

Mycoplasma Encephalitis ?

Pediatric Neurology Noon Conference

Dr. Hemang Shah

Patient 1

- MM is 14 yo RH WF developed HA for 1 month, 1 week before admission 2 ER visit for HA with N/V. 2 days prior to admission became disoriented.
- Exam encephalopathic, rt. Lower face weakness, rt. leg numbness, focal seizure?
- CSF: 3 WBC, 2 RBC, 23 protein, 70 glucose
- Prolonged hospital course with status epilepticus, pentobarb coma for 6 weeks, brain biopsy, shunt placement and concern for herniation
- Mycoplasma Ig G and Ig M +ve
- Went to rehab after 2 months and then home 2 weeks later (PEG, Trach out)

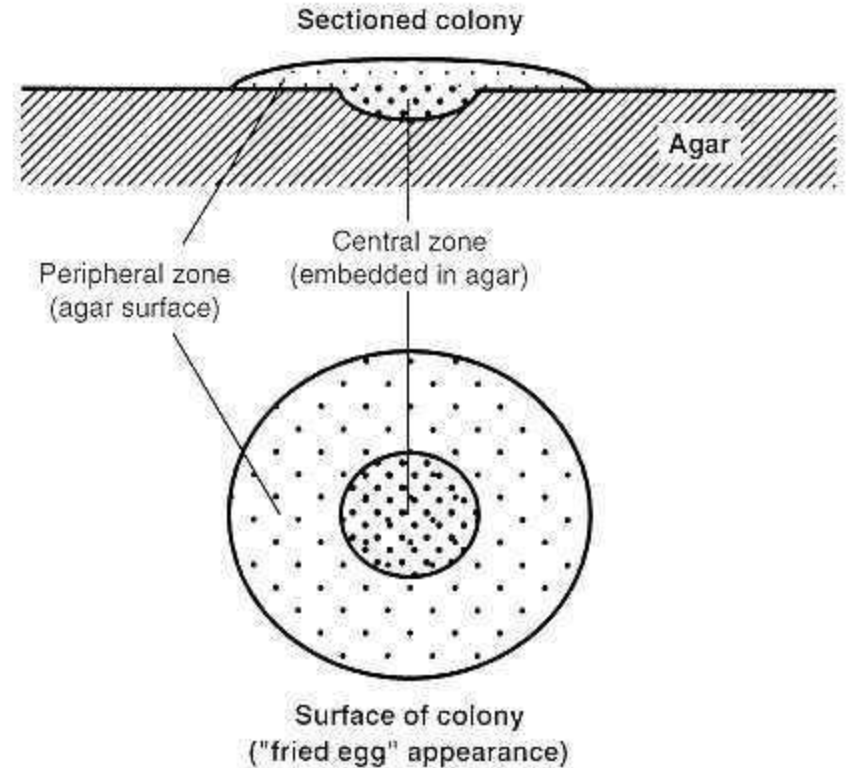
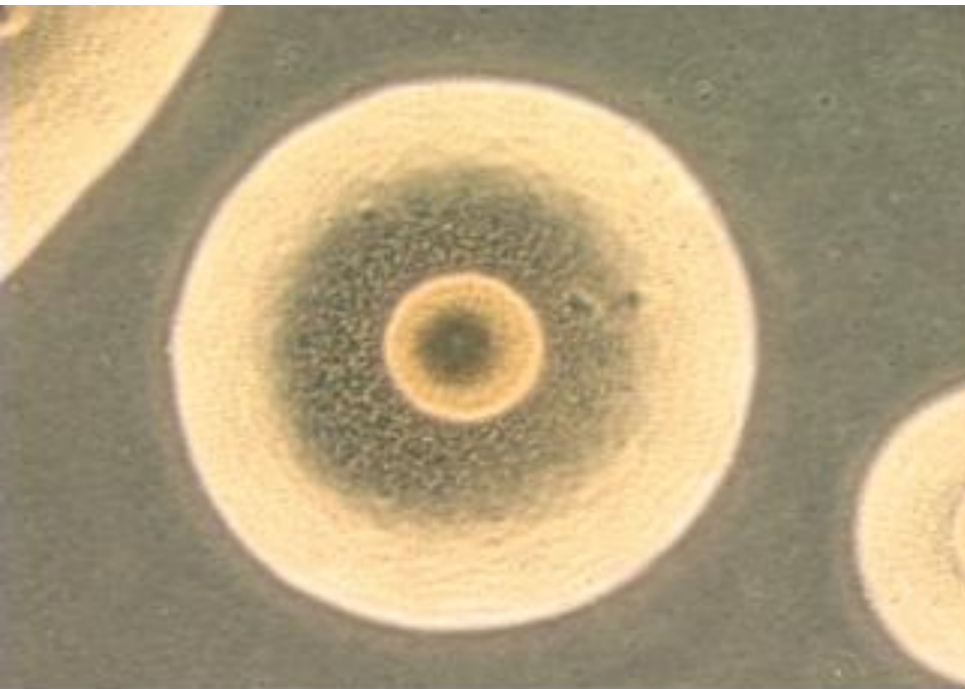
Patient 2

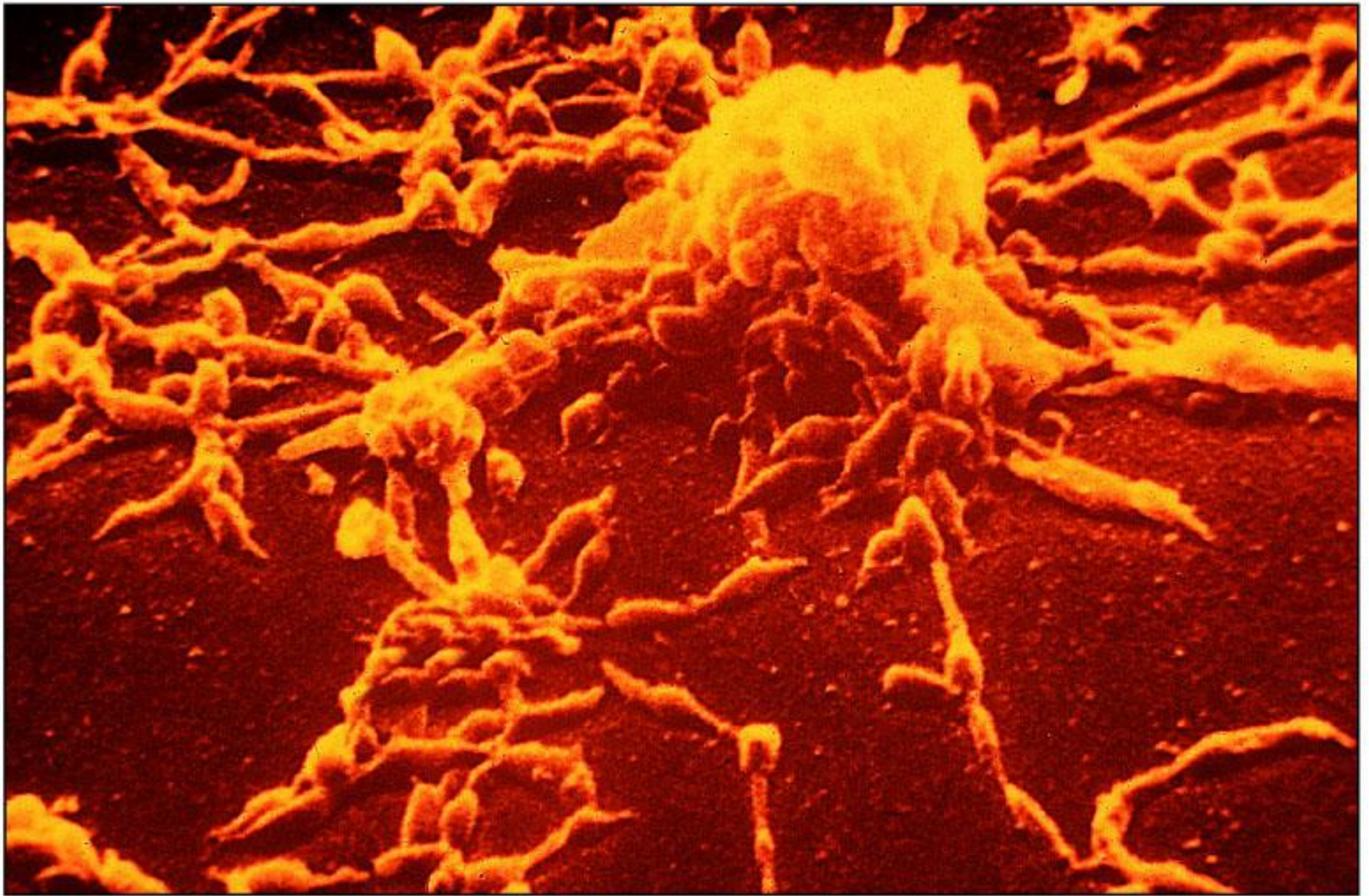
- LK is 14 yo RH AAF with HA 2 weeks, feeling of vertigo, became ataxic and dysarthric 2 days prior to admission. No preceding febrile/viral illness
- Exam had cerebellar signs
- Show MRI – stroke – tumor – biopsy – chronic inflammatory changes
- CSF: 50 WBC, 7 RBC, 79 glucose, 14 protein
- Mycoplasma IgM and IgG +ve, mycoplasma CSF PCR neg.

Lets' talk about Mycoplasma first

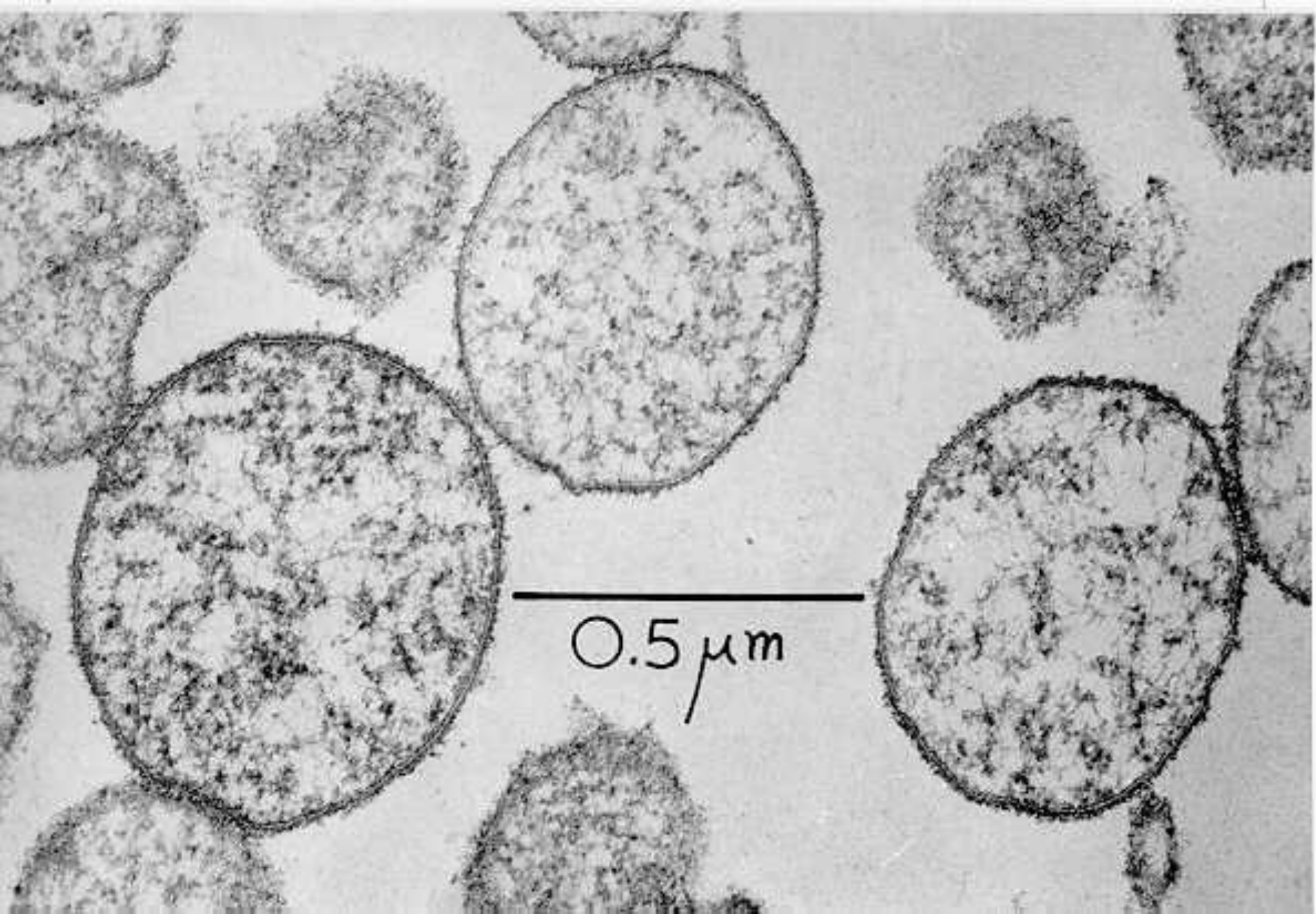
- Smallest self-replicating organism
- Surface parasite, can walk on water
- Evolved by degenerative evolution from Gram +ve bacteria
- Phylogenetically most closely related to clostridia, (Prokaryote? Fungus? – Mollicutes)
- What do their colonies look like?
- We will not talk about *Ureaplasma Urealyticum*

Fried – egg appearance



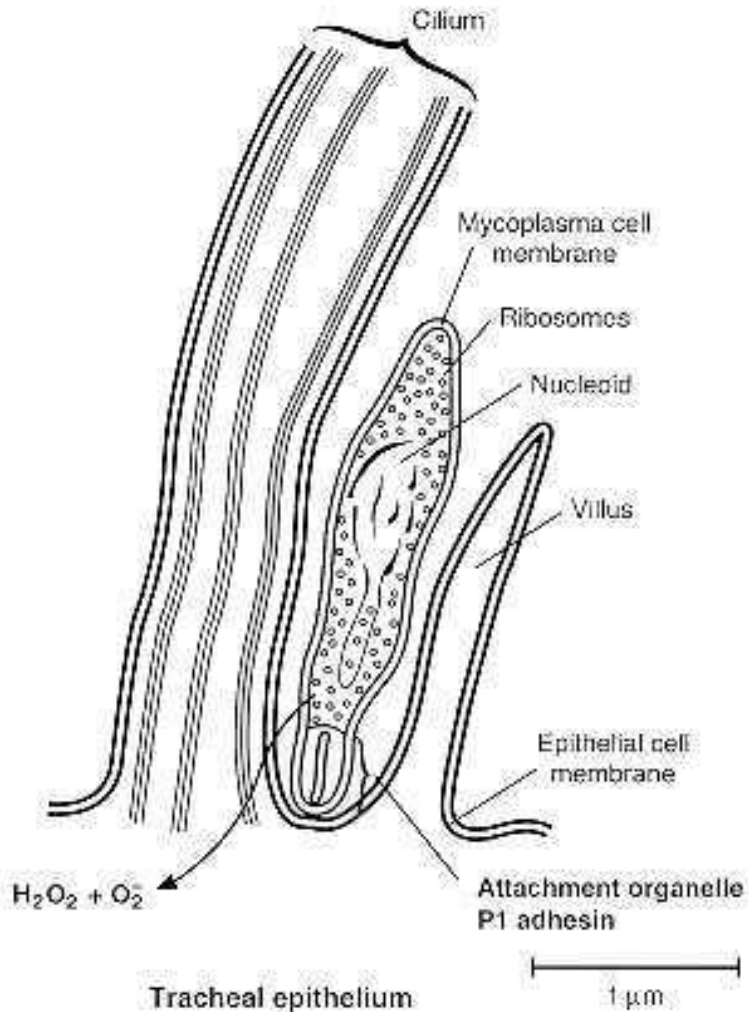


(b)



Courtesy of RM Cole, Bethesda, Maryland

Pathogenesis and Host Defenses



- Adhesins – P1
- Fusion
- Antigenic variability systems
- Host factors

Lets talk about encephalitis

- Immunocompetent children beyond the neonatal age group
- Definition ? – acute CNS dysfunction with radiographic or laboratory evidence of brain inflammation
- What is the significance of infectious agent found outside CNS?
- Mimics of encephalitis
- Primary encephalitis: direct invasion – GM – e.g. *Arbovirus, HSV, Rabies, Polio, Naegleria fowleri.*
- Location: Rabies, Japanese encephalitis, HSV.
- Post/para infectious encephalitis: aberrant immune response against brain antigen - e.g. myelin basic protein.

Table 1. Pathogens of Encephalitis

Viruses

- Adenovirus
- Arboviruses
- Encephalomyocarditis virus
- Enteroviruses
- Hepatitis A, B
- Herpesvirus (HSV) group
 - HSV 1 and 2
 - Varicella-zoster virus
 - Epstein-Barr virus
 - Cytomegalovirus
 - Human herpesvirus 6
 - Herpesvirus B
- Influenza
- Lymphocytic choriomeningitis virus
- Measles
- Mumps
- Parainfluenza
- Parvovirus
- Rabies
- Rotavirus
- Respiratory syncytial virus
- Rubella
- Smallpox
- Vesicular stomatitis virus

Bacteria

- *Actinomyces* sp
- *Bartonella henselae*
- *Brucella* sp
- *Chlamydia* sp
- *Ehrlichia* (aka *Anaplasma*) sp
- *Listeria monocytogenes*
- *Mycoplasma pneumoniae*
- *Nocardia* sp
- Q fever
- *Rickettsia* sp
- Spirochetes
 - Treponema pallidum*
 - Leptospira* sp
 - Borrelia* sp
- Whipples bacillus

Fungi

- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*

Protozoa

- *Acanthamoeba* sp
- *Balamuthai mandrillaris*
- Malaria sp
- *Naegleria fowleri*
- *Toxoplasma gondii*
- *Trypanosoma* sp
- Parasites
 - Baylisascaris procyonis*
 - Cysticercosis
 - Schistosoma* sp
 - Strongyloides stercoralis*
 - Trichinella spiralis*

Table 4. Risk Factors for Encephalitis

Risk Factor/Exposure	Possible Cause
Mosquito bites	Alphavirus: Western equine, Eastern equine, Venezuelan equine Flavivirus: St. Louis, West Nile Bunyavirus: La Crosse, California
Tick bite	Colorado tick fever, Powassan virus, <i>Anaplasma</i> (aka <i>Ehrlichia</i>), Rocky mountain spotted fever, tick-borne encephalitis
Raccoon feces	<i>Baylisascaris procyonis</i>
Wild/domestic animals	Leptospirosis
Bats	Rabies
Pigs	Nipah virus
Cats	<i>Bartonella hensalae</i>
Rodents	Lymphochoriomeningitis virus
Sheep/goats	Q fever
Travel	
Asia	Japanese encephalitis, Nipah virus
Europe	Tick-borne encephalitis
Africa	Lassa fever
Illness-exposures	
Chickenpox	
Measles	
Influenza	
Pneumonia	<i>Mycoplasma</i>
Fresh water	<i>Naegleria fowleri</i> , leptospirosis
Soil	<i>Balamuthia mandrillaris</i>
Vaccination	Measles-mumps-rubella, vaccinia
Season	
Spring/Summer	Mosquito-borne, tick-borne
Other systemic illness	Evaluate as needed for neoplastic and rheumatologic disease

Table 2. Commonly Diagnosed Causes and Mimics of Encephalitis

Diagnosed Cause	Recommended Testing
Sporadic	
<i>Bartonella henselae</i>	Serum <i>Bartonella</i> IgG
Enterovirus (EV)	CSF EV PCR, CSF viral culture
Epstein-Barr virus (EBV)	CSF EBV PCR, serum EBV serology
Herpes simplex virus (HSV)-1	CSF HSV PCR
Measles/Subacute sclerosing panencephalitis	Serum/CSF IgG
<i>Mycoplasma pneumoniae</i> (MP)	CSF MP PCR, serum MP IgM
Seasonal	
West Nile virus	Serum/CSF IgM (after fourth day of illness)
La Crosse Encephalitis	Serum/CSF IgM
Infectious Mimic	Recommended Testing
Bacterial meningitis	CSF Gram stain and culture
Tuberculosis (MTb)	CSF AFB stain/culture CSF MTb PCR PPD
Cryptococcal meningitis	CSF/serum antigen detection CSF fungal culture
Syphilis	CSF/serum VDRL, serum FTA
Rickettsial disease	Acute/convalescent serology
<i>Ehrlichia/Anaplasma</i> sp	Peripheral blood smear Acute/convalescent serology
Malaria	Peripheral blood smear
Ig=immunoglobulin, CSF=cerebrospinal fluid, PCR=polymerase chain reaction, AFB=acid-fast bacillus, PPD=purified protein derivative, FTA=fluorescent treponemal antibody absorption.	

Table 5. Initial Laboratory Testing for Encephalitis and Its Mimics

Cerebrospinal Fluid

- Glucose, protein, cell count, differential count
- Routine bacterial culture
- Viral culture
- Herpes simplex virus polymerase chain reaction (PCR)
- Cryptococcal antigen
- Enteroviral PCR
- *Mycoplasma* PCR
- Tuberculosis culture and PCR
- Epstein-Barr virus PCR
- West Nile virus immunoglobulin (Ig) M

Blood

- *Bartonella henselae* Ig G
- Epstein-Barr virus serology panel
- Lyme IgG (in endemic areas if cranial neuropathy present)
- *Mycoplasma* IgM
- West Nile virus IgM (during mosquito season)
- La Crosse virus IgM (in endemic areas, during mosquito season)
- Complete blood count, differential count
- Serum to be saved for comparison with convalescent specimen

Other

- Viral cultures of nasopharynx and stool
- Purified protein derivative skin test

• Don't forget opening pressure on LP, VDRL, ACE level, KOH stain and fungal culture.

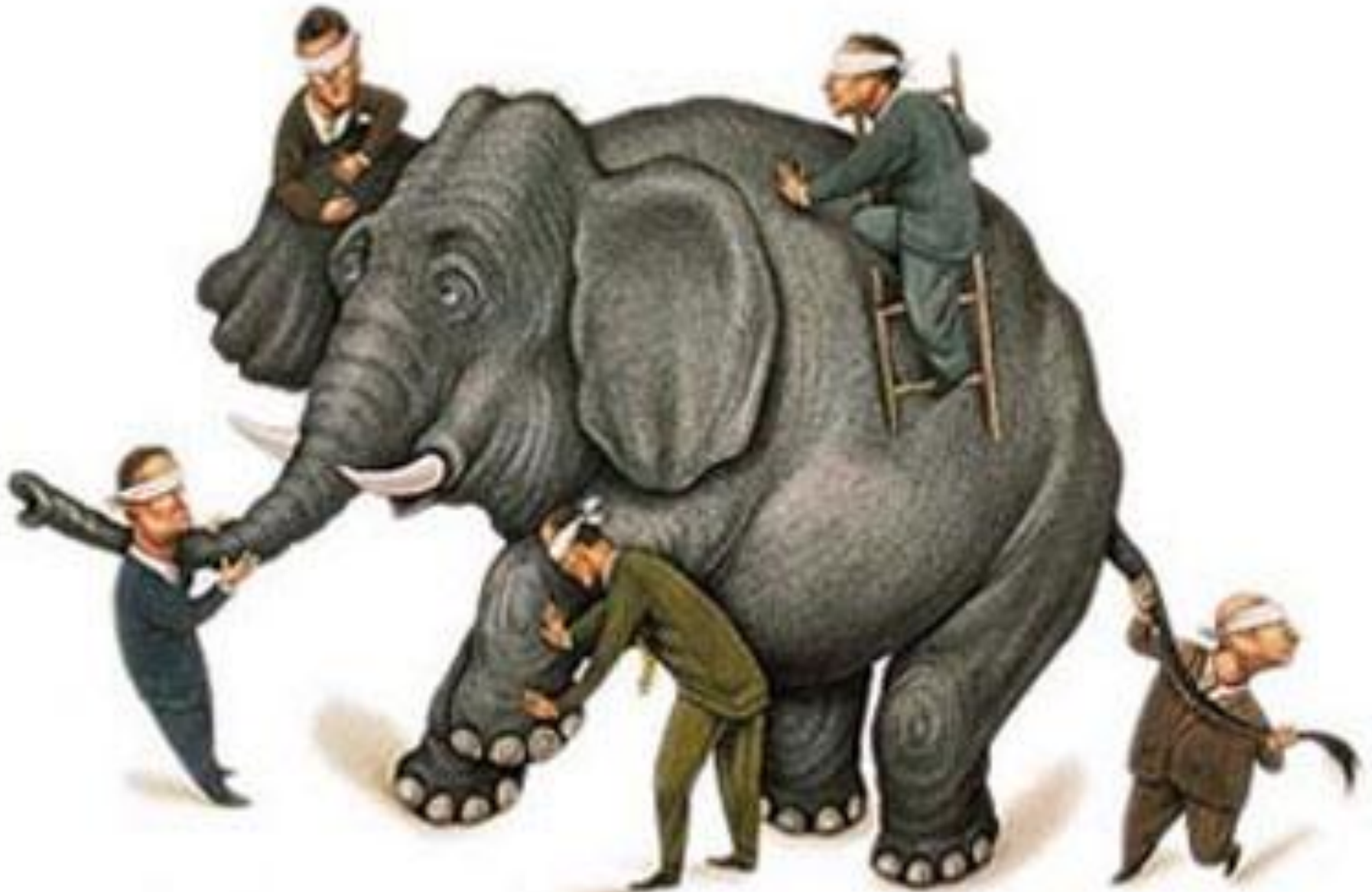
• Think about non infectious causes and send TPO antibodies, ovarian teratoma – NMDA receptor antibody

• ID consult

• Look at images yourself

• If pt. looks bad and CT/MRI/LP negative – repeat it.

We trying to know ENCEPHALITIS



Some stolen slides from:

In Search of Encephalitis Etiologies: Diagnostic Challenges in the California Encephalitis Project, 1998–2000

**Carol A. Glaser,¹ Sabrina Gilliam,¹ David Schnurr,¹ Bagher Forghani,¹ Somayeh Honarmand,¹ Nino Khetsuriani,²
Marc Fischer,³ Cynthia K. Cossen,¹ and Larry J. Anderson²**

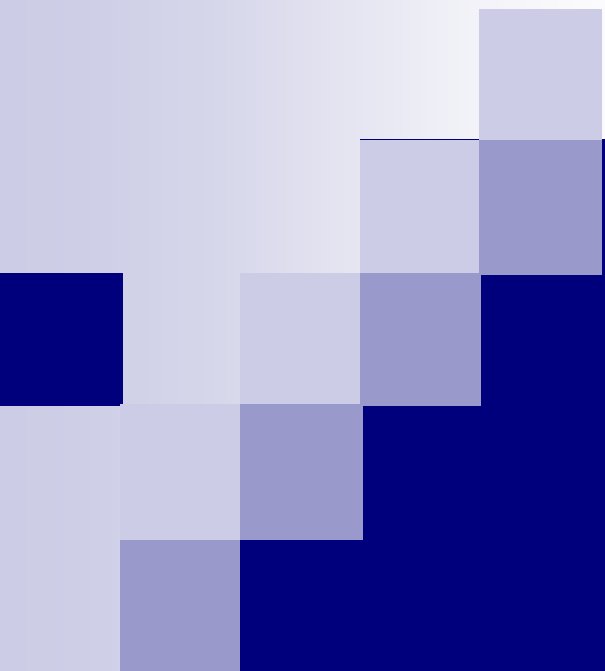
¹Viral and Rickettsial Disease Laboratory, California Department of Health Services, Richmond, California; and ²Respiratory and Enteric Viruses Branch and ³Meningitis and Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

The California Encephalitis Project was initiated in June 1998 to identify the causes and characterize the clinical and epidemiologic features of encephalitis in California. Testing for ≥ 13 agents, including herpesviruses, enteroviruses, arboviruses, *Bartonella* species, *Chlamydia* species, and *Mycoplasma pneumoniae*, was performed at the Viral and Rickettsial Disease Laboratory (Richmond, California). Epidemiologic and clinical information collected for each case guided further testing. From June 1998 through December 2000, 334 patients who met our case definition of encephalitis were enrolled. A confirmed or probable viral agent of encephalitis was found in 31 cases (9%), a bacterial agent was found in 9 cases (3%), and a parasitic agent was found in 2 cases (1%). A possible etiology was identified in 41 cases (12%). A noninfectious etiology was identified in 32 cases (10%), and a nonencephalitis infection was identified in 11 (3%). Despite extensive testing and evaluation, the etiology of 208 cases (62%) remained unexplained.

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California Encephalitis Project: What we have learned...

Carol Glaser

Somayeh Honarmand

Viral and Rickettsial Disease Laboratory

CA Dept of Health Services



California Encephalitis Project (CEP)

- June 1998 to December 2000
- Viral and Rickettsial Disease Laboratory
- Funding from the Centers for Disease Control, Emerging Infection Program
- Cases referred from physicians throughout CA - not population-based (biased toward more severe and diagnostically difficult cases)
- Similar sites in TN, NY

Encephalitis case definition

- Hospitalized w/encephalopathy (depressed or altered consciousness \geq 24 hrs) or ataxia

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



- **Submit the following specimens:**

- CSF

- acute serum

- respiratory sample (NP/throat swab)

- convalescent serum (10-14 days after collection of acute serum)

Core Testing

15 agents

■ CSF

- Molecular - enteroviruses, HSV1/2, VZV, EBV, CMV, HHV6
- Antibody – measles (HSV, VZV if indicated)

■ Acute serum**

- Arboviruses (St. Louis encephalitis, Western equine encephalitis, and West Nile virus), Epstein Barr virus, Mycoplasma pneumonia, Measles
- rabies when indicated

**Bartonella sp./Balamuthia previous core

Core Testing - continued

15 agents

■ Respiratory sample (NP/throat)

- Molecular: PCR – enterovirus, Mycoplasma pneumonia, Influenza A & B (Oct – Mar only)
- General viral isolation

■ Convalescent serum (paired sera)

- Arboviruses (St. Louis encephalitis, Western equine encephalitis, and West Nile virus), HSV, VZV, Mycoplasma pneumonia, Chlamydia sp., adenovirus,
- Influenza A & B (Oct-Mar only)

Expanded testing

- Based on exposures, travel, clinical symptomatology and laboratory values
- Examples
 - exposures
 - foreign travel -- additional arboviruses, rabies
 - lab values
 - low WBC/platelets -- rickettsia
 - eosinophilia -- parasites

About the cases...

- Not population based
 - Large sampling of cases throughout the State
 - Biased toward
 - More difficult to diagnosis
 - ~3-4% HSV 1 in CEP vs. 10-20% in other studies
 - More severe
 - overall short-term mortality ~12% vs. 4-6% other studies



CEP findings....

CEP Findings

1998-2004, N=1243

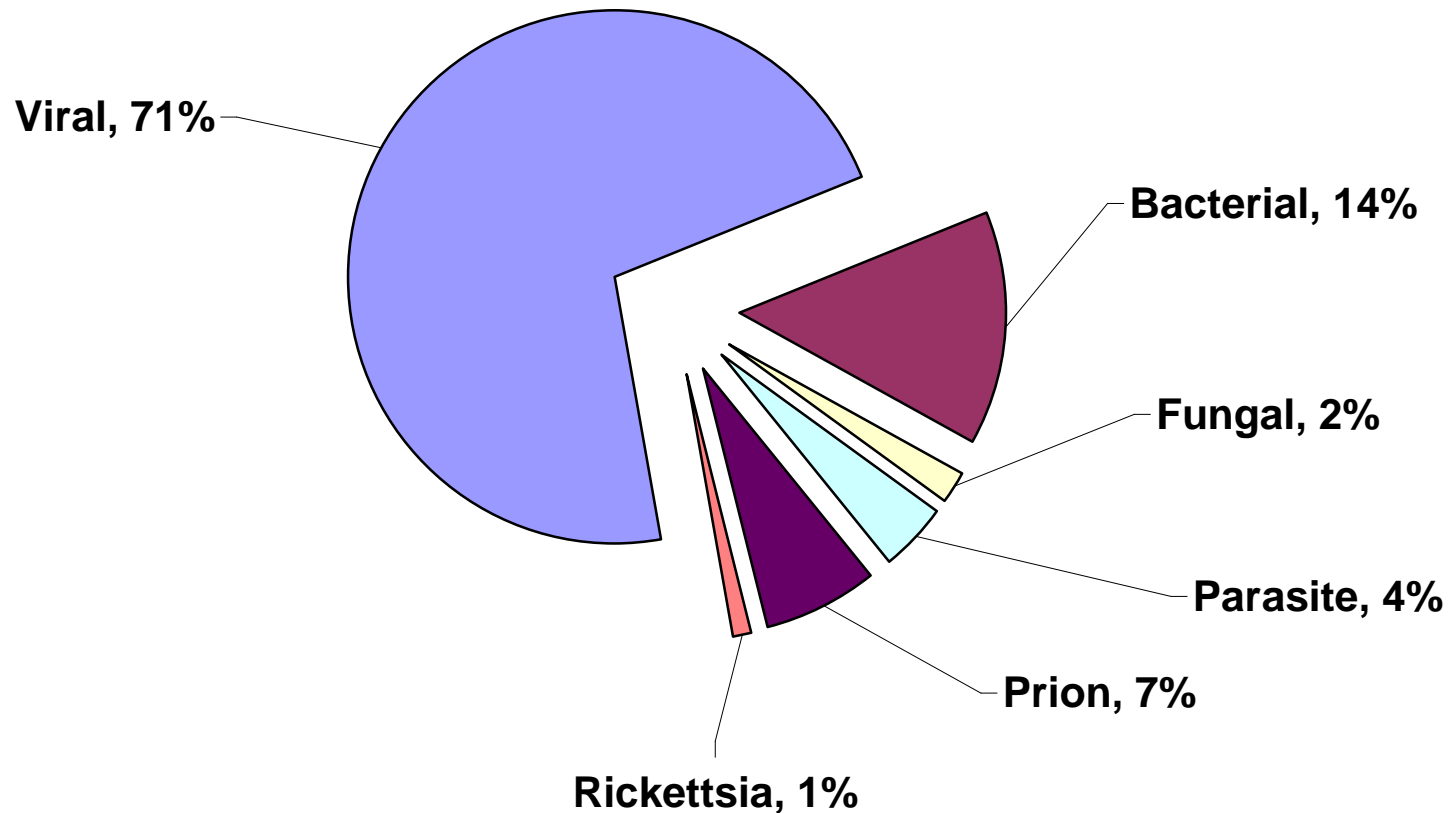
- **Infectious: 24%**
 - **confirmed/probable: 13%**
 - **possible: 11%**

- **Mimickers: 9%**
 - **Infectious but not encephalitis: 1%**
 - **Non-infectious: 8%**

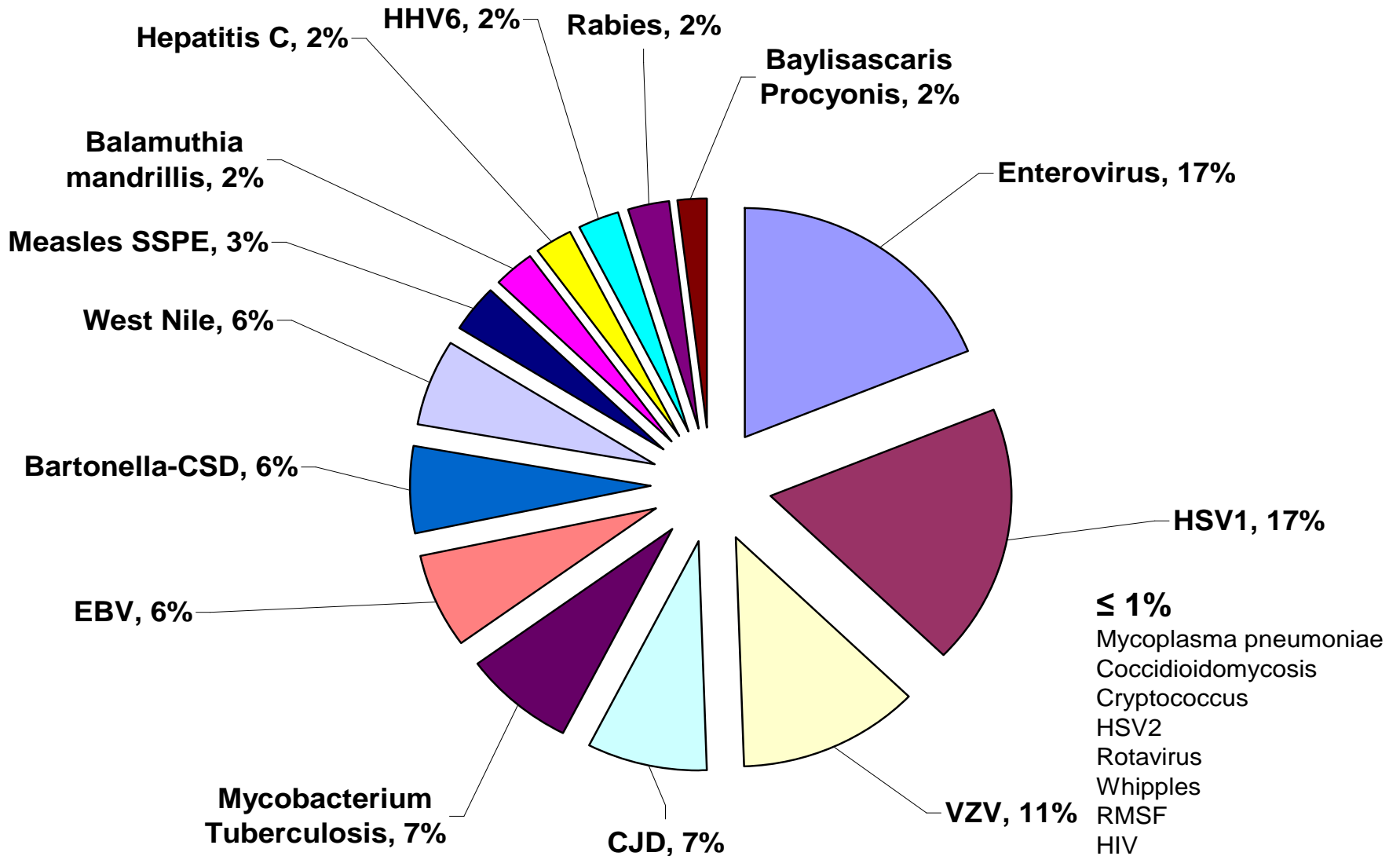
- **Unknown: 67%**

- *Similar results in TN, NY studies*

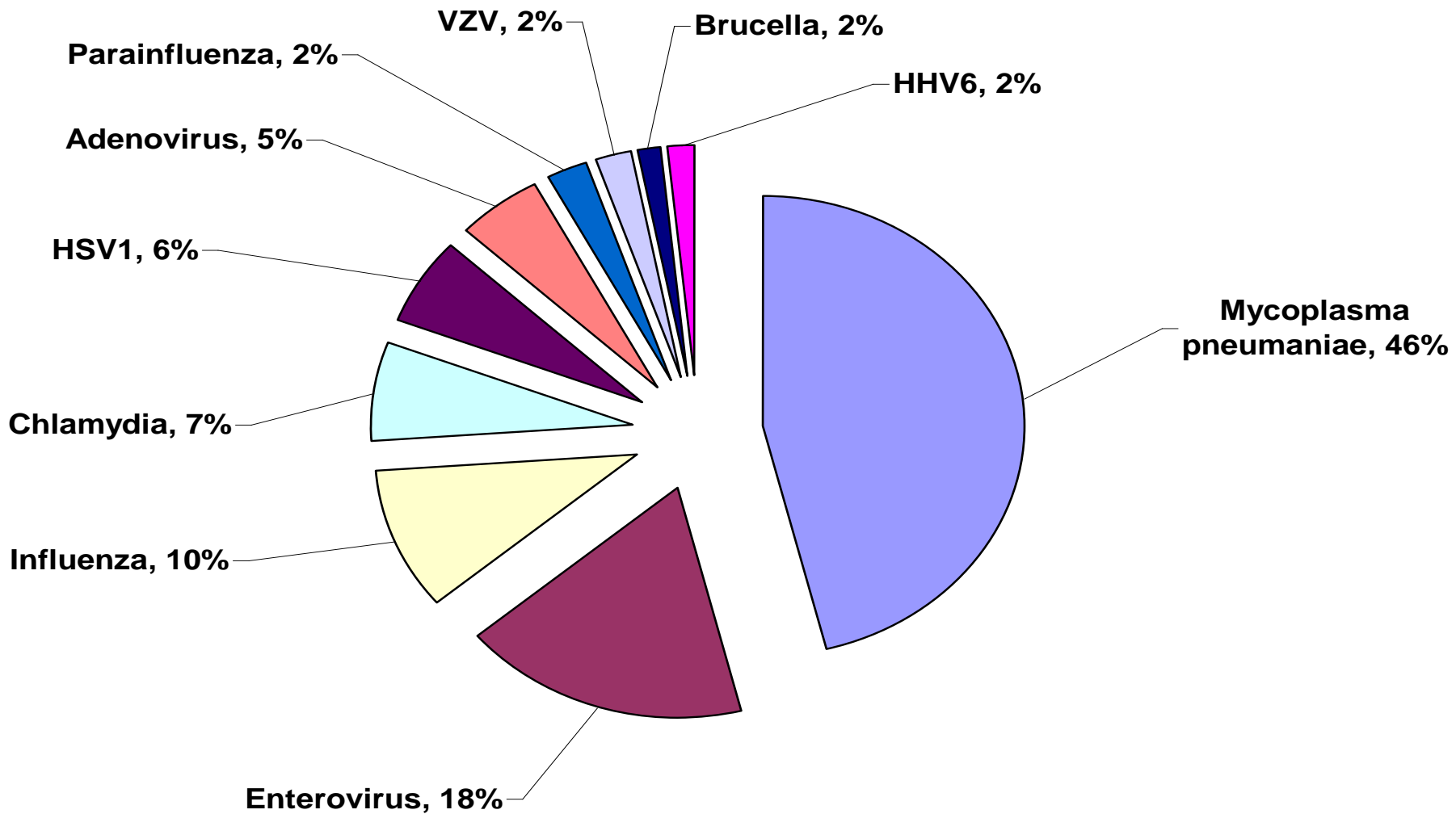
Breakdown of Confirmed/Probable



Breakdown of Confirmed/Probable Agents



Breakdown of Possible cases



Some interesting Observations

- *Varicella* was among the most common causes of encephalitis in 1980s (22 % – 25%). In our study 1%, immunization?
- Most common bacterial species associated with encephalitis was *Bartonella*
- *M. Pneumoniae* serology was positive in 11 pts but only 2 of them had positive CSF PCR (post-infectious process OR deep parenchymal infection only)
- Similar problem for *Chlamydia* infection



Case presentations/series:



Case presentation #1

- 12 year Hispanic male with history of developmental delay, attention deficit disorder
- Presented 6 month history of ataxia, 3 month history of idiopathic seizures
- Hospitalized with lethargy/fever/altered consciousness and somnolence

Case presentation #1

- LP#1: WBC = 9 WBCs/mm³
Protein = 47 mg/dL
- MRI: high signal intensity and swelling in left parietal, temporal and occipital lobes
- Developed coma → died (~3 weeks after admission)

Case presentation #1

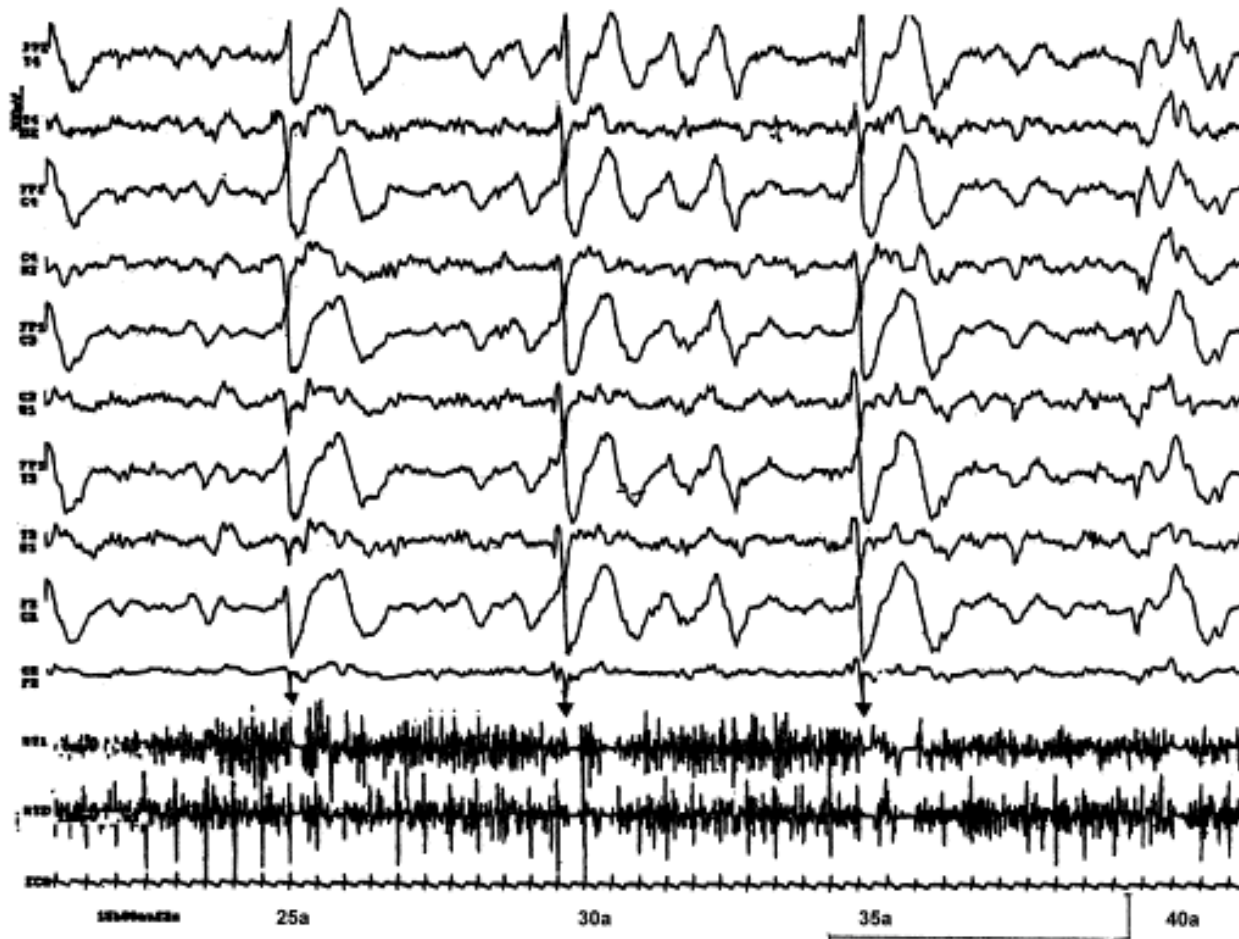
- CEP results:

- CSF

- Herpes consensus PCR = NEG
 - Mycoplasma PCR = NEG
 - Enterovirus PCR = NEG

- Serum

- St. Louis encephalitis/Western Equine Encephalitis/
EBV/Adenovirus/Mycoplasma/Chlamydia = NEG



EEG and electromyogram (EMG) in a 18 month old child, with eyes closed. Periodic, long-interval, diffuse, synchronous and stereotyped paroxysmal discharges correlated with brief episodes of axial atonia. 1 cm, 300 μ V; 15 mm, 1 s; MY 1, right trapezius; MY 2, left trapezius. The arrow corresponds to the beginning of the loss of muscle tone.

Case presentation #1

- Measles antibody
 - serum: IgG=21.0
 - CSF: IgG=18.0
- Diagnosis: measles subacute sclerosing panencephalitis (SSPE)
- No history of measles on initial presentation, received MMR vaccine
- Retrospective history: history of rash illness at 8 months of age

SSPE background

- Considered rare disease
- Most often due to measles, less commonly rubella
- Natural infection with measles usually at early age
- Incubation period for SSPE 7-10+ years
- Often 3 phases, steadily progressive:
 - Behavioral changes -- school performance decline
 - Movement disorder -- myoclonus and other involuntary movements
 - Complete neurologic decline
- California (and US) had epidemic of measles 1989-1991

SSPE: lessons learned

- Utility of screening for measles, especially in high-risk population
- Simple, rapid, inexpensive antibody test
- History doesn't always indicate insidious onset
- Absence of measles history should not preclude consideration of SSPE

VACCINATE



Case presentation #2

- 21 year old Hispanic female
 - Acute onset of fever and seizures
 - College student
 - Recent travel to Europe
 - Cat at home
 - Reptiles in backyard

Case presentation #2

- Admitted to ICU
- LP: WBC = 0 WBC/mm³,
Protein = 33 mg/dL, Glucose = 60 mg/dL
- MRI: normal
- Seizures aggressively managed → by hospital day 4 much improved and discharged to home



Case presentation #2

- CEP results
 - Positive Bartonella sp. titers
 - Negative Bartonella PCR (experimental)
- Cervical lymphadenopathy identified in retrospect



Cat-Scratch Disease (CSD) encephalopathy background

- *Bartonella henselae* and other *Bartonella* sp.
- Encephalopathy may occur within 6 weeks of initial symptoms
- Encephalopathy may be the initial manifestations of CSD
- Laboratory studies often unremarkable
- Outcomes good

Cat-Scratch Disease (CSD)

Lessons learned

- Fairly distinctive presentation: often seizures, CSF normal
- Cat contact often but not always (1 case with dog/rabbit, 1 case with rat)
- Lymphadenopathy not always present
- Serology very helpful, utility of PCR?

Case presentation #3

- 4 year old White female:
 - Admitted with 1 day of fever, lethargy, change in behavior, stiff neck and somnolence
 - 5 days prior to onset -- had spent 10 days in Maui where she swam in ponds, waterfalls
 - Grandmother also ill with similar illness

Case presentation #3

- LP: WBC = 101 WBCs/mm³ (88%P)
Protein = 33 mg/dL
- No ICU care
- discharged to home at baseline 8 days after onset

Case presentation #3

- CEP results:

- CSF:

- Herpes consensus PCR: NEG
 - Mycoplasma PCR: NEG

- Serology:

- SLE/WEE/Mycoplasma/Chlamydia/Adenovirus/EBV=NEG

- Enterovirus PCR spinal fluid: Positive

- Enterovirus IgM serum = 8.0 (high)



Enterovirus background

- Common cause of aseptic meningitis (60-90%)
- Especially in pediatrics
- Hypothesis: with more sensitive assays available -- would be a leading cause of encephalitis



Enterovirus

Lessons learned

- Mostly pediatric cases
- Most in summer/fall, but not always
- Most with pleocytosis
- Milder disease generally (less ICU, shorter length of stay, and no deaths)

Case presentation #4

- 14 year old white female presented with:
 - 5 days of fever, emesis and headache
 - Ataxia
 - Alert and oriented

 - LP results: WBC = 3 WBCs/mm³
Protein = 29 mg/dL, Glucose = 56 mg/dL



Case presentation #4

- Mono spot positive from referring facility
- CEP results:
 - EBV serology: positive acute infection
 - EBV PCR: negative at our laboratory, sent to another laboratory -- also negative



EBV background

- Generally good outcomes
- PCR useful tool for diagnosis
- Often in adolescent patients



EBV: Lessons learned

- Serology probably more accurate than PCR for diagnosis (because of mechanism?)
- Mostly pediatrics and young adults
- Outcomes generally good, but not always

Case Presentation #5

- 72 y/o male with possible encephalitis, referred into CEP
 - onset of headache/fever
 - 5 days later hospitalized with lethargy, somnolence and focal right-sided weakness
 - LP: WBC = 10 WBCs/mm³, Protein = 172 mg/dL, Glucose = 60 mg/dL
 - CT/MRI: mild atrophy, otherwise normal
 - Died 11 days after hospitalization
 - No autopsy
 - cause of death : “cerebral vascular accident”

Case Presentation #5

- California Encephalitis Project (CEP):
 - Deceased core testing includes rabies testing
- rabies antibody positive
- Cause of death or due to prior vaccine??

Case Presentation #5

- brain specimen not available
- throat swab
 - tested at Centers for Disease Control
 - PCR positive for rabies: sequenced strain: canine strain/Philippines
 - contaminated with saliva
- Patient originally from Philippines, was there 10 months prior to onset of illness

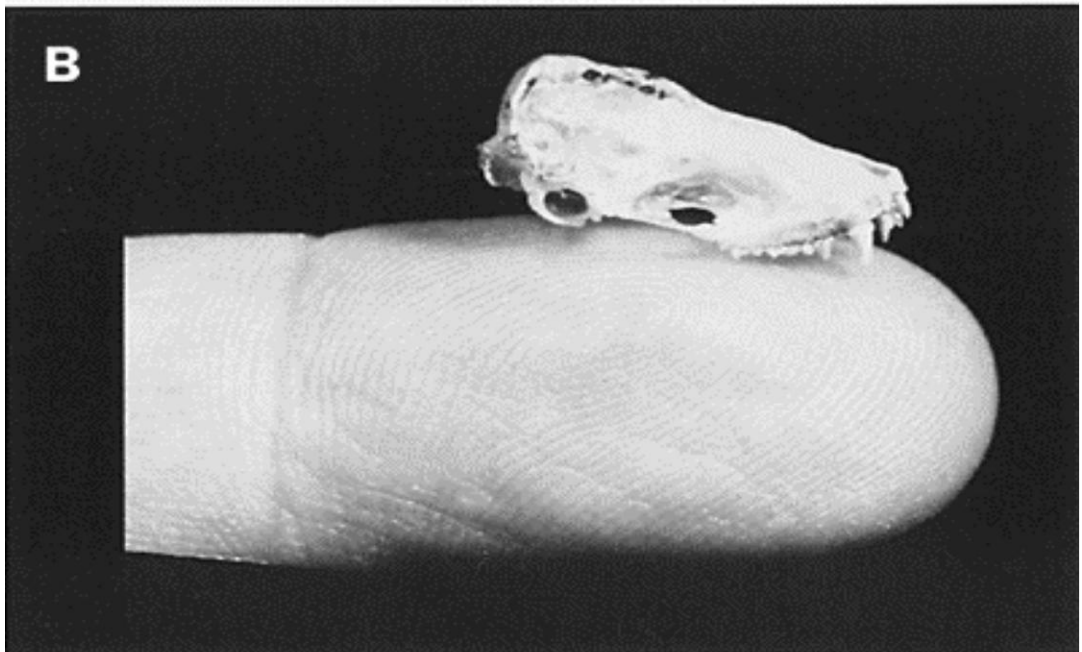
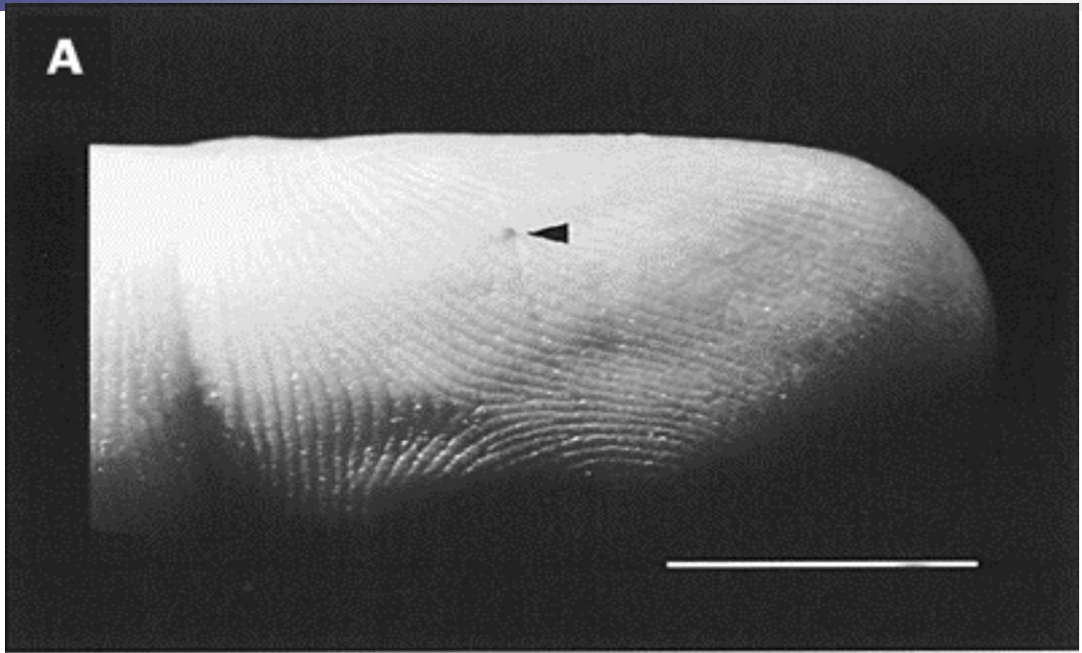
Rabies background

- Acute, rapidly progressive encephalitis
- Always fatal
- Variable incubation period (up to 20 years)
- Worldwide: estimated 100,000 cases
- Rare in US, 1-2 cases/year
 - US 1990-2001:
 - 36 human cases: 29 associated with bats
- 2 forms
 - Furious (70%)
 - Paralytic (30%)

Rabies

Summary of Cases

- 4 cases total
 - All adults
 - All male
 - Ages: 66 years (2003), 28 years (2002), 72 years (2001), and 49 years (2000)
 - 1 associated with dog strain (Philippines) and 3 associated with bat strain





Rabies

Lessons learned

- Rabies testing should be done on all severe, rapidly progressive encephalitis even if no animal bite history
- Ante-mortem testing is possible but tricky

Case Presentation #6

- 10 year old previously healthy female;
 - 2 day prior to admission: episode of vomiting, somnolent and upper respiratory infection
 - Seen in ER: fever and lethargy
 - Admitted and noted to be inattentive, drooling and ‘difficulty finding words’

Case Presentation #6

- Exposure history: dog and cat, no other animal contact but lived in rural area
- Admit labs
 - CSF WBC=90 WBC/ml (75%L/14%M/11%P)
Protein=26 mg/dL, Glucose=59 mg/dL
 - CT Scan: Left frontal lobe with mass effect

Case Presentation #6

- CSF studies; negative viral isolation, negative HSV1 PCR at hospital, commercial and VRDL
- Negative arboviruses (SLE/WEE/WNV)
- Negative EBV
- Negative Mycoplasma pneumonia

Case Presentation #6

- Hospital Day #3: partial seizure
- 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(83%L), Protein=107 mg/dL, Glucose=57 mg/dL



Case Presentation #6

- CSF PCR HSV-1:
 - Hospital lab: Positive HSV-1
 - VRDL: Positive HSV-1

Herpes Background

- HSV-1 leading cause of encephalitis (HSE)
- Acute necrotizing encephalitis
- Estimated frequency; 1/250,000
- Most common cause of sporadic encephalitis
- Without Rx: mortality up to 70%
- PCR; considered sensitive and specific

Herpes (HSE) Background

- How common false negative?
 - Prospective study, 10 cases HSE
 - 8/10 CSF PCR pos, 2/10 CSF PCR neg(2nd tap positive)—20% false negative
 - Scan J Inf Dis 1998
 - Retrospective study, 22 cases HSE
 - 21/22 HSV PCR positive 1st tap, 2 days later: pos—4.5% false negative
 - Clin Inf Dis 1994
- CEP study, 28 HSE cases
 - 7/28 HSV PCR positive 1st tap, later tap pos—25% false negative (CEP biased toward diagnostically difficult)

Basis for analysis

- Some agents have characteristic clinical manifestations
 - Herpes Simplex 1: temporal lobe
 - Japanese encephalitis virus: brainstem
 - Varicella zoster: cerebellar signs/symptoms
- recognize some agents with broad clinical spectrum
- recognize that each profile won't necessarily be relevant
- Maybe more than just infectious
 - Reyes syndrome

Usual work up

- History: fever, headache, AMS, focal neurological signs, seizure. Don't let gradual onset fool you.
- Exam: look for focal findings
- Labs: think why not to tap, lymphocytic pleocytosis, elevated protein (usually < 200). Regular labs are usually OK
- Always send acute serum to be stored/frozen for future use
- Neuro-imaging: CT noncontrast – fast but most of the time doesn't give answer
- MRI with/without contrast
- EEG
- Empiric acyclovir 10 mg/kg/dose iv q 8 hrs for 2-3 weeks OR negative HSV PCR
- Empiric coverage for bacterial meningitis ?
- How about IVIg, steroids, immunomodulators
- Rehab should start on day one – PT/OT/ST

Quiz

- 1) Most common diagnosed cause of sporadic encephalitis
- 2) This virus was first seen in US (NYC) in 1999, became widespread in the summer of 2002 causing 284 deaths, transmitted by?, reservoir?
- 3) Regional adenopathy – encephalitis
- 4) Hand, foot and mouth disease – encephalitis
- 5) Non traumatic CSF shows plenty of RBC
- 6) We have vaccine to prevent encephalitis for this virus (4)
- 7) Acute flaccid paralysis can be presentation of this virus infection
- 8) Paresthesia at/near inoculation site, if you get this right you will save lives of other contacts (clue: hydrophobia)
- 9) Which stat has highest and second highest number of human cases of H1N1 flu (as of 5/11/09)
<http://www.cdc.gov/h1n1flu/update.htm#statetable>