Acute Infectious Encephalitis
Challenges in Clinical and Biological Diagnosis

The Value of New Tools and Trusted Recipes
In the Etiological Diagnosis of Viral encephalitis:

« A Virologist’s Point of View »

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ESCMID Course Grenoble, October 2014
(no conflict of interest)
Acute encephalitis:
Infection is still the most commonly demonstrated pathogenic mechanism

- ≈ 50% of cases are due to infectious agents (mainly viruses)
- demonstrated? = confirmed / probable / possible
- importance of molecular methods (real time PCR) in CSF
- serology still useful (intrathecal synthesis, serum)
### ROUTINE STUDIES

**CSF**
- 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
- Gram stain and bacterial culture
- **HSV-1/2 PCR** (if test available, consider HSV CSF IgG and IgM in addition)
- **VZV PCR** (sensitivity may be low; if test available, consider VZV CSF IgG and IgM in addition)
- **Enterovirus PCR**
- Cryptococcal antigen and/or India Ink staining
- Oligoclonal bands and IgG index
- VDRL

**SERUM**
- Routine blood cultures
- **HIV serology (consider RNA)**
- Treponemal testing (RPR, specific treponemal test)
- **Hold acute serum and collect convalescent serum 10–14 d later for paired antibody testing**

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**Conditionnal studies:**
- Host Factors / Geographic Factors / Season and exposure/ Specifics signs

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*Venkatesan A, Clin Infec Dis 2013*
Acute encephalitis:
Increasing description of autoimmune encephalitis
new pathophysiological concepts between virus and autoimmunity

HSV could be involved in autoimmune encephalitis

Increasing description of autoimmune encephalitis
What is the real frequency of autoimmune encephalitis?

The Frequency of Autoimmune N-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project

Gable M, Clin Infect Dis 2012

761 encephalitis < 30 years “diagnostically challenging”

→ 42 viral causes
  (30 entero, 7HSV, 5 WNV)

→ 32 NMDAR encephalitis

Autoimmune N-methyl-D-aspartate receptor encephalitis is a differential diagnosis of infectious encephalitis

Thomas L, J Infect 2012

108 encephalitis
(6mo-88years median 55)

→ 38 infectious causes

→ Autoantibody screening:
  . 2 NMDAR (1.8%)
  13 and 77 year old
  .No MDR in the 17
  HSV encephalitis
Acute encephalitis:
Still 40-50% of acute encephalitis with no clear etiological diagnosis in spite of new molecular tools:

Diagnostic Strategy Used To Establish Etiologies of Encephalitis in a Prospective Cohort of Patients in England

“…. Viral metagenomic studies using next-generation sequencing were undertaken to try to identify any novel pathogens present in 36 samples with no other etiology. Although no new viral sequences were identified, the possibility of their presence at a low titer in some of the samples cannot be excluded.

Ambrose H, J Clin Microbiol 2011
**PCR is the gold standard for the diagnosis of CNS Viral Infections**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Reported sensitivity and specificity of CSF PCR</th>
<th>Evidence class and level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus (HSV)-I Encephalitis</td>
<td>96% and 99% [15]</td>
<td>Class I Level A</td>
</tr>
<tr>
<td>Varicella-Zoster virus (VZV)</td>
<td>80% and 98% [25]</td>
<td>Class III Level C</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>92% and 94% [32]</td>
<td>Class II Level B</td>
</tr>
<tr>
<td>Epstein–Barr Virus (EBV)</td>
<td>97–100% and 98.5% [33,34,36]</td>
<td>Class IV Level C</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>31–95% and 92–100% [37,40, 41]</td>
<td>Class II Level B</td>
</tr>
<tr>
<td>JC virus (JCV)</td>
<td>50–82% and 98.5–100% [48–50]</td>
<td>Class II Level B</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Diagnosis will already have been made on the blood</td>
<td>Class III Level C</td>
</tr>
<tr>
<td>Human T-cell lymphotropic Virus (HTLV-I)</td>
<td>75–99.4% and 98.5% [40,57]</td>
<td>Combination of CSF PCR and anti-HTLV-1 antibody index useful in diagnosis</td>
</tr>
</tbody>
</table>

*Steiner I, Euro J Neurol 2012*
## Virological Diagnosis of Central Nervous System Infections by Use of PCR Coupled with Mass Spectrometry Analysis of Cerebrospinal Fluid Samples

*Leveque N, J Clin Microbiol 2014*

### TABLE 4 Comparison of neurotropic virus detection in CSF samples using routine PCR and PCR-MS assays

<table>
<thead>
<tr>
<th>PCR-MS result</th>
<th>HSV</th>
<th>VZV</th>
<th>CMV</th>
<th>EBV</th>
<th>HHV-6</th>
<th>JCV</th>
<th>Enterovirus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of samples with indicated result in routine PCR assay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>23</td>
<td>8</td>
<td>15</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Neg</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>294</td>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>307</td>
<td>0</td>
<td>326</td>
<td>18&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kappa test (95% CI)</td>
<td>0.80 (0.69–0.92)</td>
<td>0.85 (0.71–0.98)</td>
<td>NC</td>
<td>0.34 (0.10–0.58)</td>
<td>NC</td>
<td>NC</td>
<td>0.84 (0.78–0.90)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>92</td>
<td>94</td>
<td>NC</td>
<td>31</td>
<td>NC</td>
<td>NC</td>
<td>84</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>97</td>
<td>99</td>
<td>NC</td>
<td>97</td>
<td>NC</td>
<td>NC</td>
<td>99</td>
</tr>
</tbody>
</table>
PCR is the gold standard:
What Else?: Use of staged molecular analysis

- Antibacterial or antiviral treatment
- Identify pathogens by routine CSF study
- Stored CSF of persons with viral meningitis or encephalitis cases of unknown etiology
- Multiplex MassTag PCR
- 16S ribosomal RNA
- Pan-viral microarray
- High-throughput pyrosequencing

Meningitis 165
Encephalitis 47

77
131 unexplained meningitis or encephalitis

Hsu CC, Emerg Infec Dis 2013
. **Multiplex Mass tag PCR + 16 s rRNA + MicroArray**: 
  → 31 new diagnosis (23%) / 131

. **After Multiplex Mass tag PCR + 16 s rRNA + MicroArray**: 
  → no need of next generation sequencing

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**Table 3: Pathogens identified by a staged molecular approach**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. (%) cases</th>
<th>No. HIV positive</th>
<th>Molecular method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Meningitis</td>
<td>Encephalitis</td>
</tr>
<tr>
<td><strong>Virus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus*</td>
<td>2 (6)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus 1</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus 2</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>3 (10)</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>16 (52)</td>
<td>16 (64)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>5 (16)</td>
<td>5 (20)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>31 (100)</td>
<td>25 (100)</td>
<td>6 (100)</td>
</tr>
</tbody>
</table>

*Sequences of enteroviruses showed 1 infection each of echovirus 11 and echovirus 30.*

†For 1 case, human herpesvirus 1 was identified by MassTag PCR; in the other, by DNA microarray.
Are there some pitfalls/limits with HSV PCR during Herpes simplex encephalitis?

PCR in CSF: the gold standard since 1995:

- Sensitivities 96-98% (less in children?)
- Specificities 95-99%
- Positive predictive values ≈ 100%
- Negative predictive values ≈ 98%

→ PCR negative and clinical suspicion of HSE:
  → Maintain ACV
  → Perform a second HSV PCR at day 3 - 7: if neg stop acycl.
### Table 3: Number of correct qualitative results per panel member and technology type

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample content</th>
<th>Sample conc. Copies/ml</th>
<th>Total datasets n=227</th>
<th>Conventional</th>
<th>PCR</th>
<th>Real time</th>
<th>NASBA a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Commercial a</td>
<td>n=9</td>
<td>n=79</td>
<td>n=121</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-house b</td>
<td>n=13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n=13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Commercial c</td>
<td>n=79</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-house d</td>
<td>n=121</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n=121</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n=5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **False negative with low viral load HSV 1 = 22 %**
- **False negative with low viral load HSV2 = 77 %**
- **False Positive = 2.5 %**
Herpes Simplex Encephalitis with Two False-Negative Cerebrospinal Fluid PCR Tests and Review of Negative PCR Results in the Clinical Setting

Adler A, Case Rep Neurol 2011

CLINICAL PROBLEM-SOLVING
Caren G. Solomon, M.D., M.P.H., Editor

A Creeping Suspicion


Figure 2. Findings in the Brain-Biopsy Specimen.
Panel A shows diffuse infiltration by foamy macrophages, with patchy perivascular lymphocytic infiltration (hematoxylin and eosin). No intranuclear inclusions are evident. Panel B shows positive immunohistochemical staining (brown) for herpes simplex virus.
## Intrathecal Ab synthesis and herpes simplex encephalit. with neg HSV PCR

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, age</strong></td>
<td>M, 54</td>
<td>F, 67</td>
<td>F, 31</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>38.8°C</td>
<td>38°C</td>
<td>38.5°C</td>
</tr>
<tr>
<td><strong>Neurological signs</strong></td>
<td>Confusion, Coma, Seizures, Personality change</td>
<td>Confusion, Time and place Disorientation, Speech disorder</td>
<td>Confusion, Seizures, Memory loss</td>
</tr>
<tr>
<td><strong>Delay between first</strong></td>
<td>Less than 2 days</td>
<td>Less than 2 days</td>
<td>Less than 2 days but probably symptoms for about 10 days</td>
</tr>
<tr>
<td>signs and hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First CSF</strong></td>
<td>White blood cells: 89/mm³ (lymphocytes: 32%)</td>
<td>White blood cells: 610/mm³ (lymphocytes: 96%)</td>
<td>White blood cells: 190/mm³ (lymphocytes: 87%)</td>
</tr>
<tr>
<td></td>
<td>Protein: 0.53 g/L, Glucose: normal</td>
<td>Protein: 1.24 g/L, Glucose: normal</td>
<td>Protein: 0.98 g/L, Glucose: normal</td>
</tr>
<tr>
<td><strong>EEG recording</strong></td>
<td>Focal periodic discharges in right temporal area (day 1)</td>
<td>Periodic laterised epileptiform discharges in left temporal area (Day 3)</td>
<td>Periodic laterised epileptiform discharges in left temporal area (Day 1)</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Signs of encephalitis (day 20)</td>
<td>Signs of encephalitis (Day 3)</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>PCR for HSV</strong></td>
<td>Negative: day 1, 20</td>
<td>Negative: day 5, 10, 15, 22</td>
<td>Negative: day 1, 3, 7, 17</td>
</tr>
<tr>
<td><strong>Specific Intrathecal</strong></td>
<td>Positive on day 21 after any clinical signs onset.</td>
<td>Positive on day 10 after any clinical signs onset.</td>
<td>Positive on day 17 after any clinical signs onset.</td>
</tr>
<tr>
<td>synthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tibbling-Link index</strong></td>
<td>1.14</td>
<td>8.65</td>
<td>1.40</td>
</tr>
</tbody>
</table>

**Tibbling-link index**: \( \frac{\text{IgG HSV}_{\text{CSF}}}{\text{IgG HSV}_{\text{serum}}} \) / \( \frac{\text{Albumine}_{\text{CSF}}}{\text{Albumine}_{\text{serum}}} \)

**Intrathecal synthesis or Passive transfer?**

*Denes E, Swiss Med Wkl, 2010*
Are there some pitfalls/limits with HSV PCR during Herpes simplex encephalitis?

. Role of viral load monitoring (quantitative PCR) for prognosis?

. one study with a positive corelation:
  *Domingues R, J Clin Microbiol 1998*

. current studies: no correlation
  *Hjalmarsson A, J Neurol 2009*
  *Schloss L, J Med Virol 2009*

. no other biological surrogate markers for outcome?

. Usefulness of a PCR at the end of the treatment?
PCR  HSV positive and non response to Acyclovir Therapy?

- False positive PCR?

- Associated autoimmune encephalitis?

- HSV resistance?

Acyclovir-resistant herpes simplex encephalitis in a patient treated with anti-tumor necrosis factor-α monoclonal antibodies

Schepers k, J Clin Virol 2014

Acyclovir Resistance in Herpes Simplex Encephalitis

Schulte E, Ann Neurol 2010

Herpes simplex virus drug-resistance: new mutations and insights

Andrei G, Curr Opin Infect Dis 2013
Hospital admission, 1st lumbar punctation

1st MRI

Acyclovir: 10mg/kg/8h

2nd MRI: injury progression

2nd lumbar punctation

Neurological deterioration

Acyclovir: 15mg/kg/8h

Foscarvir: 40mg/kg/8h

3rd lumbar punctation

Clinical improvement

Hospital discharge

Fever

23/02*  25/02  01/03*  02/03  03/03  05/03  17/03*  25/03  04/04

RV-171

TK: Wild-type

TK: Adenosine (A) del. in a string of 4As (Nts 184-187)

DNA pol: Wild-type

RV-172

TK: Wild-type

TK: Adenosine (A) del. in a string of 4As (Nts 184-187)

DNA pol: N.A.

RV-178

TK: Adenosine (A) del. in a string of 4As (Nts 133-137)

DNA pol: N.A.

Viral samples

TK and DNA pol genotyping

Schepers k, J Clin Virol 2014
Helicase–Primase Inhibitor Pritelivir for HSV-2 Infection


Viral encephalitis after allogenic stem cell transplantation: rare and different

2 628 patients (1999-2009, retrospective study)
.32 patients: positive PCR for virus in CSF (1.2%):
HHV6 > EBV > HSV
Co-infections
. Viral encephalitis associated with T cell depletion OKT3 or alemtuzumab
. Poor survival

*Including CMV + HHV-6 + JC virus; HHV-6 + HHV-7; CMV + HHV-6; HSV + EBV; CMV + VZV + HSV + EBV.

Schmidt-Hieber M, Haematologica 2011
EBV encephalitis after allogeneic hematopoietic stem cell transplantation

. Prospective survey 172 patients (2008-2011)

. 3-y cumulative incidence of EBV-associated CNS diseases: 8.6 ± 2.4%

. 12 cases EBV-associated CNS disease:

. 8 Post Transplant Lymphoproliferative Disease (PTLD)
  . 4 isolated CNS PTLD,
  . 4 systemic PTLD with brain involvement of whom 2 encephalitis

. 3 encephalitis

. 1 myelitis

Liu QF, Transpl Infect Dis 2013
EBV load in CSF: which **threshold**?
EBV load in CSF: which threshold?

Weinberg A et al, Ann Neurol 2002
How differentiate isolated CNS PTLD from EBV encephalitis when Biopsy is impossible

.11 patients with CNS PTLD :

→ 7/11 CD19 CD20 B cell

→ 3/11 clonal rearrangement of Ig Gene

. 8 patients without PTLD :

→ no predominance of CD19 CD20 B cell

→ no clonal rearrangement of Ig Gene

Wu M, PLOS ONE 2013
Case report

40 year old patient renal transplantation in 2004
February 2008 Hospitalization for seizure

Impossibility of lumbar puncture
Cerebral biopsy : inconclusive histology

EBV load in biopsy $> 2 \times 10^6$ copies/ ug d’ADN
Post Transplantation Lymphoproliferative Disease
Case report

Mr X 40 year old, August 2011 after Corsica holydays and notion of mosquito bites
febrile encephalitis with cerebellitis
maculo papular rash

- Normal CT scan and MRI TDM / IRM normale

- CSF: 12 cell /mm³ (80 % lymphocytes) /
  negative gram stain
  protein 0.56 g/L
  glucose: normal

- Hepatic Cytolysis ( Transaminases X6)
. Hepatitis E encephalitis:
  positive IgM)
  HEV PCR positive in blood / CSF / stools

. Notion de Figatelle in Corse +++
Today and Tomorrow:
rapid and easy to use syndrome-based multiplex PCR

The Day after Tomorrow:
DNA microarrays and mass spectrometry?
Next Generation Sequencing?.

Serology still helpful

*always*: «… recommended tests should not supplant clinical judgment … »
Progressive multifocal leukoencephalopathy (PML) and JC virus

Debiasy Clin Microbiol Rev 2004,

. CSF PCR:
  . Sensitivity 50-95% (better on centrifuged CSF)
  . Specificity around 100%
  . High viral load in CSF (> 4.7 log units) correlated shorter survival

. JCV PCR in urine or blood not predictive of PML
Progressive multifocal leukoencephalopathy (PML) and HIV

1. **HAART**: Significant decrease of JC viral load:
   - reduced rate of positive detection
   - risk of false negative PCR correlated with CD4 > 100 µl

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results for:</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-HAART era</td>
<td>HAART era</td>
</tr>
<tr>
<td>Positive detection rate (%)</td>
<td>17/19 (89.5 [75.5–103.5])</td>
<td>23/40 (57.5 [42.1–72.9])</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>82/83 (98.8 [96.4–101.2])</td>
<td>141/141 (100)</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>98</td>
<td>69</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>95</td>
<td>100</td>
</tr>
</tbody>
</table>

2. **Immune reconstitution inflammatory syndrome (IRIS)**

up to 23% of PML in HIV patients
low or negative viral load

Marzochetti A et Al, J Clin Microbiol, 2005
Tans CS et al, Lancet Neurol 2010
Progressive multifocal leukoencephalopathy (PML)

3. immunomodulatory medications (Tans CS et al, Lancet Neurol 2010)
   - Natalizumab and MS or Crohn
   - Efalizumab and psoriasis
   - Rituximab

4. PCR and virus variability (Landry MI et al, J Clin Virol 2008)

   31-year-old woman
   .corticosteroid for suspicion of Multiple sclerosis
   aggravation: clinical and MRI: MS/ADEM/PLM/Vasculitis

   First CSF negative for JC PCR (VP1): negative

   Deterioration (intravenous immunoglobulin/plasma exchange)

   cerebral biopsy: polyoma particles by EM

   Control of the CSF with another JC PCR (large T antigen): highly +

   Suspicion of PLM with first PCR negative:
   Repeated test with the same or different PCR targets
   If PCR repeatedly negative consider brain biopsy
VZV encephalitis: the unknown (?) second etiology of infectious encephalitis

8 % (n=20) of the cases in the 253 French cases

- 16 PCR + in CSF:
  8 adults without cutaneous involvement
  7 adults with cutaneous involvement
  1 boy with chicken pox

- 4 PCR negative
  2 boys with acute encephalitis within varicella (1 day, 1 week)
  2 adults acute encephalitis within or after zoster (3 days, 3 weeks after)

- 15 % of mortality (>75 year-old) (vs 5% in our HSV cases)

- 3 year outcome: 41 % moderate to severe sequelae (glasgow outcome scale)

De Brouker T, 2012
VZV CNS diseases still persist but change with and varicella vaccine:

1. USA: VZV vaccine coverage (at least one dose) 90% in 2007

2. California Encephalitis project 1998-2009:

\[
\frac{43}{4021} \text{ CSF} = \text{PCR VZV positive (1%)}
\]

- 26 CSF analyzed (7 patients <16 year-old, 4 vaccinated):
  - 13 meningitis
  - 11 encephalitis (7 without Rash)
  - 2 ADEM (1 without rash)

decrease of VZV encephalitis in childhood

one case (meningitis) with the Oka vaccine strain

≈10 cases of CNS disease associated with VZV vaccine in the literature (mostly meningitis)

Pahud BA et al, J Infect Dis 2011
Autoimmune N-methyl-D-aspartate receptor encephalitis is a differential diagnosis of infectious encephalitis

Thomas L, J infect 2012

<table>
<thead>
<tr>
<th>Etiology</th>
<th>N. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>17</td>
<td>15.7</td>
</tr>
<tr>
<td>VZV</td>
<td>7</td>
<td>6.5</td>
</tr>
<tr>
<td>CMV</td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>Toscana virus</td>
<td>1</td>
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<tr>
<td>Enterovirus</td>
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<td><strong>Bacteria</strong></td>
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<td>Mycobacterium tuberculosis</td>
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