011
Interactions between HLA-DRB1 and viral status in predicting MS

- Interaction for HSV-1 and *HLA-DRB1* (*p*<0.001)
- using neurological controls *p*=0.024,
- using healthy controls *p*<0.001.
- In *HLA-DRB1 -*:
  - OR=4.11, 95%CI 1.17, 14.37; *p*=0.03
- In *HLA-DRB1 +*:
  - OR=0.07, 95%CI 0.02, 0.32; *p*=0.001

Waubant, 2011.

Environmental Factors

- Exposure to viruses
  - EBV seropositivity: 3-5 fold increased likelihood of MS
- Parental smoking
  - Risk 2 fold higher if parents smoke
- Vitamin D status
- Obesity
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Anticipatory Guidance

• In the case of uncertain diagnosis, present a plan for surveillance
• Involve school personnel and establish an Individualized Education Plan or 504 plan
• Establish neuropsychologic “baseline”
• Recognize that anticipatory guidance will change as the patient matures in his/her disease
• Stay connected!
Anticipatory Guidance for Peds MS

• Natural history of disease
  – Number of relapses within the first 2 years portends worse prognosis
    • Each additional relapse increases rate of disability by 31-41%

• Cognitive sequelae

Natural History of Disease
Natural History of Disease

EDSS 4

EDSS 6

EDSS 7

Cognitive Outcomes

- N=37 patients with pediatric MS
- Within 19 months of diagnosis, 30% with deficits seen in:
  - Attention
  - Memory
  - Confrontational naming
- Correlations with EDSS, number of relapses and disease duration
- 50% with depressive symptoms

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Pediatric patients exist within a system

• Diagnosis of a chronic disease affects:
  – Parents
  – Siblings
  – Patient, self identity
Summary Points

• Acquired demyelinating syndromes of childhood have distinct diagnostic criteria yet overlap commonly at onset
• Differential diagnosis of ADS is broad, and includes genetic, metabolic, neoplastic and infectious causes
• Clinical presentation of ADS in pre-pubertal children often includes encephalopathy
• Recovery from attacks is robust in early MS disease, yet these children reach disability at younger ages

Summary points

• Environmental and genetic triggers are similar to those of adults
  – Epidemiologic studies of children with pediatric onset disease may provide clues
• Psychosocial impact of a chronic disease is huge, and impacts the entire family
Thank you for your attention

Radiographic evaluation

- Gray and white matter?
- Venous sinus thrombosis?
- Persistent contrast enhancement?
- Distribution of disease?
  - Diffuse?
  - Hypothalamic?
  - Periventricular?
  - Brainstem, thalamic or basal ganglia involvement?
  - Meningeal involvement?

Consider: Neurosarcoidosis, NMO, Langerhans Cell Histiocytosis

Case #2

- 11 yo F presented with bilateral, painless vision loss, vomiting
- Past medical history: ADHD, Mood d/o, HTN
- Family history: MGM with rheumatoid arthritis
- Neurologic exam:
  - No light perception left eye, + APD
  - Nystagmus
  - Dysmetria

Laboratory Confirmation

- CSF: unremarkable, no oligoclonal bands
- MRI brain and orbits, spinal cord: optic nerve atrophy (L), bilateral enhancement, periventricular lesions adjacent to middle cerebellar peduncle
- NMO antibody: POSITIVE
Case #2 Red Flags

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Antibody mediated Disorders

• Encephalopathies:
  – Anti-NMDAR encephalitis
  – Voltage gated potassium channel-complex
  – Glutamic acid decarboxylase
• Neuromyelitis optica

Location, Location, Location

• Pediatric MS
  – More frequent involvement of brainstem or cerebellum at disease onset
• Transverse myelitis
  – Short, peripheral, circumscribed lesions are more common in CIS/MS