Case 31 - 2019: A 45-Year-Old Woman with Headache and Somnolence

Julia Beck, Michael Oropeza, Rayna Martinson, & Matt McClintock
Introduction to the Patient

- Female, 45 experiencing a severe headache (pounding sensation) from occiput to retro-orbital area and forehead along with lethargy
- Married, mother of three school-age children
- On disability benefits, spends most time indoors
- Smoked 10 cigarettes/day (quit 22 years prior), alcohol use in moderation, no use of illicit drugs
- Family history of coronary artery disease, diabetes, migraines, hypertension, atrial fibrillation, and multiple sclerosis (MS)
Migraines are recurring types of headaches that cause moderate to severe throbbing or pulsing pain. Other symptoms associated with it are nausea, weakness, and optical/auditory sensitivity. Which of the following is not true of migraines?

A) Migraines can be caused by tumors, abnormal brain structures, or stroke.
B) Neurostimulation surgeries can provide relief.
C) Caffeine can cause a migraine.
D) In order to be considered a migraine, you must experience an aura.
E) None of the above.
Migraines are recurring types of headaches that cause moderate to severe throbbing or pulsing pain. Other symptoms associated with it are nausea, weakness, and optical/auditory sensitivity. Which of the following is not true of migraines?

A) Migraines can be caused by tumors, abnormal brain structures, or stroke.
B) Neurostimulation surgeries can provide relief.
C) Caffeine can cause a migraine.
D) In order to be considered a migraine, you must experience an aura.
E) None of the above.
Patient History

- MS
- Seronegative inflammatory polyarthritis (progressive despite immunosuppressive therapies)
- Hypertension
- Depression
- Anxiety
- Melanoma
- Inflammatory flexor tenosynovitis (extended carpal tunnel release and radical flexor tenosynovectomy)
- Current medications: rituximab, hydroxychloroquine, leflunomide, methylprednisolone, butalbital-acetaminophen-caffeine tablets, diclofenac, hydrocodone-acetaminophen, inhaled albuterol, duloxetine, bupropion, quetiapine, trazodone, lisinopril, nifedipine, cholecalciferol, and folic acid
Seronegative rheumatoid arthritis is a diagnosis of rheumatoid arthritis without the presence of the rheumatoid factor (RF) antibody. Along with the RF antibody, which auto-antibody is used to detect rheumatoid arthritis serologically?

A) Anti-thrombin  
B) Anti-citrullinated peptide  
C) Anti-Smith  
D) Anti-smooth muscle  
E) All of the above
Seronegative rheumatoid arthritis is a diagnosis of rheumatoid arthritis without the presence of the rheumatoid factor (RF) antibody. Along with the RF antibody, which auto-antibody is used to detect rheumatoid arthritis serologically?

A) Anti-thrombin
B) Anti-citrullinated peptide
C) Anti-Smith
D) Anti-smooth muscle
E) All of the above
History of Current Illness

- Experienced chronic migraines (last happened 10 years ago)
  - Symptoms sometimes come back (relieved with butalbital-acetaminophen-caffeine therapy)
- No history of head injury
- 13 days prior to admission to Massachusetts General
  - Went to another hospital and reported photophobia, nausea and vomiting
  - Received medications to relieve symptoms and sent home
- 7 days prior to admission
  - Headache and nausea return
- 3 days prior to admission
  - Lethargic, disoriented, decreased verbal output
Photophobia is an intolerance of light. Which of the following is not a common cause of photophobia?

A) Narcolepsy
B) Migraines
C) Supranuclear palsy
D) Pituitary tumors
E) Meningitis
Photophobia is an intolerance of light. Which of the following is not a common cause of photophobia?

A) Narcolepsy
B) Migraines
C) Supranuclear palsy
D) Pituitary tumors
E) Meningitis
Presentation Upon Transfer to Massachusetts General Hospital
Appearance and Physical/Mental Exams

- Repetitive blinking and squinting of left eye, but no ptosis or facial droop
- Mild resistance to neck flexion was noted
- Ulcers on distal fingers, but no rashes
- Mild postural tremor (from MS)
- Patient wrote “magical” when asked to write her name
- Could follow simple but not complex commands
- Persistently poor mental function
Vitals

- Temperature: **36.3°C**
  - (ref. 36.5 - 37.3)
- Pulse: **90bpm**
  - (ref. 60-100)
- Blood pressure **106/65 mmHg**
  - (ref. 90/60 - 120/80)
- Respiratory rate **18 breaths/min**
  - (ref. 12-18)
- Oxygen saturation **98%**

Fairly normal vitals despite abnormal vitals during previous hospital visits
  - BP as high as 160/110 mmHg, pulse 110 beats per minute

- Upon admission to Massachusetts General Hospital
  - Blood work
  - Lumbar puncture
  - MRI of the head
  - Given antimicrobials including doxycycline, acyclovir, and meropenem

- 10 days after admission to MGH
  - Repeat MRI
The patient in this case study has multiple sclerosis. MS is an autoimmune disease in which neurons become demyelinated, leading to a reduced efficiency of signal conduction between neurons and nerve damage. Which of the following is false regarding myelin?

A) Myelination begins in the brainstem and cerebellum before birth, and it continues through adolescence in normal development.
B) Oligodendrocytes are responsible for myelination in the PNS, and Schwann cells myelinate axons in the CNS.
C) Myelination increases axonal membrane resistance and decreases membrane capacitance.
D) Myelin is made up of protein and fatty substances.
E) The gaps within the myelin sheath are called Nodes of Ranvier.
The patient in this case study has multiple sclerosis. MS is an autoimmune disease in which neurons become demyelinated, leading to a reduced efficiency of signal conduction between neurons and nerve damage. **Which of the following is false regarding myelin?**

A) Myelination begins in the brainstem and cerebellum before birth, and it continues through adolescence in normal development.

B) **Oligodendrocytes are responsible for myelination in the PNS, and Schwann cells myelinate axons in the CNS.**

C) Myelination increases axonal membrane resistance and decreases membrane capacitance.

D) Myelin is made up of protein and fatty substances.

E) The gaps within the myelin sheath are called Nodes of Ranvier.
Labs and Imaging
<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Other Hospital</th>
<th>7 Days before Admission, Other Hospital</th>
<th>3 Days before Admission, Other Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-cell count (per mm(^3))</td>
<td>4000–11,000</td>
<td>6490</td>
<td>8450</td>
</tr>
<tr>
<td>Platelet count (per mm(^3))</td>
<td>135,000–400,000</td>
<td>260,000</td>
<td>166,000</td>
</tr>
<tr>
<td><strong>Differential count (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>45–68</td>
<td>59.8</td>
<td>71.3</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>25–44</td>
<td>26.8</td>
<td>17.3</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2.5–8.1</td>
<td>10.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.0–3.6</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.0–1.8</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Immature granulocytes</td>
<td>0.0–0.9</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>120–246</td>
<td></td>
<td>304</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td>0–20</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>C-reactive protein (mg/liter)</td>
<td>0–8.0</td>
<td>6.0</td>
<td>48.5</td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td>0–0.08</td>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>
# Lumbar Puncture Results at 1st Hospital (before MGH)

<table>
<thead>
<tr>
<th>Cerebrospinal fluid</th>
<th>Colorless</th>
<th>Colorless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>Colorless</td>
</tr>
<tr>
<td>Turbidity</td>
<td>Clear</td>
<td>Clear</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>40–70</td>
<td>45</td>
</tr>
<tr>
<td>Total protein (mg/dl)</td>
<td>15–45</td>
<td>190</td>
</tr>
<tr>
<td>Red-cell count (per mm³)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>0–5</td>
<td>63</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Xanthochromia</td>
<td>Not present</td>
<td>Not present</td>
</tr>
</tbody>
</table>

* To convert the values for glucose to millimoles per liter, multiply by 0.05551.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
## Table 1. Laboratory Data.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, This Hospital</th>
<th>On Admission, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4500–11,000</td>
<td>5710</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–400,000</td>
<td>93,000</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>40–70</td>
<td>68.1</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>22–44</td>
<td>20.0</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4–11</td>
<td>7.5</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–8</td>
<td>1.9</td>
</tr>
<tr>
<td>Basophils</td>
<td>0–3</td>
<td>0.7</td>
</tr>
<tr>
<td>Immature granulocytes</td>
<td>0.0–0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>110–210</td>
<td>424</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td>0–20</td>
<td>5</td>
</tr>
<tr>
<td>C-reactive protein (mg/liter)</td>
<td>0–8.0</td>
<td>47.3</td>
</tr>
</tbody>
</table>

* Values in red indicate abnormal ranges.

*Reference intervals taken from the Laboratory Medicine handbook.
**CSF tested additionally for autoantibodies, but results were negative**
(can indicate certain autoimmune disorders if positive)
The patient in this case had high levels of protein in her cerebrospinal fluid, which was determined after a lumbar puncture (spinal tap). Which of the following is NOT a possible cause of high protein levels in CSF?

A) Brain tumor
B) Meningitis
C) Cerebral hemorrhage
D) Multiple sclerosis
E) All of the above can cause high CSF protein levels.
The patient in this case had high levels of protein in her cerebrospinal fluid, which was determined after a lumbar puncture (spinal tap). Which of the following is NOT a possible cause of high protein levels in CSF?

A) Brain tumor
B) Meningitis
C) Cerebral hemorrhage
D) Multiple sclerosis
E) All of the above can cause high CSF protein levels.
Magnetic Resonance Imaging (MRI) Scan #1

- Taken upon admission to MGH
- Leptomeningeal enhancement in the posterior fossa (A,B,C)
- Signal hyperintensity in sulci of temporal and occipital lobes (MS)

Figure 1. Initial MRI of the Head.
MRI of the head was performed on admission to this hospital. Shown are images obtained at the level of the dentate nuclei, third ventricle, and lateral ventricles (left, middle, and right columns, respectively). T1-weighted contrast-enhanced images (Panels A, B, and C) show subtle leptomeningeal enhancement in the posterior fossa. T2-weighted fluid-attenuated inversion recovery (FLAIR) images (Panels D, E, and F) show signal hyperintensity in the sulci of the temporal and occipital lobes, as well as signal hyperintensity in the right posterior periaqueductal region that corresponds to a punctate focus of restricted diffusion on diffusion-weighted images (Panels G, H, and I).
The brain is covered with 3 membranous layers called the meninges, found just underneath the cranium. From outermost to innermost, what is the order of these 3 layers found in the brain?

A) Dura mater, arachnoid mater, pia mater  
B) Arachnoid mater, pia mater, dura mater  
C) Pia mater, arachnoid mater, dura mater  
D) Dura mater, pia mater, arachnoid mater  
E) Pia mater, dura mater, arachnoid mater
The brain is covered with 3 membranous layers called the meninges, found just underneath the cranium. **From outermost to innermost, what is the order of these 3 layers found in the brain?**

A) **Dura mater, arachnoid mater, pia mater**

B) Arachnoid mater, pia mater, dura mater

C) Pia mater, arachnoid mater, dura mater

D) Dura mater, pia mater, arachnoid mater

E) Pia mater, dura mater, arachnoid mater
MRI Scan #2

-Performed to see if condition had progressed or if any changes could be seen
-Repeat MRI 10 days after admission
-Leptomeningeal enhancement and hydrocephalus
-Hyperintensity (basal ganglia, hippocampi, dentate nuclei, etc)
Comparing MRI Scans (10 days apart)
Differential Diagnosis
Key Considerations

- This patient is immunocompromised due to the following:
  - Multiple sclerosis
  - Seronegative inflammatory polyarthritis

- Lumbar Puncture
  - Elevated opening pressure of 28 cm H$_2$O
    - Reference range: 6 - 25 cm
  - Elevated white-cell count: 298 per mm$^3$
  - Elevated glucose concentration: 107 mg/dl
  - Elevated total protein concentration: 572 mg/dl

- MRI
  - Hydrocephalus (“water on the brain”)
  - 5-mm lesion in the splenium of the corpus callosum
  - Plaques of demyelination and axonal loss
Where is cerebrospinal fluid (CSF) produced in the brain?

A) Choroid plexus
B) Cerebellum
C) Pons
D) Medulla
E) Subarachnoid space
Where is cerebrospinal fluid (CSF) produced in the brain?

A) Choroid plexus
B) Cerebellum
C) Pons
D) Medulla
E) Subarachnoid space
Noninfectious Causes

- Autoimmune encephalopathy
- Paraneoplastic encephalopathy
- Carcinomatous meningitis
- Lymphocytic meningitis
- Use of certain medications (NSAIDs)
Noninfectious Causes

- **Autoimmune encephalopathy**
  - *Encephalopathy*: a broad term for any brain disease or damage that alters brain structure and/or function
  - The body’s immune system attacks healthy brain cells, leading to brain inflammation
  - **Fitting diagnosis?**
    - Rapid progression of impaired memory and cognition, speech and vision problems, and nuchal rigidity
    - MRI results

- **Paraneoplastic encephalopathy**
  - Occurs when T-cells mistakenly attack normal cells in the nervous system
  - Triggered by an abnormal immune response to a tumor
  - **Fitting diagnosis?**
    - Lesion in the spenium
    - Rapid onset of neurologic symptoms
Noninfectious Causes

- **Carcinomatous meningitis**
  - Cancer cells from a primary tumor undergo metastasis to the meninges
  - CSF provides a habitable environment for the growth of these cells
  - *Fitting diagnosis?*
    - History of melanoma
    - Headache, confusion, speech problems, somnolence

- **Lymphocytic meningitis**
  - Recurring form of aseptic meningitis, usually caused by herpes simplex virus 2
  - *Fitting diagnosis?*
    - Migraine-like symptoms

- **Nonsteroidal antiinflammatory drugs**
  - Uncommon disease that leads to meningitis
  - *Fitting diagnosis?*
    - Seen in patients with autoimmune diseases
    - Prescribed diclofenac to treat headaches
Infectious Acute Meningoencephalitis

- **Protozoa**
  - Acanthamoeba species

- **Viral infection**
  - Influenza
  - Insect-borne virus
  - Adenovirus

- **Bacterial meningitis**
  - *Mycobacterium tuberculosis*

- **Fungal meningoencephalitis**
  - *Cryptococcus neoformans*
Infectious Causes - Protozoa

- Single-celled eukaryotes that feed on organic matter, including tissue
- Acanthamoeba species can cause disease in immunocompromised patients

**Fitting diagnosis?**
- Patient is immunocompromised by MS and RA
- Lesion was visible on corpus callosum
- Photophobia, blinking and twitching left eye
Infectious Causes - Virus

- **Influenza-associated encephalopathy**
  - Respiratory symptoms that progress with altered mental state, confusion, and seizures
  - Transmitted through droplets in the air

- **Fitting diagnosis?**
  - Symptoms associated with encephalopathy
  - High protein concentration in CSF
  - Age of patient
Infectious Causes - Virus

- Mosquito-borne viruses
  - West Nile virus
  - St. Louis encephalitis virus
  - La Crosse virus
  - Eastern equine encephalitis virus
- Tickborne Powassan virus
- Fitting diagnosis?
  - Location of patient’s second home
  - Time of year
Infectious Causes - Virus

- Adenovirus meningoencephalitis
  - Extremely rare condition that affects the brain and spinal cord, notably inflammation and decreased cognitive functioning
  - Transmitted through droplets in the air, similar to the flu
  - Normally is presented by respiratory symptoms, flu-like symptoms, conjunctivitis, and pneumonia
  - Immunocompromised population is at a greater risk for developing more severe symptoms

- Fitting diagnosis?
  - Meningitis seen in MRI
  - Patient is immunocompromised
  - Adenovirus causes meningitis and/or meningoencephalitis as a primary infection
Infectious Causes - Bacteria

- *Mycobacterium tuberculosis* meningitis
  - Slow developing meningitis (1-2% of TB cases) following initiation of infection in lungs
  - At-risk populations include the homeless, those with HIV, and other immunocompromised individuals
  - Spread through droplets in the air
  - **Fitting diagnosis?**
    - Patient did not respond to antimicrobial therapy
    - Hydrocephalus
    - CSF glucose level
      - Typically low in TB meningitis
Infectious Causes - Fungi

- **Fungal meningoencephalitis**
  - Usually subacute or chronic
  - Depends on species
    - *Cryptococcus neoformans*
      - Infects brain and spinal cord
      - Patients with compromised immune systems are at risk
      - Transmitted through inhalation of fungal particles
  - **Fitting diagnosis?**
    - Treated with methylprednisolone due to MS
    - Tested for cryptococcal polysaccharide in CSF
Based on the information provided on each differential diagnosis and this patient’s labs and imaging, what is your final diagnosis?

A) Carcinomatous meningitis
B) Adenovirus meningoencephalitis
C) Diclofenac-induced (NSAID) aseptic meningitis
D) Bacterial meningitis
E) Rapid progression of MS
Final Diagnosis

Adenovirus meningoencephalitis
Treatment
Treatment

- Lab grew a viral culture of CSF from spinal tap taken at 1st hospital and after 8 days of incubation, results came back positive for the growth of adenovirus type 2. PCR ran to confirm.
- Patient received 1 dose of cidofovir (5mg/kg) to be taken weekly.
  - Used to treat eye infections (Cytomegalovirus (CMV)).
  - Associated with renal tubular cellular injury and nephrotoxicity.
  - Given with aggressive IV for hydration
- IV of immune globulin of 0.5/kg was prescribed for 5 days.
What do you think is the mechanism by which the drug Cidofovir acts?

A) Prevents the virus from entering cells.
B) Induces the virus to go dormant.
C) Interferes with DNA replication.
D) Destroys the virus capsule.
E) None of the above.
What do you think is the mechanism by which the drug Cidofovir acts?

A) Prevents the virus from entering cells.
B) Induces the virus to go dormant.
C) **Interferes with DNA replication.**
D) Destroys the virus capsule.
E) None of the above.

Cidofovir acts by interfering with DNA polymerase during replication.
Treatment

- Patient’s clinical status continued to decline despite the use of Cidofovir and the immune globulin.
- Physicians put in an application for the experimental antiviral drug brincidofovir, a prodrug of cidofovir.
  - This drug was still in clinical trials but was showing promising results against DNA viruses such as CMV, adenovirus, varicella zoster virus, herpes simplex virus, and papillomaviruses.
  - Brincidofovir was considered to have broad antiviral activity with a low risk of renal and marrow toxicity, which is good for immunosuppressed patients.
What is true regarding a prodrug?

A) It is a drug that has more side effects than the original drug.
B) It is a drug that binds to the first drug to make it have higher affinity for the target.
C) It is a drug that allows the original drug to get into the host easier.
D) It is an inactive drug that is activated during metabolism.
E) All of the above are true.
What is true regarding a prodrug?

A) It is a drug that has more side effects than the original drug.
B) It is a drug that binds to the first drug to make it have higher affinity for the target.
C) It is a drug that allows the original drug to get into the host easier.
D) It is an inactive drug that is activated during metabolism.
E) All of the above are true.

This prodrug is converted to cidofovir diphosphate by cleavage of the lipid moiety and phosphorylation during metabolism in the body.
Resolution

- While awaiting the arrival of brincidofovir from the pharmaceutical company, the patient’s condition continued to worsen.
  - Follow up MRI on the 10th day.
  - Patient’s cognitive function was declining.
- Patient was moved to comfort measures only.
- On the 12th day of being at the hospital, the patient passed away.
- An autopsy was performed.
Autopsy Findings
Autopsy Findings
Autopsy Findings
Autopsy Findings
Clinical Relevance

- Adenovirus meningoencephalitis is extremely rare and is generally only seen in immunocompromised hosts and published reports of the neuropathological features are scarce.
- It is rare that the spinal cord and roots are involved.
- No approved antiviral agents for the prevention or treatments of adenovirus
- Vaccine for the adenovirus serotypes 4 and 7 are available for U.S. military use only.
- The use of brincidofovir for the treatment of adenovirus diseases has been terminated and is now only available for approved patients with adenovirus.
- Researchers are now looking into using cytotoxic T cells to treat adenovirus infectious diseases.
Clinical Relevance

● Subtle abnormalities in lab or imaging results could shift a clinician’s direction to finding a diagnosis
  ○ Aside from the leptomeningeal enhancement seen on the MRI, all other symptoms were indicative of MS

● Some diseases are not definitively diagnosed until post-mortem analysis
  ○ Empathy is an essential skill for healthcare professionals when delivering difficult news to family members

● Cases are not black and white
  ○ Requires flexibility and open-minded collaboration between medical teams