The “gold” standard? A 4-year-old boy with somnolence and focal weakness

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Disclosures

• I have no conflicts of interest or financial obligations to disclose.
History of Present Illness

• 4-year-old previously healthy boy presents with headache, abdominal pain, unresponsiveness, left-sided weakness, and right eye deviation
• Recently diagnosed with post-viral ileus while admitted with 2 weeks of abdominal pain and emesis
  ▪ Unremarkable abdominal imaging
• ROS: + fever, + emesis, - abnormal movements
• FHx: 2.5 yo sister with developmental delay
• SHx: Lives with mom, dad, and 2 younger siblings. Attends preschool. Recently played with chickens and a puppy. No notable travel within the past year. Eats dairy products from the farmer’s market.

Physical Exam

• Vitals: T 37.1, HR 61, RR 22, BP 117/81, SpO2 100%, Wt 18.1 kg (69%ile)
• GEN: somnolent, intermittently awakens complaining of abd pain
• HEENT: NCAT, PERRL (3mm), Nares clear, MMM, keeps head preferentially turned to right
• NECK: supple, no LAD
• CHEST: Lungs CTAB, no rales or wheezes, no increased WOB
• CV: Bradycardic, regular rhythm, normal S1, S2, no MRGs, cap refill < 3 sec, 2+ peripheral pulses
• ABD: Soft, NTND, +BS, no masses, no HSM
• NEURO: Eyes and head deviated to right, will intermittently follow commands, left facial droop, increased tone L > R, 4+ reflexes on left, 2+ on right, multiple beats of ankle clonus on left
• SKIN: Warm, no rashes
Laboratory Findings

<table>
<thead>
<tr>
<th>WBC</th>
<th>Protein</th>
<th>Glucose</th>
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</thead>
<tbody>
<tr>
<td>134</td>
<td>102</td>
<td>&lt;5</td>
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<tr>
<td>4.2</td>
<td>22</td>
<td>0.4</td>
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Diff: 82% N, 18% L, 7% M, 0 E, 0 B

- **LP**
  - **WBC 66** (52% lymphs, 46% neutrophils)
  - Protein 41
  - **Glucose < 20**
  - Gram Stain negative, Enterovirus PCR negative

Imaging

- **CXR**
  - Patchy calcific density in right lung base unchanged from previous CXR.

- **CT Head W/O Contrast**
  - Ill-defined high attenuation material noted in several sulci in right parietal cortex.
  - Differential includes subarachnoid hemorrhage vs. hemorrhagic infarct within parenchyma.

- Decision made to obtain MRI in ER
Imaging - MRI

Axial TRACE Weighted  T2 Axial

Imaging - MRI

T1 Axial  T1 Axial
Audience Question

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- Which broad category of diagnoses seems most likely?
  a. Infectious
  b. Inflammatory/rheumatologic
  c. Hematologic
  d. Oncologic

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Differential Diagnosis

- Thromboembolism
- Meningitis
  - Bacterial
  - Tuberculosis
  - Viral
  - Fungal
  - Rickettsial
- Encephalitis
- Vasculitis
- Malignancy

NOTE: Further history revealed child had lived in Tanzania for the first year of life.

Hospital Course

- Intubated on admission but extubated 12 hours later and weaned to RA
- Started on empiric Vancomycin and Ceftriaxone
- Persistent fevers, abdominal pain
- Persistent bradycardia with PVCs
- Persistent hyponatremia (129-131)

- ECHO, carotid dopplers, LE venous dopplers normal

- Multiple consults: Neurology, Gastroenterology, Infectious Disease, Immunology, Rheumatology, Hematology/Oncology, Genetics/Metabolism
Hospital Course- Lab Findings

- Quantiferon and PPD negative
- HIV, RPR negative
- Hypercoagulability labs (Protein C, S, lupus anticoagulant, factor V leiden, anticardiolipin Ab's)
- Autoimmune labs (dsDNA, ANCA, C3, C4, ENA screen) negative

- Repeat LP on HD 3
  - 194 Nucleated cells (69% neutrophils, 26% lymphs)
  - Protein 73
  - Glucose < 20
  - Cytology negative
  - TB, Enterovirus, HSV, EBV, CMV, VZV PCR's negative
  - Opening pressure not done

Hospital Course, continued

- HD 4: Added fluconazole
- HD 6: Added doxycycline, ampicillin coverage
- HD 7: Pulse dose steroids with concern for vasculitis
- HD 8: Added rifampin, INH, pyrazinamide, ethambutol

- Blood Cx, Urine Cx, CSF Cx (x 2), CSF AFB Cx, CSF Fungal Cx (x2) all negative

- Repeat MRI on HD 7 and HD 11 with progressive and new infarcts, worsening hydrocephalus
Differential Diagnosis Revisited

- Thromboembolism
- Meningitis
  - Bacterial
    - Tuberculosis
  - Viral
  - Fungal
  - Rickettsial
- Encephalitis
- Vasculitis
- Malignancy

Audience Question

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  4. Select “Finish” to submit your answer.
- Which of the following is the most likely diagnosis?
  a. Viral Meningitis
  b. TB Meningitis
  c. Vasculitis
  d. Encephalitis

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Differential Diagnosis Revisited

- Thromboembolism
- Meningitis
  - Bacterial
    - Tuberculosis
  - Viral
  - Fungal
  - Rickettsial
- Encephalitis
- Vasculitis
- Malignancy

Clinical features supportive of TB meningitis
- History
  - Lived in TB-endemic area
  - Abdominal pain, fever
- Labs
  - Low CSF glucose
  - CSF pleocytosis
  - Hyponatremia
- Imaging
  - Multifocal basilar infarcts
  - Leptomeningeal enhancement
  - Hydrocephalus

Specific TB Testing
- Quantiferon negative
- PPD negative
- CSF AFB culture negative
- CSF TB PCR negative

Which of the following is the most likely diagnosis?

Viral Meningitis  0%
TB Meningitis  0%
Outcome

• Brain biopsy performed on HD 10
  ▪ Caseating granulomas and rare AFB+ organisms in the center of granulomas

• CSF AFB culture later grew M. Tuberculosis complex on HD 17

Diagnosis

*Mycobacterium Tuberculosis Meningitis*
TB Meningitis

- Children represent 5% of TB diagnoses in the U.S.
  - Majority age 1-4 with foreign-born parents or prior residence outside U.S.

- Pulmonary TB 2/3, Extrapulmonary TB 1/3
  - Extrapulmonary TB most commonly presents as CNS or LAD

- CSF analysis shows elevated protein, low CSF glucose, pleocytosis

- Many cases of TB in children < 5 are never microbiologically confirmed

Complications of TB Meningitis

- Ischemic stroke
- Hyponatremia
- Hydrocephalus
- Initial worsening after initiation of anti-TB therapy
Testing for TB Meningitis

• PPD and Quantiferon
  ▪ More sensitive when used in combination
  ▪ Overwhelming TB infection can cause false negative

• PCR assays
  ▪ Subject to sampling error
  ▪ Limited sensitivity in children (25%)

Quantiferon-TB Gold

• Nil tube
  ▪ Negative control for background IFN-γ
• Mitogen tube
  ▪ Positive control for baseline immune status
  ▪ Non-specific T cell response
• TB Antigen tube
  ▪ Detects specific CD4+ T cell response
Follow-up

- Treated with Rifampin, INH, Moxifloxacin, Ethionamide
  - Moxifloxacin due to Pyrazinamide resistance

- Repeat MRI on HD 39 with no new infarcts, resolution of leptomeningeal enhancement

- CSF AFB culture later confirmed by CDC as Mycobacterium Tuberculosis
  - Genetic analysis revealed most likely origin as Africa

- Discharged to inpatient rehab and completed DOT

Take Home Points

- Constellation of fever, abdominal pain, CNS infarcts, low CSF glucose, hyponatremia, and hydrocephalus should raise suspicion for TB meningitis.

- It is important to obtain a thorough exposure history in children, including travel history beyond the past year.

- Negative TB testing may provide false reassurance. Be aware of the sensitivity and specificity of the tests you are sending in clinical context and initiate anti-TB treatment early if high suspicion.
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Questions?
References


