

Mycobacterial and fungal infections of the CNS

Ariane Soldatos, MD, MPH

Pediatric Neuro-ID and Autoimmune Neurology

National Institute of Neurological Disorders and Stroke (NINDS), USA



Douala, Cameroon, October 20

13th Regional
Teaching Course

in Sub-Saharan Africa
in cooperation with AFAN



Case #1

- 5 month-old male presents with prolonged afebrile seizures
- immunocompetent, born in the UK, previously healthy and neurotypical
- brain MRI on day 2 of admission: extensive basal leptomeningeal enhancement with multiple areas of diffusion restriction
- CSF: lymphocytic pleocytosis, elevated protein, low glucose
- BioFire PCR for bacteria and viruses and Xpert MTB/RIF assay for TB negative on the initial small volume CSF sample
- chest X-ray with upper lobe consolidation and CT chest showing lymphadenopathy
- negative staining for acid-fast bacilli from endotracheal secretions
- empiric anti-TB treatment started on day 3 of admission and dexamethasone

- Mycobacterium tuberculosis detected 2 days later using Xpert MTB/RIF from 1 of 3 respiratory samples obtained from bronchoalveolar lavage (negative on cultures)
- no resistance markers to rifampicin on molecular testing and the isolate was confirmed to be fully sensitive on whole-genome sequencing on the second sample
- TB cultures from CSF also remained negative
- HIV negative
- On day 6 of admission, repeat neuroimaging was done due to increasing hypertonia and nystagmus: new left middle cerebral artery territory infarct; patient deceased
- The father was later found to have pulmonary TB

TB meningitis

- Disproportionately affects children under 5 years
- And patients with HIV, especially with $CD4 < 100$
- contact tracing:
 - the father had a productive cough for 1 month, fever and night sweats
 - no previous personal or family history of TB, and there was no recent travel.
 - chest radiograph showed widespread nodularity throughout both lungs with a small unilateral pleural effusion
 - pulmonary TB was confirmed by positive smear microscopy, TB culture and Xpert MTB/RIF on a sputum sample, and he commenced treatment.
 - father was from Albania, a low incidence country for MTB, therefore the infant had not been recommended the BCG vaccine at birth
- the risk of developing tuberculosis following close exposure to a positive case is highest in children under 5 years

Diagnostics in TB Meningitis

- traditional Ziehl-Neelsen smear microscopy has a low sensitivity on CSF due to the paucibacillary nature of TB meningitis.
- Mycobacterial culture is slow. While large CSF volumes and repeat samples can improve the diagnostic yield, this can be impractical in infants and children.
- Nucleic acid amplification tests, such as the Xpert MTB/RIF and the Xpert MTB/RIF Ultra, are more specific and sensitive than microscopy and provide results quicker than culture.
- the Xpert MTB/RIF Ultra was developed as the next-generation assay to overcome the suboptimal sensitivity in smear-negative TB patients when using the Xpert MTB/RIF assay
- Xpert MTB/RIF Ultra is now recommended by the WHO as the first-line diagnostic test of CSF for children with suspected TB meningitis.
- Nucleic acid amplification tests still lack the high sensitivity in CSF needed to exclude TB meningitis when negative.
- Effort should also be made to identify TB in extraneural sites such as respiratory sampling through gastric aspiration, induced sputum or bronchoalveolar lavage

Treatment in adults

- Initial intensive phase (4 drugs administered for 2 months)
 - isoniazid, rifampin, pyrazinamide
 - 4th drug options: ethambutol, streptomycin, levofloxacin, ethionamide
- Continuation phase (usually 2 drugs for an additional 7-10 months)
 - Isoniazid, rifampin
- Total tx duration 9-12 months
- Initiation of ART should be delayed for the first 8 weeks of antituberculous tx to avoid IRIS
- WHO recommends 6-8 weeks of adjunctive steroids

Treatment

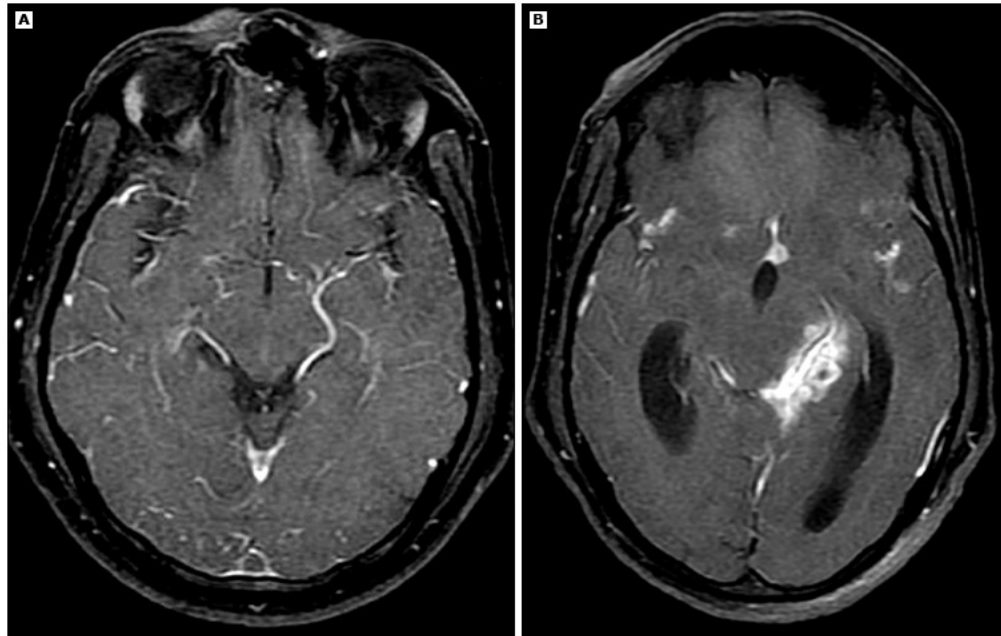
- 2022 WHO Pediatric TB guideline:
 - Mortality was lower in the children treated with the intensive 6-month regimen compared to those treated with the standard WHO-recommended 12-month regimen
 - isoniazid, rifampin and pyrazinamide, given at higher dosages, combined with ethionamide (in children monitoring for ethambutol associated optic neuritis is difficult)
 - given for 6 months if HIV-negative and for 9 months if HIV-positive
 - hepatotoxicity, gastrointestinal irritability and hypothyroidism are recognized complications of ethionamide.

Short Intensive Treatment for Children with Tuberculous Meningitis (SURE) trial

- randomized trial with a factorial design of enhanced antituberculosis and anti-inflammatory treatment for children with TBM.
- Children are first randomized to either the standard WHO recommended 12-month TBM regimen or to an optimized regimen consisting of rifampin (30mg/kg), isoniazid (20 mg/kg), pyrazinamide (40mg/kg) and levofloxacin (20mg/kg) daily for 6 months.
- Each child is then randomized to receive either aspirin or a placebo for the first 8 weeks of treatment.
- The study will recruit 400 children until 2023
- in Zambia, Zimbabwe, Uganda, India and Vietnam and is coordinated by the MRC Clinical Trials Unit at UCL, UK

TB-IRIS (Immune Reconstitution Inflammatory Syndrome)

Tuberculous meningitis paradoxical reaction



(Panel A) Initial brain magnetic resonance imaging in patient with tuberculous meningitis.

(Panel B) Follow-up imaging 8 weeks after initiation of antituberculous treatment demonstrates paradoxical worsening including hydrocephalus, tuberculoma and exudates in peri-mesencephalic cistern.

Outcomes

- Complications such as tuberculous vasculitis and stroke, hydrocephalus, hyponatremia, optochiasmatic arachnoiditis
- A systematic review on outcomes in childhood TB meningitis, including 1636 children in mainly TB endemic countries, identified that the risk of death despite treatment was 19.3%, with neurological sequelae seen in 53.9%
- Younger age, presentation with seizures and large or bilateral cerebral infarcts are associated with particularly poor outcomes
- Given the limitations with current diagnostics and poor prognosis, prevention is crucial:
 - BCG provides significant protection against TB meningitis and disseminated TB with the greatest protection when given in infancy or at school age (75%–92% vaccine efficacy)

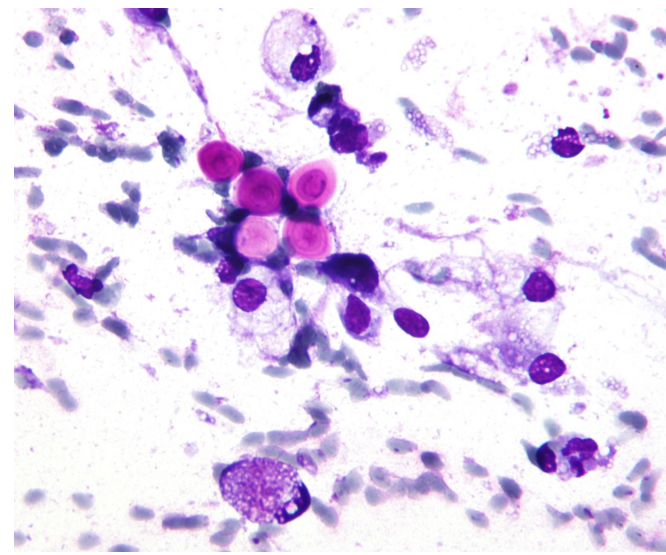
Case #2

- 15-year-old, previously healthy boy, presents for evaluation of:
 - a 4-week history of nausea, vomiting, weight loss, and imbalance
 - along with a 3-week history of vision changes (blurry and double vision)
 - also described intermittent headache with progressive neck stiffness, photophobia, and tactile temperatures.
- Examination was notable for meningismus and right lateral rectus nerve palsy.
- Magnetic resonance imaging (MRI) of the brain:
 - abnormal FLAIR (fluid-attenuated inversion recovery) signal scattered throughout multiple cerebral sulci along with punctate foci of abnormal FLAIR signal within subcortical white matter associated with subtle leptomeningeal enhancement.
- CSF: elevated opening pressure, lymphocyte-predominant pleocytosis, low glucose, and elevated protein.
- *Cryptococcus gattii* was identified on multiplex PCR (and confirmed on fungal culture of CSF fluid)
- HIV neg, normal CD4 count and immunologic work-up, no iatrogenic immunosuppressant drugs, primary immunodeficiency genetic panel negative

- Therapy was initiated with intravenous liposomal amphotericin B (5mg/kg/day) and oral flucytosine
- Serial therapeutic lumbar punctures
- 10 days after initiation of antifungal therapy, he had neurological decline with increased somnolence, anisocoria, and new fevers
- CSF was PCR and culture negative
- Dexamethasone initiated at 0.3mg/kg/day with improvement
- after completion of 6 weeks of intravenous liposomal amphotericin B and oral flucytosine, he was transitioned to planned fluconazole tx (for 12-month total antifungal tx) and discharged on a continued steroid wean

- 9 months later, while still on maintenance antifungal tx and toward the end of his steroid wean, readmitted for right-sided weakness
- MRI: new leptomeningeal enhancement in the left parietal lobe
- CSF studies negative for *Cryptococcus*
- Restarted on higher steroids with a slower wean over 8 months
- 4 months after completion of his second steroid wean (and without current antifungal tx), he developed new left-sided weakness
- CSF neg for infection
- MRI: new right-sided leptomeningeal enhancement
- Tx again with pulse steroids followed by a prolonged taper

Cryptococcal Meningitis (CM)



- HIV-associated
- Idiopathic CD4 lymphopenia-associated
- Caused by encapsulated yeast *Cryptococcus neoformans* (patients with CD4+ deficiency) or *Cryptococcus gattii* (previously healthy pts)
- Prevention: serum CrAg screening in HIV pts with CD4<100 and preemptive tx with fluconazole
- Diagnosis:
 - Lumbar puncture: elevated protein, hypoglycorrhachia, lymphocytic pleocytosis (may be normal in HIV patients), elevated opening pressure
 - CSF Cryptococcal Antigen-very sensitive and specific in CSF
 - Culture: takes 3-5 days to grow, larger volumes of CSF yield better growth
 - PCR: Less sensitive in HIV negative patients with CM (lower burden)

Treatment

- Induction:
 - In 2018, WHO issued guidelines for the diagnosis, prevention, and management of HIV-related cryptococcal meningitis in LMICs:
 - 1 week of amphotericin B plus flucytosine
 - the alternative therapy is 2 weeks of fluconazole plus flucytosine.
 - In the ACTA trial, 1-week (short course) amphotericin B plus flucytosine resulted in a 10-week mortality of 24% (95% CI –16 to 32) and 2 weeks of fluconazole and flucytosine resulted in a 10-week mortality of 35% (95% CI –29 to 41).
 - However, with widely used fluconazole monotherapy, mortality because of HIV-related cryptococcal meningitis is approximately 70% in many African LMIC settings.
- Consolidation: at least 8 weeks fluconazole 400-800 mg/day
- Maintenance: fluconazole 200 mg/day for minimum 1 year
- ART: for patients with HIV not yet on ART, ART should be delayed at least 4 weeks post induction therapy to minimize the risk of IRIS (immune reconstitution syndrome)
- ICP: Elevated ICP must be managed with serial lumbar punctures, sometimes shunting

PIIRS: Post-infectious Inflammatory Immune Response Syndrome

- Deterioration in neurologic status in previously-healthy patients with CM after appropriate treatment and conversion of CSF fungal culture to negative
- Potentially due to response to release of fungal antigens during therapy
- Thought to be caused by an appropriate pro-inflammatory response including IFN- γ and IL-6 stimulating T Helper cells, which leads to immune-mediated host damage
- Neurologic manifestations: worsening mental status, changes in gait, cerebellar signs, cranial nerve abnormalities (hearing loss, facial palsies), evidence of increased ICP (VI nerve palsy, papilledema)
- Treatment includes steroids; sometimes requires VP shunting
- Some patients being trialed on tocilizumab (monoclonal antibody that binds to IL-6 receptor)



Case Report: Paradoxical Inflammatory Response Syndrome in a Previously Healthy, HIV-Negative, Pediatric Patient With *Cryptococcus gatii* Meningitis

Jessica H. Cheng¹, Ritu Cheema², Peter R. Williamson³ and Victoria R. Dimitriadis^{4*}

¹ Department of Pediatrics, UIC Davis Health, Sacramento, CA, United States; ² Division of Pediatric Infectious Diseases, Department of Pediatric Microbiology, National Institutes of Health, Bethesda, MD, United States; ³ Department of Pediatrics, National Institutes of Health, Bethesda, MD, United States; ⁴ Department of Pediatrics, National Institutes of Health, Bethesda, MD, United States

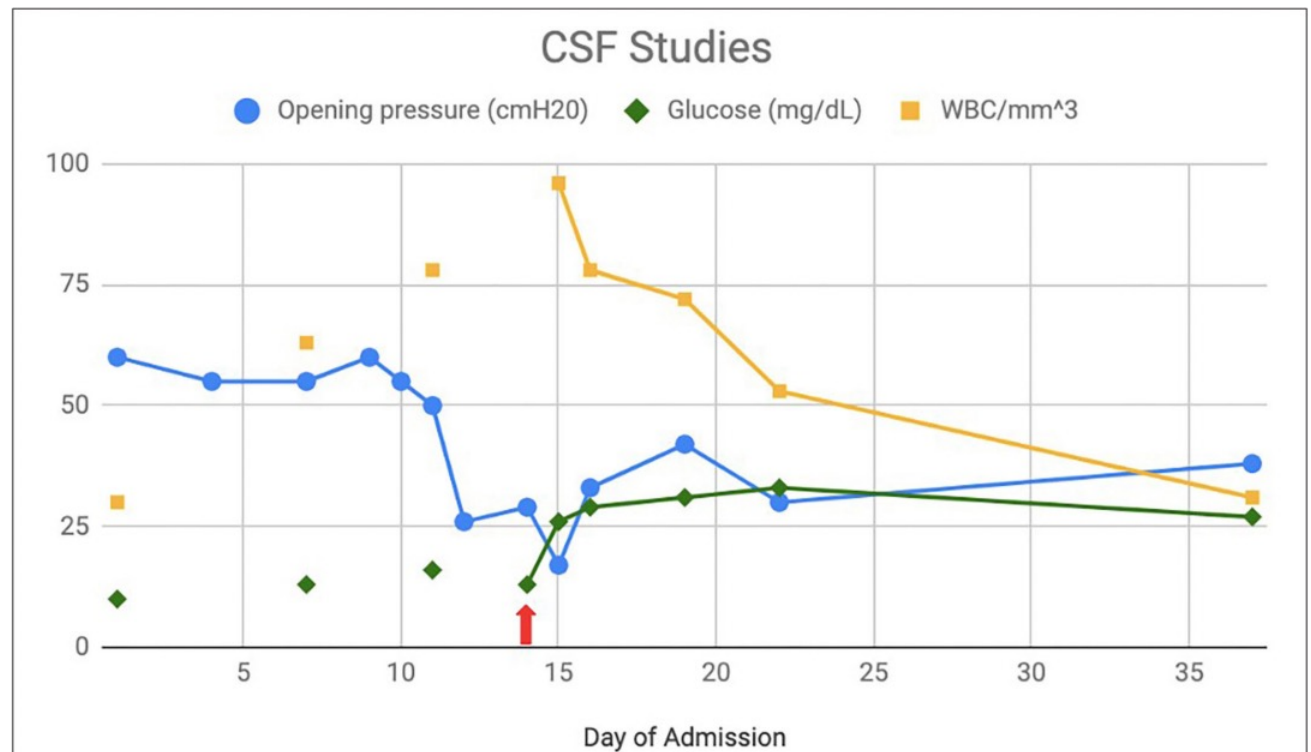


FIGURE 1 | Cerebrospinal fluid (CSF) studies: CSF opening pressure, glucose, and WBC count over the course of initial hospitalization with initiation of steroids on day 13 (red arrow).

Pediatric CM

- The Pediatric Health Information System, a database containing administrative information from 42 United States children's hospitals, was used to identify children admitted for the treatment of Cryptococcal Infection (CI) between 2003 and 2008. All pediatric inpatients less than 19 years of age who received an ICD-9 code for cryptococcosis or cryptococcal meningitis (CM) were included.
- a total of 63 cases of CI were identified, for a CI admission frequency of 6.2 cases per million hospitalizations.
- 63.5% had an underlying immunocompromising medical condition, whereas 21% were immunocompetent and 16% were infected with HIV.
- Cryptococcosis not involving the central nervous system was more common than CM (62% vs. 38%).
- The overall in-hospital case fatality rate was 9.5%.

Selected References

- Solomons RS et al. Update on the Treatment of Pediatric Tuberculous Meningitis. *The Pediatric Infectious Disease Journal*. 2022
- Khambati N et al. Fatal tuberculous meningitis in an infant presenting with seizures in the UK. *BMJ Case Rep* 2021.
- World Health Organization. Who meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTB/RIF ultra compared to Xpert MTB/RIF. Geneva: WHO, 2017.
- World Health Organization. Next-Generation Xpert® MTB/RIF ultra assay recommended by WHO Geneva, 2017. Available: https://www.who.int/tb/features_archive/Xpert-Ultra/en
- Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014;14:947–57
- Loyse A et al. Leave no one behind: response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle-income countries. *Lancet Infect Dis*. 2019
- Cheng JH et al. Case Report: Paradoxical Inflammatory Response Syndrome in a Previously Healthy, HIV-Negative, Pediatric Patient With *Cryptococcus gatii* Meningitis. *Front. Pediatr.* 2021
- Joshi NS et al. Epidemiology of cryptococcal infection in hospitalized children. *Pediatric Infect Dis J*. 2010



- Home
- About the Clinical Center
- Clinical Trials & You
- Participate in a Study
- Referring a Patient
- How to Search
- Contact Us

About Clinical research

Research participants are partners in discovery at the Clinical Center, the nation's clinical research hospital. Clinical research is medical research involving people. The Clinical Center's mission is to rapidly translate scientific observations and laboratory discoveries into new ways to diagnose, treat and prevent disease. More than 500,000 individuals from around the world have participated in clinical research at the Clinical Center since the hospital opened in 1953. The Clinical Center does not charge patients for participation and treatment in clinical studies at NIH. In addition, in certain emergency circumstances, you may qualify for help with travel and other expenses. For more information: [Click here.](#)

Medical Information Disclaimer



Find NIH Clinical Center Trials

The National Institutes of Health (NIH) Clinical Center Search the Studies site is a clinical studies conducted mostly in Bethesda, MD.

Keyword:

Search

[Browse by institute of the principal investigator](#)

01-I-0202

Natural History, Genetics, Phenotype, and Treatment of Mycobacterial Infections

19-I-0133

Paradoxical Tuberculosis Reactions in Patients without HIV Infection

93-I-0106

Cryptococcosis in Previously Healthy Adults

Participants currently recruited/enrolled

14-I-0146	The Pathogenesis and Genetics of Disseminated or Refractory Coccidioidomycosis	Participants currently recruited/enrolled	2-100 Years	NIAID
11-I-0187	The Natural History and Pathogenesis of Human Fungal Infections	Participants currently recruited/enrolled	0-125 Years	NIAID
10-I-0216	Studies of Disorders with Increased Susceptibility to Fungal Infections	Participants currently recruited/enrolled	0-125 Years	NIAID
07-I-0033	Screening Protocol for Detection and Characterization of Infections and Infection Susceptibility	Participants currently recruited/enrolled	0-125 Years	NIAID

Acknowledgments

- **NIAID**

Steve Holland, Gigi Notarangelo, Michalis Lionakis, Alexandra Freeman

- **NINDS:**

Avindra Nath, Bridgette Jeanne Billioux, Bryan Smith



ariane.soldatos@nih.gov