Clinicopathological Conference

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History
Malaise
Bilateral leg numbness and weakness
Urinary retention

Examination
Temp = 38.8
1.7 liters of urine in bladder
Palpable red rash on legs

[Image of a person smoking a pipe]
Neurological Examination

Low tone and 0 power in bilateral legs

T10 sensory level

0+ patella and ankle reflex

Question #1

Knowing only the initial history and examination, the most likely diagnosis is:

A. first bout of MS
B. acute transverse myelitis
C. viral myelitis
D. dural AV fistula
E. another type of acute myelopathy

Acute transverse myelitis

Two Basic Questions:

1) Complete or Incomplete?
2) Inflammatory or not?
Acute transverse myelitis

Classification:

1. Post-infectious / Post-vaccination

2. Direct infection (viral, bacterial, fungal, parasitic)

3. Secondary to systemic autoimmune disease
   a. SLE
   b. Sjögren's
   c. Neurosarcoidosis
   d. Behcet's
   e. Mixed connective tissue disorder
   f. Scleroderma

4. Idiopathic

2002 Transverse Myelitis Consortium criteria:

A. Clinical:
   1) bilateral sensory, motor or autonomic dysfunction
   2) cord sensory level
   3) progresses to nadir over 4-21 days from onset

B. Neuroimaging: r/o structural cause

C. Inflammatory etiology
   1) gadolinium enhancement
   2) CSF pleocytosis or IgG index elevation

Laboratories I

CBC
   WBC 15.1

CSF
   WBC 35 (57% P)
   RBC 136
   Gluc 49 (188 serum)
   Protein 699
   OCB 0
   IgG index 0.60
Laboratories II

Mycoplasma (serum)
Acute IgM=Negative
Acute IgG=6.51
Convales IgM=Positive
Convales IgG=4.98
Mycoplasma (CSF)
Not run
Mycoplasma throat
Negative
Peripheral leukocytosis with normal platelet count
- Mildly increased magnesium and mildly decreased phosphate
- Increased alkaline phosphatase
- Mild increased AST and total bilirubin

**CSF protein** = 699
- glucose = 49/118
- rbc = 136  wbc = 35 (57P/30M/13L)
- OCB = 0   IgG Index = 0.6

- **Cord MRI:** extensive, diffuse increased T2 signal, central > peripheral
- **Brain MRI:** patchy increased T2 signal
  - Bilateral high posterior frontal subcortical white (? right enhancing)
  - Right posterior limb internal capsule
  - Left middle cerebellar peduncle
  - ? Right midbrain

**Mycoplasma pneumoniae titers:**

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgM</th>
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<tbody>
<tr>
<td>Acute</td>
<td>6.51</td>
<td>negative</td>
</tr>
<tr>
<td>Convalescent</td>
<td>4.98</td>
<td>positive</td>
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Chest x-ray: no infiltrate

M. pneumoniae nasopharynx/throat culture: Negative

**Question #2:** Which of the following statements about Mycoplasma pneumoniae is **not** true?

A. *M. pneumoniae infections are usually mild and easy to treat.*
B. *Serious M. pneumoniae infections are best diagnosed by the combination of an infiltrate on chest x-ray and a positive nasopharynx or throat culture.*
C. *The likelihood of dermatologic, arthritic and/or neurologic complications of a M. pneumoniae infection is not correlated with the severity of the infection.*
D. *M. pneumoniae is one of the major causes of encephalitis in children.*
E. *Thomboembolic phenomena are one of the pathways by which M. pneumoniae is associated with neurological disease in adults.*
M. pneumoniae: neurologic complications

- Immune-mediated; spinal cord and brain
- Anti-neuronal antibodies detectable 2-4 weeks after systemic infection
- Usual interval between systemic infection and myelitis 10 days
- Myelitis: dramatic and severe
  - Complete paraplegia, loss of sensation and sphincter function within 1-3 days
  - Most commonly thoracic, but extensive cord in 3 cases
- CSF: 10-200 wbc, nl glucose, protein 100-250

Question #3

On the basis of the data available up to this point, including the neuroimaging and the M. pneumoniae titers, the most likely diagnosis is:

A. ADEM precipitated by acute M. pneumoniae infection
B. ADEM following coincidental acute M. pneumoniae infection
C. NMO spectrum disorder
D. Longitudinally extensive transverse myelitis (LETM)
E. Something else we have not discussed

Acute disseminated encephalomyelitis

- Infections
  - mycoplasma mumps infectious mononucleosis
  - measles influenza parainfluenza
  - rubella varicella typhoid
  - ...and many other upper respiratory and febrile diseases
- Vaccinations...especially smallpox
- brain > cord > brainstem = cerebellum

NMO diagnostic criteria: 1999

A. 3 absolute requirements:
   1) Optic neuritis
   2) Acute myelitis
   3) No symptoms implicating other CNS regions

B. at least 1 of 3 major supportive criteria:
   1) Brain MRI at onset normal or does not fulfill MS criteria
   2) Spinal cord MRI lesion greater than or equal to 3 vertebral segments
   3) CSF greater than 50 WBC or 5 neutrophils

C. or 2 of 3 minor supportive criteria:
   1) Bilateral optic neuritis
   2) Severe residual visual loss
   3) Severe fixed, post-attack weakness
**NMO diagnostic criteria: 2006**

1) Optic neuritis

2) Acute myelitis

3) At least 2 of 3 supportive criteria:
   a. Contiguous cord MRI lesion 3 or more vertebral segments
   b. Brain MRI not meeting MS criteria
   c. NMO-IgG positive

These criteria are 99% sensitive and 90% specific for differentiating NMO from MS with optic nerve and spinal cord presentations.

**Significance of NMO-IgG antibody**

- NMO has a different pathogenesis than MS
- 73% sensitive, 91% specific for distinguishing NMO from optic spinal presentations of classical MS
- Predictive: another event w/in 1 yr
  - + NMO-IgG: 55%
  - - NMO-IgG: 0%

Significance of NMO-IgG antibody

- Brain lesions present in up to 50% of patients with NMO-IgG
  - Many asymptomatic
  - Hypothalamic involvement, endocrinopathies

- 1 in 4 NMO patients are NMO-IgG negative
  - Path more complicated than complement-mediated tissue damage from this antibody
  - Other as yet undiscovered antibodies involved
  - Aquaporin-4 water channel is also prominent in the kidney and stomach... but the CNS aquaporin-4 isoform has prominent astroglial surface representation

Significance of NMO-IgG antibody

- Treatment implications:
  - NMO → immunosuppression
  - MS → immunomodulation

- NMO spectrum disorders

Interval History

Persistent urinary retention

Perianal numbness
Dr. Cuneo

Relapse

- ? Partially treated a monophasic illness
- ? Recurring illness

5 months

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tr>
<td>9/10</td>
<td>Initial illness</td>
</tr>
<tr>
<td>10/1</td>
<td>Hospital discharge</td>
</tr>
<tr>
<td>12/7</td>
<td>Ambulating with device; urinary retention</td>
</tr>
<tr>
<td>2/11</td>
<td>Paraplegia</td>
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Question #4
The most important additional clue is:

A. Palpable petechial skin rash
B. Markedly elevated CSF protein
C. Diffuse osteopenia
D. Mild elevated Mg/mild decreased phosphate/increased alkaline phosphatase
E. None of the above; you’re looking in the wrong direction

Revisiting the mystery clues:

Major:
- Palpable petechial skin rash
- CSF protein 699

Minor:
- Diffuse osteopenia
- Mild elevated magnesium/mild decreased phosphate
- Increased alkaline phosphatase
Revisiting the mystery clues:
1. Palpable red rash

Purpura
- Bleeding into the skin (petechiae or ecchymosis)
- Classification:
  a) Extravascular...trauma
  b) Intravascular...coagulopathy - non-palpable
- a) Vascular...inflammation
  • Immune complex formation
  • Complement activation
  • Neutrophilic infiltration - palpable; leukocytoclastic vasculitis

Revisiting the mystery clues:
2. CSF protein 699

Triggers of leukocytoclastic vasculitis:
- Infections
  - Rocky mountain spotted fever
  - Meningococcemia
- Medications
  - Nonsteroidal anti-inflammatory drugs, antibiotics, allopurinol, phenytoin and thiazide diuretics
  - Immunofluorescence negative
- Autoimmune disorders
  - Immunofluorescence positive
  - Prototype Henoch-Schönlein purpura (classical triad of purpura, abdominal pain and arthritis)
  - Malignancies

Possibly relevant clues about immune status not provided:
- ANA..............................SLE; MCTD
- DSDNA..........................SLE
- Antiphospholipid antibodies......SLE
- SSA..............................Sjögren’s
- ANCA-P; ANCA-C...............2 cases of ANCA-associated myelitis
Revisiting the mystery clues:

3. Diffuse osteopenia
   - Mild elevated magnesium/mild decreased phosphate
   - Increased alkaline phosphatase

   - Diffuse osteopenia...? Vitamin D deficiency
   - Low phosphate
     - phosphate resides in bone as mineralized extracellular matrix
     - Vitamin D deficiency can lead to decreased absorption
   - Increased magnesium
     - Rarely seen outside of renal insufficiency
   - Increased alkaline phosphatase
     - Bone or liver

Question #5
The Audience of Neurologists Pounders:

A. Did the original mycoplasma infection cause monophasic ATM/ADEM, that came back after inadequate rx?
B. Was the original mycoplasma infection the primer for chronic relapsing ATM/ADEM?
C. Does the patient have a connective tissue disorder causing chronic relapsing ATM/ADEM?
D. Does the patient ‘simply’ have NMO/NMO spectrum disorder?
E. Does the patient have something else I haven’t considered?

Things it would be nice to know at this point...

- From the patient
  - ? prior good health
    - Energy, weight stability
    - Immune status
    - Exposures
  - ? prior visual symptoms
- and from the lab...
  - NMO-IgG
  - ANA, SSA, DSDNA, ANCA-P, ANCA-C

In a nutshell...

1. Relapsing CNS disorder
   - cord > brain
2. Systemic illness............................................ANA, SSA
   - initial prodrome
   - Autoimmune response to M. pneumoniae
   - palpable rash ...leukocytoclastic vasculitis

- NMO spectrum disorder..................................NMO-IgG
  - ? overlapping with asymptomatic connective tissue disease
Interval History
FINAL DIAGNOSIS:
Vascular myelopathy secondary to tandem intracranial and spinal dural arteriovenous fistulae
Dr. Bollen
NEUROPATHOLOGY

ANDREW BOLLEN
PROFESSOR OF NEUROPATHOLOGY
UCSF
Symptoms of arteriovenous fistulae are precipitated or aggravated by minor systemic illness with fever, posture, valsalva.

- Aminoff and Logue, 1974