Profiles of Clinical Syndromes in Patients with Unexplained Encephalitis

Carol Glaser, DVM, MD
Viral and Rickettsial Disease Laboratory
California State Health Department
CDC-ICEID
March 2002
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 > 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 ≥24 hours, lethargy, or change in personality) or ataxia, AND have 1 or more of the following: fever (T≥38°C), seizure(s), focal neurologic findings, CSF pleocytosis, abnormal EEG or neuroimaging study. Case patients must be ≥6 months of age and immunocompetent.

**Patient Information:**

<table>
<thead>
<tr>
<th>Last name</th>
<th>First name</th>
<th>DOB / /</th>
<th>Medical Record #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Street Address: __________________________ City: ____________________ Zip Code: __________

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

### Race:
- o White
- o Black
- o Native American
- o Asian/Pacific Islander
- o Other
- o Unknown

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

<table>
<thead>
<tr>
<th>Exposures</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any animal contact (including pets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tick bites/exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosquito bites/exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other insect bites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day care (patient or siblings)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunizations up to date?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunizations in last month?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications (including OTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxins or illicit drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh water (swimming or drinking)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingestion of soil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish Ingestion (marine, freshwater)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outdoor activity (camping, hiking, etc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick Contacts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Ethnicity:
- o Hispanic
- o Non-hispanic

### Sex:
- o Female
- o Male

### Travel 1 mo before onset (specify location, dates, and mode of transportation):

<table>
<thead>
<tr>
<th>Travel</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside of United States</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In United States</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In State (out of local area)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Additional Information (please provide details):

<table>
<thead>
<tr>
<th>Information</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient homeless?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever traveled outside the US?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known TB exposures?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous PPD test?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Miscellaneous exposures or potentially pertinent information:

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---
**Patient Name:**

**Clinical:**

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

Date of hospital admission: _/__/__

Do the following apply anytime during current illness:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>In ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever &gt;38°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alt. conscious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme irritability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiff neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal neuro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intractable?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pheno/pentobarb?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>URI or ILI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Brain MRI** date _/__/__ o Normal o Abnormal oND
If abnormal: o temporal lobe involvement
  o white matter involvement
  o hydrocephalus
  o other

**Brain CT** date _/__/__ o Normal o Abnormal oND
If abnormal: o temporal lobe involvement
  o white matter involvement
  o hydrocephalus
  o other

**EEG** date _/__/__ o Normal o Abnormal oND
If abnormal: o diffuse slowing
  o focal temporal epileptiform activity
  o PLEDS
  o other

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Diff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDRL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Was HSV PCR sent? o Yes o No
If yes, please give result & CSF date:

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN/Cr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tox screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy metals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Microbiologic studies/results:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- Antiviral agents
- Antibacterial agents
- Steroids/IVIG

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Facility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 ≥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:
  - Sydenham's 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 inflx: CJD (3), Whipples (1)
  - 2 noninflx: Astrocytoma (1), MS (1)

- Profile 10 (recurrent)
  - 4 unknown
  - 2 non-inflx: vasculitis (1), Atypical MS (1)