Encephalitis & Other CNS Infections

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I have no disclosures
• Background
  - Encephalitis
  - California Encephalitis Project (CEP)
  - Diagnostic algorithms-International Encephalitis Consortium

• Case vignettes
  - Highlights of agent-specific findings with focus on diagnostics (rather than Rx)
  - CEP experience and lessons learned, particularly as it relates to diagnostic testing
  - Present variety of cases:
    - some relatively common where diagnostic problems arose and
    - other rare, but important, causes
    - As well as ‘mimickers’

• Wide range of incidence rates depending on country, age-group etc
  - 0.7-13.8/100,000
• Generally higher pediatric population > adults
• Higher in tropical areas > “Western” countries
• Comparable to ‘purulent meningitis’

Jmor F et al., Jour Virol 2008
Granerod J et al., Lancet Infect Dis 2010
Michael BD et al., Epilepsia, 2010
1998-2010
- 20,258 encephalitis-associated hospitalizations/year
- 5.8% fatal
- Total charges in 2010; — 2 billion

Vora NM, Neurology, 2014
Encephalitis

One of the most challenging syndromes for clinicians to diagnose and manage:

• Severity of syndrome with high morbidity/mortality
• Vast number of infectious agents
• Large number of non-infectious mimickers
• Specific pathogen/underlying cause is identified < 50% of cases

About encephalitis

• Not a single disease entity
• Often an uncommon presentation of a common infection
• But sometimes a rare infection
• Lots of misconceptions about diagnostic testing
About management and treatment

**DIAGNOSIS IS KEY**

**Encephalitis - Viral**

- Togavirus: EEE, VEE, WEE
- Flavivirus: SLE, WN, JV, Dengue
- Bunyaviruses: LaCrosse
- Paramyxoviridae: mumps, measles
- Arenaviruses: LCM, Machupo, etc
- Enteroviruses: Polio, coxsacki, etc
- Reoviruses: CTF
- Rhabdovirus: rabies
- Filoviridae: Ebola, Marburg
- Retroviridae: HIV
- Herpes: HSV1/2,VZV,EBV,CMV,HHV6
- Adenovirus
Non-Viral Causes

- Rickettsial
- Bacterial
- Fungal
- Parasites
- Prion

- Non-infectious “mimickers”

With so many pathogens....

Where do you begin?
**California Encephalitis Project (CEP)**

- 1998 – 2011
- Viral and Rickettsial Disease Laboratory, State of CA
- Funding from CDC Emerging Infections Program
- Cases referred from MDs throughout CA
  - Not population-based (e.g., large sampling throughout CA)
  - Biased toward more severe and diagnostically difficult cases
- TN and NY had similar programs

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**Encephalitis Case Definition**

- Hospitalized w/ encephalopathy (depressed or ALOC > 24 hours)
  - AND
- 1 or more of the following:
  - fever (38°C)
  - seizure(s)
  - focal neurological findings
  - CSF pleocytosis
  - EEG findings c/w encephalitis
  - abnormal neuroimaging
- Exclusions: <6 months old or immunocompromised
• Molecular, serologic, isolation
• Multiple specimen types (CSF, sera, respiratory, brain if available)

Core testing:
  ▪ Arboviruses (WNV, SLE, WEE)
  ▪ Herpesviruses (HSV1, HSV2, VZ, EBV, HHV6)
  ▪ Enteroviruses
  ▪ Respiratory viruses (Flu A/B, Paraflu 1-3, adenovirus, HMPV)
  ▪ *Mycoplasma pneumoniae*

• Expanded testing - exposures, clinical symptomatology, laboratory
Approach to the individual patient....

Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium

Background. Encephalitis continues to result in substantial morbidity and mortality worldwide. Advances in diagnosis and management have been limited, in part, by a lack of consensus on case definitions, standardized diagnostic approaches, and priorities for research.

Methods. In March 2012, the International Encephalitis Consortium, a committee begun in 2010 with members worldwide, held a meeting in Atlanta to discuss recent advances in encephalitis and to set priorities for future study.

Very Brief Case Vignettes
Case 1
Young female with fever and somnolence

- 10 year old, previously healthy, white female
  - Admitted with 2 day history fever and upper respiratory illness, increasing lethargy and somnolence
  - Admission exam - inattentive, drooling, and had difficulty finding words
Case 1

- Exposure history:
  - Owns dog and cat
  - Residence in rural area
  - No sick contacts
  - No recent travel

- Admit labs/Neuroimaging
  - LP: WBC = 90 cells/mm³ (75%L, 14%M), Protein = 26 mg/ml, Glucose = 59 mg/ml
  - CT Scan: Left frontal lobe enhancement, mass effect

Case 1

CEP results

- CSF PCR
  - HSV-1, HSV-2: Negative (HSV-1 PCR also negative outside hospital)
  - VZ: Negative
  - Mycoplasma: Negative
  - Enterovirus: Negative

- Serology:
  - Arboviruses/Mycoplasma/Chlamydia/Adenovirus/EBV: Not significant

- Respiratory PCR
  - Influenza A/B, Adenovirus, Mycoplasma, Enterovirus: Negative
**Case 1**

- On HD#3 developed seizures
- EEG: slowing L>R, sharp wave in left parietal
- MRI: multifocal T2 prolongation with patchy enhancement, most pronounced in left temporal lobe
- HD#4 LP repeated:
  - CSF WBC=113 WBC cells/mm³ (83%L)
  - Protein=107 mg/dl, Glucose=57 mg/dl

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**Diagnostic Testing Algorithm**

**Selected Etiology-specific Considerations**

*Herpes Simplex Virus (HSV)*

Case series and studies have shown that HSV polymerase chain reaction (PCR) can be falsely negative, especially among children and early in the disease course [18, 21, 31]. If testing from the first LP is negative and herpes simplex encephalitis (HSE) is still of concern (eg, temporal lobe involvement seen on neuro-imaging), a second LP should be repeated within 3–7 days with CSF sent for HSV PCR [1]. Testing for intrathecal HSV antibodies may complement molecular testing but is not typically useful for acute patient management [32].

Herpes Simplex Encephalitis

- HSV-1 considered to be leading cause of encephalitis
- Acute necrotizing encephalitis
- PCR: considered sensitive and specific

Tunkel AR et al., Clin Inf Dis, 2008

Herpes Simplex Encephalitis
CEP Experience

- CEP: 100 cases --~ 20% had initial PCR negative (biased toward more difficult cases)
- Of those with false negative 1st CSF, CSFs were relatively bland:
  - Initial CSF lab values:
    - Median CSF WBC=17 WBCs/mm³ (range: 0-330)
    - Median CSF Protein=34 mg/dL (range: 22-87)
55 year old male with DM type 1 who was admitted with 3 day history of malaise, weakness, fevers, body aches and upper extremity weakness.

Reports difficulty lifting R arm off of bed and being unable to bend L arm. He also reported severe weakness in bilateral shoulders.

He also reported nausea and poor appetite, but denied vomiting, diarrhea. He also c/o dry cough x several days.
Case 2

• Social History
  — Married with 2 grown children
  — lives with spouse in Central CA
  — No EtOH, Tob, or other drug use

• Exposure History
  — Owns 2 dogs/healthy
  — recent history of mosquito bites
  — No international travel, traveled to Minnesota 3 months prior

• Initial work-up only revealed hyperglycemia, which corrected with insulin. CXR and CT Head were negative

• febrile to 38.5 and started on Ceftriaxone and Levoquin for presumed CAP

• By HD#3 - less coherent (didn’t know his name, where he was) and his weakness progressed
Case 2

Exam
- Febrile 101, rest vital signs wnl
- Incoherent, minimal response to painful stimuli
- Absent reflexes upper extremities, diminished lower extremities
- No grimace to painful stimuli upper extremities, does grimace to painful stimuli lower extremities

Case 2-Laboratory Studies

CSF
RBC 53
WBC 23 (80L, 1Large Lymph, 19M)
Gluc 128 (serum 218)  Prot 75

No oligoclonal Ig Bands detected

MRI unremarkable

Testing at hospital:

CSF PCR for HSV and VZ     : negative
CSF PCR for West Nile       : negative
CSF bacterial culture      : negative
Case 2

• He had respiratory arrest HD #4 and was emergently intubated. CT Chest showed large bilateral R>L infiltrates thought to be secondary to aspiration.

• CEP contacted, request for polio testing

CEP results
• CSF PCR
  ▪ HSV-1, HSV-2: Negative (HSV-1 PCR also negative outside hospital)
  ▪ VZ: Negative
  ▪ Mycoplasma: Negative
  ▪ Enterovirus: Negative

• Serology:
  ▪ West Nile **CSF West Nile IgM +**;
  ▪ **=West Nile Neuroinvasive Disease (WNND)**
  Adenovirus/EBV: Not significant

• Respiratory PCR
  ▪ Influenza A/B, Adenovirus, *Mycoplasma*, Enterovirus: Negative
West Nile Virus

- Flaviviridae (RNA virus)
  - Yellow Fever
  - Dengue
  - St Louis Encephalitis (SLE)
- First identified in Uganda, 1937
- First seen in United States, 1999

West Nile Virus in birds

- birds are primary amplifier hosts
- migratory birds can expand endemic region
- WN isolated from numerous wild birds
  - both wetland and terrestrial species
  - >200 bird species affected
- strain highly infectious for North American birds, causing mortality and high viremia
  - ranges from no clinical signs in some species to over 90% fatality
West Nile Virus transmission cycle

- Mosquito vector
- Incidental infections
- Bird reservoir hosts
- Incidental infections

West Nile Virus—"Classical" Clinical Description

- Incubation period of 2-15 days
- Most illness: "West Nile fever"
  - Self-limited dengue-like illness
  - Fever, headache
  - Rash, lymphadenopathy
  - Nausea, vomiting
- Rarely pancreatitis, hepatitis, myocarditis
Asymptomatic ~20%

"West Nile Fever" <1%

CNS disease ~10% fatal (<0.1% of total infections)

WNV Human Infection “Iceberg”

1 CNS disease case = ~150 total infections

~80% Asymptomatic

West Nile Virus—”Classical” Clinical Description

- Severe neurologic illness categories (WNND)
  - Meningitis
    - Fever, nuchal rigidity, CSF pleocytosis
  - Encephalitis
    - Altered mental status
  - Acute Flaccid Paralysis
    - Polio like syndrome

West Nile leading arbovirus and neurologic illnesses in US
West Nile Virus

Since 1999 in U.S.
- Human cases every state except Hawaii, Alaska and Maine
- Variation year to year, hot spots

- Over 17,000 WNND/over 1500 deaths
- In 2012; 2,873 WNND, 270 deaths
In 2014; 1,283 WNND, 85 deaths

Diagnosis, Treatment and Prevention

Diagnosis
- Serology (CSF IgM) rather than PCR
  [PCR has role immunocompromised host]

Treatment
- Supportive case only
  - No anti-viral for WNV (despite multiple early trials)

Prevention
- Still no vaccine (several under development)
- Avoid mosquito bites
Case 3
43 year old male with viral meningitis vs. CNS fungal

43 year old male

- Presented with one+ week of progressively worsening headache, fever, nausea and vomiting

- Seen in ER, diagnosed (initially) with viral meningitis, told to take fluids
Case 3

- Exposure history
  - S California resident
  - Fire fighter-windy conditions
  - Notes a lot of construction around home recently
  - No foreign travel

- PMH
  - History of splenectomy due to ITP several years prior

Work up

- CSF bacterial Cx: neg
- CSF AFB smears: neg
- CSF fungal smear/Cx: neg
- CSF Enterovirus PCR: neg
- CSF HSV PCR: neg
- CSF N. mening Ag neg
- CSF GBS Ag neg
- CSF S. pneumo Ag neg
- CSF Hib Ag neg
- CSF viral Cx: neg
- Lyme serologies: neg
- CSF Lyme dz PCR neg
- West Nile IgM ELISA neg
- California Encephalitis Project: serum/CSF negative
- Cocci CF/ID neg
- HIV RNA neg
- PPD neg
- CSF cytology negative
Case 3

• ~ 2 weeks later presents again with worsening HA, now febrile 103 and admitted
  — LP WBC 533 WBC (90% mononuclear), glucose 28 and protein 180
  — Several subsequent LPs
• Discharged (on Fluconazole)
• But condition worsened;
  — Last LP (~1 week later)
    • WBC 300 (99% lymphocytes)
    • Protein = 674, Glucose = 42
Biopsy done
~ 6 weeks initial presentation

- Kansagra AP, J Neurosurg, Nov 2008

**Case 3**

- *Balamuthia mandrillaris* testing positive

- Rx with ‘cocktail’ of different Rx with initial improvement but died a few months after initial presentation
Balamuthia mandrillaris

- Found in soil and water
- Worldwide distribution
- Inhalation or direct contamination of skin lesion

- Type of free-living amoeba (living single-celled organisms)
  - Dozen of types of free-living amoeba, few are pathogenic

- Two distinct CNS presentations of free-living amoeba:
  - Fulminant, rapid progressive, fatal encephalitis — *Naegleria fowleri* (diving in brackish water)
  - Granulomatous amoebic encephalitis
    - Acanthoembia sp.,
    - Balamuthia mandrillaris

- Considered to be a rare cause of encephalitis
- 200 + worldwide, 70 in U.S.
Balamuthia mandrillaris

• Subacute to chronic presentation
  - Imaging: ring-enhancing, hydrocephalus, or parenchymal mass
  - Often lymphocytic CSF pleocytosis
  - Insidious onset -- headache, nausea, low-grade fever, lethargy, & confusion

• Can mimic
  - Brain tumor
  - ADEM
  - Mycobacterium tuberculosis
  - Neurocysticercosis
  - Viral encephalitis

18 confirmed cases identified by CEP since 1990:
(possibly additional cases but no brain tissue)

Positive serology often the ‘tip-off’ but brain biopsy needed for confirmation

Demographics
  - Median age = 17 years (1-84 years)
  - 71% Hispanic
  - Is this because of exposure vs. genetic susceptibility vs. ?
  - 88% male
  - Most immunocompetent

Balamuthia mandrillaris
CEP summary and Lessons learned
Balamuthia mandrillis
CEP summary and Lessons learned

- CSF: lymphocytic or neutrophilic predominance, normal-high protein, normal-low glucose
- All had abnormal neuroimaging: ring-enhancing, mass lesions, hydrocephalus
- Exposure/risk factor:
  - Not clear but most with soil exposure such as gardener, construction worker, jeeping/motorcycling in dusty area
- Most died but 2 still living (one lost-to-follow-up)

Diagnostic studies

<table>
<thead>
<tr>
<th>LABORATORY FEATURES</th>
<th>NEUROIMAGING FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated transaminases—Rickettsia serology, tick borne diseases testing³</td>
<td>Frontal lobe—Aeobtia favierii testing (CSF wet mount and PCR³)</td>
</tr>
<tr>
<td>CSF protein &gt;100 mg/dL or CSF glucose &lt;20 peripheral glucose, or lymphocytic pleocytosis with subacute symptom onset—MTB testing³, fungal testing³</td>
<td>Temporal lobe—VZV antibodies (serum and CSF), HSV 67 PCR (CSF)</td>
</tr>
<tr>
<td>CSF protein &gt;100 mg/dL or CSF glucose &lt;20 peripheral glucose and neutrophilic predominance with acute symptom onset and recent antibiotic use—CSF PCR for E. pneumoniæa and N. meningitidis</td>
<td>Basal ganglia and/ or thalamus—Adenovirus¹ testing, MTB testing³</td>
</tr>
<tr>
<td>CSF eosinophilia—MTB testing³, fungal testing³, Batrachochytrium dendrobatidum antibody (serum), A. cantonensis and G. hominis sp. testing³</td>
<td>Brainstem—Adenovirus testing³, Listeria PCR if available, Brucella antibody (serum), MTB testing³</td>
</tr>
<tr>
<td>RBCs in CSF—Aeobtia favierii testing³</td>
<td>Cerebellum—EBV PCR (CSF) and serology</td>
</tr>
<tr>
<td>Hyporexia—anti-VGDC antibody (serum), MTB testing³</td>
<td>Diffuse cerebral edema—Respiratory virus testing³</td>
</tr>
<tr>
<td></td>
<td>Space occupying and/ or ring-enhancing lesions—MTB testing³, fungal testing³, Balamuthia mandrillis and A. cantonensis testing³</td>
</tr>
<tr>
<td></td>
<td>Toxoplasma serology</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus and/ or basal meningal enhancement—MTB testing³, fungal testing³</td>
</tr>
</tbody>
</table>

Testing and Treatment

Consult with CDC National Center for Emerging and Zoonotic Infectious Diseases Waterborne Disease Prevention Branch, CDC

(or if in California, consult with California State Health Dept)

• Testing

Brain material for IHC and molecular (serology can be helpful as well)

• Treatment recommendations
  ▪ Combination of Sulfadiazine, Flucytosine, Azole, Azithromycin and Pentamidine
  ▪ CEP cases survivors

Not so rare after all....two recent transplant clusters in U.S.
Case 4
..just one more reason to be crazy..
Young Asian female with fever, confusion, tremors

22 y/o Asian female,
• Admitted to psychiatric unit for odd behavior, “completely out of her mind”
• Abnormal movements
• High heart rate, hypotension

•California Encephalitis Project contacted because clinicians were concerned about rabies
**The workup before referral**

- CSF PCR
  - HSV 1&2 (-)
  - VZV (-)
  - HHV6 (-)
  - Enterovirus (-)
- Parvo B19 DNA (-)
  - IgG 5.3 IgM <0.1
- West Nile (-)
- HIV-1 PCR <50
- CMV IgG (+), IgM (-)
- EBV IgM <0.90, IgG 3.27
- VRDL NR
- Strongyloides Ab 0.29
- Schistosoma Ab 0.0
- G. lamblia Ag (-)
- Tropheryma whippelii (-)
- Bartonella panel (-)
- Cryptococcus (-)
- C. immitis (-)
- RPR NR
- Hbc IgM NR
- HBV DNA <40
- Hbc Ab (+)
- HCV Ab NR
- HAV IgG (+)
- Mumps Ab (+)

**Workup of case - continued...**

- Rickettsia panel IFA
  - Typhus IgG (-)
  - RMS IgG (-)
  - E. chaffeensis IgG (-)
  - A. phagocytophilia IgG (-)
  - Q fever phase I and II IgG (-)
- Arbo Panel pending
- M. pneu mo IgM 307, IgG 1.24
- H. capsulatum Ab <8
- pANCA (-)
- cANCA (-)
- Heavy metal screen (WNL)
- β-HCG (-)
- α-fetoprotein 1.5
- VGCC Ab
- Pemphigus Ab Screen
- ANNA titers
- GAD 65 Ab <0.5
- Neuroimm
- Thyroid Peroxidase Ab <10
- TSH 2.93 T4 1.65
- DS DNA Ab (-)
- ANA (-)
**CEP contacted**

- **Suggested:**
  - Anti-N-methyl-D-aspartate receptor (anti-NMDAR) testing
  - Abdominal/pelvic ultrasound

- **Results:**
  - U/S – teratoma
  - Antibody positive for anti-NMDAR antibody

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### Diagnostic studies

**CONDITIONAL STUDIES**

- **HOST FACTORS:**
  - Immunocompromised—CMV PCR, HHV-6 PCR, HIV PCR (CSF), Toxoplasma gondii serology and/or PCR; MTB testing; fungal testing; WNV testing

- **GEOGRAPHIC FACTORS:**
  - Africa—malaria blood smear, typhoid fever blood/CNS CSF, serology from serum and CSF; dengue testing
  - Asia—Japanese encephalitis virus testing, dengue testing; malaria (blood smear); hantavirus testing (serology from serum and CSF; PCR, immunohistochemistry, and virus isolation in a BSL-4 lab can also be used to substantiate diagnosis)
  - Australia–Malaysia: TBE encephalitis virus testing, Kunjin virus testing, Australian Bat Lyssavirus (ABLV) testing
  - Europe—Tick-borne encephalitis virus testing if Southern Europe, consider WNV testing, Toscana virus testing
  - Central and South America—dengue testing; malaria (blood smear); WNV, Venezuelan encephalitis testing
  - North America—Geographically appropriate arboviral testing (eg, WNV, Powassan, LaCrosse, Eastern Equine Encephalitis viruses, Lyme (serum ELISA and Western blot)

- **SEASON AND EXPOSURE:**
  - Summer fever, Afebrile and tick-borne disease testing
  - Cat (particularly if with seizures, paraneoplastic CSF)—Bartonella antibody (serum, CSF), ophtalmologic evaluation
  - Tick exposure—tick borne disease testing
  - Animal bite/bite exposure—rabies testing
  - Swimming or diving in water—Aeromonas species (serum, CSF) wet mount and PCR

**SPECIFIC ILLNESS AND SYMPTOMS**

- Psychotic features or movement disorder—anti-NMDAR antibody (serum, CSF); rabies testing; CSF screen for malignancy, Creutzfeldt-Jakob disease
- Pronounced disturbance in affect or behavior—anti-NMDAR antibodies; MTB PCR CSF; screen for malignancy
- Rapid deterioration, particularly with mental status change or prior travel to tick-endemic areas—rabies testing
- Respiratory symptoms—Mycoplasma pneumoniae serology and throat PCR (if either positive, then do CSF PCR); respiratory virus testing
- Acute flaccid paralysis—Arbovirus testing; rabies testing
- Parkinsonism—Arbovirus testing; Toxoplasma serology
- Unexplained skin lesions—Bakerella micans; Acanthamoeba testing

Anti-NMDAR encephalitis

- Initially recognized ~ 8 years ago in young Asian females, often with teratoma
- Initially considered a ‘paraneoplastic syndrome’
- Immune form of encephalitis
- Some have teratomas, but the young children and males generally do not

Comparison to Viral Agents
CEP data (2007-2011)

< 30 years of age

- Gable M et al, CID, 2012
August 2012 — 29 y/o male with acute flaccid paralysis
— Unvaccinated
— No history of international travel
— Physician requested polio testing
And then

- Within 2 weeks
  - 2 additional reports of AFP with anterior horn myelitis of unknown etiology
- Extensive testing at VRDL
  - All negative
- Alerts posted via CDPH communications to local health departments in California
  - Dec 2012, July 2013 and Feb 2014 asking LHDs to submit cases that met definition

AFP causes

**Infectious**
- Poliomyelitis-like syndrome

**Post-infectious/inflammatory**
- GBS (axonal motor subtype)
- Transverse myelitis

**Vascular**
- Spinal AVF, anterior spinal artery stroke

**Toxin**
- Diphtheria polyneuropathy
- Botulism
**AFP/anterior horn**

**FIGURE 1.** Algorithm for the evaluation of patients with limb or respiratory weakness. NMU, neuromuscular junction; CK, creatine kinase; AMAN, acute motor axonal neuropathy; AIIDP, acute inflammatory demyelinating polyneuropathy; ICU, intensive care unit.

Epidemiol Rev Vol. 22, No. 2, 2000
Data on AFP

- AFP is not reportable per se so data are limited
- In countries that monitor AFP
  - 1/100,000 (ALL Causes)

IS THIS REALLY THAT UNUSUAL...?
Data from California study

Zangwill K, Ped Neurology, 2010

What they looked for

Table 1. Clinical diagnoses and International Classification of Diseases-9 codes used for screening of computerized diagnoses data to detect potential cases of acute flaccid paralysis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-9 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Flaccid Paralysis</td>
<td>335.29, 335.8, 335.9, 336.9</td>
</tr>
<tr>
<td>Multiple-sclerosis-debilitating disease</td>
<td>340, 341</td>
</tr>
<tr>
<td>Nervous system diseases: related, solubilizable, nonautoimmune, noninfectious cerebral palsy</td>
<td>342, 343.4, 343.8</td>
</tr>
<tr>
<td>Other paralysis, ataxia, quadriplegia, no. specified</td>
<td>344</td>
</tr>
<tr>
<td>Unspecified disorders of the nervous system</td>
<td>340.9</td>
</tr>
<tr>
<td>Cerebral atrophy, encephalopathy, and related lesions</td>
<td>346, 351, 362, 383</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>356, 355</td>
</tr>
<tr>
<td>Peripheral neurosensory neuropathy, including sensory, motor, and mixed neuropathy</td>
<td>356</td>
</tr>
<tr>
<td>Inflammatory and toxic neuropathy</td>
<td>357.9</td>
</tr>
<tr>
<td>Myasthenia gravis, other myasthenic conditions</td>
<td>358, 358.8</td>
</tr>
<tr>
<td>Muscular dystrophy, channelopathies, and other myopathies</td>
<td>359</td>
</tr>
<tr>
<td>Acute encephalomyelitis</td>
<td>366</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>365.3, 710.4, 729.1</td>
</tr>
<tr>
<td>Dementia, cerebral atrophy, and related neurodegenerative disorders</td>
<td>722.9, 723.4, 724.4, 729.2</td>
</tr>
<tr>
<td>Infective encephalopathy, cerebrospinal fluid, and lymphoid tissue</td>
<td>722.4</td>
</tr>
<tr>
<td>Trauma of spinal cord, nerve plexuses, peripheral nerves</td>
<td>850.5-857.9</td>
</tr>
<tr>
<td>Other peripheral nerve disorders</td>
<td>858.5-859.1</td>
</tr>
</tbody>
</table>

Zangwill K, Ped Neurology, 2010
• Study within Kaiser population (1992-1998) identified
  - 1.4/100,000 in pediatric population (suggesting 800-900 cases/year in US)
  - Included GBS, Botulism, Stroke, Myasthenia gravis and transverse myelitis
  - However NONE were “anterior horn cell” disease

» Zangwill K, Ped Neurology, 2010

Was this above baseline?

No way to know, but we thought it was suspicious
Additional case finding

- Call for cases through our regular communications with Local Health Departments

<table>
<thead>
<tr>
<th>Acute flaccid paralysis, including absent or significantly diminished reflexes in one or more limbs AND</th>
</tr>
</thead>
<tbody>
<tr>
<td>o MRI showing grey matter involvement of the spinal cord OR</td>
</tr>
<tr>
<td>o EMG showing anterior horn cell disease</td>
</tr>
<tr>
<td>o With or without accompanying mental status changes</td>
</tr>
<tr>
<td>o Without a confirmed traumatic, neoplastic, arboviral, or vascular etiology</td>
</tr>
</tbody>
</table>

Testing

- Extensive infectious disease testing
  - Arboviruses
  - Adenoviruses
  - Enteroviruses
  - Parechoviruses
  - Other respiratory viruses
  - Mycoplasma pneumonia
Our first hypothesis

• Enterovirus
  ▪ Likely EV71

Enterovirus 71 aka "the new polio"

• Outbreaks in Asian countries
  ▪ Malaysia, 1997
  ▪ Taiwan, 1998
  ▪ China, 2008
• Many AFP cases
• Often with concurrent HFMD
• Sporadic cases in the U.S.
However

- Extensive EV testing
  - Very few EV positives
  - No EV71
- However we did have a few EV-D68...
  - EV-D68 is a cause of respiratory illnesses
- What did this mean?

Enteroviruses
What do we know about EV-D68 and AFP?

A Fatal Central Nervous System Enterovirus 68 Infection

John D. Kreuter, MD, MPH, N飞翔, MD, Joseph L. McCarty, MD, Joseph T. Schaffzin, MD, and Steven Colier, MD, RN

Case Report

• And an additional case reported through national surveillance

Kreuter JD, Arch Path Lab Med, 2011
CDC, Enterovirus surveillance, MMWR, 2006

Would we ever sort this out?....
Several reports from some of these same states...

Polio-like illness causing mystery paralysis in Colorado kids

Polio-like symptoms found in three Kansas City children

Polio-Like Cases in Massachusetts Similar To Colorado Cases

Update doctors wonder if enterovirus-D68 caused limb weakness in two children

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Centers for Disease Control and Prevention

MMWR Early Release

Vol. 63, Early Release

October 3, 2014

Morbidity and Mortality Weekly Report (MMWR)

Acute Neurologic Illness of Unknown Etiology in Children — Colorado, August-September 2014

Early Release

On September 12, 2014, CDC was notified by the Colorado Department of Public Health and Environment of a cluster of five children evaluated at Children’s Hospital Colorado with acute neurologic illness characterized by upper respiratory symptoms, including upper respiratory symptoms, occurring 2-16 days (median = 7 days) before onset of neurologic illness. Seven of eight patients with magnetic resonance imaging of the spinal cord had nonenhancing lesions of the gray matter of the spinal cord spanning multiple levels, and seven of nine with magnetic resonance imaging of the brain had nonenhancing brainstem lesions (most commonly the dorsal pons). Two of five with magnetic resonance imaging of the lumbar spinal region had gadolinium enhancement of the ventral nerve roots of the cauda equina. Eight children were up to date on polio vaccination. Eight have not yet fully recovered neurologically.
35 cases Calif

- Median age 9 years (range 0.4-73 years)/mostly pediatrics but 25% adults
- 54% female
- Pre-existing condition:
  - None 51%
  - Asthma 17%
- ~same as California population
- Diverse geographic areas of the State
Summary
n=35

- 91% with respiratory or GI prodrome
- Ventilator: 43%, several were still on ventilator at time of discharge
- Hospital stays, median =17 days (some >>100 days)

If this was really all EVD68

- Why weren’t more of our specimens positive?
  - Very few respiratory samples collected within one week of respiratory symptom onset
  - And perhaps we should re-think our ‘paradigm’ for EV detection for this particular EV
  - Not necessarily high yield in stool
The personal side

34 states

• Herpes simplex virus
  — Leading cause of sporadic encephalitis
  — Example of uncommon presentation of a common infection
  — PCR is good but not perfect

• West Nile virus
  — Recently emerging virus in the US, now leading arboviral encephalitis
  — Serology is generally best for diagnosis

• Balamuthia mandrillis
  ▪ Although not common, probably not so rare
  ▪ Consider testing in patients with parenchymal lesions especially if CSF profile "MTB/fungal-ish"
  ▪ Example of rare

• Rabies
  ▪ Should be considered in any rapidly progressive encephalitis
  ▪ Probably also being missed
Summary

- Anti-NMDAR encephalitis
  - The leading entity in CEP, consider in patients with movement disorders, seizures and/or autonomic instability
- Polio-like illness
  - We still have a lot of work to do-likely related to EVD-68 but don’t know mechanism and more important don’t know what to do about it!

What are we missing?—probably a combination of...

- Missed diagnosis of relatively common known agent (e.g. HSV or EV)
- Rare disease not considered (e.g., Balamuthia)
- Non-infectious mimicker (e.g., anti-NMDAR)
- Novel agent/entity not yet discovered (e.g. new virus)
THE END

Diagnostic Algorithm

CEP input + Lessons learned

Similar projects + Other international experts

Diagnostic Algorithm
Approach to the individual patient...

Clinical Infectious Diseases Advance Access published August 6, 2013

Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium


Background. Encephalitis continues to result in substantial morbidity and mortality worldwide. Advances in diagnosis and management have been limited, in part, by a lack of consensus on case definitions, standardized diagnostic approaches, and priorities for research.

Methods. In March 2012, the International Encephalitis Consortium, a committee began in 2010 with members worldwide, held a meeting in Atlanta to discuss recent advances in encephalitis and to set priorities for future study.

Diagnostic algorithm

(Adults)

<table>
<thead>
<tr>
<th>ROUTINE STUDIES</th>
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<tbody>
<tr>
<td>CSF</td>
<td>Collect at least 20 cc fluid, if possible; freeze at least 5-10 cc fluid, if possible. Opening pressure, WBC count with differential, RBC count, protein, glucose.</td>
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<tr>
<td>Gram stain and bacterial culture</td>
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<tr>
<td>HSV-1/2 PCR (if test available, consider HSV CSF IgG and IgM in addition).</td>
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<tr>
<td>CMV PCR (sensitivity may be low; if test available, consider CMV CSF IgG and IgM in addition).</td>
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<tr>
<td>Enterovirus PCR</td>
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<tr>
<td>Cryptococcal antigen and/or India ink staining</td>
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<tr>
<td>CSF pleocytosis and IgG index</td>
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<tr>
<td>VDRL</td>
<td></td>
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<tr>
<td>SERUM</td>
<td></td>
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<tr>
<td>Routine blood cultures</td>
<td></td>
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<tr>
<td>HIV serology (consider RNA)</td>
<td></td>
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<tr>
<td>Treponemal testing (RPR, specific treponemal test)</td>
<td></td>
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<tr>
<td>Hold acute serum and collect convalescent serum 10-14 d later for paired antibody testing</td>
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<tr>
<td>IMAGING</td>
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<tr>
<td>Neuroimaging (MRI preferred to CT, if available)</td>
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<tr>
<td>Chest imaging (Chest x-ray and/or CT)</td>
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<tr>
<td>NEUROPHYSIOLOGY</td>
<td></td>
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<tr>
<td>EEG</td>
<td></td>
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<tr>
<td>OTHER TISSUES/FLUIDS</td>
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</table>

When clinical features of extra-CNS involvement are present, we recommend additional testing (eg, biopsy of skin lesions; bronchoalveolar lavage and/or endobronchial biopsy in those with pneumonic/pulmonary lesions; throat swab PCR culture in those with upper respiratory illness; sputal culture in those with dermatitis); also see below.

Diagnostic studies

**CONDITIONAL STUDIES**

**HOST FACTORS**
- Immune compromised—CMV PCR, HHV6/7 PCR, HHV6 PCR (CSF), Toxoplasma gondii serology and/or PCR, MTB testing; fungal testing; - VNN testing

**GEOGRAPHIC FACTORS**
- Africa—malaria (blood smear), typhus/typhoid (blood), dengue (virus testing), malaria (blood smear), HIV virus testing (serology from serum and CSF), MTB PCR, immunohistochemistry, and virus isolation in a BSL4 lab can also be used to substantiate diagnosis
- Asia—Japanese encephalitis virus testing, dengue testing, malaria (blood smear), dengue virus testing (serology from serum and CSF), PCR, immunohistochemistry, and virus isolation in a BSL4 lab can also be used to substantiate diagnosis
- Australia—African trypanosomiasis testing, dengue virus testing
- Europe—Tick-borne encephalitis virus testing, If Southern Europe, consider WNV testing, Toscana virus testing, dengue virus testing
- Central and South America—dengue testing, malaria (blood smear), WNV, Venezuelan equine encephalitis testing
- North America—Geographically appropriate arboviral testing (eg, WNV, Powassan, LaCrosse, Eastern Equine Encephalitis viruses), Lyme disease (serum ELSA and Western blot)

**SEASON AND EXPOSURE**
- Summer/fall—Arbovirus* and tick-borne disease* testing
- Cat (particularly if with fleas, psoroptes catum CSF—Bartonella antibody (serum), ophthalmologic evaluation
- Tick exposure—tick borne disease testing
- Animal bite/exposure—rabies testing
- Swimming/exposure in warm freshwater or near marine incursion—Neoglena flexilis (CSF, wet mount and POCs)

**SPECIFIC SIGNS AND SYMPTOMS**
- Psychotic features or movement disorder—anti-NMDAR antibody (serum, CSF); rabies testing*; screen for malignancy, Creutzfeldt-Jakob disease
- Prominent limbic symptoms—Autoimmune limbic encephalitis testing, HHV6/7 PCR (CSF); screen for malignancy
- Rapid decomposition (earliest with animal bite history or prior travel to rabies-endemic areas)—rabies testing*.
- Respiratory symptoms—Mycoplasma pneumoniae serology and throat PCR (if either positive, then do CSF PCR); respiratory virus testing
- Acute flaccid paralysis—Arbovirus testing*; rabies testing*
- Paraneoplastic—Arbovirus testing*; Toxoplasma serology
- Neurological skin lesions—Balantidium mandrillaris; Acanthamoeba testing

**LABORATORY FEATURES**
- Elevated transaminases—Rickettsia serology, tick borne diseases testing
- CSF protein > 100 mg/dL, or CSF glucose < 30 mg/dL, or lymphocytic pleocytosis with subacute symptom onset—MTB testing, fungal testing
- CSF protein > 100 mg/dL, or CSF glucose < 30 mg/dL, or lymphocytic pleocytosis with acute symptom onset and recent antibiotic use—MTB PCR for S. pneumoniae and N. meningitidis
- CSF eosinophilia—MTB testing, fungal testing, Baylisascaris procyonoides antibody (serum); Angiostrongyulus cantonensis and Gnathostoma sp. testing
- RBCs in CSF—Neoglena flexilis testing
- Hypofibrinogenemia—anti-VGKC antibody (serum); MTB testing

**NEUROMAGING FEATURES**
- Frontal lobe—Neoglena flexilis testing (CSF wet mount and POCs)
- Temporal lobe—VGKC antibodies (serum and CSF); HHV 6, 7 PCR (CSF)
- Basal ganglia and/or thalamus—Arbovirus* testing; MTB testing
- Brainstem—Arbovirus testing*; Listeria PCR/RFLP available, Brucella antibody (serum); MTB testing
- Cerebellum—EBV PCR (CSF) and serology
- Diffuse cerebral edema—Respiratory virus testing
- Space occupying and/or ring-enhancing lesions—MTB testing, fungal testing, Balantidium mandrillaris and Acanthamoeba testing, Toxoplasma serology
- Hydrocephalus and/or basal meningeal enhancement—MTB testing, fungal testing, respiratory virus testing

Figure. Approach to management of patients with suspected encephalitis

   - Consider ICU admission

2. Initiate diagnostic evaluation
   - No evidence of encephalitis
   - Suggestive of encephalitis
   - Alternate diagnosis confirmed?

3. Acyclovir +/- antiviral
   - Yes: Closely monitor mental status
   - No: Repeat diagnostic evaluation in 24-48 hours

4. Decrease or altered level of consciousness?
   - Yes: Evaluate for seizures and status epilepticus
   - No: Evaluate for other causes of encephalopathy

5. Rapidly progressing?
   - Yes: Treat seizures and status epilepticus
   - No: Medical management

6. Evidence for cerebral edema?
   - Yes: Medical management, ICP Monitoring/Wentz Monitor
   - No: If refractory cerebral edema, consider further neurosurgical intervention i.e. hemicraniectomy, lobectomy

7. Evidence of ongoing inflammation or deterioration: brain biopsy
   - Yes: Provide adequate ventilatory and hemodynamic support
   - No: Continuous EEG monitoring

8. HSIV/VZV confirmed: Continue acyclovir
   - Other infections: Identify and treat with appropriate antimicrobial
   - Autimmune encephalitis confirmed: Immunosuppression
   - Unknown etiology: Obtain further history, consider empiric immnosuppression
   - Evidence of ongoing inflammation or deterioration: brain biopsy

Agents Identified in CEP

- Respiratory Viruses: 10%
- HSV 6%
- VZV 6%
- West Nile Virus 5%
- HSVI 11%
- Enterovirus 11%
- EBV 10%
- RSV 5%
- Herpesvirus 5%
- Micovirus 10%
- Chlamydia 1%
- Chagas 1%
- Influenza 1%
- Measles 1%
- Mumps 1%
- HPV 1%
- Rhinovirus 1%

Excludes <5% each of Acute HIV, ARS, Bartonella, Babesia, Cryptococcus, Cytomegalovirus, Hepatitis B, and Epstein-Barr, Pneumonia, Others, and Infections with <5% contamination with these agents.
Specimens

- CSF
- Acute serum
- Respiratory sample (NP/throat swab)
- Convalescent serum (10-14 days > acute serum)
- Brain tissue if available

Case 2

T37.1; HR 102 BP 107/62; RR 18 AC PEEP 5 Fi02 0.70 O2 sat 98%

Gen Does not open eyes to voice or painful stimuli
HEENT mmm, ETT in place
C/V RRR nl SLS2. No m/r/g
Pulm coarse BS bilaterally
Abd soft, NT, ND, NABS

Neurologic

  Cranial Nerves: PERRL, has roving eye movements and fine horizontal nystagmus with gaze fixation, normal corneal reflexes, symmetric grimace, weak cough/gag
  Motor: nl tone, normal bulk
  UE (R/L): no movement of upper extremities with painful stimulus
  LE (R/L): purposeful withdrawal of legs to painful stimulus
  Reflexes (R/L): biceps 0/0, triceps 0/0, brachioradialis 0/0, patellars 2+/2+, AJs 2+/2+; plantars flexor bilateral.
  Sensation: no grimace to painful stimuli in upper extremities, does grimace to painful stimuli in the lower extremities.
### Neurologic features (n=35)

<table>
<thead>
<tr>
<th>Neurologic Symptoms</th>
<th>Total or Median (N=35)</th>
<th>% or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache at onset of neurologic symptoms</td>
<td>19</td>
<td>54</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>14</td>
<td>40%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12</td>
<td>34%</td>
</tr>
<tr>
<td>Pain or paresthesia of limbs</td>
<td>23</td>
<td>66%</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>10</td>
<td>29%</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>Limb weakness or paralysis</td>
<td>35</td>
<td>100%</td>
</tr>
<tr>
<td>1 limb affected</td>
<td>5</td>
<td>14%</td>
</tr>
<tr>
<td>2 or 3 limbs affected</td>
<td>14</td>
<td>40%</td>
</tr>
<tr>
<td>4 limbs affected</td>
<td>16</td>
<td>46%</td>
</tr>
<tr>
<td>Upper limb/s affected</td>
<td>26</td>
<td>74%</td>
</tr>
<tr>
<td>Any documented sensory involvement</td>
<td>12</td>
<td>34%</td>
</tr>
<tr>
<td>Intubated</td>
<td>15</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Laboratory features (n=35)

<table>
<thead>
<tr>
<th>Diagnostic studies</th>
<th>Total or Median</th>
<th>% or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF pleocytosis (WBC &gt; 5 cells/μL)</td>
<td>26</td>
<td>74%</td>
</tr>
<tr>
<td>Median CSF WBC from first LP</td>
<td>49</td>
<td>0-455</td>
</tr>
<tr>
<td>CSF hyperproteinemia (&gt;45 mg/dL)</td>
<td>14</td>
<td>40%</td>
</tr>
<tr>
<td>Median CSF protein from first LP</td>
<td>38</td>
<td>13-234</td>
</tr>
<tr>
<td>Pathogenic virus isolated (n=31)</td>
<td>8</td>
<td>26%</td>
</tr>
<tr>
<td>Enterovirus D68</td>
<td>6</td>
<td>26%</td>
</tr>
<tr>
<td>Coxsackie virus A16</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Coxsackie virus B3</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Enterovirus, untyped</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>
# Neuroimaging & Motor Recovery

<table>
<thead>
<tr>
<th>Neuroimaging &amp; Neurophysiology</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 lesion of central gray matter of spine</td>
<td>33</td>
<td>94%</td>
</tr>
<tr>
<td>Lesion &gt;3 vertebral lengths</td>
<td>30</td>
<td>94%</td>
</tr>
<tr>
<td>Nerve root enhancement on MRI</td>
<td>9</td>
<td>26%</td>
</tr>
<tr>
<td>Supratentorial lesions on brain MRI (n=31)</td>
<td>10</td>
<td>32%</td>
</tr>
<tr>
<td>Patients with EMG report available</td>
<td>12</td>
<td>34%</td>
</tr>
</tbody>
</table>

## Motor Recovery

| Flaccid weakness at > 30days (n=16)                                 | 15    | 94%        |
| Flaccid weakness at > 1 year (n=10)                                 | 9     | 90%        |