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DR|TB TRAINING NETWORK

PEDIATRIC DR-TB MENINGITIS: CASE-BASED DISCUSSION

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Sentinel Project on pediatric drug-resistant tuberculosis

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(GMT -5:00)

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Learning points

- The diagnosis of DR-TB meningitis in children
- Strategies to manage complications and reduce mortality
- Anti-TB drug regimen selection and empiric therapy

Pediatric DR-TB meningitis is an underappreciated problem

- Estimated 33,00 incident cases of childhood MDR-TB annually
- As many as 1-3% of pediatric cases present with meningitis.
- More common manifestation in children than adults

Jenkins H, et al. Incidence of multidrug resistant TB disease in children: systematic review and global estimates. The Lancet. May 3;383(9928):1572-9, 2014.

Rallis D, et al. Current epidemiology of childhood tuberculous meningitis in Greece: a 10-year population-based study. ILTLD. 17(6):847-8, 2013.

Pediatric TBM is bad and drug resistance makes it even worse

- Near complete mortality in untreated disease
- 80% of children with advanced disease will have permanent neurologic sequelae despite treatment.
- Drug resistance associated with poor outcomes

Outcome	Characteristics in Model	Variable	Number in Analysis	Odds Ratio	95% Confidence Interval	*P*
Unfavorable outcome	Age		122			0.013
	DST	Isoniazid monoresistant	122	0.22	0.03–1.87	0.17
		Rifampin monoresistant	122*	—	—	—
		Multidrug-resistant	122	12.4	1.17–132.3	0.037
Mortality	HIV status		88	6.17	0.92–41.3	0.061
	DST	Isoniazid monoresistant	88†	—	—	—
		Rifampin monoresistant	88*	—	—	—
		Multidrug-resistant	88	63.9	4.84–843.2	0.002

Seddon JA., et al. Impact of drug resistance on clinical outcome in children with tuberculous meningitis. Pediatric Infectious Disease Journal. 31(7):711-6, 2012

Outcomes in pediatric MDR-TB meningitis are poor

Patient	Age (yr)	History of TB Contact*	BMRC Grading (on Admission)	HIV Status	Steroids Used	Time to Confirmation of MDR-TBM (wk)	Time on Effective Therapy (wk)	Outcome
1	3	Unknown	1	Negative	No	16	0	Died
2	2.5	No	3	Positive	Yes	12	0	Died
3	2.5	Yes	3	Positive	No	13	0	Died
4	8	Yes	1	Positive	No	10	48	Survived
5	0.8	Unknown	3	Negative	No	12	0	Died
6	11	Unknown	1	Positive	Unknown	10	2	Died
7	4	Yes	2	Positive	No	20	8	Died
8	2	Unknown	2	Positive	No	10	8	Died

- Mortality 87.5%
- Delay in diagnosis
- Low rates of contact tracing
- Low rates of steroid use

Padayatchi N, et al. Multidrug-resistant tuberculous meningitis in children in Durban, South Africa. Pediatric Infectious Disease Journal. 25(2):147-50, 2006.

Georgia has a high burden of MDR-TB

- TB incidence – 116 cases per 100,000
- TB prevalence – 158 cases per 100,000

- MDR TB prevalence:
  - 11% among new cases
  - 38% previously treated cases

Patient 1 – History of present illness

- 9-year-old girl living in a former Soviet Republic with a high incidence of MDR-TB.
- No past medical history; BCG vaccinated at birth.
- Lives with her mother, who is well. Father has MDR-TB.
- Developed fever, fatigue and severe, persistent headaches over a two week period.

Patient 1 - Physical and laboratory examination

- **Weight:** 22 kg
- **Temperature:** > 38°C
- **Neurologic exam:** delirious, neck with limited range of flexion and extension, photophobia

- **Creatinine:** 0.6 mg/dl
- **AST:** 22 IU/L
- **ALT:** 18 IU/L
- **HIV serology:** unknown, but presumed negative

Patient 1 – CSF examination

- **Cell count:** 400 WBC/ml3 (90% lymphocytes)
- **Protein:** 0.66 mg/dl (normal 15-60 mg/dl)

- **CSF microscopy:** AFB negative
- **CSF culture:** positive

  <u>Drug susceptibility testing:</u>

  Resistant – INH, Rif, S, Ofx, Eth

  Sensitive – Km, Cm

Patient 1 – Treatment regimen

- Pyrazinamide 600mg PO daily
- Capreomycin 0.6 g IM daily
- Levofloxacin 250 mg PO daily
- Cycloserine 250 mg PO daily
- Prothionamide 250mg PO daily
- PAS 4.0 g PO daily
- Amoxicillin/clavulanate 1 g PO daily
- Clarithromycin 1 g PO daily
- Clofazimine 250mg PO daily

Patient 1 – Persistent symptoms despite treatment

- Patient continued to complain of fatigue one month into treatment
- Physical exam revealed persistent neurologic signs.
- Repeat lumbar puncture:
  - CSF cell counts increased to 824 cells/mm3
  - Protein increased to 0.99 mg/dl

Patient 1 – Imaging while on treatment

- Head MRI at month two of treatment showed obstructive hydrocephalus, paraventricular swelling and inflammation of the inner capsule.

- Dexamethasone was subsequently started in an attempt to decrease inflammation.

Patient 1 – Further worsening

- Clinical condition did not improve. The patient developed seizures, nausea and vomiting.
- Repeat MRI showed increased hydrocephaly.

- Subsequently underwent placement of an extra-ventricular drain by neurosurgery with good results.
  - Seizures and headaches resolved.
  - Nausea and vomiting continued.

Patient 1 – Outcome

- Regimen was modified : capreomycin, levofloxacin, cycloserine, prothionamide
- Subsequently gained weight, temperature normalized, headache did not recur.
- Completed 20 months of treatment.

Delay in diagnosis

- Delay in diagnosis is common, leading to increased morbidity and morality.
- Highest risk: very young patients, patients with co-existing illness and those from non-TB endemic regions.
- Single most important factor in predicting outcome.

Early stage pediatric TBM is difficult to recognize

- Peak incidence between 2 and 4 years of age
- Presents with nonspecific symptoms of ill health
  - poor weight gain
  - low-grade fever
  - listlessness
- Classic neurologic signs are usually seen only in advanced disease

van Toom R, et al. Update on the diagnosis and management of tuberculous meningitis in children. Seminar in Pediatric Neurology 21(1): 12-18, 2014

Classic CSF finding of TBM

- Low glucose: less than 45 mg/dL in 80 percent of cases
- High protein: ranges from 100 to 500 mg/dL in most patients; however, patients with subarachnoid block may show extremely high levels (2 to 6 g/dL)
- Lymphocytic pleocytosis: between 100 and 500 cells/microL

Hristea A, et al. Clinical prediction rule for differentiating tuberculous from viral meningitis. IJTLD. 16: 793-8, 2012

CSF microscopy

- Ziehl-Neelsen microscopy staining of CSF is the most widely applied rapid diagnostic technique for TBM.

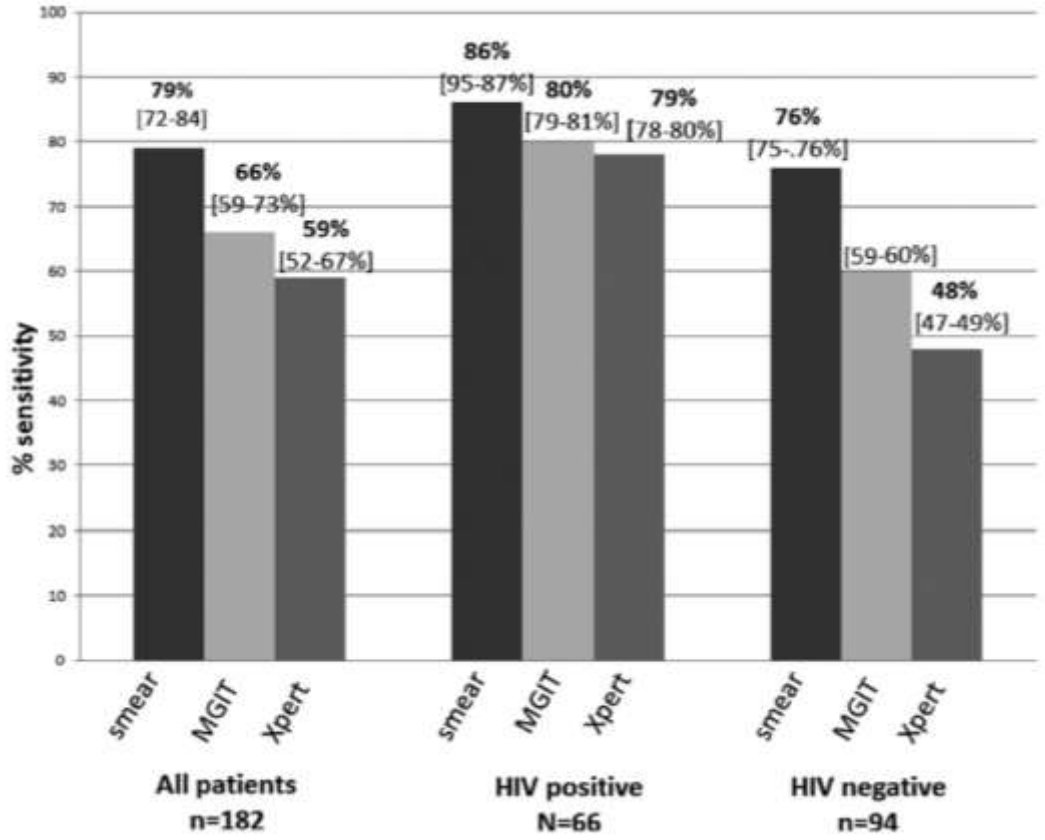
- Sensitivity usually below 20%
- Analysis of a large volume (7 ml) of CSF and examination time of 30 minutes per slide improves sensitivity

CSF culture

- Sensitivity of almost 60%
- Not feasible to rule in or rule out disease because test take weeks to return positive results.
- Requires robust laboratory facilities

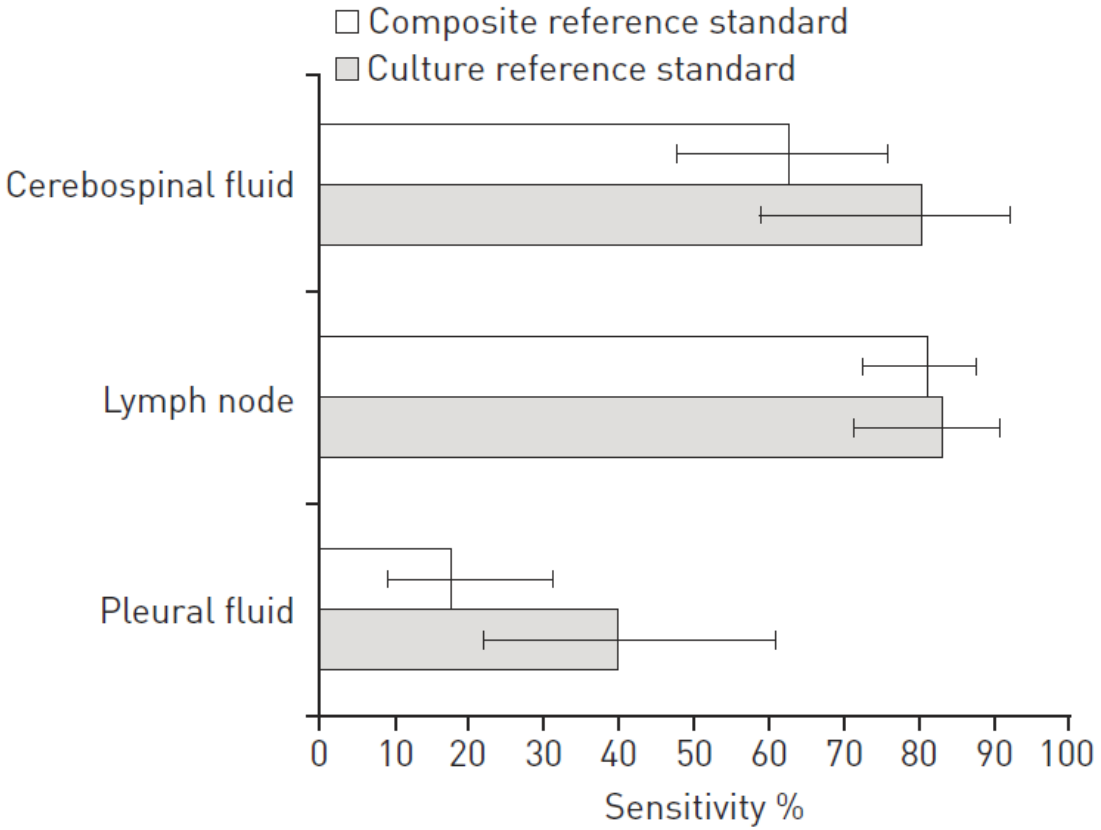

GeneXpert
Lot xxxxx
xxxx xx xx
MTB/RIF Assay
For Research Use Only
Cepheid

Sensitivity of Xpert for TBM compared to other diagnostic tests



Nhu NT, et al. Evaluation of GeneXpert MTB/RIF for the diagnosis of tuberculous meningitis. J Clin Micro. 2014 Jan;52(1):226-33

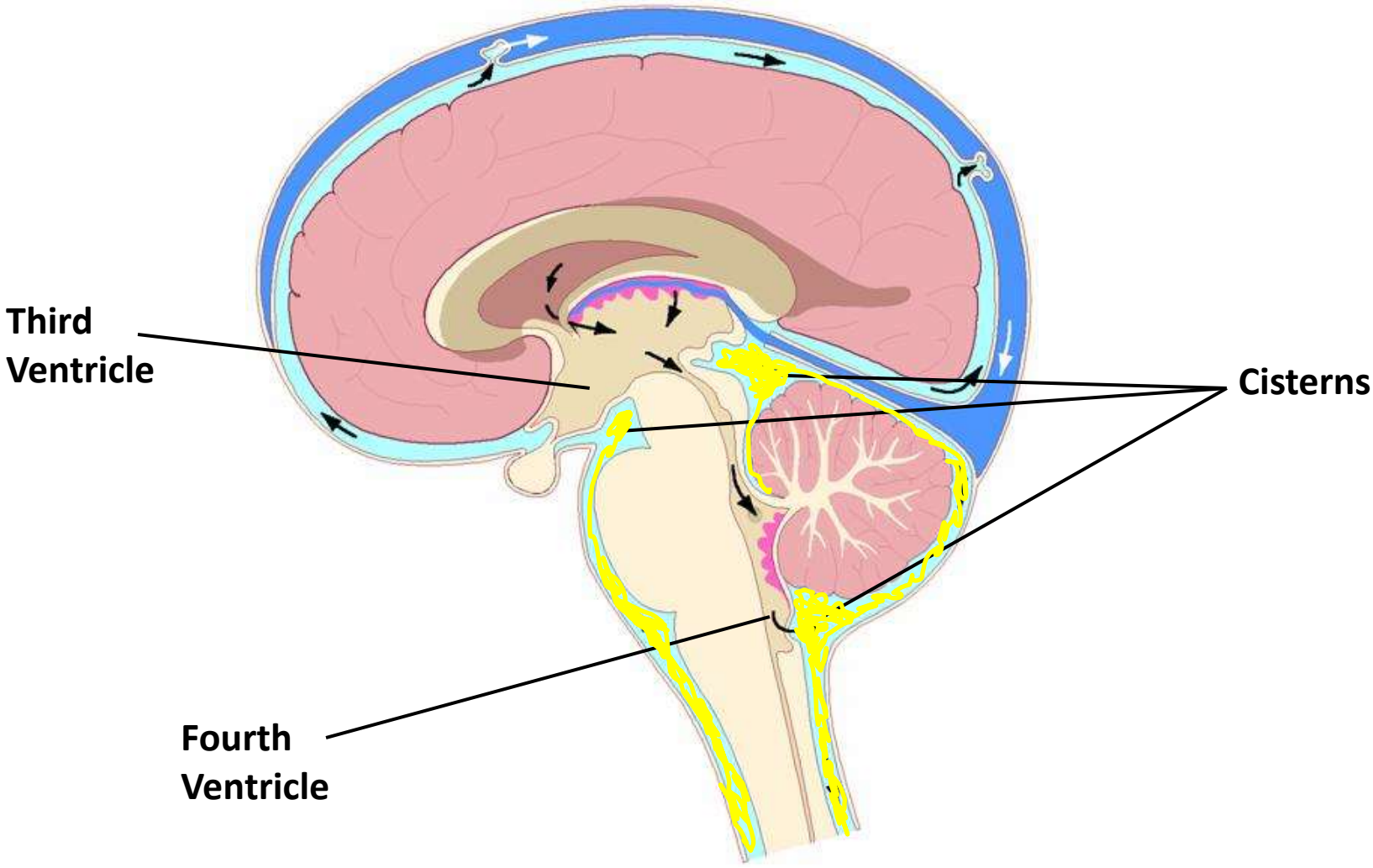
Xpert sensitivity across sample types



Denkinger C, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2014


TRUTH
C. Barsotti

Pathogenesis of TBM

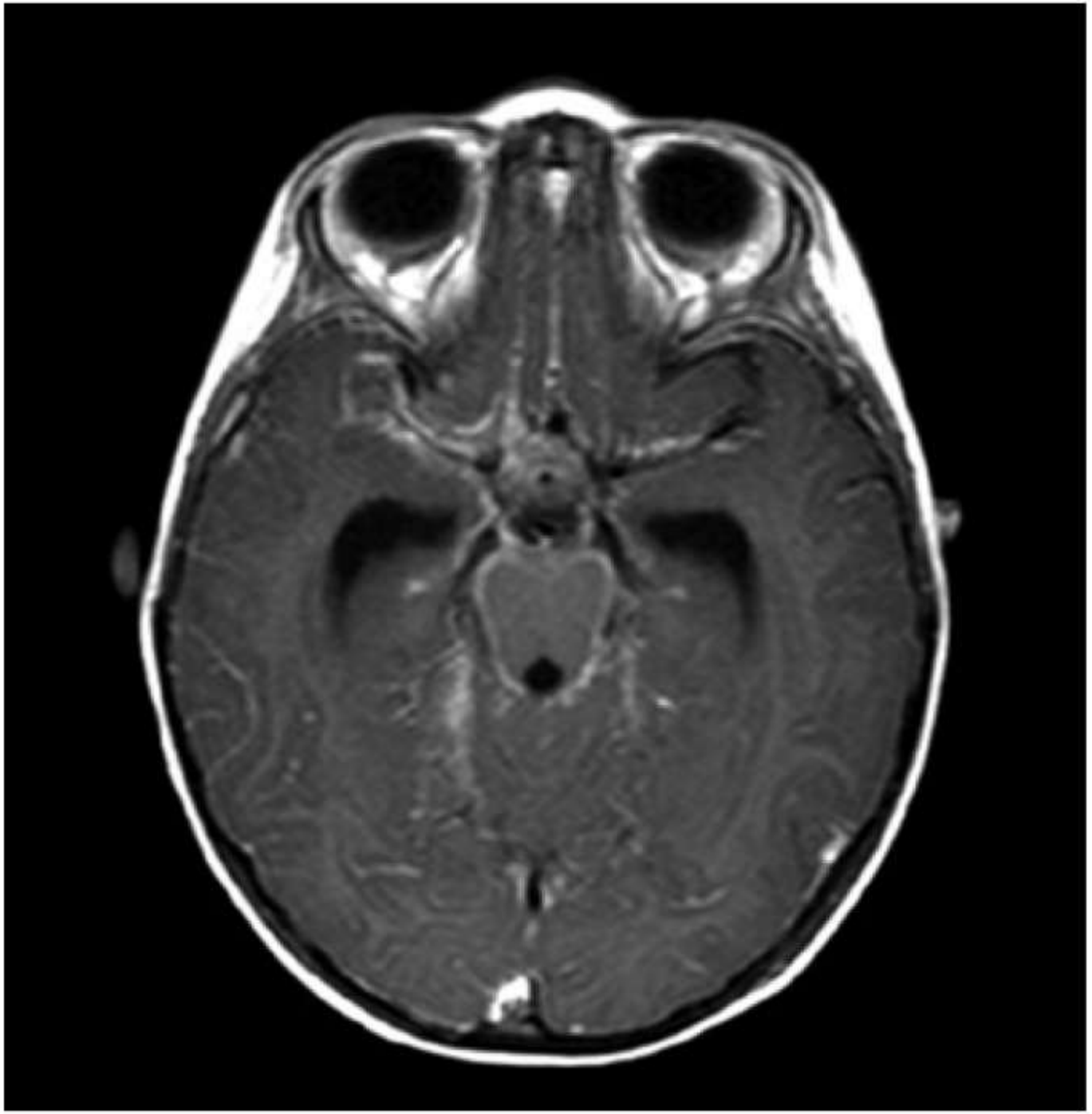


Complications of TBM

- Tuberculous hydrocephalus and raised intracranial pressure
- Tuberculosis cerebrovascular disease
- Hyponatremia
- TB mass lesions
- TB-immune reconstitution inflammatory syndrome

Grading of TBM

- Grade 1: Fully conscious, rational and no neurologic signs
- Grade 2: Confused but not comatose; neurologic signs limited to hemiparesis or single cranial nerve palsy
- Grade 3: comatose or stuporous; multiple cranial nerve palsies or complete hemiplegia or paraplegia



Low cost interventions to manage complications of pediatric TBM

- Control of hyponatremia and cerebral salt wasting
- Intravascular volume support
- Elevation of the head of bed
- Acetazolamide and furosemide for communicating hydrocephalus

Vadivelu S, et al. A review of the neurological and neurosurgical implications of tuberculosis in children. Clinical Pediatrics 52(12): 1135-43, 2013.

Systemic steroids for anti-inflammatory therapy

- Cochrane meta analysis of corticosteroids in 1140 HIV uninfected participants.
  - Reduced the risk of death (relative risk = 0.78, 95% CI: 0.67 – 0.91)
  - Reduced risk of disabling neurological deficit (relative risk = 0.82, 95% CI 0.70 – 0.97)

- Prednisone: 2 to 4 mg/kg per day (max 60 mg/day) for the first month of treatment, then wean.
- Dexamethasone can be used as an alternative.

Thalidomide can be effective against tuberculomas

- Thalidomide moderates the production of TNF-alpha, which can reduce abscess size.

- Dose 3-5 mg/kg/day orally in children who develop life threatening TB mass lesions despite corticosteroids.

Ventricular drains

- To decompress the ventricular system and reduce intracranial pressure.
- Requires neurosurgical placement
- Serial lumbar puncture as a temporizing measure if neurosurgery isn’t available

Patient 2 – History of present illness

- 15-year-old girl living in a former Soviet Republic with a high incidence of MDR-TB.
- No past medical history; BCG vaccinated at birth. HIV negative.
- No close contact with an active case of DR-TB.
- Developed fever, fatigue and severe, persistent headaches over a one week period.

Patient 2 - Physical and laboratory examination

- **Weight:** 50 kg
- **Temperature:** > 38°C
- **Neurologic exam:** neck with limited range of flexion and extension, positive Kerning sign, remainder of physical exam not documented

- **Chest x-ray:** normal

Patient 2 – CSF examination

- **Cell count:** 580 WBC/ml3 (90% lymphocytes)
- **Protein:** 0.63 mg/dl (normal 15-60 mg/dl)

- **CSF microscopy:** AFB negative
- **CSF culture:** negative

Patient 2 – Treatment regimen

- Izoniazid 300 mg PO daily
- Rifampicin 600 mg PO daily
- Pyrazinamide 1600mg PO daily
- Ethambutol 1200mg PO daily

Patient 2 – Failure to improve

- Condition did not improve on first-line TB treatment
- Clinical picture was concerning for MDR-TB
- Patient was hospitalized and her treatment regimen was modified to include first-line anti-TB drugs and empiric MDR-TB therapy:

  isoniazid, rifampicin, ethambutol, pyrazinamide, capreomycin, ofloxacin, cycloserine and PAS.

Patient 2 – Outcome

- Patient's temperature normalized and she gained weight.
- Patient was discharged from the hospital and was treated as an outpatient.
- Completed 20 months of treatment

Contact tracing

- Critical in children with TB meningitis, especially for those whose diagnosis is not confirmed microbiologically.
- Consider Xpert MTB/RIF testing to quickly identify MDR-TB in the contact, thereby helping to guide therapy in the index pediatric patient.

Empiric therapy

- The *a priori* risk for MDR-TB should be assessed.
- Low risk patients without microbiologic diagnosis should be initiated on empiric first-line therapy and then switched to MDR-TB therapy after failing to respond in the first month of therapy.
- The threshold for switching regimens should be relatively low in patients in highly endemic MDR-TB settings who fail to respond to first-line drugs.

Dosing and CNS penetration

- The MDR-TB regimen should include an injectable, a quinolone and at least other two likely active second line drugs plus pyrazinamide.
- Controlled trials to determine the optimal drug regimen and treatment duration for TBM have not been conducted.
- There is no good data on CNS penetration.

Conclusions I

- Pediatric DR-TB is an unrecognized problem with fatal consequences for children
- Poor outcomes mainly associated with delays in diagnosis
- Need high index of suspicion and look for isolated vomiting, headache, fatigue and decreased play
- Contact history is key in making the diagnosis, but need to ask additional questions about contacts to assess risks

Conclusions II

- NAAT (i.e. Xpert) are preferred diagnostic test under program conditions, although culture should also be done if possible
- Principles follow management of pulmonary MDRTB in children, but may need adjuvant steroids, drainage/EVD; thalidomide may have a possible role in cases complicated by brain abscess
- Empiric MDR-TB therapy when risk of disease is moderate

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