

# A Headache of a Headache

(A CPC Presentation)

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**Mentor:** Begem Lee, MD

# The Setup

# CC: Headache and vomiting

## HPI:

- 13 yo previously healthy F presenting with **headache, nausea, and vomiting**. She also has one day of **intermittent extremity weakness** and paresthesias.
- Headaches, N/V started 5 days ago. Headaches are constant, bilateral location, no exacerbating or relieving factors. Emesis is NBNB, several times a day, had some loose stools, now improved. No AMS or confusion. Seen in UC where she was diagnosed with viral illness.
- On day of admission, started to have weakness/numbness and tingling of left arm and leg.

# CC: Headache and vomiting

- **ROS:** +decreased activity, fatigue, N/V, diarrhea, +weakness, headache. Negative for fever, weight loss, URI sxs, resp sxs, neck stiffness, seizures, facial asymmetry, confusion.
- **Medical, Surgical and Family history:** No pertinents.
- **Social history:** Lives with family.
- No home meds, immunizations UTD, no known drug allergies, development normal.

# Vitals

Temp 37.6, HR 73, RR 21, O2 99% on RA, BP 136/59, BMI 49 kg/m<sup>2</sup>

# Physical Exam

- **Constitutional:** She is oriented to person, place, and time. She appears well-developed and well-nourished. No distress. Pleasant and cooperative. **Obese.**
- **HEENT:**
  - **Head:** Normocephalic and atraumatic.
  - **Nose:** Nose normal.
  - **Eyes:** Conjunctivae and EOM are normal. Pupils are equal, round, and reactive to light. Right eye exhibits no discharge. Left eye exhibits no discharge. No scleral icterus.
  - **Neck:** Normal range of motion. Neck supple.
  - **Mouth/Throat:** Oropharynx is clear and moist. No oropharyngeal exudate.
- **Cardiovascular:** Normal rate, regular rhythm, normal heart sounds and intact distal pulses. No murmur heard.
- **Pulmonary/Chest:** Effort normal and breath sounds normal. No stridor. No respiratory distress. She has no wheezes. She exhibits no tenderness.
- **Abdominal:** Soft. Bowel sounds are normal. She exhibits no distension. There is no tenderness. There is no rebound and no guarding.
- **Musculoskeletal:** Normal range of motion. She exhibits no edema or tenderness.
- **Lymphadenopathy:** She has no cervical adenopathy.
- **Neurological:** She is alert and oriented to person, place, and time. **No cranial nerve deficit.** She exhibits normal muscle tone. Coordination normal. **Strength and sensation intact in bilateral upper and lower extremities.**
- **Skin:** Skin is warm. **No rash noted.** She is not diaphoretic. No erythema. No pallor.
- **Psychiatric:** She has a normal mood and affect. Her behavior is normal.

# Labs

- Serum

- Na 138, K 3.5, Cl 98, CO2 29, BUN 12, Cr 0.53, Glu 156
- AST/ALT 38/60
- Tbili 0.8
- Dbili 0.1
- Alb 4.8

- Coags: INR 1.1

- Lipase 23

- Lactate 1.7

- CBC

- WBC 13.4, Hgb 14.9, PLT 481
- Neutrophils 72%, Lymphocytes 18%, Monocytes 3%, Bands not reported

- UA

- SG 1.015, Ketones 1+
- Negative glucose, protein, bili, leukocytes, nitrites

- CSF

- RBC 3, WBC 461, PMN 0%, Mononuclear 100%
- Glucose 81, Protein 212

- CXR: normal

- EKG: normal

- CT head non-contrast: normal

- Brain and spine MRI

- Normal (without contrast)
- Limited due to length of MRI, so there is some mild artifact

- Rapid flu A/B negative

# Review

What we have so far



# History and Physical

- Headache

- Started x5 days ago
- Accompanied by N/V
- Constant
- Bilateral
- No exacerbating/relieving factors

- Vomiting

- NBNB

- Numbness/tingling

- Started x1 day ago
- Localized to L arm and leg

- Loose stools

- Spontaneously resolved

- No PMHx or family history

- On presentation

- Hypertensive
- Obese
- No abnormalities on neuro exam

# Labs

- Serum glucose 156 (high)
- WBCs 13.4 (elevated)
- UA 1+ ketones

# CSF Studies

- 461 WBCs, all lymphocytes
  - Lymphocytes rarely predominate in the early phases of bacterial meningitis
- Elevated protein
  - Normal ranges up to 58 in adults
  - Up to 170 in preterm neonates
- Glucose 81
  - **< 18** strongly predictive of bacterial meningitis
- 3 RBCs
  - **Subtract 1 WBC for every 500 to 1500 RBCs**
  - Non-traumatic tap

# CSF Lymphocytic Pleocytosis

## Bacterial meningitis

- WBC > 1000/uL
- Usually *neutrophilic* predominance
- Protein > 250 mg/dL
- Glucose < 45 mg/dL

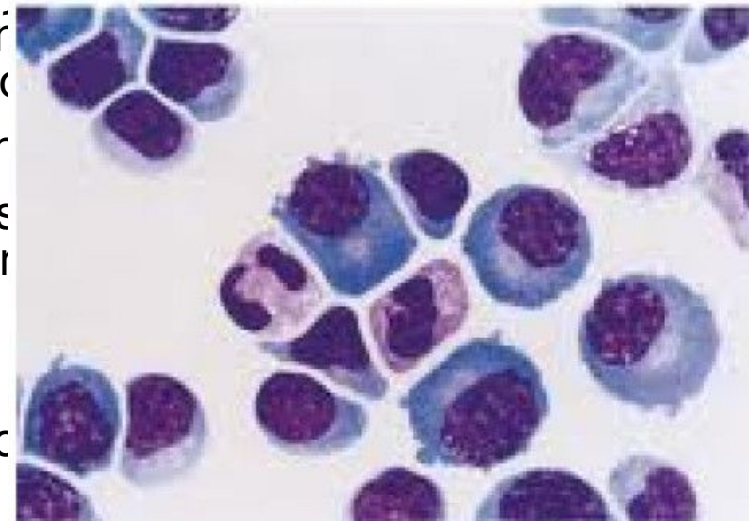
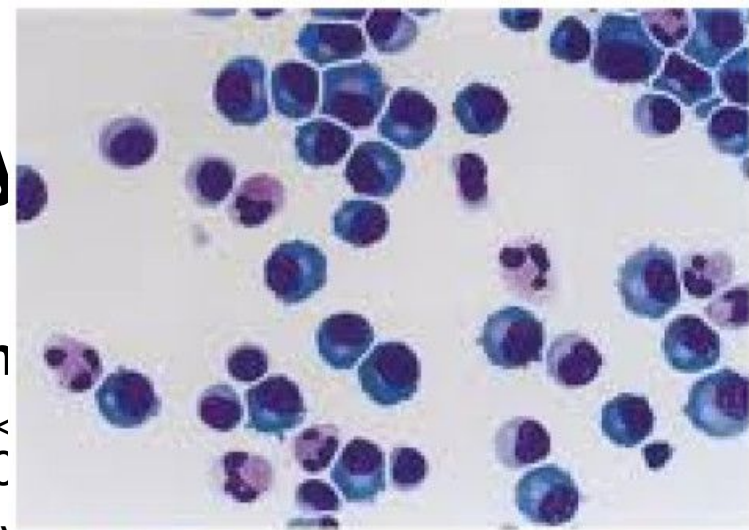
• WBCs: **461**

• Glucose:  $156/2 = 78$ ; **81 > 78**

• Protein: **212**. Protein > 220 mg/dL reduces protein to 1% or less.

## Viral meningitis

- WBC < 1000/uL  
< 2000
- Usually *lymphocytic* predominance
- Protein < 250 mg/dL
- Glucose concentration > 45 mg/dL



# Differential Diagnosis

What could it be?



## Infectious

- Bacterial meningitis (less likely)
- Viral meningitis or encephalitis
  - *N/V, constant bilateral headache, symptoms x5 days, leukocytosis, lymphocytic pleocytosis on LP w/ elevated protein*

## Vascular

- Vasculopathy
- Intracranial hemorrhage
- Coagulopathy

## Oncologic

- Space-occupying lesion

## Neurologic

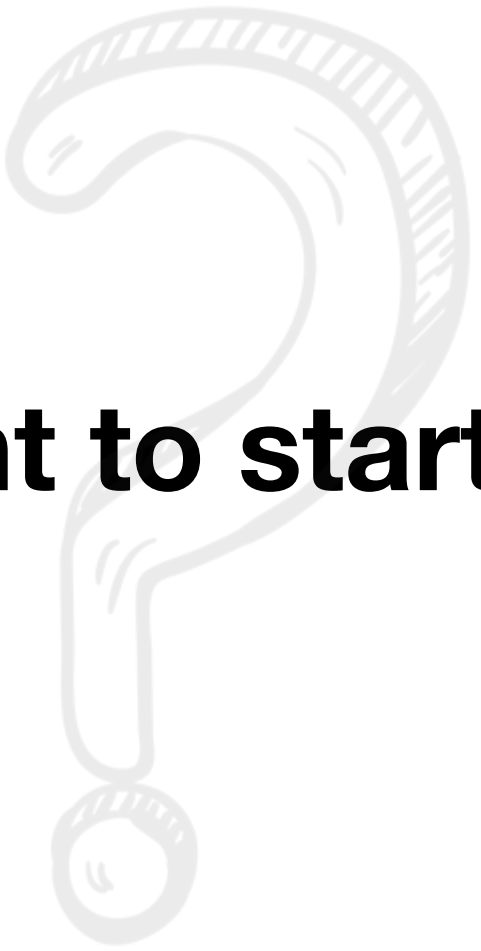
- Primary headache (migraine, complex migraine)
  - *Pain, nausea, vomiting, numbness/tingling, although nonfocal pain and CSF pleocytosis*
- Early onset MS
  - *Headache, intermittent weakness/numbness/tingling in periphery, teenage female, pleocytosis on LP, no fever*
- Idiopathic intracranial hypertension
- Partial/focal seizures

## Rheumatologic

- CNS lupus
- Autoimmune vasculopathy

# Treatments

- Migraine cocktail
  - Saline bolus
  - IV diphenhydramine
  - Ketorolac
  - Metoclopramide or prochlorperazine
  - At our hospital would be more likely to order metoclopramide for dopamine antagonism although may be more evidence for prochlorperazine.
- Pt is dehydrated (1+ ketones on UA)
  - Start mIVF and consider second bolus.
- NPO due to nausea/vomiting
- Re-assess nausea/vomiting after migraine cocktail
- May add ondansetron PRN



**“Do you want to start  
antibiotics?”**

—Begem Lee



~~“Nah.”~~ “Yes!”

—Smarter Michael Castello

# Bacterial Meningitis

## Most common pathogens

- Neonates: GBS, *E. coli*
- 1-3 months: GBS, *E. coli*, *Listeria monocytogenes*
- 3+ months (if immunized): *S. pneumoniae*, *N meningitidis*
- *N. meningitidis* most likely in a 13 year old

## Appropriate <sup>empiric</sup> treatment

- Ampicillin + gentamicin (+ cefotaxime or ceftazidime)
- Vancomycin + ceftriaxone or cefotaxime
- Vancomycin + ceftriaxone or cefotaxime

# Additional Treatments

- Vancomycin + ceftriaxone

# Wish List

- Imaging

- Repeat MRI brain/spine w/w contrast
- MRA head/neck
- MRI orbits

- CSF

- Save specimen
- Opening pressure
- Oligoclonal bands
- Encephalitis panel including HSV

- Other

- RVP

- Blood

- dsDNA
- SS-A and SS-B Ab
- Antiphospholipid Ab
- Coags
- Iron studies
- Peripheral smear
- bHCG
- Ca, Mg, phos
- MMA
- Vitamin D
- CMV/EBV

# Wish List

- Physical Exam

- Fundoscopic exam
- Visual fields
- Strength exam

- History

- Sexually active?
- Regular periods/LMP?
- New hair growth?
- Recent weight loss/gain?
- Diet or dietary restrictions?
- Drug/alcohol use?
- Recent travel/camping?

# **Patient Update**

- Still with headache after migraine cocktail, feels better lying down.
- Developed some possible blurry vision that is intermittent.
- Noted to have possible CN VI palsy
- Ophthalmology consulted and exam significant for full optic nerves but no frank papilledema
- Strength exam wnl
- History
  - Sexually active? No
  - Regular periods? LMP? Regular periods, LMP 2 weeks ago
  - New hair growth? No
  - Recent weight loss/gain? No
  - Dietary restrictions? Regular diet
  - Drug/alcohol use? No
  - Recent travel/camping? Travels to Mexico occasionally, no recent camping.

# Labs

- Negative meningoencephalitis panel
  - Eastern Equine, St. Louis, West Nile, Western Equine, Measles, HSV, Varicella, Cocksackie, Echovirus, Influenza, Mumps, LCM, CMV, Adenovirus
- No oligoclonal bands
- Ca, Mg, phos normal
- Upreg negative
- dsDNA < 1, cardiolipin < 11 (both negative)
- Vitamin D normal
- Coags normal
- No additional CSF, no opening pressure
- Not sent:
  - No MMA
  - No EBV/CMV
  - No RVP
  - No iron studies
  - No peripheral smear



# Repeat Brain MRI with MRV

- Dural sinuses

- There is diffuse compression and attenuation of the dural venous sinuses, most prominent along the anterior half of the superior sagittal sinus and the bilateral transverse and sigmoid sinuses. No convincing filling defect visualized on accompanying postcontrast MRI brain sequences. A prominent right suboccipital dural sinus is again seen which is a normal anatomic variant. The jugular veins are patent bilaterally.

- Brain

- Limited pre and postcontrast images of the brain demonstrate robust diffuse leptomeningeal enhancement which is most prominent along the cerebellar vermis. More subtle abnormal enhancement extending along the left internal auditory canal. Moderate diffuse sulcal effacement is again seen and unchanged compared to the prior examination without evidence of evolving hydrocephalus. No inferior tonsillar ectopia. The callosal rostrum is mildly dysplastic, which may represent a mild congenital malformation of unclear clinical significance. The midline structures are otherwise normal in appearance and stable compared to the prior examination.

# Repeat Brain MRI with MRV

## Radiologist's impression

- Brain

- Moderate diffuse sulcal and ventricular effacement with robust diffuse abnormal leptomeningeal enhancement. Appearance is most compatible with meningeal inflammation, reported suspicion for meningitis and increased intracranial pressure. Correlation with the CSF analysis would be helpful. Diffuse compression and attenuation of the dural venous sinuses without convincing thrombosis.
- This is likely on the basis of external compression of the dural sinuses due to increased intracranial pressure.

- Spine

- Mild diffuse leptomeningeal enhancement extending along the thoracic cord superiorly to level of the cervicothoracic junction, nonspecific in appearance but likely reflecting infectious versus inflammatory leptomeningeal disease as described in the companion MRI brain, which is separately reported.

# Review

Where are we now?



- Increased ICP, likely still increasing
  - Even without opening pressure, we are seeing progression to possible CN VI palsy (most commonly affected with increased ICP), full optic nerves (although no papilledema), and possible blurry vision
  - Imaging VERY consistent with increased ICP with sinus compression, ventricular effacement.
  - Hypertension could also be due to increased ICP
  - Nausea/vomiting consistent with increased ICP
- Everything so far appears to be pointing to some kind of meningitis...

# ...but not bacterial meningitis

- Imaging consistent with **meningitis** with signs of **inflammation**.
- Patient continues to be **afebrile** (although increased white count on CBC).
- While hard to differentiate bacterial from viral only on CSF, she has decently high glucose which makes bacterial less likely.
- Also would expect bacterial to have a **neutrophil** predominance, she has **lymphocytes**.
- It's been at least 5 days, would expect bacterial meningitis to progress much faster.

## Infectious

- Bacterial meningitis
- Viral meningitis
- Encephalitis

## Vascular

- Vasculopathy
- Intracranial hemorrhage
- Coagulopathy

## Oncologic

- Space-occupying lesion

## Neurologic

- Primary headache (migraine, complex migraine)
  - *Pain, nausea, vomiting, numbness/tingling, although nonfocal pain and CSF pleocytosis*
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## Rheumatologic

- CNS lupus
- Autoimmune vasculopathy

## Infectious

- ~~Bacterial meningitis~~
- Viral meningitis
- Encephalitis

## Vascular

- Vasculopathy
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## Oncologic

- Space-occupying lesion

## Neurologic

- Primary headache (migraine, complex migraine)
- Early onset MS
- Idiopathic intracranial hypertension
- Partial/focal seizures

## Rheumatologic

- CNS lupus
- Autoimmune vasculopathy

# Infectious

- ~~Bacterial meningitis~~
- Viral meningitis
- Encephalitis



# Infectious

- ~~Bacterial meningitis~~
- ~~Viral meningitis~~
  - Many known viruses were negative, including HSV
- Encephalitis
  - Acute disseminated encephalomyelitis (ADEM)
    - Pt did get previously diagnosed with a viral infection.
    - Typical CSF abnormalities in ADEM are nonspecific and include a lymphocytic pleocytosis

## Infectious

- ~~Bacterial meningitis~~
- ~~Viral meningitis~~
- Encephalitis
  - Acute disseminated encephalomyelitis (ADEM)

## Vascular

- Vasculopathy
- ~~Intracranial hemorrhage~~
- ~~Coagulopathy~~

## Oncologic

- ~~Space occupying lesion~~
- Carcinomatous meningitis
  - Diffuse leptomeningeal glioneuronal tumor

## Neurologic

- ~~Primary headache (migraine, complex migraine)~~
- ~~Early onset MS~~
- ~~Idiopathic intracranial hypertension~~
- ~~Partial/focal seizures~~

## Rheumatologic

- CNS lupus
- Autoimmune vasculopathy

# Wish List

- CSF
  - CSF gram stain and culture
  - CSF fungal culture
  - Fungitell / Candida, Cocci, aspergillus, Moraxella, mucor Ab
  - CSF AFB
- Blood
  - Blood culture
  - Fungitell / Candida, Cocci, aspergillus, Moraxella, mucor Ab
- Quantiferon or place PPD
- History
  - Traveling: around workers? Homeless? Prisoners? Family members who travel a lot?
  - Environment: location of primary houses in US and Mexico? Going through deserts? Construction nearby?
- Wild shot: Meningeal biopsy...

# Treatments/interventions

- Migraine cocktail didn't seem to do anything
- Treat ICP/prevent it from getting worse
  - Hypertonic saline
  - Mannitol
  - Acetazolamide
  - Glucocorticoids
    - Cannot start if oncologic diagnosis suspected
- Keep a close eye on blood pressure and breathing, watch for Cushing's triad

# **Patient Update**

# Labs

- CSF gram stain: no organisms, no acid fast bacilli
- CSF culture: no growth after 5 days
- CSF fungal culture: negative
- Mycobacterium TB PCR CSF: not detected
- Cryptococcus: not detected
- Coccidioides Ab: < 1:2 (not detected)
- Quantiferon/PPD: negative
- Blood culture: negative

# Additional History

- No exposure to homeless, prisoners.
- Family does not travel a lot.
- No further info about travel in Mexico.

# Aseptic Meningitis

When it isn't bacterial (or lupus)






TABLE. Infectious and Noninfectious Etiologies of Aseptic Meningitis

| Infectious   | Noninfectious  |
|--|--|
| <p><b>Bacteria:</b></p> <ul style="list-style-type: none"> <li>Bacterial endocarditis</li> <li>Bartonellosis</li> <li>Brain abscess</li> <li>Brucellosis</li> <li>Ehrlichiosis</li> <li>Leptospirosis</li> <li>Lyme disease</li> <li>Subarachnoid hemorrhage</li> <li>Subarachnoid infection</li> <li>Untreated bacterial meningitis</li> <li>Rocky Mountain Spotted Fever</li> <li>Syphilis</li> <li>Typhus</li> </ul> <p><b>Fungi:</b></p> <ul style="list-style-type: none"> <li>Blastomycosis</li> <li>Cryptococcosis</li> <li>Coccidioidomycosis</li> <li>Histoplasmosis</li> </ul> <p><b>Mycobacterial:</b></p> <ul style="list-style-type: none"> <li>Tuberculosis</li> <li>Disseminated Mycobacterium</li> </ul> <p><b>Parasites:</b></p> <ul style="list-style-type: none"> <li>Angiostrongylus cantonensis</li> <li>Neurocysticercosis</li> <li>Primary amoebic meningoencephalitis (Naegleria)</li> <li>Toxoplasmosis</li> <li>Trichinosis</li> </ul> <p><b>Viruses:</b></p> <ul style="list-style-type: none"> <li>Adenovirus</li> <li>Arbovirus (ie, West Nile, Laccrose, California, Equine Encephalitis, Japanese Encephalitis)</li> <li>Enteroviruses (poliovirus, coxsackie virus, echo/parecho)</li> <li>Herpes Viruses (HSV 1 and 2, VZV, CMV, EBV, HHV-6)</li> <li>HIV</li> <li>Influenza A &amp; B</li> <li>Lymphocytic choriomeningitis</li> <li>Measles</li> <li>Mumps</li> </ul> | <p><b>Drugs/Blood Products:</b></p> <ul style="list-style-type: none"> <li>Allopurinol</li> <li>Anti-CD3 monoclonal antibody</li> <li>Azathioprine</li> <li>Beta lactams (Amoxicillin)</li> <li>Carbamazepine</li> <li>Intrathecal drugs</li> <li>Intravenous immunoglobulin</li> <li>Isoniazid</li> <li>Nonsteroidal anti-inflammatory drugs (NSAIDs)</li> <li>Trimethoprim-sulfamethoxazole</li> </ul> <p><b>Inflammatory:</b></p> <ul style="list-style-type: none"> <li>Autoimmune encephalitis</li> <li>Behçet's disease</li> <li>CNS vasculitis</li> <li>Granulomatosis with polyarteritis</li> <li>Kawasaki's disease</li> <li>Multiple sclerosis</li> <li>Rheumatoid arthritis</li> <li>Sarcoidosis</li> <li>Systemic lupus erythematosus</li> <li>Mediterranean Fever</li> <li>Croptin-associated periodic syndrome (CAPS)</li> <li>Cogan syndrome</li> <li>Muckle-Wells syndrome</li> <li>Neonatal-onset multisystem inflammatory disease (NOMID)</li> <li>Chronic infantile neurological cutaneous articular syndrome (CINCA)</li> </ul> <p><b>Neoplastic:</b></p> <ul style="list-style-type: none"> <li>Carinomatous meningitis</li> <li>CNS Lymphoma</li> <li>Leukemia</li> <li>Posttransplantation lymphoproliferative disorder</li> </ul> <p><b>Vaccine Related:</b></p> <ul style="list-style-type: none"> <li>Live attenuated</li> <li>Epidemiology</li> <li>Rathke's cleft cyst</li> <li>Migraines</li> <li>Postsurgical</li> </ul> |

Abbreviations: CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HHV, Human Herpesvirus; HIV, human immunodeficiency virus; HSV, Herpes simplex virus

# Aseptic meningitis

- Infectious
    - Viral
      - Herpes class (HSV, VZV, CMV, EBV, HHV-6)
      - Enteroviruses
      - Arbovirus class (West Nile, Japanese Encephalitis)
    - Fungal
      - Cryptococcus
      - Coccidioides
    - Mycobacterial
      - TB
      - MAC
    - Parasitic
      - Cysticercosis
      - Amoebae (*Naegleria*)
      - Toxoplasmosis
- 

# Noninfectious Causes

- Postinfectious, vaccines
- Anatomic/Other
  - Cysts
  - Migraines
- Neoplastic
  - Carcinomatous meningitis
  - CNS leukemia/lymphoma
- Inflammatory
  - Autoimmune encephalitis
  - Behçet's disease
  - CNS vasculitis
  - Granulomatosis with polyarteritis
  - Kawasaki's disease
  - Multiple sclerosis
  - Rheumatoid arthritis
  - Sarcoidosis
  - Systemic lupus erythematosus
  - Genetic or neonatal onset periodic fevers

# Review

Now where are we?



- Not infectious
- Inflammatory?
- Malignant?
  
- Repeat LP for increasing ICP
- Flow cytometry on CSF
- *Brain biopsy...*

# **Patient Update**

- Repeat LP

- Opening pressure was 29. Approximately 10cc clear CSF were collected and sent for laboratory.
- Closing pressure was 13 mm water

- CSF cytology

- Glucose: 55
- Protein: **309**
- RBCs: 10
- WBCs: **790**
  - **92% lymphocytes**, 8% monocytes, 0% neuts

- Repeat CSF findings

- CSF cytology – no malignant cells
- CSF Leukemia/Lymphoma flow – negative
- C3 154 (normal 75-118)
- C4 35 (normal 20-38)
- Smith antibody < 1 (negative)
- RNP antibody < 1 (negative)
- ANCA negative
- CSF ACE < 5 (normal)

# Head CT Angiogram

The intracranial internal carotid arteries, vertebrobasilar system and their proximal branches are patent. No hemodynamically significant stenoses, aneurysms or other vascular malformations seen.



# Review

The possibilities are dwindling...



# Neoplastic

- No blasts on initial CBC
- CSF flow cytometry negative for leukemia/lymphoma
- **Carcinomatous meningitis**
  - Diffuse leptomeningeal glioma

# Inflammatory

- Sarcoid
  - ACE negative
  - CXR negative
- SLE, RA, KD, Cogan syndrome, Muckle-Wells syndrome, periodic fevers
  - Does not meet diagnostic criteria
- Vasculitis
  - Negative CT angio, MRI, MRA
  - Negative ANCAs



[Ther Adv Neurol Disord](#). 2010 Jan; 3(1): 29–42.

doi: [10.1177/1756285609347123](https://doi.org/10.1177/1756285609347123)

PMCID: PMC3002614

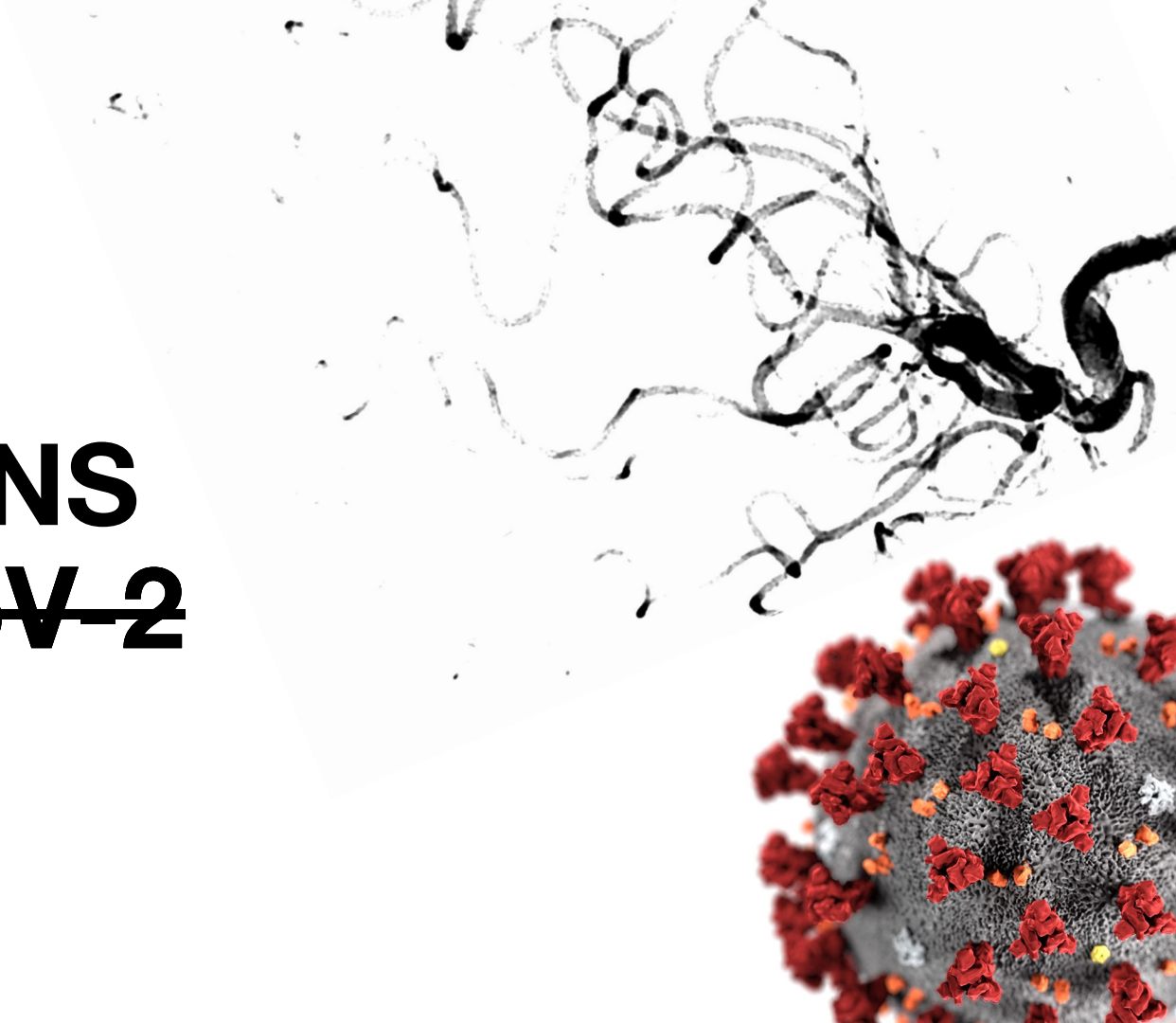
PMID: [21180634](https://pubmed.ncbi.nlm.nih.gov/21180634/)

## Diagnosis and treatment of cerebral vasculitis

[Peter Berlit](#)

- Behçet's, Polyarteritis nodosa
  - No systemic involvement
- GPA, microscopic polyarteritis
  - No ANCA
- Primary angiitis of the CNS (PACNS)
  - Small vessel childhood PACNS (SV-cPACNS)

**SV-cPACNS**  
**~~SARS-CoV-2~~**





# Diagnostic Tests

- Brain and leptomeningeal biopsy = gold standard
- Improves with steroids



## **SV-PACNS**

- Biopsy needed for definitive diagnosis
- Improves with steroids

## **Carcinomatous meningitis**

- Biopsy needed for definitive diagnosis
- Would not treat with steroids

**“We’re going to need  
some of your brain...”**



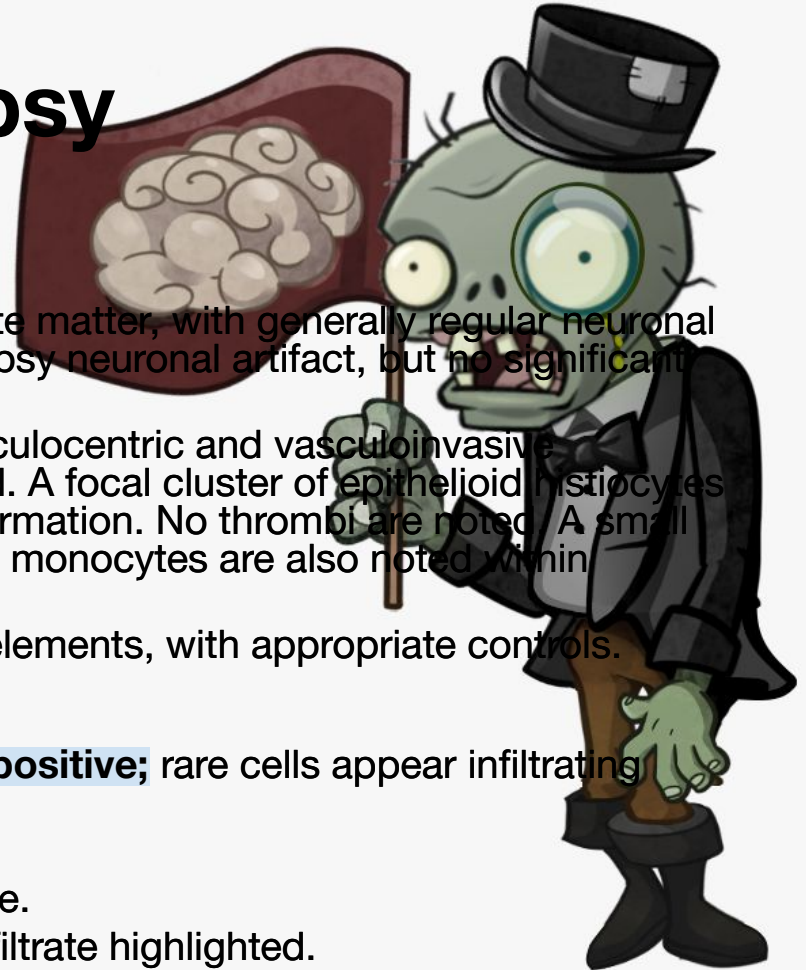
# Leptomeningeal Biopsy

- Microscopic description

- Sections show a portion of cortex and white matter, with generally regular neuronal laminations and populations, with mild biopsy neuronal artifact, but no significant edema.
- A few, small foci of surface meningeal vasulocentric and vasculoinvasive **lymphohistiocytic infiltrates** are identified. A focal cluster of epithelioid histiocytes is seen consistent with loose granuloma formation. No thrombi are noted. A small number of **perivascular lymphocytes** and monocytes are also noted within superficial Virchow-Robin spaces.
- A GMS (silver) stain is negative for fungal elements, with appropriate controls.

- Immunohistochemistry

- **CD3: Majority of inflammatory infiltrate positive;** rare cells appear infiltrating vessel walls.
- CD20: Rare inflammatory cells positive.
- CD68: Subset of inflammatory cells positive.
- CD31: Endothelium within inflammatory infiltrate highlighted.



# **T-cell inflammation of the small vessels**

Start treatment with steroids, cyclophosphamide

Review

> [Ther Adv Neurol Disord.](#) 2018 Jul 9;11:1756286418785071.

doi: [10.1177/1756286418785071](https://doi.org/10.1177/1756286418785071). eCollection 2018.

# Primary Angiitis of the Central Nervous System: Diagnosis and Treatment

[Carolin Beuker](#)<sup>1</sup>, [Antje Schmidt](#)<sup>2</sup>, [Daniel Strunk](#)<sup>2</sup>, [Peter B Sporns](#)<sup>3</sup>, [Heinz Wiendl](#)<sup>2</sup>, [Sven G Meuth](#)<sup>2</sup>, [Jens Minnerup](#)<sup>2</sup>

Affiliations + expand

PMID: 30034536 PMCID: [PMC6048610](#) DOI: [10.1177/1756286418785071](https://doi.org/10.1177/1756286418785071)

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- “Thanks a lot” to COVID-19 for *ruining everything*, no one likes you.



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- Rachel Castello
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# Thank you!

Michael A. Castello, MD, PhD  
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