Acute Encephalitis: What is New?
Howard Faden and Osman Farooq

Definitions of Encephalitis and Meningitis

<table>
<thead>
<tr>
<th>Encephalitis</th>
<th>Meningitis</th>
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<tbody>
<tr>
<td>Inflammation of the brain parenchyma</td>
<td>Inflammation of the meninges</td>
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</table>

Distinguishing Characteristic of Encephalitis and Meningitis

**Encephalitis**
- Change in level of consciousness
- Change in behavior
- EEG changes
- CSF normal or abnormal

**Meningitis**
- Stiff neck
- CSF abnormal

Basic Work-Up

- History
- Age
- Season: Summer and Fall-arboviruses and enteroviruses
- Ill contacts: Enteroviruses and EBV
- Animal contact: Cats, bats, rodents, etc.
- Travel: Regional outbreaks

Basic Laboratory Work-Up

- CBC with differential
- CSF for cells, glucose protein
- Acute (IgG and IgM) specific antibodies and convalescent antibody titers (IgG, +/- IgM)
- Respiratory screen (<3 years)/ Throat culture (>3 years) for respiratory viruses
- NP/Throat for enterovirus PCR
- Stool culture for enteroviruses
Basic Laboratory Work-Up

- CSF PCR for HSV 1 and 2 and enteroviruses
- Anti-N-Methyl-D-Aspartate Receptor Antibody

### California Encephalitis Project, 1998-2011 (Confirmed or Probable Cases)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>HSV 1, 2a</td>
<td>40, 5</td>
<td>7, 0</td>
</tr>
<tr>
<td>VSV</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Mycoplasma a</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Enteroviruses b</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>SLE, WEE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WNV</td>
<td>19</td>
<td>5 a</td>
</tr>
<tr>
<td>EBV</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Bartonella</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Anti-NMDAR</td>
<td>ND</td>
<td>32</td>
</tr>
</tbody>
</table>

aCID 2006:43, 1565  
bCID 2012:54, 899  
cCID 2012:54, 899  
dCID 2006:43, 1565  
pPediatrics 2007:120,305, additional 109 possible cases  
q2012 - 238 epidemic cases

Map of WNV Cases 11/6/2012

West Nile Virus 11/6/2012

<table>
<thead>
<tr>
<th>State</th>
<th>CNS cases</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texas</td>
<td>765</td>
<td>1684</td>
</tr>
<tr>
<td>California</td>
<td>238</td>
<td>395</td>
</tr>
<tr>
<td>New York</td>
<td>55</td>
<td>98</td>
</tr>
<tr>
<td>All States</td>
<td>2559</td>
<td>5054</td>
</tr>
</tbody>
</table>

West Nile Virus

- Clinical manifestations in children: 80% asymptomatic, 20% fever and <1% CNS disease (adults >30%).
- CNS manifestations: meningitis, encephalitis (may resemble HSV) and flaccid paralysis (anterior horn neurons destroyed as in polio)
- CNS outcomes: 60% of adults persist with issues such as weakness, confusion and light headedness at 1 year

Lyme Disease 2012
Neurological Diseases of Lyme Disease

- Facial nerve palsy
- Meningitis
- Other cranial nerve palsy
- Radiculopathy
- Cognitive deficits

Post-Lyme Disease Syndrome (PLDS)

PLDS includes fatigue, musculoskeletal pain, headache, cognitive difficulty changes; however, No evidence of Lyme disease causing PLDS if treated appropriately

Medical letter 2007, 49:49
Pediatric Infectious Disease Journal 2008, 27:1089
Pediatrics 2012, 130:256

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis

Case

- 17y previously healthy female presents with confusion, agitation, auditory hallucinations and suicidal ideation
- PE and lab parameters were normal
- Discharged home with a diagnosis of Brief Psychotic Disorder

Case: Work up

- Symptoms progressed → admitted to psych hospital
- On admission, was noted to have hyperventilation
- Days later: apnea, seizure → transferred to tertiary care center
- Brain CT & MRI normal
- CSF showed mildly elevated lymphocytes and protein → Rx acyclovir presumed viral enceph

Case: Hospital Course

- 4 days later: 2nd seizure, decreased LOC → intubated, ICU
- Developed orofacial dyskinesias and involuntary movements of the upper extremities
- EEG: non-convulsive status epilepticus
- Repeat labs & CSF unchanged
- Paraneoplastic antibody panel revealed Anti-NMDA-R antibodies in the serum and CSF
Case: treatment
- Search for a primary tumor: right ovarian teratoma
- Right oophorectomy performed
- Rx: plasma exchange followed by IVIG
- No improvement in neurological status

Case: Outcome
- ICU course complicated by diabetes insipidus, Staph aureus pneumonia, C diff colitis and bacteremia
- 3 months after initial presentation: 3rd degree heart block with hypotension
- Pace maker
- >14 weeks following admission: cardiac arrest → death despite aggressive resuscitation attempts

NMDAR Encephalitis
- Autoimmune disorder characterized by:
  - Neuropsychiatric disturbances
    - changes of mood, behavior, and personality, resembling acute psychosis
  - Progresses to include seizures, decreased level of consciousness, dyskinesias, autonomic instability, and hypoventilation

N-Methyl-D-Aspartate Receptor (NMDAR)
- The NMDA receptor is a glutamate and aspartate receptor found throughout the brain.
- It participates in learning, memory and is responsible, in large part, for the plasticity of the brain.

Historically
- Initially identified in young women with ovarian teratoma who presented with psychosis or memory problems, rapidly progressing to multiple neurological deficits
- 59% had tumor
- Despite severity → patients often recovered after tumor removal and immunotherapy, suggesting an immune-mediated pathogenesis

OVERVIEW
- Frequency: Unclear
- Several features
  - Involvement of relatively young women. (20-50 yrs, median 25.8)
  - Unusual presentation with prominent psychiatric manifestations.
  - Normal or atypical MRI findings.
    - (75% of cases consist of mild, transient T2 of FLAIR abnormalities outside the medial temporal lobes, sometimes with cortical enhancement)
  - Benign appearance of the ovarian tumors. (About 59% of the patients)
  - High prevalence of prodromal viral-like symptoms (part of early immune reaction)
Clinical Presentation

I. Prodromal phase
- Nonspecific cold or viral-like symptoms (fever, fatigue or headache) and, after a mean period of 5 days, developed psycho-behavioral symptoms.

Clinical Presentation

II. Psychotic phase:
Within 2 weeks (mean 6.8 days) of developing symptoms
- Emotional disturbance (apathy, lack of emotion, depression, loneliness, fear)
- Cognitive decline
  - (difficulty in using a cellular phone or passing through an automatic ticket gate)
- Prominent schizophrenia-like symptoms
  - (disorganized thinking, compulsive ideation, delusions, hallucinations, and loss of self-awareness)
- Amnesia (not prominent at onset)
- Strange behavior: staring at their reflection in a mirror with an odd smile

Clinical Presentation

III. Unresponsive phase
- Catatpsy-like symptoms
  - (Mute, akinetic, unresponsive to verbal commands while keeping their eye open)
- Bizarre and inappropriate smiling
- Athetoid dystonic postures, echo phenomenon
  - (mimicking the examiner’s movement)
- Normal Brainstem reflexes, but no eye movement with visual threat

Clinical Presentation

IV. Hyperkinetic phase
- All patients gradually develop orolingual dyskinesias such as lip licking or chewing, and athetoid dystonic postures of the fingers.
- Intractable bizarre orofacial-limb dyskinesias
  - Sustained jaw movements, bruxism, jaw-opening dystonia, grimacing, intermittent ocular deviation or disconjugation, athetoid choreiform movements of the limbs.
  - Varied in speed, distribution, and motor pattern (like psychogenic movement disorder)
- All patients had symptoms of autonomic instability
  - Labile blood pressure, bradycardia or tachycardia, hyperthermia, and diaphoresis.

NMDAR Encephalitis in Children
- 40% of cases <18 years
  - 25% had tumor (all ovarian teratomas)
  - The younger the pt, the less likely a tumor present
- Sx: Behavior and speech problems, seizures, abnormal movements
  - Dysautonomia and hypoventilation are less frequent or severe
- Recognition of psychosis in children is challenging
  - Tantrums, aggression, agitation, speech problems
Clinical Presentation

**V. Gradual recovery phase**

- Typically slow, symptoms may relapse, especially in patient with undetected or recurrent tumors and patients with no associated tumors.
- Duration of the hospital stay: 2-14 month (mean 7 months)
- Spontaneous progressive improvement until recovery
- Characteristic features of patients who recovered from encephalitis
  - Persisting amnesia of the entire process
  - Compatible with disruption of the mechanism of synaptic plasticity, thought to underlie learning and memory

**Antibody Titer**

- Correlation between antibody titers and neurological outcome and by the decrease in number of postsynaptic clusters of NMDA receptors caused by patient’s antibodies
- Reversed by removing the antibodies from the cultures, explaining the potential reversibility of patient’s symptoms

**Diagnosis**

- Characteristic clinical features – psychotic symptoms, pelvic tumor...
- Antibodies to NR1/NR2B heteromers of the NMDAR in the serum and CSF
- Diagnostic Brain Imaging
  - MRI: Less predictable (about 55% has abnormality)
  - SPECT, FDG-PET
- Others: CSF pleocytosis, EEG...
  - EEG: diffuse delta activity without paroxysmal discharges (usually)

**Management**

- Decrease antibody titer: NMDA receptor antagonist
  - SMKI01, Ketamine, Phencyclidine
- Immune modulating therapy
  - Corticosteroids, Plasma exchange, IVIG – rapid & sustained control of the immune response within CNS
- Long lasting dyskinesia: responded to propofol and midazolam
- Conservative management: hypoventilation, autonomic instability
Prognosis

• Better prognosis than most other paraneoplastic encephalitis.
  – Despite the severity of the disorder, 25% of the patients had severe deficits or died.

• Resection of the tumor appeared important to attain final recovery or sustain the improvement that in some cases started soon after immunotherapy (Corticosteroid, Plasma exchange, IVIG).

References

