Encephalitis & Other CNS Infections

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I HAVE NOTHING TO DISCLOSE

Outline
- 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'

Epidemiology
- 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

“Incidences” of Encephalitis and Bacterial Meningitis*

Burden of disease in U.S.
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

Encephalitis - Viral

- Togavirus: EEE, VEE, WEE
- Flavivirus: SLE, WN, JV, Dengue
- Bunyaviruses: LaCrosse, La Crosse
- 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”

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
Encephalitis Case Definition

- Hospitalized with 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

CEP Testing Algorithm

- 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)
- Expanded testing - exposures, clinical symptomatology, laboratory

Specimens

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

Diagnostic Algorithm

- CEP input
- Lessons learned
- Similar projects
- Other international experts

Approach to the individual patient....

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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 “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

Case 1

- CSF PCR HSV-1 repeated on 2nd CSF:
  - Hospital lab: Positive HSV-1
  - VRDL: Positive HSV-1
- Diagnosis: Herpes Simplex Encephalitis (HSE)
**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

**CEP Experience & Lessons Learned**

- CEP: 80 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)

**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 neuroimaging), 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].


**Case 2**

- 70 year old male with rapidly progressive dementia

**Case 2**

- 70 year old Asian male presented with rapidly progressive dementia
- Clinical course over last few weeks—forgetfulness, tremors, and fevers
- LP#1; 12 WBC cells/mm³ Pr=137 mg/dL, G=52 mg/dL
- MRI; multiple focal lesions in temporal and parietal lobes

- CSF PCRs; negative for HSV 1/2, varicella, enterovirus
- Serology; negative for WNV, SLE, WEE, adenovirus, parvovirus
- Respiratory PCRs: negative for enterovirus, Mycoplasma pneumonia, adenovirus, RSV
Conclusions ...unlikely infectious.....CEP testing completed.........(we thought...)
—Hospital contacted us to tell us...

Brain biopsy: “florid meningoencephalitis…”

Paraffin blocks sent to CEP;
• special extraction method from paraffin blocks, positive by PCR detection for enterovirus (EV)

Also sent to Centers for Disease Control
• Positive for enterovirus (EV) -- IHC AND PCR positive

Enterovirus Encephalitis
CEP Experience & Lessons Learned
• Leading cause of viral meningitis
• Role in encephalitis was previously unknown
• CEP ~ 4% of all cases (>100 confirmed cases)
• Median age = 11.0 years (mean=20.5 yrs)
• Tend to be less severe > other types however 32% ICU admission, 5% died
• 65% pediatric, 35% adult

CSF EV PCR good, but...not perfect
• Important to examine for enterovirus in multiple specimens:
  • Brain biopsy if possible
  • Throat/Nasopharyngeal
  • Stool
• ~60 additional cases considered probable or possible -- CSF EV PCR negative but positive in respiratory and/or stool
• Suspect we are missing EV cases due to unsuitable or incomplete specimens

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 S. pneumonia 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

**Case 3**

Biopsy done ~ 6 weeks initial presentation
**Balamuthia mandrillaris**

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

**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

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**Balamuthia mandrillaris**

- 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 — Acanthamoeba sp., Balamuthia mandrillaris
- Considered to be a rare cause of encephalitis

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**Balamuthia mandrillaris**

- 17 confirmed cases identified by CEP since 1990: (probably 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
  - 88% male
  - Most immunocompetent

**Balamuthia mandrillaris**

- 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)
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

CDC website

Not so rare after all...two recent transplant clusters in U.S.

Case 4

16 year old male with sore throat and not eating

Case 4

16 y/o male from Mexico

- Brought by family to ER in Southern California
- Sore throat and loss of appetite
- In ER
  - Temp 100.6 and tachycardia
  - Awake and alert but agitated and crying
  - Given IV fluids and discharged with diagnosis of pharyngitis and abdominal pain

Case 4

Several hours later..presented to same ED

- Nausea, vomiting, fever and sore throat
- Agitated and uncooperative
- Refused to take fluids, noted to be spitting frequently
- Given IV fluids
- Discharged ;
  - Diagnosis: Viral pharyngitis, depression and anorexia
  - also Psych evaluation recommended

Case 4

Following day

- vomiting and shaking and collapsed
- 911 called
- Paramedics arrived, resuscitation efforts unsuccessful
Case 4

- Exposure history:
  - Had recently arrived to California from Mexico, at the time of death no animal bites known
  - Rabies testing done, positive on brain,
  - Rabies virus identified as variant most closely related to Mexican free-tailed bat variant
  - Family then interviewed and two potential bite prior bite exposures

Rabies

- Causes a severe acute progressive encephalitis
- "most deadly virus"
- Latin for: to “be mad”/"madness"
- Worldwide importance as cause of encephalitis and also the “quintessential” zoonosis—discussed further in Zoonoses lecture

Epidemiology

- Only 1-2 recognized cases/year in the United States...so why is it so important?
  - Many encephalitis cases are ‘rule out’ rabies ...on the other hand, cases are missed
  - World: 50,000-100,000 cases/year

Bites from bats may be overlooked

Jackson A, Lancet, 2001

CEP Summary & Lessons Learned

- 7 cases identified
  - Median age = 39 years [8-72]
  - 86% male
  - 6 fatal
  - "imported" vs acquired in U.S. cases

Case 5

19 year old college student with fever and double vision
Case 5

- URI illness approximately 2 weeks pta
- Then developed fever, headache, double vision, vomiting and body aches, wax and waning course
- Seen in urgent care
- Returned with severe headache, difficulty concentrating and diplopia

Admitted to hospital
- LP
  - 290 WBCs (75% PMNs), Glucose 20 and Protein 171
  - Bacterial cultures (CSF and blood negative)
  - No pre-treatment
  - Brain MRI shows diffuse cerebral edema

Case 5

- CEP contacted because of concerns of encephalitis
- Routed specimens for bacterial PCR and Free-living amoeba testing

Bacterial meningitis

- Neisseria meningitidis
- Leading cause of bacterial meningitis:

Neisseria meningitidis

- Produces a polysaccharide capsule which is basis of serogroup typing
  - At least 13 serogroups have been identified
- Majority of disease worldwide is due to serogroups A, B, C, Y, and W135
- Serogroups B, C and Y most common in U.S.
- Currently no vaccine for serogroup B licensed for use in most countries (there are strain specific serogroup B vaccines in New Zealand and Cuba)
Meningococcal Disease

- ~10% colonization rate, transmitted human-to-human through direct contact/inhalation of respiratory secretions
- Incubation period 1-10 days (usually <4 days)
- Even with proper treatment, may progress rapidly and result in death
- Causes substantial morbidity: 10-20% survivors have sequelae (neurologic disability, limb loss, hearing loss)
- Outbreaks are rare but do occasionally occur

Bacterial meningitis
CEP Summary & Lessons Learned

Not common but can ‘mimic’ encephalitis
- Neisseria meningitidis (6)
- Strep pneumoniae (5)
- miscellaneous (8)

Case 6

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. phagocytophila IgG (-)
  - Q fever phase I and II IgG (-)
- Arbo Panel pending
- M. pneumonia IgM 307, IgG 1.24
- H. capsulatum Ab <8
- pANCA (-)
- cANCA (-)
- Heavy metal screen (WNL)
- B-HCG (-)
- a-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

**Anti-NMDAR encephalitis**

- Initially recognized ~ 5 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

**Summary**

**Common infections (with rare presentation)**

- Herpes simplex:
  - Limitations of CSF PCR testing, consider re-tap if temporal lobe involvement
- Enterovirus
  - Another leading cause of encephalitis
  - More often in pediatrics but still important in adults
  - Multiple specimen types needed to optimize yield

**Rare infections**

- *Balamuthia mandrillis*
  - Although not common, probably not so rare
  - Consider testing in patients with parenchymal lesions especially if CSF profile “MTB/fungal-ish”
- *Rabies*
  - Should be considered in any rapidly progressive encephalitis
  - Probably also being missed
Summary

Encephalitis mimickers

- Bacterial meningitis
  - If CSF profile looks bacterial & bacterial culture negative; role for PCR in these cases

- Anti-NMDAR encephalitis
  - The leading entity in CEP, consider in patients with movement disorders, seizures and/or autonomic instability

Approach to the individual patient...

Diagnostic Algorithm

Similar projects

Other international experts

Diagnostic Algorithm (Adults)

Diagnostic studies

Diagnostic studies
THE END