

# Profiles of Clinical Syndromes in Patients with Unexplained Encephalitis



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CDC-ICEID

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# ~~Clusters~~ of Clinical Syndromes in Patients with Unexplained Encephalitis

- not clustered in time or place
- grouped by clinical characteristics

# Outline

- Background California Encephalitis Project
- Purpose of Profile development
- Profile descriptions
- First steps to various profiles

# California Encephalitis Project

- Viral and Rickettsial Disease Laboratory, California Department of Health Services
- Collaboration with Respiratory and Enteric Viruses Branch and Emerging Infections Program, Centers for Disease Control
- New York and Tennessee also sites

# Objectives of Project

- Increase understanding of epidemiologic, clinical, laboratory features of encephalitis by:
  - Providing state-of-the art , rapid, diagnostic tests
  - Collection of data:
    - demographics
    - exposures
    - clinical symptoms
    - laboratory tests
    - neuroimaging

# Encephalitis case definition

- Hospitalized with encephalopathy (depressed or altered consciousness  $\geq$  24 hrs)
- 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

# Encephalitis Case History Form

Serum, CSF & this case history form are required for testing (specimens will not be tested without this form)!

Consent is required for advanced diagnostic testing

**NP/throat and stool/rectal** specimens are recommended

Case patients must be hospitalized with encephalopathy (depressed or altered level of consciousness  $\geq 24$  hours, lethargy, or change in personality) or ataxia, **AND** have 1 or more of the following: fever ( $T \geq 38C$ ), seizure(s), focal neurologic findings, CSF pleocytosis, abnormal EEG or neuroimaging study. Case patients must be  $\geq 6$  months of age and immunocompetent.

## Patient Information:

Last name \_\_\_\_\_ First name \_\_\_\_\_ DOB \_\_\_\_/\_\_\_\_/\_\_\_\_ Medical Record # \_\_\_\_\_

Street Address: \_\_\_\_\_ City \_\_\_\_\_ Zip Code \_\_\_\_\_ Occupation \_\_\_\_\_

Telephone #: \_\_\_\_\_ Name of Surrogate decision-maker and/or Guardian: \_\_\_\_\_

**Race:**  White  Black  Native American  
 Asian/Pacific Islander  Other  Unknown

**Exposures 1 mo before onset** (specify details):

Any animal contact (including pets):  No  Yes

Tick bites/exposure:  No  Yes

Mosquito bites/exposure:  No  Yes

Other insect bites:  No  Yes

Day care (patient or siblings):  No  Yes

Immunizations up to date?:  No  Yes

Immunizations in last month?:  No  Yes

Medications (including OTC):  No  Yes

Toxins or illicit drugs:  No  Yes

Fresh water (swimming or drinking)  No  Yes

Ingestion of soil  No  Yes

Fish Ingestion (marine, freshwater)  No  Yes

Head Trauma  No  Yes

Outdoor activity (camping, hiking, etc)  No  Yes

Sick Contacts  No  Yes

**Ethnicity:**  Hispanic  Non-hispanic

**Sex:**  Female  Male

**Travel 1 mo before onset**

(specify location, dates, and mode of transportation):

Outside of United States:  No  Yes

In United States:  No  Yes

In State (out of local area):  No  Yes

**Additional Information** (please provide details):

Is the patient homeless?  No  Yes

Ever traveled outside the US?  No  Yes

Known TB exposures?  No  Yes

Previous PPD test?  No  Yes

**Significant Past History (medical, social, family, including rheumatologic disorders, early organ failure):**

**Miscellaneous exposures or potentially pertinent information:**

**Patient Name:** \_\_\_\_\_

**Clinical:**

Date of first CNS symptom(s): \_\_\_/\_\_\_/\_\_\_

Date of hospital admission: \_\_\_/\_\_\_/\_\_\_

**Do the following apply anytime during current illness:**

In ICU  No  Yes \_\_\_\_\_

Fever  $\geq 38^\circ$   No  Yes \_\_\_\_\_

Lethargy  No  Yes \_\_\_\_\_

Alt. conscious  No  Yes \_\_\_\_\_

Personality ?  No  Yes \_\_\_\_\_

Extreme irritability  No  Yes \_\_\_\_\_

Hallucinations  No  Yes \_\_\_\_\_

Stiff neck  No  Yes \_\_\_\_\_

Ataxia  No  Yes \_\_\_\_\_

Somnolence  No  Yes \_\_\_\_\_

Focal neuro  No  Yes \_\_\_\_\_

Seizures  No  Yes \_\_\_\_\_

intractable?  No  Yes \_\_\_\_\_

Coma  No  Yes \_\_\_\_\_

pheno/pentobarb?  No  Yes \_\_\_\_\_

**Other symptoms** (1 mo before onset. Provide details)

URI or ILI  No  Yes \_\_\_\_\_

GI  No  Yes \_\_\_\_\_

CV  No  Yes \_\_\_\_\_

Rash  No  Yes \_\_\_\_\_

**Brain MRI** date \_\_\_/\_\_\_/\_\_\_  Normal  Abnormal  ND

If abnormal:  temporal lobe involvement  
 white matter involvement  
 hydrocephalus  
 other \_\_\_\_\_

**Brain CT** date \_\_\_/\_\_\_/\_\_\_  Normal  Abnormal  ND

If abnormal:  temporal lobe involvement  
 white matter involvement  
 hydrocephalus  
 other \_\_\_\_\_

**EEG** date: \_\_\_/\_\_\_/\_\_\_  Normal  Abnormal  ND

If abnormal:  diffuse slowing  
 focal temporal epileptiform activity  
 PLEDS  
 other \_\_\_\_\_

**CBC results** (first available & subsequent):

Date: \_\_\_\_\_

WBC: \_\_\_\_\_

Diff: \_\_\_\_\_

HCT \_\_\_\_\_

Plt: \_\_\_\_\_

**CSF results** (first & subsequent):

Date: \_\_\_\_\_

OP: \_\_\_\_\_

RBC: \_\_\_\_\_

WBC: \_\_\_\_\_

%Diff: \_\_\_\_\_

Protein \_\_\_\_\_

Glucose \_\_\_\_\_

CrAg \_\_\_\_\_

VDRL \_\_\_\_\_

**Was HSV PCR sent?**  No  Yes

If yes, please give result & CSF date: \_\_\_\_\_

**Other labs/Xrays** (if performed. List results if abnormal)

LFTs  Normal  Abnormal \_\_\_\_\_

BUN/Cr  Normal  Abnormal \_\_\_\_\_

ESR  Normal  Abnormal \_\_\_\_\_

ANA  Normal  Abnormal \_\_\_\_\_

Tox screen  Normal  Abnormal \_\_\_\_\_

Heavy metals  Normal  Abnormal \_\_\_\_\_

CXR  Normal  Abnormal \_\_\_\_\_

Other \_\_\_\_\_

**Microbiologic studies/results:**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Treatment** (specify type & date started):

Antiviral agents \_\_\_\_\_ Antibacterial agents \_\_\_\_\_

Steroids/IVIG \_\_\_\_\_

**Contact Physician Information (MANDATORY – FOR OBTAINING UPDATES AND RELAYING RESULTS):**

**Name:** \_\_\_\_\_ **Facility:** \_\_\_\_\_

**Pager:** \_\_\_\_\_ **Fax:** \_\_\_\_\_ **e-mail:** \_\_\_\_\_

Questions regarding project or specimens contact Somayeh Honarmand (510) 307-8608 or pager (510) 641-5286

Fax this form to (510) 307-8599 or send with specimens to:

**Specimen Receiving**

**Encephalitis Project**

**850 Marina Bay Parkway, Richmond, CA 94804**



# Core testing

- 15 different agents by complementary methods: molecular, serologic, culture
- spinal fluid/brain, serum, resp/stool samples
- Agents:
  - Herpes: HSV 1 & 2, VZ, CMV, EBV, HHV6
  - Enteroviruses
  - Respiratory viruses: Flu A/B, adenovirus, measles
  - Arboviruses: SLE, WEE, WN
  - Bacteria: Bartonella sp., Mycoplasma pneumonia, Chlamydia sp.

# Expanded testing

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

# Communication with referring facility

- Maintain frequent contact with referring physician(s) for:
  - updated infectious disease workup from referring site—bacterial cultures, serologies
  - information on non-infectious workups—e.g. autoimmune (ANA), paraneoplastic antibodies, etc.
  - updates on clinical status and further spinal taps/MRIs, etc
  - relay our results

# California Encephalitis Project


June 1998 – March 2002

- ~650 cases referred into project
- Not all met case definition (e.g. immunocompromised, not hospitalized, not encephalopathic)
- 496 cases meet definition and evaluated

# California Encephalitis Project

- **biased toward more severe** (15% mortality CEP compared to 4-6% other studies)
- **biased toward difficult to diagnosis cases** (e.g. 4% HSV1 in CEP compared with 10-20% other studies)
- **referral dependent-not population based** (>100 facilities refer)

# Summary of findings



■ Total Explained		41%
■ Not infectious	12%	
■ Infectious		
■ Viral:	16%	
■ Bacterial:	12%	
■ Parasitic:	~1%	
■ Unexplained		59%

# California Encephalitis Project

- The unexplained 59% (292) likely a number of different entities—non-infectious, infectious-known agents, unknown agents
- Unknowns not all alike—but groups among them that are similar
- Profile analysis is one approach to unknowns...

# Basis for analysis

- some agents have characteristic clinical manifestations
  - Herpes Simplex 1: temporal lobe
  - Japanese encephalitis virus: brainstem
  - Varicella zoster: cerebellum
- Recognize some agents with broad clinical spectrum
- Recognize that each profile won't necessarily be relevant



# Objectives of profile analysis (Hypothesis generating)

- Identify commonalities among groups
  - Demographics: gender, race/ethnicity
  - Exposures/Travel
- Pathogen discovery
  - Amenable to clinical groups
- Outcome/Prognosis

# Defining Profiles

- Based on combination of
  - PREDOMINANT Clinical features—
    - If none, miscellaneous profile
  - Severity of illness
  - Laboratory findings
  - Neuroimaging studies

# Profiles discussion

- highlight Profile 1, mention other profiles
- Profile analysis still in initial phases

# Profile 1 definition

- Initial case definition: Patients presented with diffuse, massive cerebral edema (CT or MRI), acellular spinal fluid, high fevers and most had rapid demise
- Note: rapid course, infection or toxin?....
  - 18 total
    - 1 infectious
  - 17 unknown

# Profile 1

## cerebral edema

- Autopsy done on almost all deceased cases
- Extensive testing at referring sites and our site: negative (including toxicology)
- Requested input from CDC on this profile

# Profile 1

## revised case definition

- All cases reviewed by single neurologist\*, medical records reviewed
- revised case definition;
- **Case definition**
  - Any person  $\geq 6$  months of age who dies with acute encephalitis and marked cerebral edema as documented by neuroimaging or pathology

\*Dr James Sejvar, EIS, CDC

# Profile 1

## revised case definition

### ■ **Exclusion criteria**

- 1) Alternative explanation for both encephalopathy and cerebral edema including:
  - a) Acute cortical demyelination consistent with Acute Disseminated Encephalomyelitis (ADEM)
  - b) Acute intraparenchymal cerebral hemorrhage in the presence of primary vascular event (as evidenced by        imaging, angiographic, or autopsy findings)
  - c) Metabolic processes (e.g., Thyrotoxic encephalopathy, hepatic/uremic encephalopathy)
  - d) Autoimmune disorders (e.g, Behcet's disease, SLE, Marburg disease), or
  - e) Exposure to selected drugs, chemicals or toxins (e.g., tacrolimus, cyclosporin, desmopressin, cisplatin)
  - f) Septic shock
- 2) Cerebral edema secondary to anoxia or ischemia as evidenced by
  - a) Severe hypotension on presentation (systolic blood pressure <90 mmHg) and
  - b) Lack of cerebral edema on initial head imaging studies
- 3) Severely immunocompromised state (HIV infection, chronic immunosuppressive medication, organ transplant)

# Revised Profile 1

- excluded 7 cases
- revised case count=10 (pediatrics, Asians)
- ongoing: interviews with family to gain more information about possible exposures...



# Profile 1

## Ongoing activities

- Pathogen discovery
  - received brain samples on most cases—amenable for pathogen discovery
- Prospective case assessment (using more specific data collection instrument)
- Case control study?
- Specimens for mitochondria structure?

# Profile 2 case definition

- Patients with encephalopathy and MRI or EEG with temporal lobe focus
- Clinically look like herpes...
  - 55 total identified
    - 19 HSV-1, 1 other infectious
    - 2 Non-infectious
  - 33 Unknown

# Profile 3 case definition

- Patients with encephalopathy and intractable seizures requiring induction of barbiturate coma
- Clinicians frequently comment on the overwhelming severity of the seizure
- 26 total
  - 3 Identified: 2 infectious, 1 non-infectious
  - 23 unknown

# Profile 6 definition

- Patients with encephalopathy, in which movement disorder is predominant
- Clinicians often note the magnitude and severity of the movements
- Previous association of movement disorders/encephalitis:
  - Sydenhams chorea/Streptococcal disease
  - Encephalitis lethargica/Influenza
- 21 total
  - 7 identified: 5 infectious, 2 non-infectious
  - 14 unknowns

# MOVEMENT DISORDER questionnaire

Patient's Name: \_\_\_\_\_

Date of Onset (movement disorder): \_\_\_\_\_

Please check all that apply:

Tremor

describe: \_\_\_\_\_

Choreoathetoid movements

describe: \_\_\_\_\_

Tics

describe: \_\_\_\_\_

Dystonia

describe: \_\_\_\_\_

Ballismus

describe: \_\_\_\_\_

Myoclonus

describe: \_\_\_\_\_

Facial tics

describe: \_\_\_\_\_

Other

describe: \_\_\_\_\_

EEG:     Abnormal             Normal     Pending/Not Done

Describe Results: \_\_\_\_\_

# Summary of all Profiles :

## Predominant Symptomatology

- Profile 1: diffuse edema, szs, acellular CSF (n=18)
- Profile 2: temporal lobe (n=55)
- Profile 3: intractable seizures (barbituate coma) (n=26)
- Profile 4: seizures, rapid recovery (n=19)

# Summary of all Profiles :

## Predominant Symptomatology

- Profile 5: cerebellar involvement (n=31)
- Profile 6: movement disorders (n=21)
- Profile 7--psychiatric component (n=26)
- Profile 8--miscellaneous
- recently added
  - Profile 9--dementia (n=9)
  - Profile 10--recurrent episodes (n=4)

# Data analysis

- Reviewed variables of unknowns in each profile for trends:
  - gender, race/ethnicity, age
  - season onset
  - animal contact, travel, recent immunizations
  - laboratory features



# Data analysis

- Calculated Odds ratio (OR) on notable trends

Profile 2:            Fall: OR=2.2 (CI: 1.1-4.6)    p=.04

Profile 6:            Male: OR=5.0 (CI: 1.1-22.3)    p=.04

                  Hispanic: OR=5.1 (CI: 1.7-15.6)    p=.004

Other profiles showed borderline OR

# Data analysis comment

- “significant” odds ratio may be result of excessive calculations
- borderline odds ratio may be result of small sample size

# Next steps

- Accumulation of more cases (our site and other sites) in the profiles
- Pathogen discovery
- Strengthen case definition in Profiles 2-8 (similar to Profile 1)
- Seek out experts in specific areas
  - cerebral edema (toxicologist, geneticist)
  - cerebellar (neurologist)
  - movement disorder (neurologist)



# *Acknowledgments*

Viral and Rickettsial Disease Laboratory

Microbial Disease Laboratory

State of California

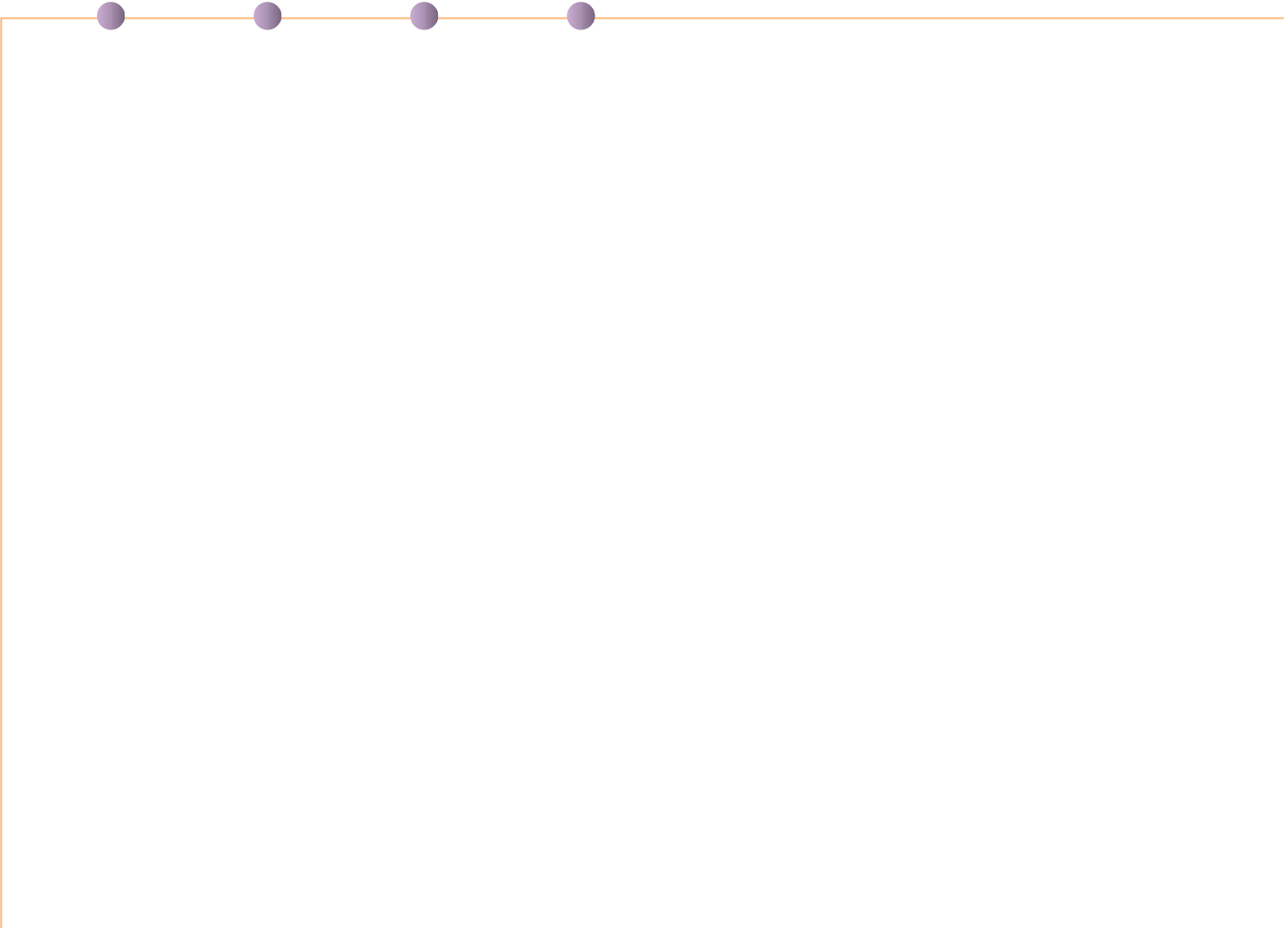


Emerging Infections Program

Respiratory and Enteric Viruses Branch

Centers for Disease Control and Prevention

California physicians



# Profiles/known

- Profile 2

- 2 infx: HSV-1 (19), Chlamydia(1)
- 2 non-infx: Astrocytoma(1), MELA(1)

- Profile 3

- 2 infx: rotavirus(1), EBV(1)
- 1 non-infx: Anti-GAD Stiff man syndrome

# Profile/knowns

- Profile 6 (7 infx)
  - infx: SSPE (2), enterovirus (1)
  - non-infx: neoplastic syndrome (1)

# Profile/known

- Profile 9 (dementia)
  - 4 infx: CJD(3), Whipples (1)
  - 2 noninfx: Astrocytoma (1), MS (1)
- Profile 10 (recurrent)
  - 4 unknown
  - 2 non-infx: vasculitis(1), Atypical MS (1)