Herpetic Encephalitides: Imaging
HSV-1 and an Uncommon Mimic

Erin Bettendorf, Harvard Medical School Year III
Gillian Lieberman, MD

March 2011
Our Patient: Presentation

- 60 year old man with 1 week of:
  - Fevers to 104
  - Severe headaches
  - Confusion & Memory difficulty
- Sleeping 20 hours per day
- “Not himself” according to his family
- His wife has also noted episodes of unresponsiveness when he appears “pale and clammy”
  - He describes a rising sensation in chest prior to these events
- Review of Systems:
  - No neck stiffness, motor or sensory changes, vertigo, shortness of breath, chest pain, abdominal pain, nausea, vomiting, dysuria, incontinence, rashes or joint pain
Our Patient: Further History

• Past Medical History
  – Temporal lobe epilepsy (last seizure in 1985), Hypertension, Depression, Hyperlipidemia
• Medications:
  – Carbamazepine, Simvastatin, Atenolol, Venlafaxine, Aspirin
• Allergies: None
• Social History:
  – Engineer, lives in a rural area. No alcohol, tobacco or recreational drugs.
• Family History: Non-contributory
Our Patient: ED Course

• Vitals: T 102, HR 54, BP 126/56, RR 18, O2 Sat 97% on 2L NC
• He became unresponsive for 30 seconds
  – After which he was more sleepy for several minutes
  – Consistent with a complex partial seizure
• Exam:
  – Well-appearing, alert, orientedx3, talkative, poor memory (short & long-term), & poor calculation
  – No other focal findings neurologically or systemically
• Some Labs on Admission:
  – WBC 4.1, Hct 38.6, Na 130, lactate 1.3
Our Patient: Next Steps

• Head imaging options for our patient:
  – Plain film
  – CT – with and/or without contrast
  – CT Angiogram
  – MRI – with and/or without contrast
  – MR Angiogram

• Consider what you would order and continue to the next slide to see the American College of Radiology’s recommendations.
# ACR Appropriateness Criteria: New Headache

## Variant 9:

**New headache. Suspected meningitis/encephalitis.**

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI head without and with contrast</td>
<td>8</td>
<td>Usage of CT vs MRI depends on local preference and availability. See statement regarding contrast in text under “Anticipated Exceptions.”</td>
<td>O</td>
</tr>
<tr>
<td>CT head without contrast</td>
<td>8</td>
<td>Usage of CT vs MRI depends on local preference and availability. To exclude signs of increased intracranial pressure, mass, or mass effect.</td>
<td>☳○○</td>
</tr>
<tr>
<td>MRI head without contrast</td>
<td>6</td>
<td>MRV should also be performed. See statement regarding contrast in text under “Anticipated Exceptions.”</td>
<td>O</td>
</tr>
<tr>
<td>MRA head with or without contrast</td>
<td>6</td>
<td>MRV should also be performed. See statement regarding contrast in text under “Anticipated Exceptions.”</td>
<td>O</td>
</tr>
<tr>
<td>CT head without and with contrast</td>
<td>6</td>
<td>MRI preferable, depending on availability.</td>
<td>☳○○</td>
</tr>
<tr>
<td>CTA head</td>
<td>3</td>
<td>Useful for problem solving or if there is a strong suspicion of vascular disease.</td>
<td>☳○○</td>
</tr>
</tbody>
</table>

**Rating Scale:** 1, 2, 3 Usually not appropriate; 4, 5, 6 May be appropriate; 7, 8, 9 Usually appropriate

*Relative Radiation Level*
Our Patient: Recommended Imaging Studies

• According to the American College of Radiology’s Appropriateness Criteria:
  – MRI with and without contrast is your first choice
  – CT without contrast is useful to look for masses, hemorrhage or increased intracranial pressure

• Our patient first had a non-contrast head CT, followed by an MRI with and without contrast

Our Patient: Head CT

- Brain window
- Read as normal
  - No evidence of hemorrhage, mass or infarction
- BUT – a limited study for many diseases within the brain parenchyma

Axial C- Head CT
Source: BIDMC PACS
Our Patient: Head CT Anatomy

- Where are we in the brain?
  - At the level of the temporal lobes
  - Midbrain (star) is visible

Axial C- Head CT
Source: BIDMC PACS
Our Patient: Head T2 MRI

- Edema in the left medial temporal lobe (arrow)
- T2 MRI
  - Both CSF & Fluid are bright

Temporal lobe edema on axial C+ FSE (fast spin echo) T2 MRI
Source: BIDMC PACS
Our Patient: Head FLAIR MRI

- Edema in the left medial temporal lobe (arrows)
- On FLAIR MRI - CSF is Dark and Edema is Light
Next let’s consider the differential diagnosis based on the imaging findings alone.

– Then we will highlight the most likely diagnosis based on our patient’s history plus imaging.
Our Patient: Differential Diagnosis Based on Imaging

- Herpes encephalitis
- Paraneoplastic Limbic Encephalitis
  - Small cell lung cancer, seminoma, thymoma, breast cancer, Hodgkin’s lymphoma
- Hypoxia
- Ganglioglioma
  - Generally benign tumor found in temporal lobe
- Mesial temporal sclerosis
  - Atrophy of hippocampus
- Post-ictal
Our Patient: Likely Diagnosis Based on Imaging plus History

- Herpes encephalitis
- Limbic encephalitis - paraneoplastic
- Hypoxia
- Ganglioglioma
- Mesial temporal sclerosis
- Post-ictal
Based on the most likely diagnosis from his history and imaging, our patient next had a **lumbar puncture** to confirm the diagnosis.
Our Patient: Diagnosis

• A lumbar puncture with elevated opening pressure showed these CSF findings:
  – Tube 4: 285 WBC, 25 RBC, 0 polys, 95 lymphs, 5 monos
  – Tube 1: 350 WBC, 25 RBC, 1 poly, 90 lymphs, 9 monos
  – PCR: HSV-1 positive

• Diagnosis: Herpes Simplex Virus type 1 Encephalitis
Our Patient: Management and Outcome

Treatment:

- **Acyclovir** 1000mg IV Q8H for 21 days
- Started on arrival in the ED and continued based on the CSF results

• Our patient’s long-term outcome:
  - Memory difficulty (long and short term)
  - Complex partial seizures
  - No other lasting deficits
Now that we have confirmed the diagnosis of HSV-1 encephalitis and treated our patient, let’s continue and look at an overview of HSV-1 encephalitis and common imaging findings.
Overview of HSV-1 Encephalitis (HSVE)

- Herpes simplex virus type 1
  - Most common cause of fatal sporadic viral encephalitis
  - No history of herpetic lesions necessary
- Clinical Presentation
  - Acute onset, febrile, headache, seizures, focal neurological deficits
  - Confusion, memory loss, altered mental status
- High Mortality – 70% without treatment
  - Decreases to 20-30% with acyclovir treatment
  - Survivors often have neurological deficits

Companion Patient #1: Common HSVE Patterns on Imaging

- Severe edema (star)
- Tissue necrosis (arrow)
- Inflammatory infiltrate
- Occasionally hemorrhage
- Can be asymmetrically bilateral (stars)
- Limbic location or temporal lobes are common

Coronal FLAIR MRI on admission

Coronal FLAIR MRI at 12 months

Companion Patient #1: Changes with Time

- Some patients have worsening MRI findings despite clinical improvement.
- The cause is unclear, but may be due to:
  - Atrophy and cystic changes over time
  - Relapsing or chronic disease
  - Immune-mediated tissue damage
  - Wallerian degeneration of nerves

Our Patient: Classic Appearance

• Before we move on, look at our patient’s MRI again and remember this appearance
  – This is **CLASSIC** for herpes simplex type 1 encephalitis
  – If this patient is febrile with headache, seizures or other neurologic findings – give acyclovir!
    • Then check a PCR of the CSF for HSV-1

Temporal lobe edema on axial C+ FLAIR MRI
Source: BIDMC PACS
Now let’s take some time to review important neuroanatomy related to HSV-1 encephalitis
Companion Patient #2: Neuroanatomy of HSVE

The most common areas involved in HSVE –
- Medial temporal lobe
- Thalamus
- Cingulate gyrus
- Insular cortex

But more widespread inflammation is often present

Neuroanatomy of the Limbic System

- HSV-1 classically attacks limbic structures:
  - Medial temporal lobes
  - Hippocampus
  - Amygdala
  - Subfrontal area
  - Cingulate gyri

- How does it enter?
  - One potential site is the olfactory nerve
  - Continue to the next slide to see more routes of infection

Cartoon of limbic system anatomy.
Levitz RE. *Heart Lung*. 1998.
Anatomy of HSVE Spread

- Primary or Reactivation of previous HSV-1 infection
  - HSV-1 can spread along the small meningeal branches of the trigeminal nerve from the trigeminal ganglion
  - Through olfactory nerves as mentioned on the last slide
- From previously infected CNS/brain tissue


Companion Patient #3: Imaging-Based Neuroanatomy, Blank MRI

- Find the following structures on the MRI and continue to the next slide to see an annotated image
  - Caudate
  - Thalamus
  - Putamen
  - Insula
  - Lateral ventricles
  - Internal capsule
Companion Patient #3: Imaging-Based Neuroanatomy Answers

- Caudate
- Thalamus
- Putamen
- Insula
- Lateral ventricles
- Internal capsule
In addition to the CT, and the T2 and FLAIR MRIs, there are several other ways that people have imaged HSV-1 encephalitis.

– Let’s review some examples now
Companion Patient #4: Other Imaging Features in HSVE

**Diffusion Weighted Image (DWI)**
- Increased intensity in areas of decreased proton movement (edema, pus, etc.)
- Potentially useful early in HSVE course because it shows more widespread damage early on compared to other MRI sequences
- Remember – Edema is Light and CSF is dark on DWI

HSV-1 encephalitis seen on four MRI modalities.
Companion Patient #5: Other Imaging Features in HSVE

• Diffusion Weighted Image (DWI)
• CT Perfusion
  – Shows flow of contrast within tissues
  – Here is an area of hyperperfusion
  – CT access may be more available in emergencies than MRI, helping to guide diagnostic decision-making
  – But it’s nonspecific, so you need more information to make a diagnosis

Companion Patient #6: Other Imaging Features in HSVE

- Diffusion weighted imaging (DWI)
- CT Perfusion
- Single photon-emission computed tomography (SPECT)
  - Nuclear medicine study using uptake of Technetium-ECD
  - More widely available & cheaper than PET scans, but less available than MRI

Correlation of T2 MRI changes in HSV-1 encephalitis (left) with increased SPECT uptake (right).
Our Patient: Imaging Recommendation

- In spite of all of these various imaging options, MRI FLAIR is still the test of choice for imaging herpes simplex type 1 encephalitis!

Temporal lobe edema on axial C+ FLAIR MRI
Source: BIDMC PACS
Now that we have discussed HSV-1 encephalitis, let’s take a look at another infection of the temporal lobes.
HSV-1 Encephalitis Mimic

• Temporal lobe changes on MRI with the right clinical picture (fever, headache, seizures, etc.) are classic for herpes simplex type 1 encephalitis…
  – However, another herpes infection can appear the same on MRI…
  – So, take a look at the imaging on the next slide, then continue on to read about this viral encephalitis
Companion Patients 7 & 8: Temporal Lobe Edema

Axial FLAIR MRI showing left temporal lobe edema

Axial FLAIR MRI showing asymmetrically bilateral temporal lobe edema

Note that the temporal lobe edema on these FLAIR MRI images appears similar to our patient’s imaging.
Companion Patients 7 & 8: Diagnosis

• These two patients were diagnosed with human herpesvirus 6 encephalitis
• Continue to the next slide to learn about HHV-6 encephalitis
Human Herpesvirus-6 Encephalitis: Overview

• Clinical presentation is the same
  – Fever, headache, focal neurologic deficits, seizure, coma
• Similar predilection for limbic system and medial temporal lobes
• BUT – HHV-6 encephalitis occurs largely in immunocompromised people
  – Especially after bone marrow transplant
• This is worth remembering because it has a different treatment than HSV-1 encephalitis
  – Ganciclovir or Foscarnet

Now that we’ve seen many patients with HSV-1 encephalitis and two with HHV-6 encephalitis showing a preference for the temporal lobes, let’s continue and examine an unusual presentation of one of these.
Companion Patient #3: Diffuse Viral Encephalitis

Remember – sometimes the appearance isn’t classic! Above you see diffuse lesions from an uncommon presentation of HHV-6 encephalitis.
Now you know how to recognize HSV-1 and HHV-6 encephalitis on imaging. Continue for a review of the important take-home points from this presentation.
Take-Home Points

• HSV-1 & HHV-6
  – Temporal lobe & limbic system
  – Fever, headache, seizures, focal neuro deficits, coma
  – Best seen on MRI
  – HSV-1 – in anyone!
  – HHV-6 – post-bone marrow transplant
  – Different treatments
    • HSV-1 – Acyclovir
    • HHV-6 – Ganciclovir or foscarnet
References

Acknowledgements

Gillian Lieberman, MD
Gul Moonis, MD
Seth Berkowitz, MD
Penny Greenstein, MD
Rafael Rojas, MD
Ciro Ramos-Estebanez, MD