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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.



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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



Diff: 82% N, **1.8% L**, 7% M, 0 E, 0 B

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

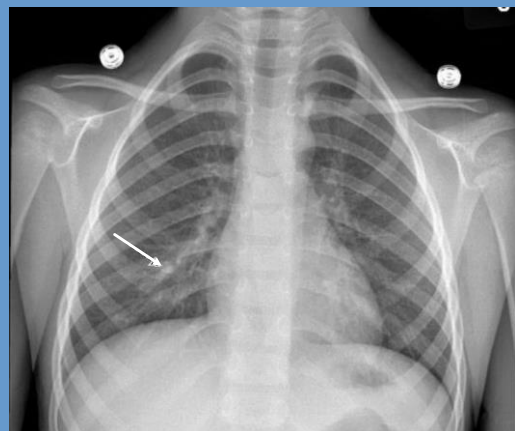


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Imaging

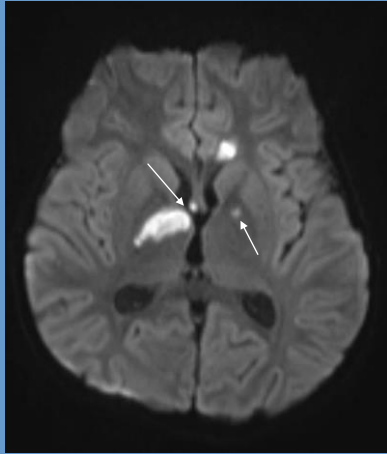
- CXR
 - Patchy calcific density in right lung base unchanged from previous CXR.
- CT Head W/O Contrast
 - Ill-defined high attenuation material noted in several sulci in right parietal cortex.
 - Differential includes subarachnoid hemorrhage vs. hemorrhagic infarct within parenchyma.
- Decision made to obtain MRI in ER



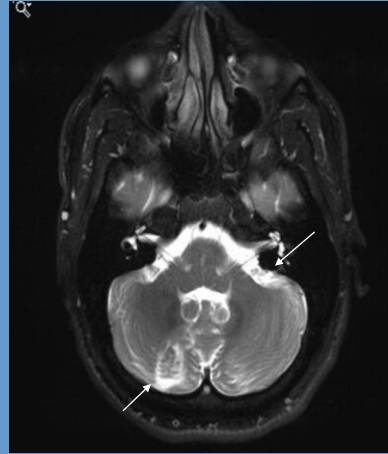
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Imaging - MRI



Axial TRACE Weighted



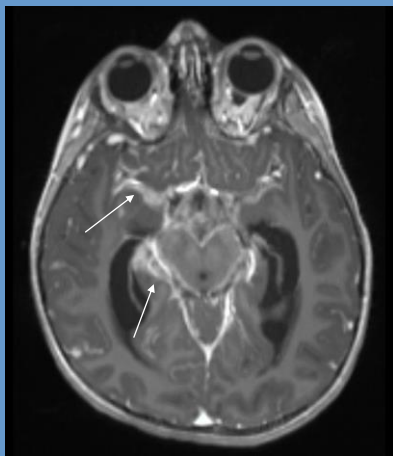
T2 Axial



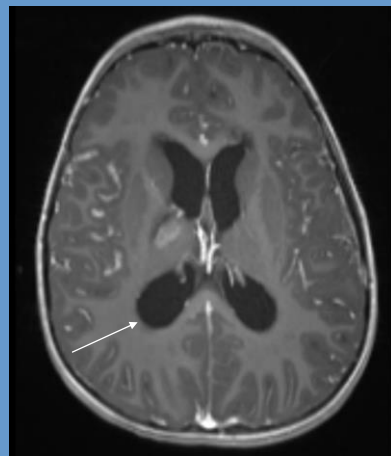
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Imaging - MRI



T1 Axial



T1 Axial



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

<https://api.cvent.com/polling/v1/api/polls/sp-mkf55g>



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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.**



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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



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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



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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



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Differential Diagnosis Revisited

- Thromboembolism
- Meningitis
 - Bacterial
 - Tuberculosis
 - Viral
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 3. Answer the question under “Live Polls” by selecting your desired answer(s).
 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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Which of the following is the most likely diagnosis?

Viral Meningitis

0%

TB Meningitis

0%

Source: <https://api.cvent.com/polling/v1/api/polls/spi9eggu>

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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

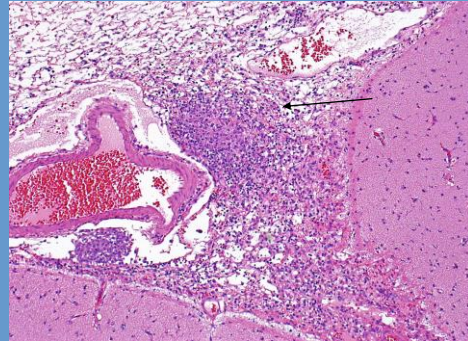
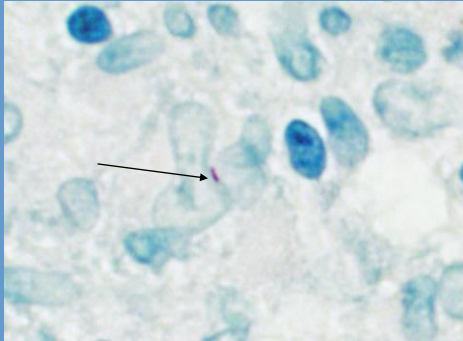


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Outcome

- 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



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Diagnosis

Mycobacterium Tuberculosis Meningitis



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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

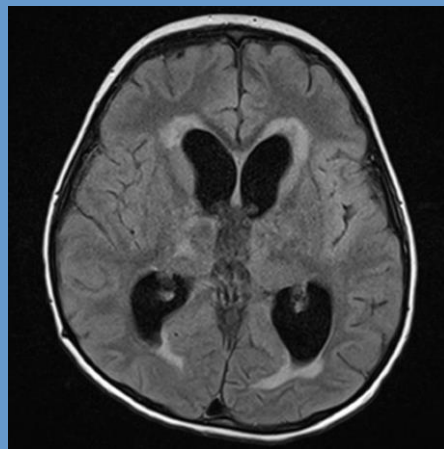


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Complications of TB Meningitis

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



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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%)



<https://phil.cdc.gov>, credit Greg Knobloch



www.inodia.co.id/quantiferon-tb-gold



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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



<http://www.quantiferon.com/us/products/quantiferon-tb-gold>



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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



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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?



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