TB meningitis: diagnosis, management and outcome

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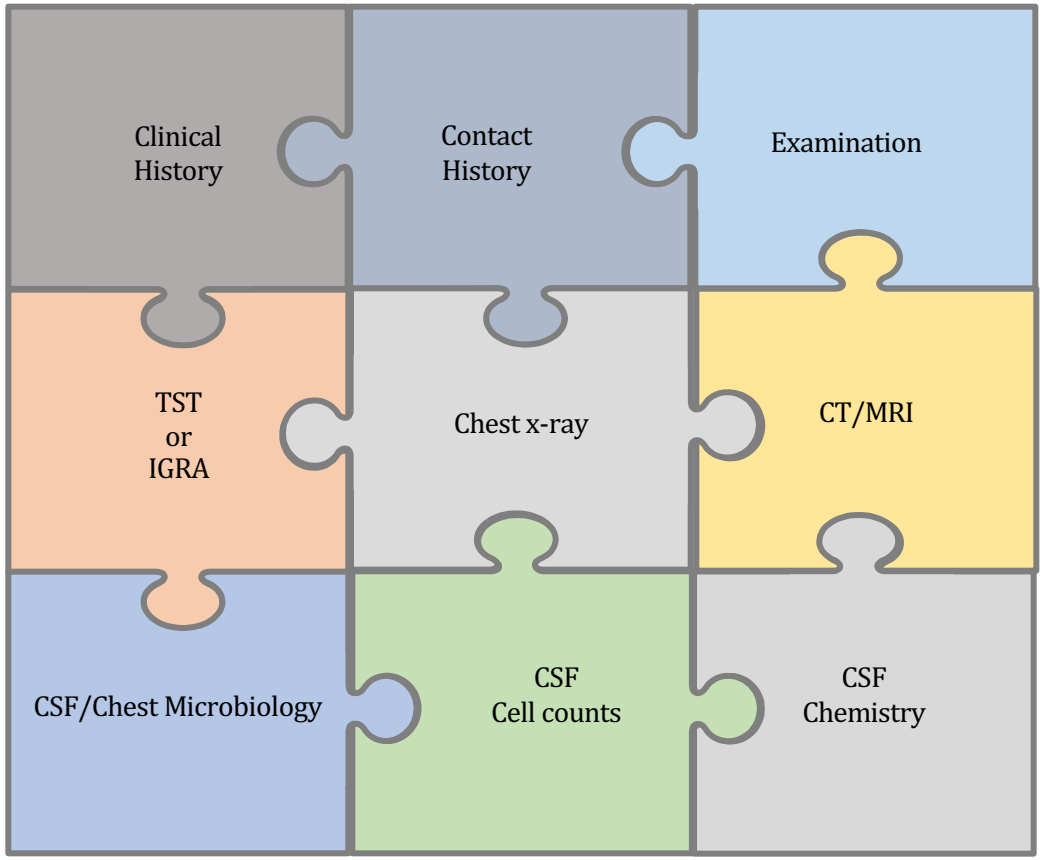
Diagnosis of TBM



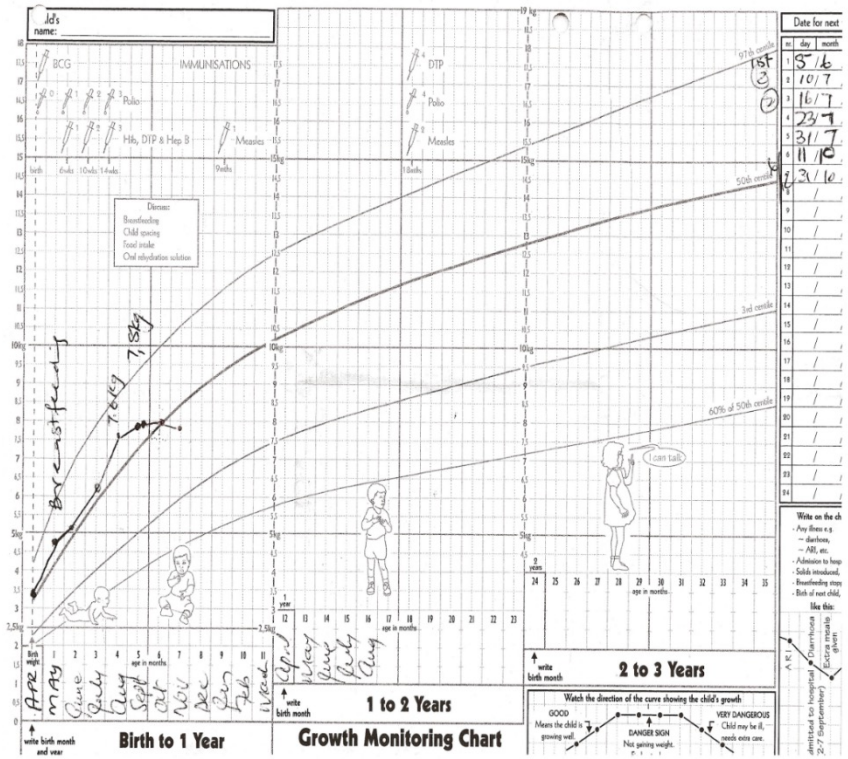
History and examination

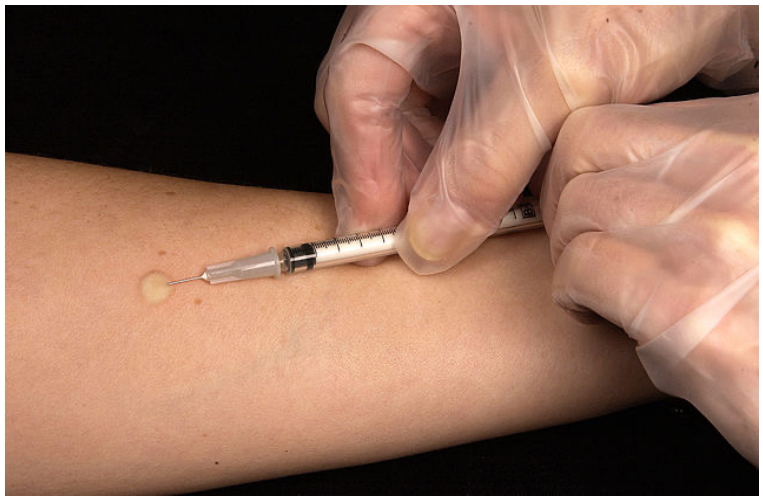
Onset is mostly insidious (days to weeks)

Early symptoms are non-specific
An important factor that differentiates the symptoms of TBM from common illnesses such as influenza is their persistence.

Neck stiffness is often absent during early disease in children
Vomiting without preceding nausea should alert physicians to the possibility of raised ICP

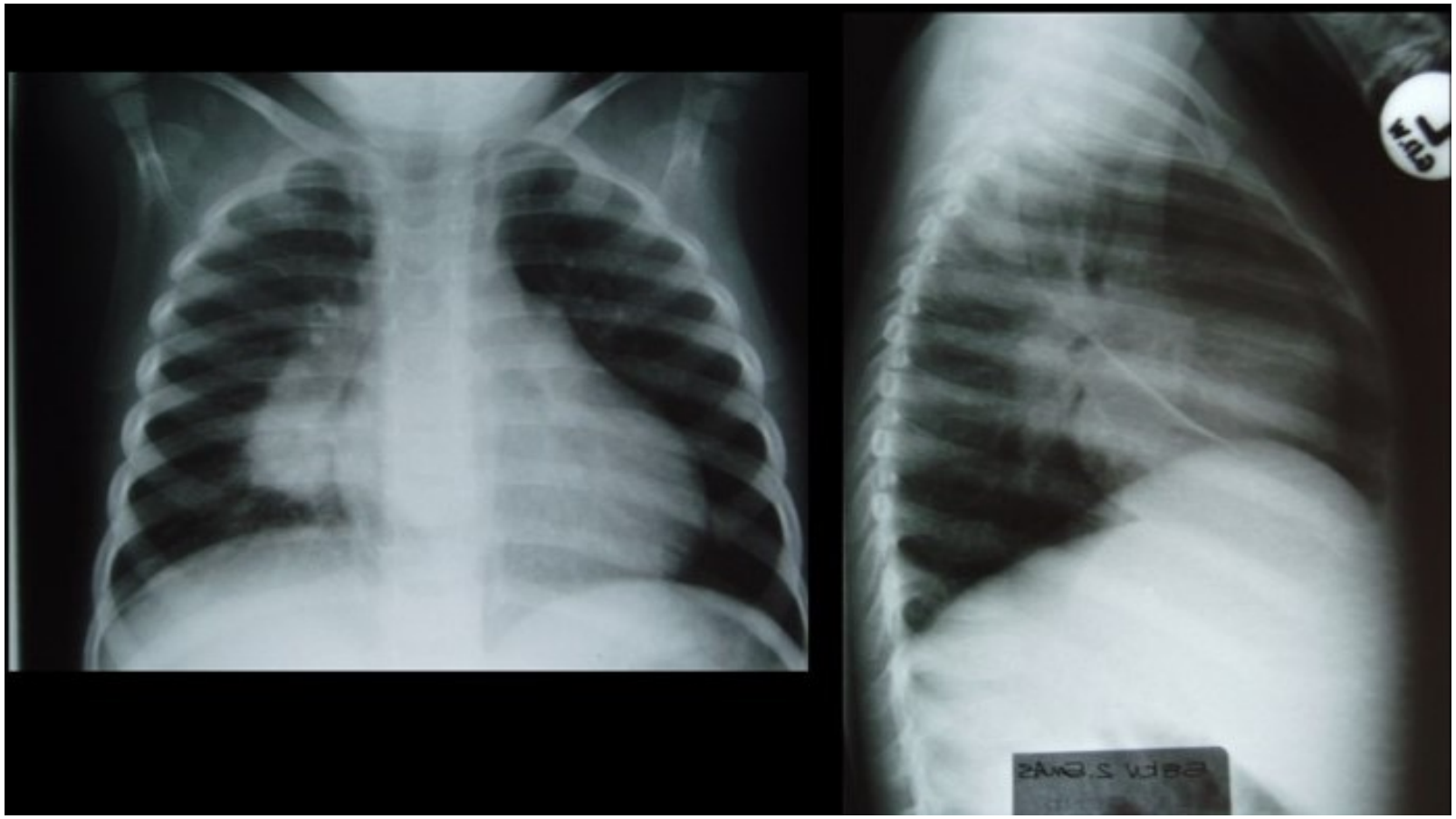
Weight faltering





Tuberculin skin testing

Chest X-Ray



Diagnosis of TBM

Routine CSF findings, healthy and meningitis

	Colour	Cell counts/ml	Protein	Glucose
Neonate	Clear to yellow	2-20 Lymphs 0 Polys	0.2-1.5 g/L	3-5 mmol/L
Infancy up to adulthood	Clear	0-5 Lymphs 0 Polys	0.2-0.4 g/L	3-5 mmol/L
Aseptic meningitis	Clear	20-100 cells Mainly Lymphs	Normal #	Normal #
Septic meningitis	Hazy to frankly purulent	➢50-1000's of cells Mainly Polys	Raised	Decreased
TB meningitis	Clear to yellow	10-500 cells Mainly Lymphs *	>1 g/L	Normal to decreased

CSF findings in Childhood TBM

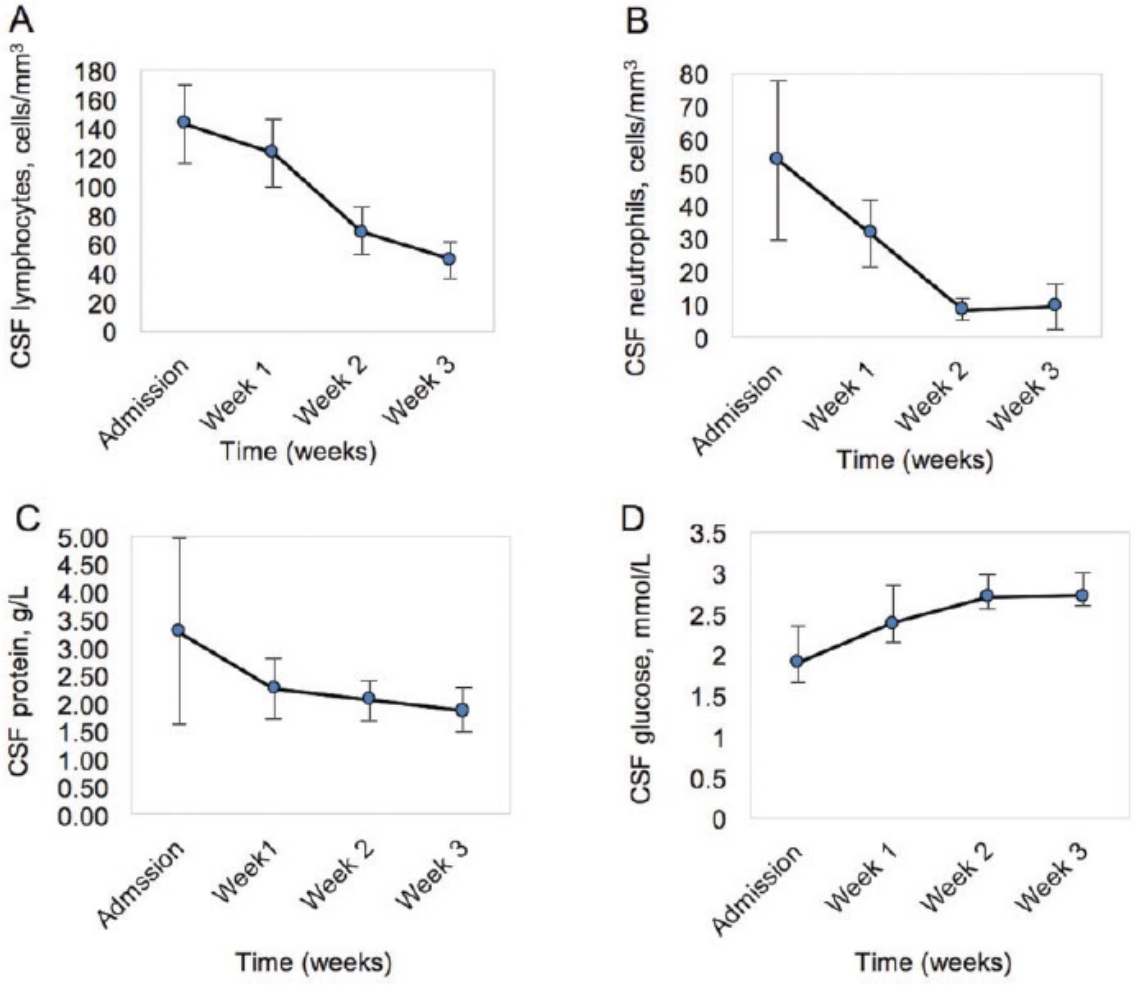
Diagnostic uncertainty remains a problem in childhood TBM
regularly based only on clinical and preliminary CSF findings

Atypical CSF findings common, including:
- normal CSF cell count,
- normal CSF protein
- normal CSF glucose levels
- CSF neutrophil predominance

Differentiating TBM from other forms of bacterial meningitis in TB-endemic areas can be challenging.

LP often repeated especially with diagnostic uncertainty (2 weeks)

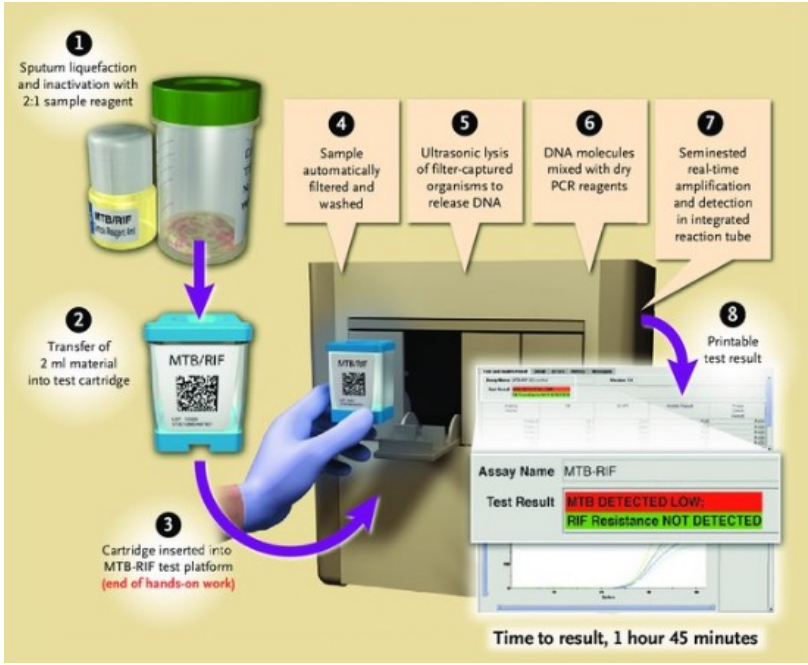
TBM Lumbar CSF Evolution



Diagnostic uncertainty → repeat LP 14 days

Nucleic Acid Amplification tests

Xpert MTB/Rif (sensitivity 61-85%)
Negative Xpert does not provide enough confidence to rule out TBM
Xpert MTB/Rif ultra
Adequate CSF volume (6ml) improves performnce



CT versus MRI

	CT	MRI	Difference
Basal enhancement	21	29	8
Hydrocephalus	23	23	0
Infarcts	21	25	4
Granuloma(s)	5	12	7

	CT (21)	MRI (25)	Difference
Basal ganglia	17	22	5
Bilateral basal ganglia	10	12	2
Thalami	2	14	12
Bilateral thalami	1	5	4
Corpus callosum	2	8	6
Brainstem	3	15	12
Cerebellum	0	1	1
Cerebral	4	14	10

Anti-microbial treatment of TBM

Clinical Review

Evidence Behind the WHO Guidelines: Hospital Care for Children: What is the Most Appropriate Anti-microbial Treatment for Tuberculous Meningitis?

Primary Reviewer: Julie Woodfield
University of Edinburgh, Scotland

Secondary Reviewer: Andrew Argent
University of Cape Town, South Africa

All trials assessing anti-microbial treatment for TBM had limited power, poor methodology and varying treatment regimens with conflicting results. Therefore, it is impossible to assess the most appropriate anti-microbial regimen for TBM from the available literature.

TBM drug regimens

		12-month regimen			6-month intensive regimen		
	CSF penetration	Dosage and range (mg/kg)	Maximum dose (mg)	Duration (months)	Dosage (mg/kg)	Maximum dose (mg)	Duration (months)
Isoniazid (H)	Good	10 (7-15)	300	12	20	300	6
Rifampin (R)	Poor (the higher dosage the higher the CSF concentration)	15 (10-20)	600	12	20	600	6
Pyrazinamide (Z)	Good	35 (30-40)	2000	2	40	2000	6
Ethambutol (E)	Poor	20 (15-25)	1000	2			
Ethionamide (Eto)	Good (>80%)	Not recommended			20	1000	6

Other 2nd line agents		
	CSF penetration	**Dosage (mg/kg)**
Levofloxacin (Lfx)	Good	20
Terizidone (Trd)	Good	15-20
Linezolid (Lzd)	Good	10
Delamanid (Dlm)/Pretomanid (Pa)	Poor	
Bedaquiline (Bdq)	Poor	

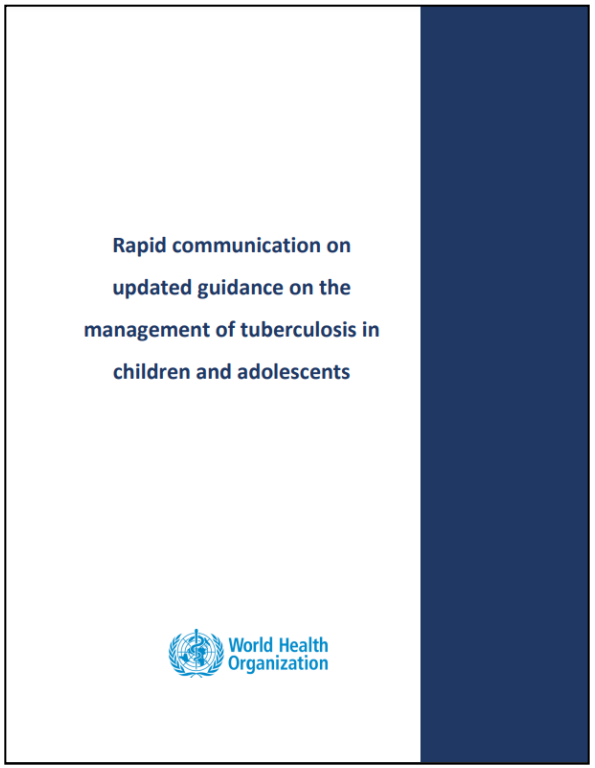
Rationale for using Ethionamide

ETH : 100% CSF penetration (healthy and inflamed meninges) compared to SM (20% inflamed meninges only) or EMB (25-50% inflamed meninges only).

Another advantage is that INH monoresistant TB meningitis is overcome when ETH and PZA are used continuously for a 6 month period. The inclusion of ETH should therefore be strongly considered in areas with high INH resistance (> 4% of primary infections) or in resource limited settings where drug susceptibility rates are unknown.

SM & EMB: Dosage-related ototoxicity and optic toxicity
ETH: Hepatotoxicity and gastrointestinal irritability with vomiting.
Monitor for hypothyroidism.

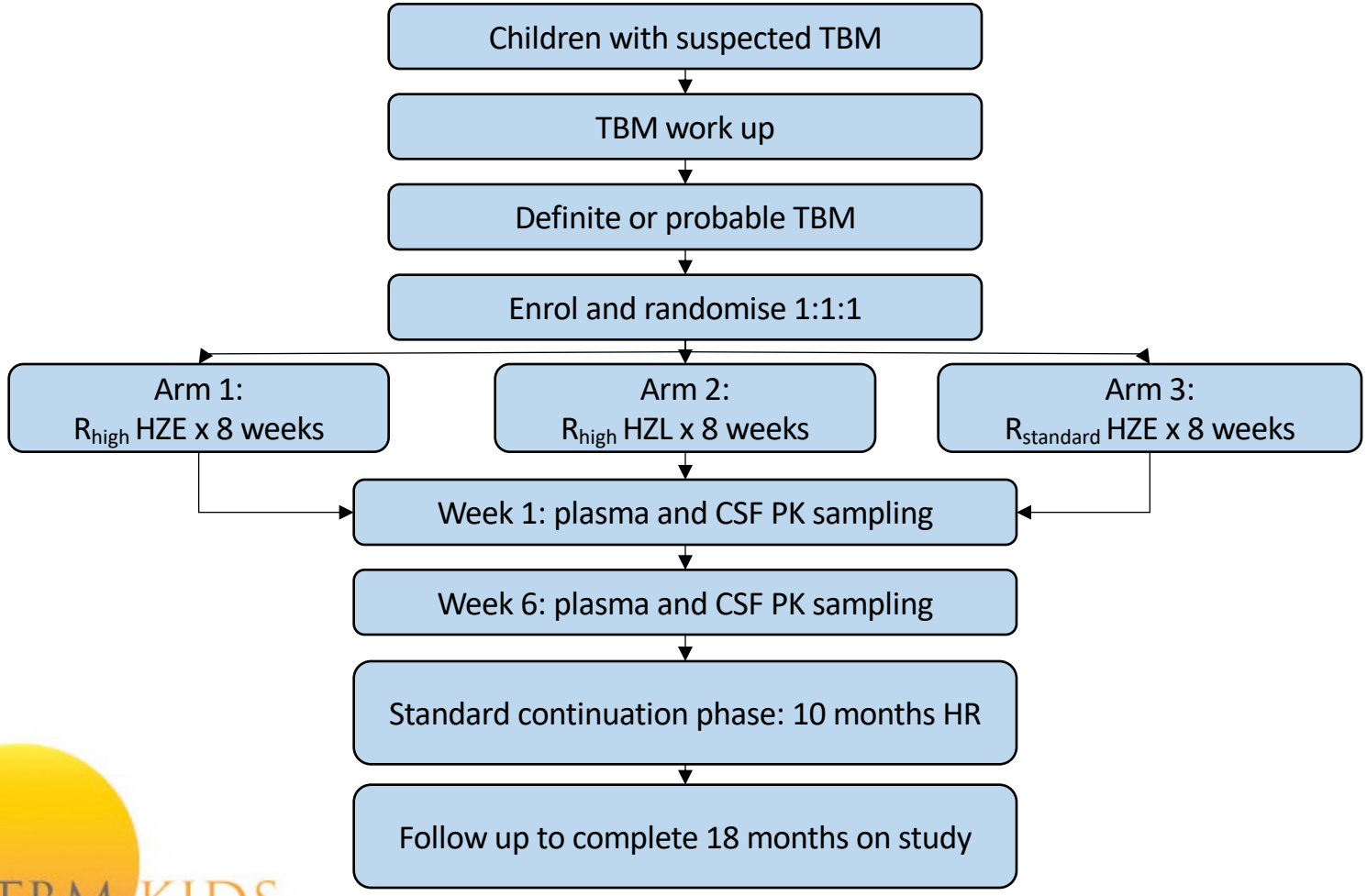
Anti-tuberculous therapy



- In children and adolescents with microbiologically confirmed or clinically diagnosed TBM, presumed to be drug susceptible, a 6-month intensive regimen composed of 6HRZEto may be used as an alternative option to the WHO recommended 12-month regimen composed of 2HRZE/10HR.

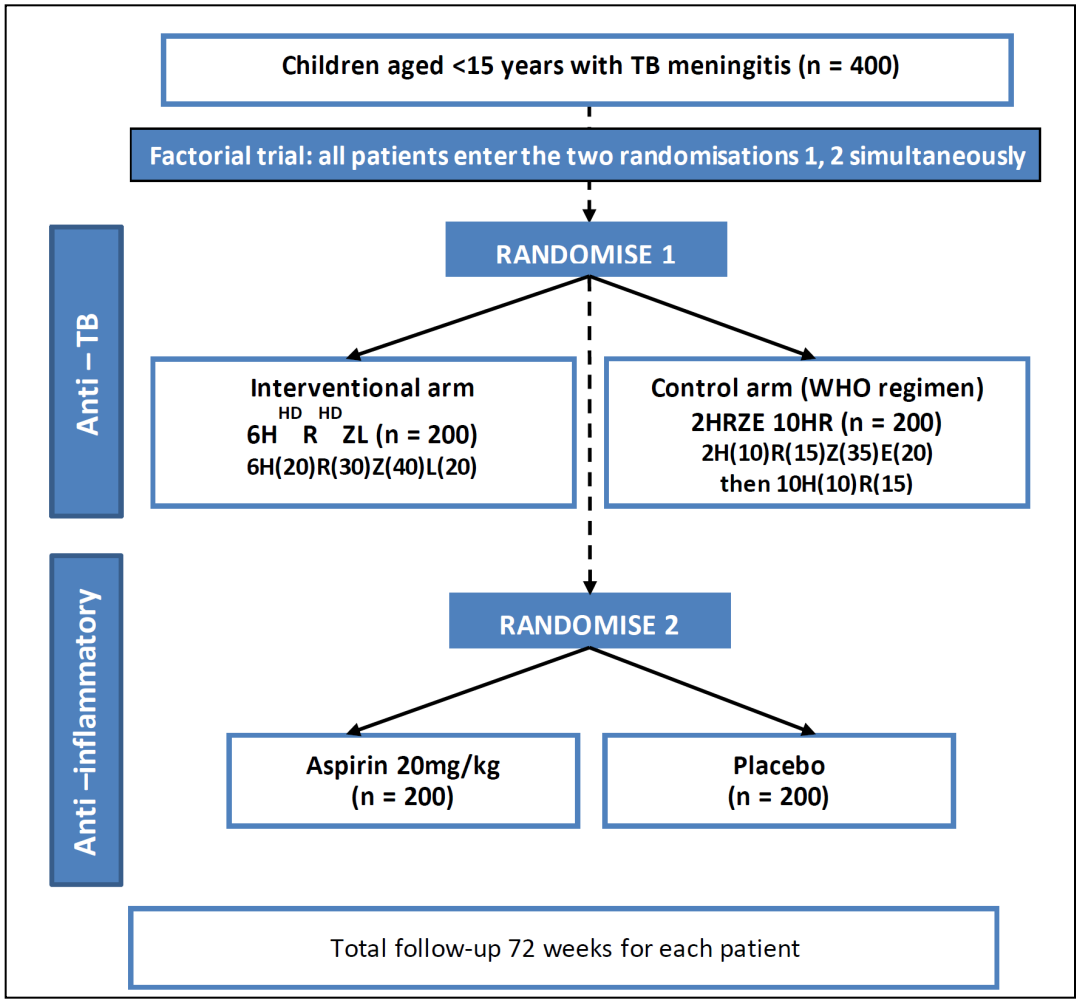
Giorgia Sulis et al Comparative effectiveness of regimens for drug Susceptible TBM in children and adolescents: Systematic review and aggregate-level meta-analysis Open forum infectious disease April 2022

Optimizing treatment to improve TBM outcomes in children



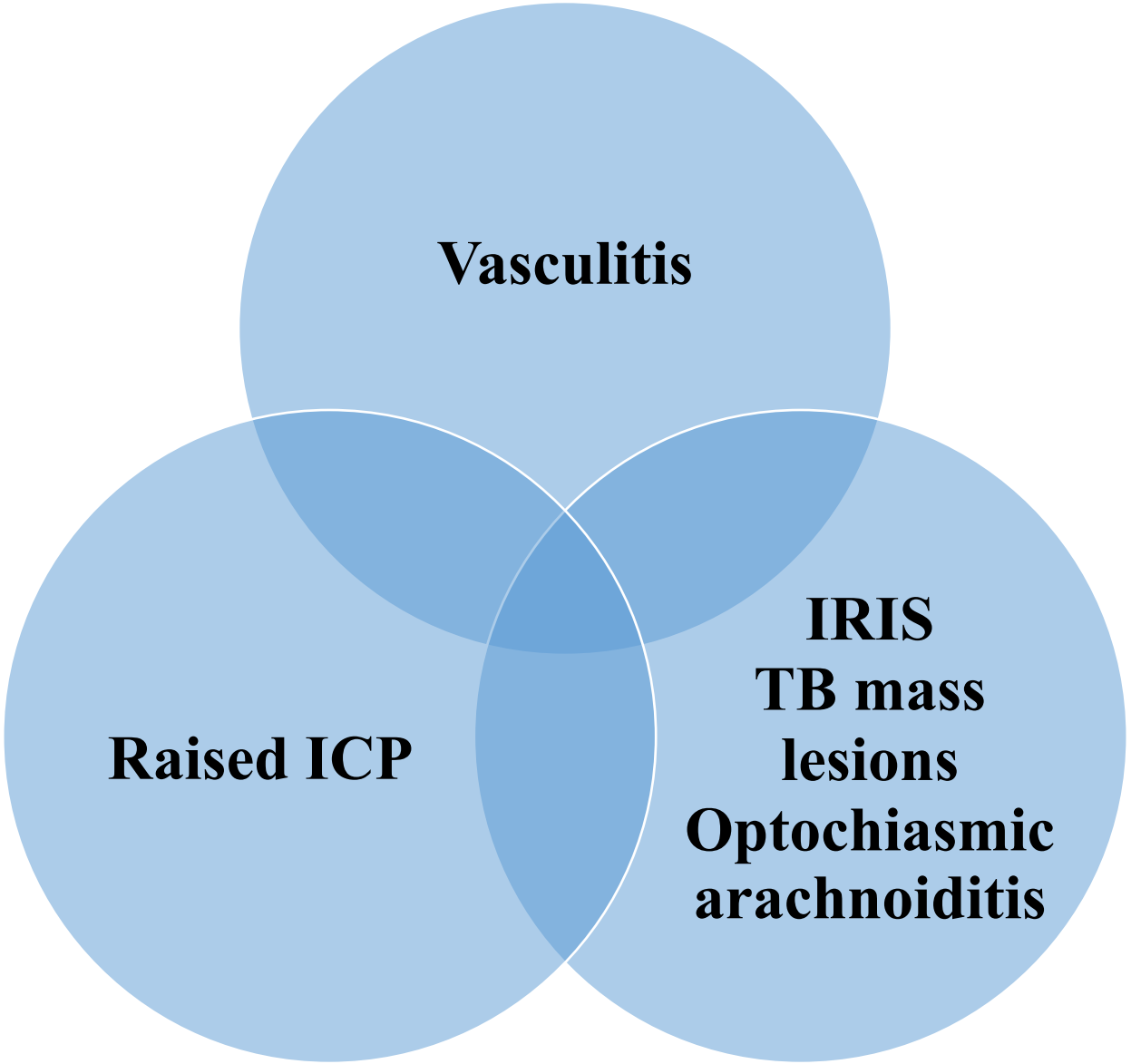
TBM KIDS

Short intensive treatment for children with tuberculous meningitis



SURE

Spectrum of pathology in TBM



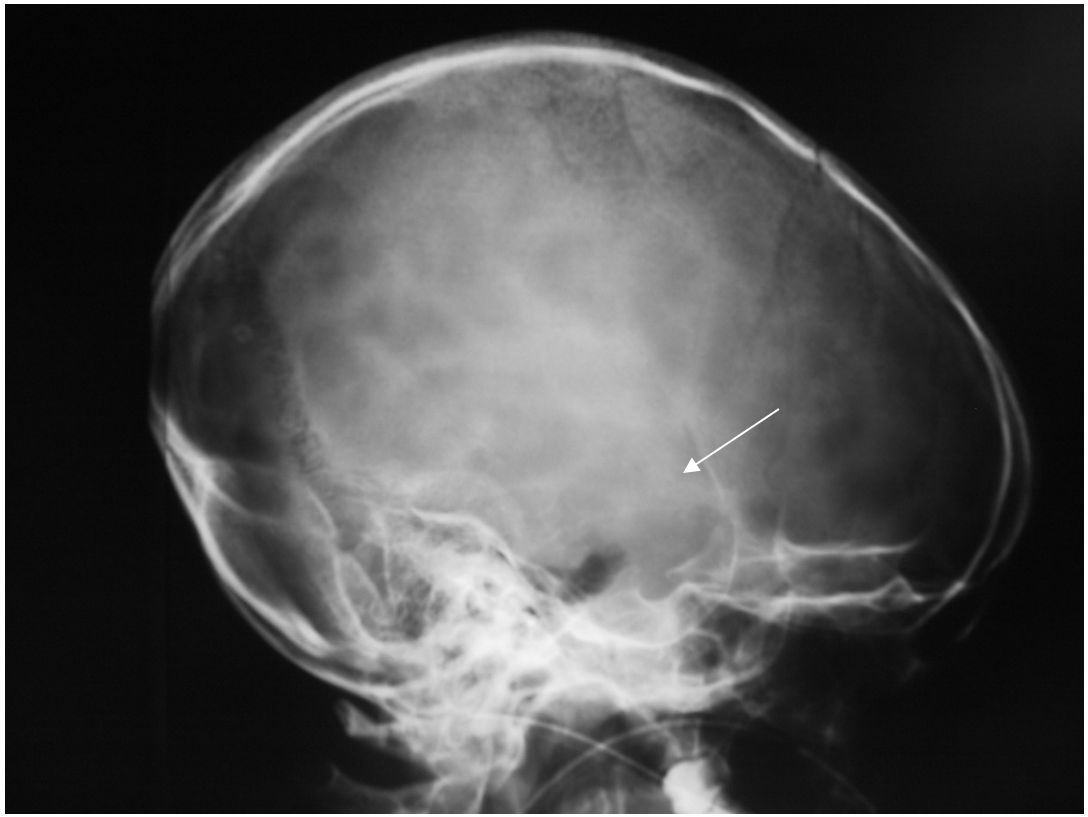
Air-encephalogram procedure

The procedure entails injection of 5 to 10 cc of air during lumbar puncture followed by a lateral radiograph of the skull within 6 hours with the patient held in elevated position. Removal of the needle and syringe at the same time after the injection of air is important otherwise leakage of air will ensue resulting in a failed procedure.

The presence of air in the lateral ventricle confirms communicating hydrocephalus whilst air at the base of the brain (prepontine cistern) without any air visible in the lateral ventricle indicates non-communicating hydrocephalus.

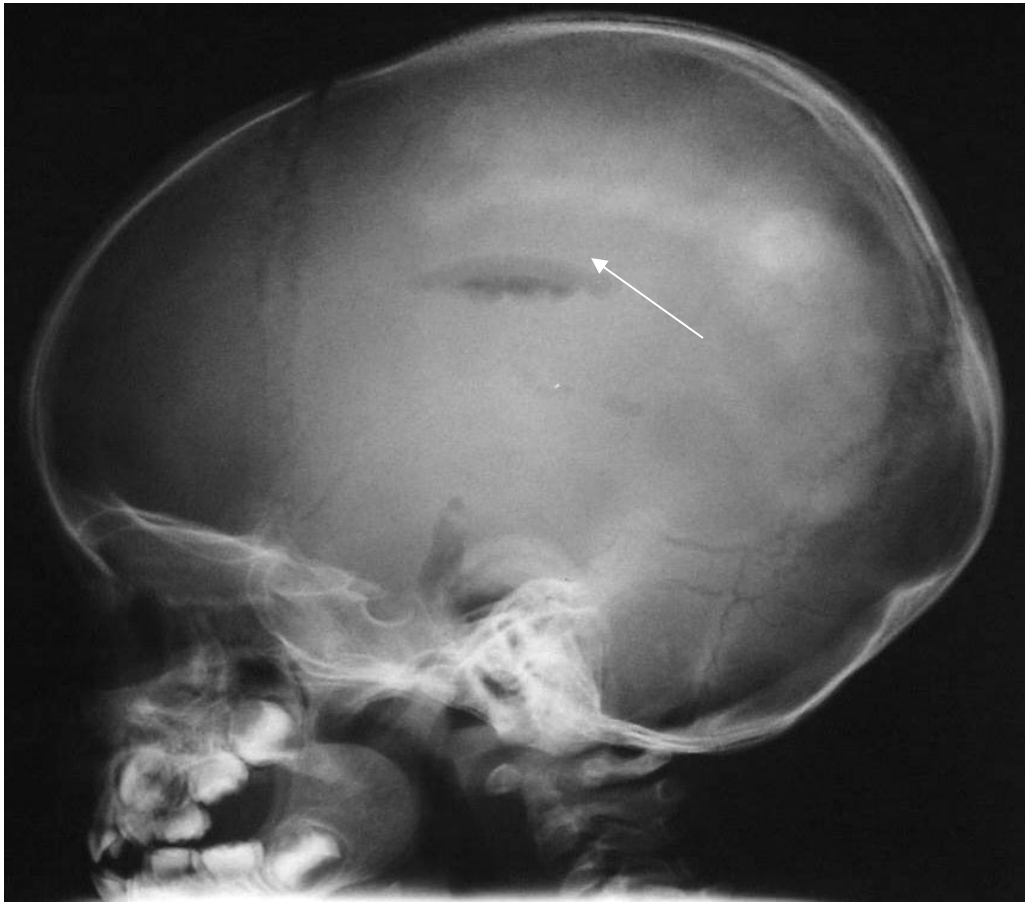
Non-communicating hydrocephalus

- Obstruction of 4th ventricular foramina
- Often sudden onset and progression of coma and brainstem signs: cerebral herniation
- Treatment: VP shunt, EVD or 3rd ventriculostomy

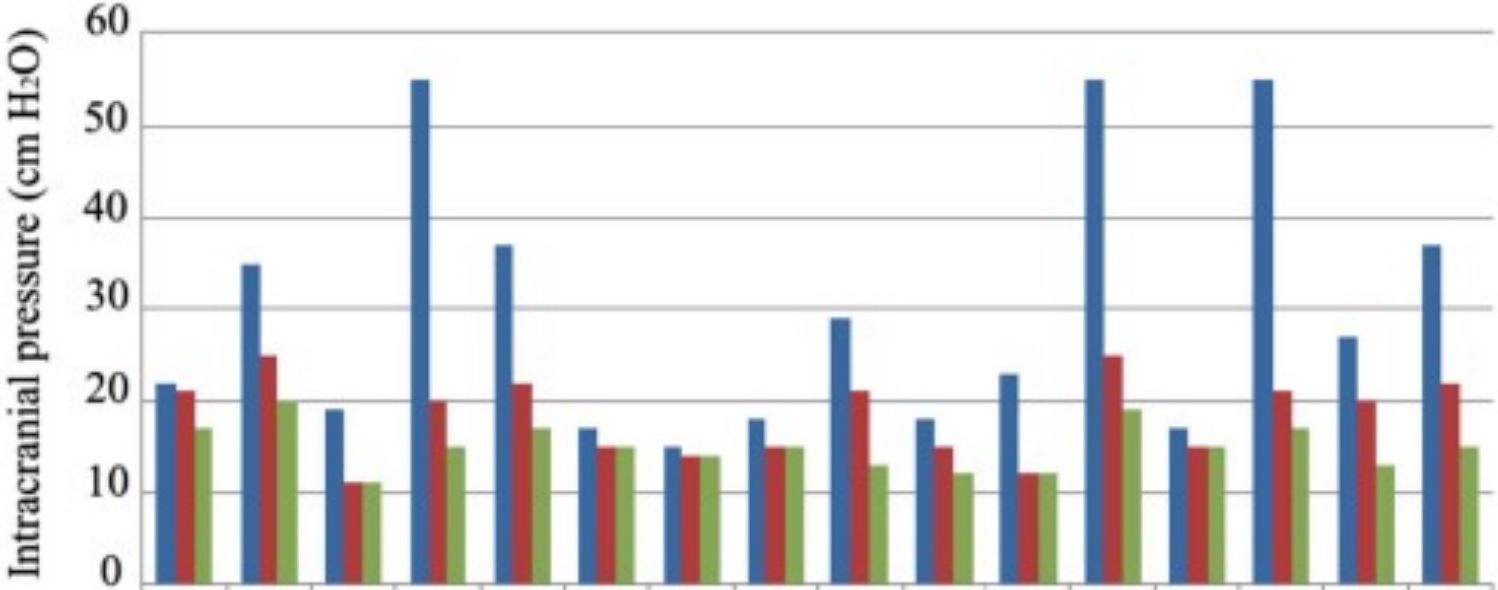


Communicating hydrocephalus

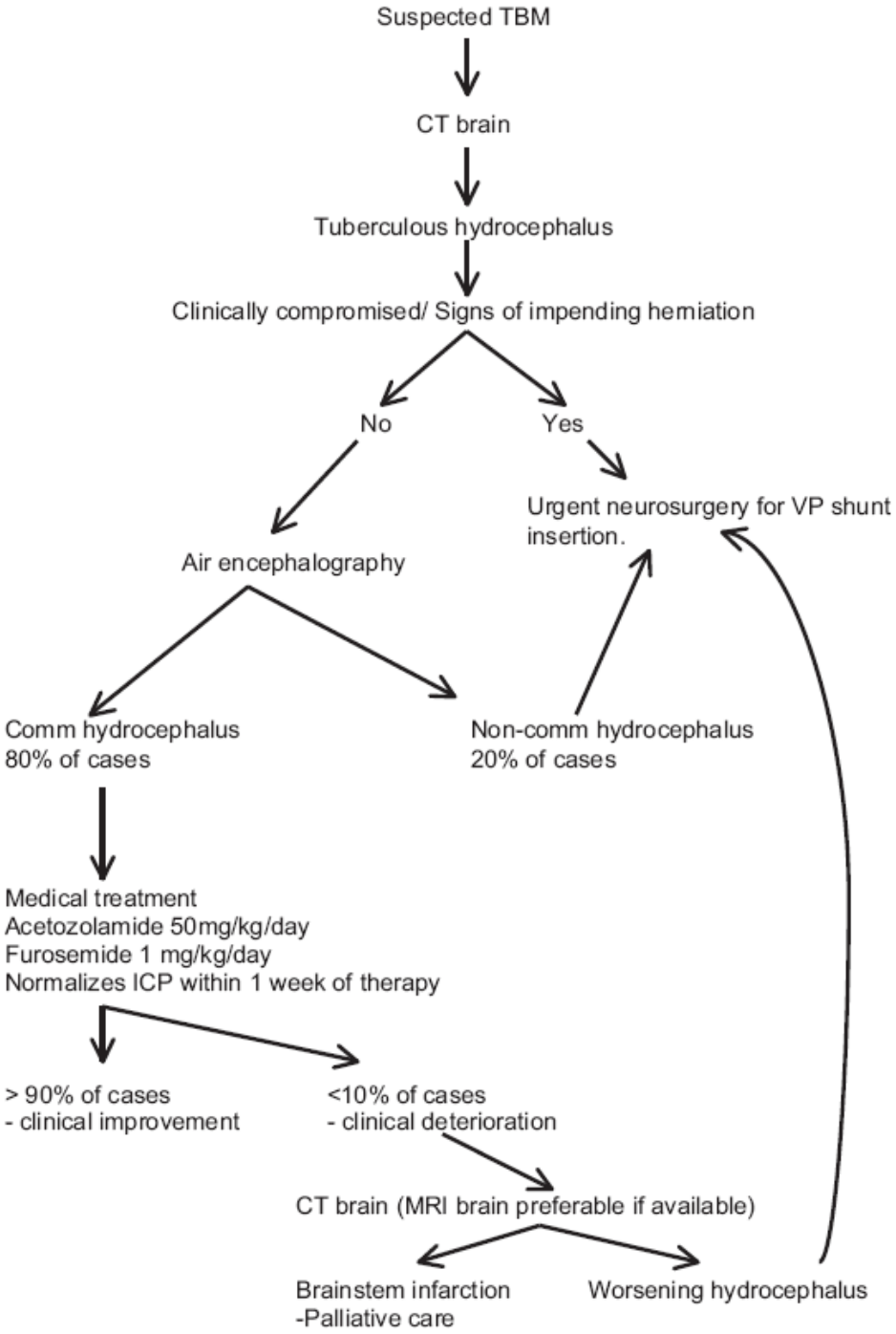
- Lumbar CSF pressure = intraventricular CSF pressure
- Medical treatment (diuretics) normalizes ICP in 90% of cases.
- Lasix 1 mg/kg/day in two divided doses. Acetazolamide 50 mg/kg/day in 3 divided doses



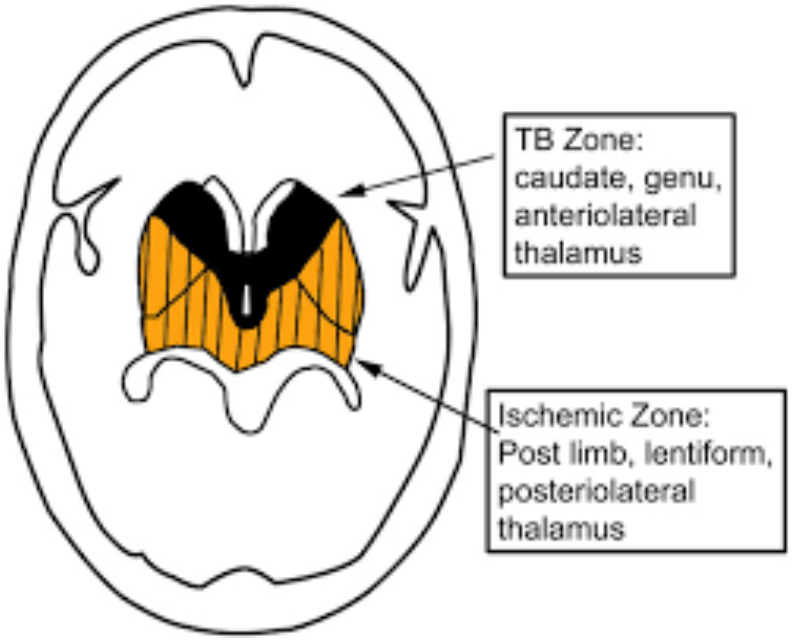
Intracranial pressure per patient on Day 1,3 & 7

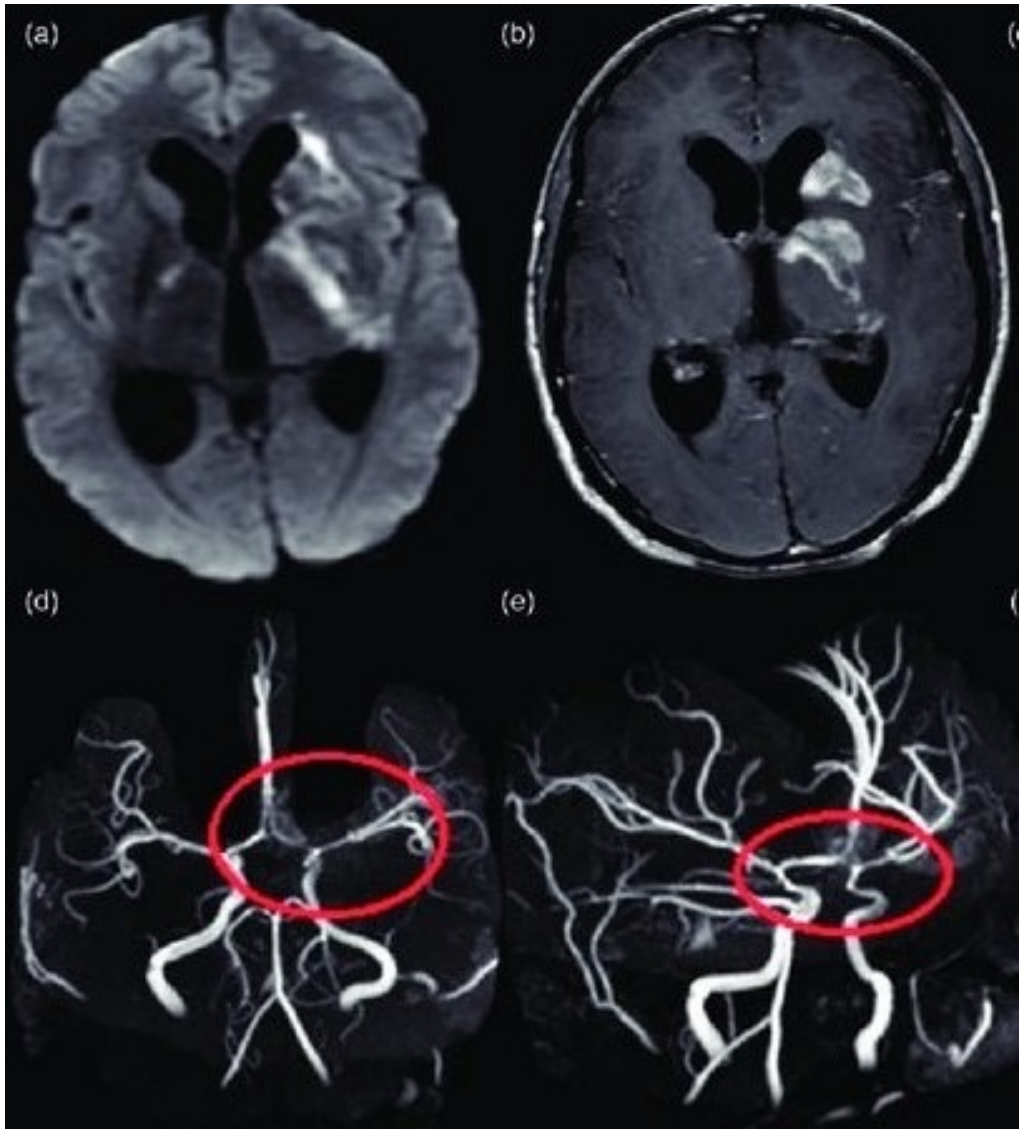


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Day 1	22	35	19	55	37	17	15	18	29	18	23	55	17	55	27	37
Day 3	21	25	11	20	22	15	14	15	21	15	12	25	15	21	20	22
Day 7	17	20	11	15	17	15	14	15	13	12	12	19	15	17	13	15


Suspected TBM
CT brain
Tuberculous hydrocephalus
Clinically compromised/ Signs of impending herniation
No
Yes
Urgent neurosurgery for VP shunt insertion.
Air encephalography
Comm hydrocephalus
80% of cases
Non-comm hydrocephalus
20% of cases
Medical treatment
Acetozolamide 50mg/kg/day
Furosemide 1 mg/kg/day
Normalizes ICP within 1 week of therapy
> 90% of cases
- clinical improvement
<10% of cases
- clinical deterioration
CT brain (MRI brain preferable if available)
Brainstem infarction
-Palliative care
Worsening hydrocephalus

Cerebral ischemia/Stroke



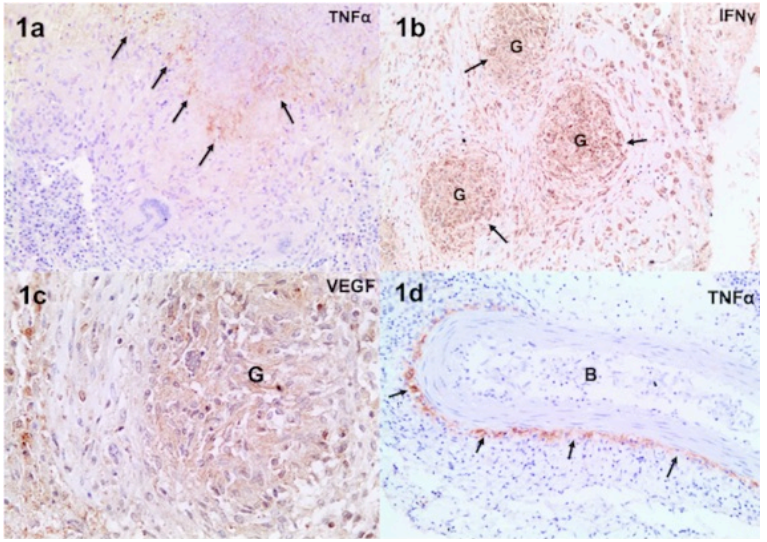


Host-directed therapies in TBM

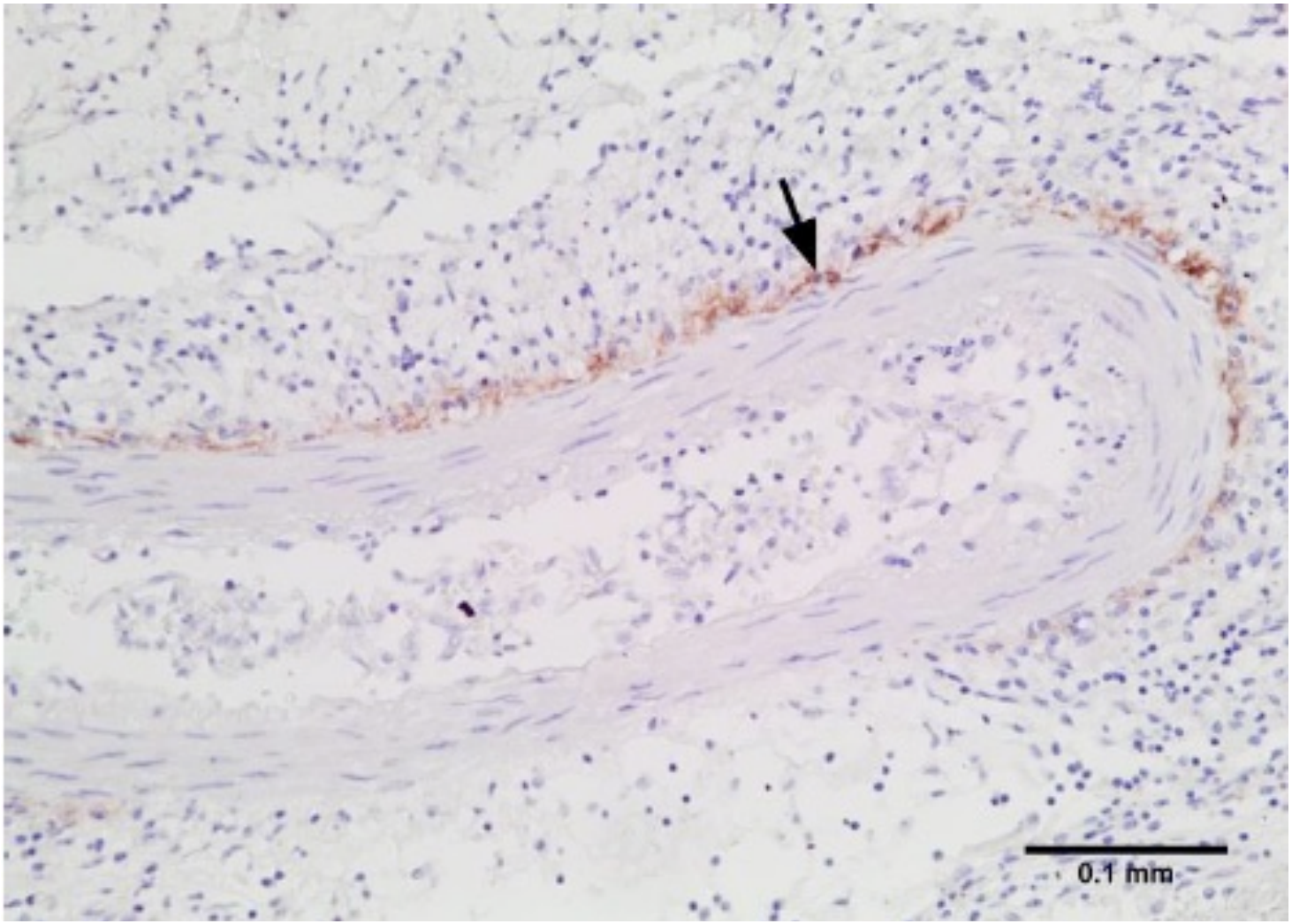
Reference	Intervention (drug, dose, duration)	Study design	Population	Primary outcome	Key findings
Mai[27]	Aspirin 81 mg vs. 1000 mg vs. placebo for 60 days	RCT: double-blind, Placebo controlled	Adults Non-HIV, Vietnam n = 120	Mortality or Stroke	No difference in 2-month mortality. Subgroup analysis showed reduction in infarcts and death with aspirin 81 mg (15%) and 1000 mg (11%) compared to placebo (34%); p = 0.06
Misra[34]	Aspirin 150mg vs. placebo	RCT: Placebo controlled	Adults n=118	Mortality or Stroke	Decreased 3-month mortality (21.7%) vs placebo (43.4%); Odds Ratio = 3.17, 95%CI 1.21 - 8.31. Aspirin resulted in absolute risk reduction of stroke in 19.1% and significant reduction in mortality compared to placebo (21.7% vs 43.4%, p=0.02)
Misra[35]	Aspirin 150mg	Retrospective cohort	n=135	Mortality	Non-statistical reduction in deaths (25%) at 3 months compared to standard TB treatment (17%).
Schoeman[36]	Aspirin 75mg or 100mg/kg	RCT	Children n=146		No improved neurological or cognitive outcomes or survival with aspirin
Schoeman[37]	Thalidomide 6mg/kg, 12mg/kg, or 24mg/kg	Dose escalating Pilot study	Children n=15	Safety and tolerability	Reduce CSF TNF-α in children with stage 2 TBM
Schoeman[38]	Thalidomide 24mg/kg for 1month	RCT: Double blinded	Children n=47		Discontinued prematurely due to side effects and deaths in thalidomide arm
Thwaites[1]	Dexamethasone	RCT: Double-blind Placebo controlled	Adult n=545 HIV and non-HIV	Mortality	Reduced risk of death through 9 months (relative risk 0.69, p=0.01) with dexamethasone
Simmons[15]	Dexamethasone	RCT: Double-blind Placebo controlled	Adult N=87		Dexamethasone did not significantly alter tested CSF cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-12) over time vs. placebo

Important cytokines in TBM

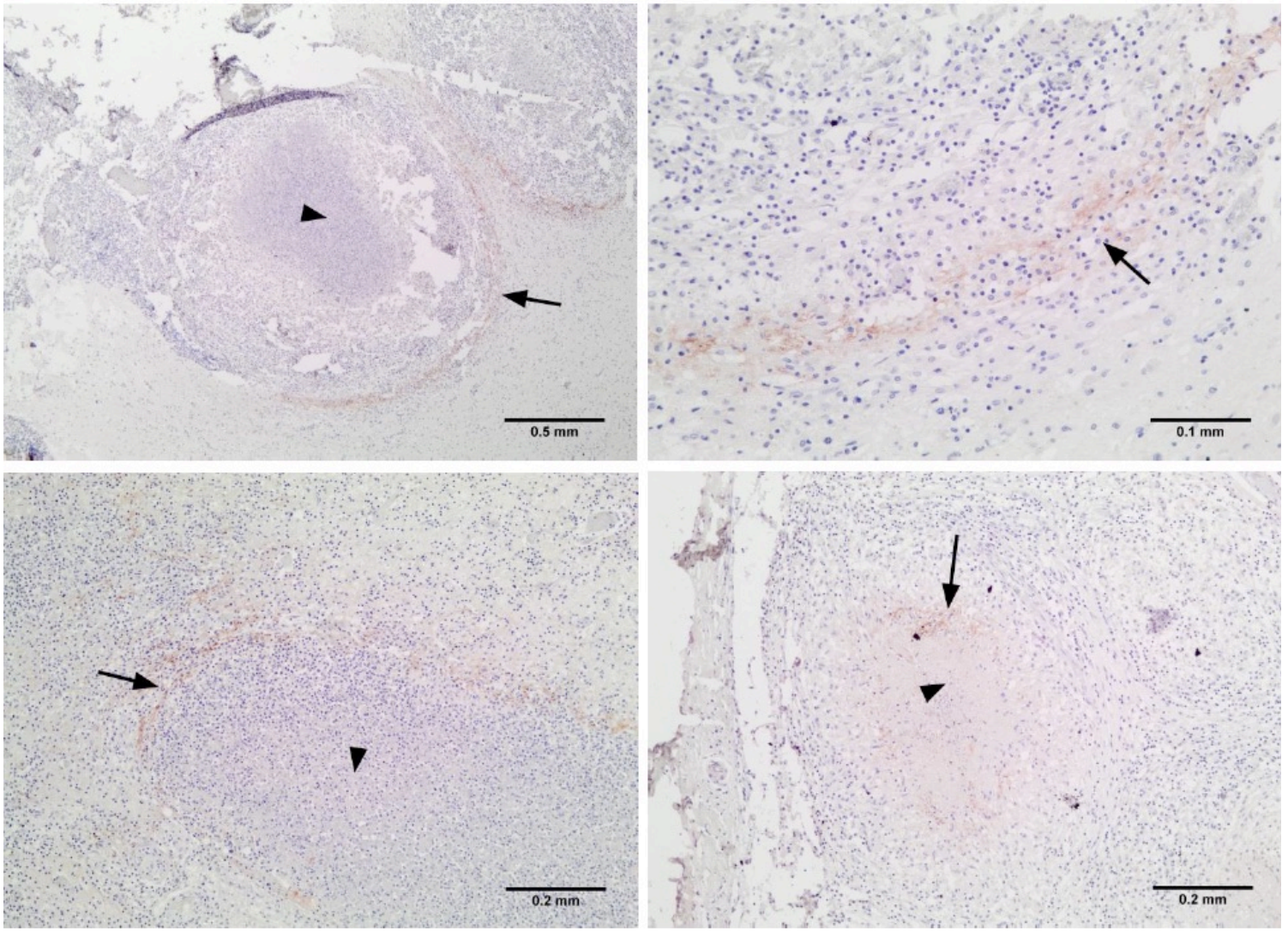
	Role in TBM disease	Impact of thalidomide
TNF-α	• Controls *M.tb* infection and replication by formation and maintenance of the granuloma: by regulating macrophage activation, phagocytosis, and the production of nitrogen and oxygen intermediates. • Inadequate TNF-α levels result in dissemination of TB disease or activation. • Excessive TNF-α levels induces a hyperinflammatory state resulting in severe tissue damage	• ↓TNF-α levels which at optimal dose confers anti-inflammatory benefits. • Reduces perilesional inflammation in TB abscesses and optochiasmatic arachnoiditis.
IFN-γ	• Critical mediator that enables macrophages to contain *M.tb* infection by stimulating maturation of phagolysosomes, by enhancing the production of nitric oxide, and by mobilizing peptides against bacteria. • Ability to induce a hyperinflammatory state. • Conversely, it also has the potential to suppress inflammatory responses secondary to down regulation of certain cytokines and chemokine genes.	• ↑IFN-γ confers anti-inflammatory benefits. • It may also improve the response to *anti*-TB drugs in cavitary cerebral TB abscesses.
VEGF	• Disrupts the permeability of the blood-brain barrier. • Drives the ectopic growth of blood vessels (vascular dysfunction) around granulomas which results in increased vascular density which serves to alleviate granuloma hypoxia. • Increases brain oedema and infarction.	• ↓VEGF results in anti-angiogenic benefit which inhibits further granuloma enlargement and allows for improved *anti*-TB drug penetration.



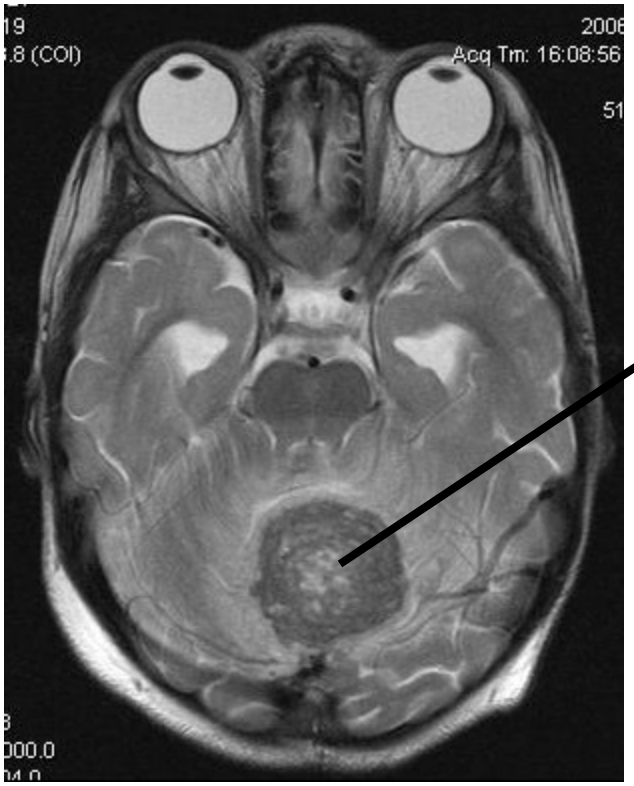
TNF-α perivascular distribution

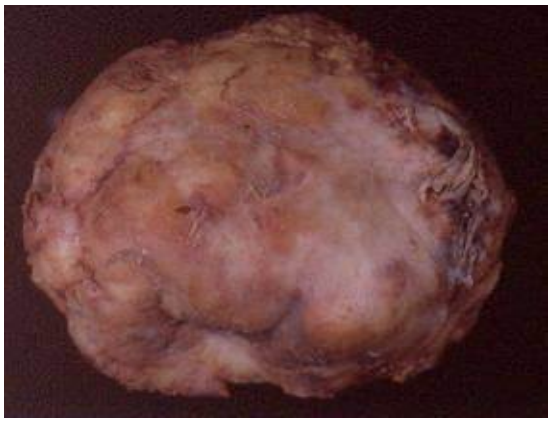


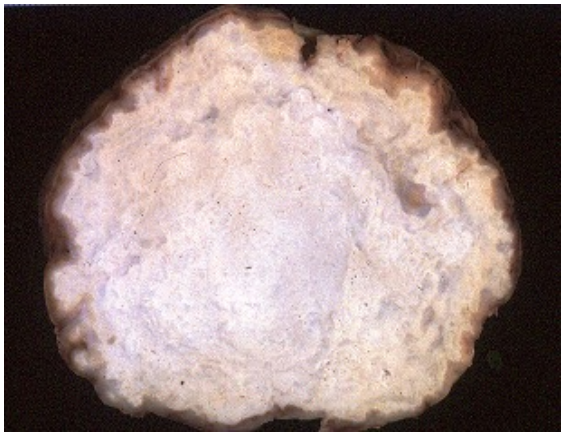
TNF-α Immunostaining TB abscess



Tuberculoma (Gumma): MRI T2-black

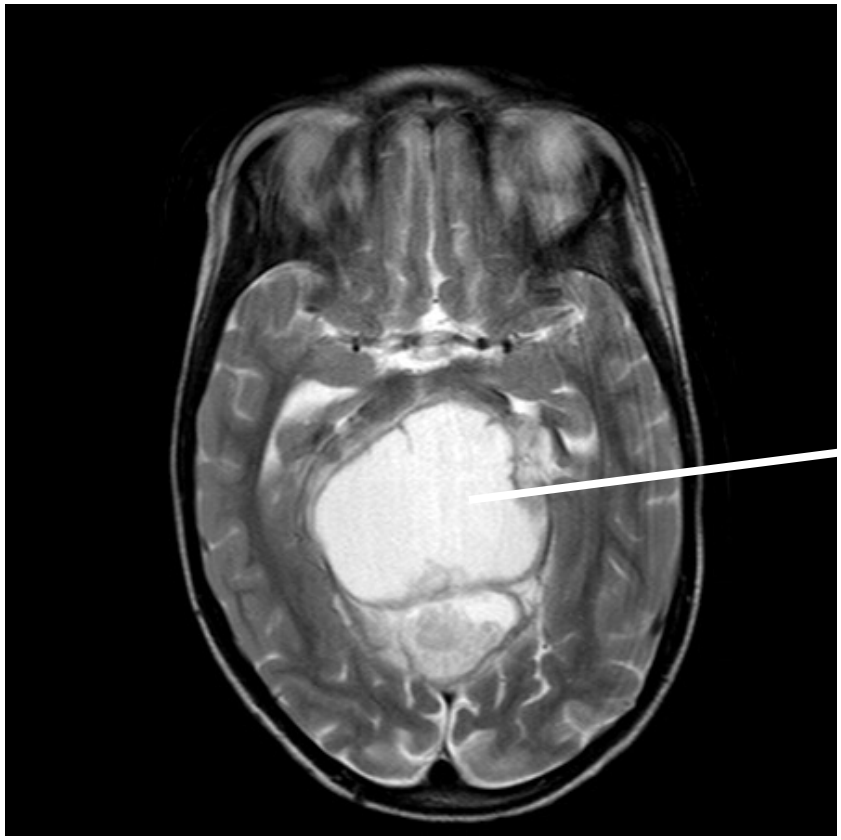


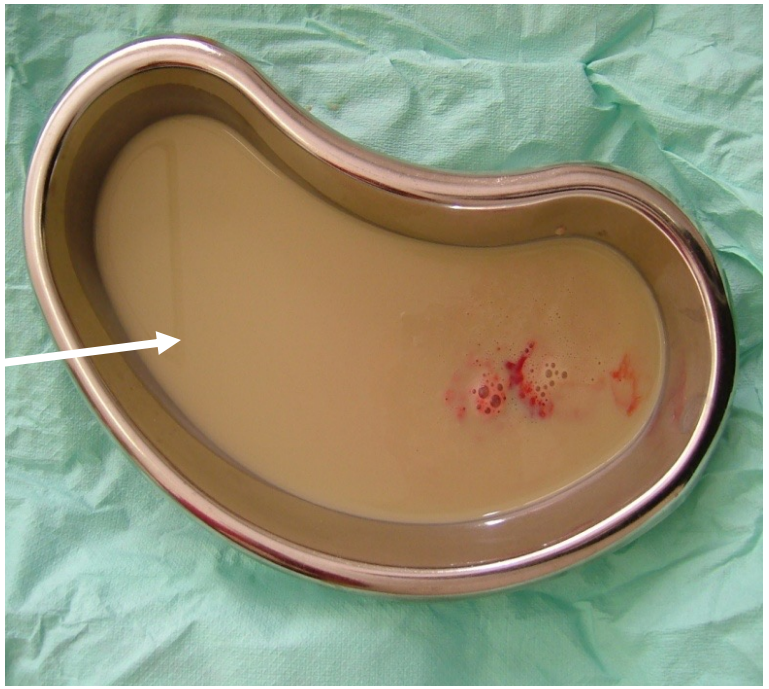




This reaction is T2 hypo intense yielding the black granuloma or gumma. Represents a satisfactory immune response. No TB bacilli visible on microscopy

TB Abscess: MRI T2 hyperintense (Bright)





The necrotic substrate is exudative/macrophage predominant
Teeming with TB bacilli +++ Gene Expert +
Unsatisfactory immune response.

Our experience with Thalidomide

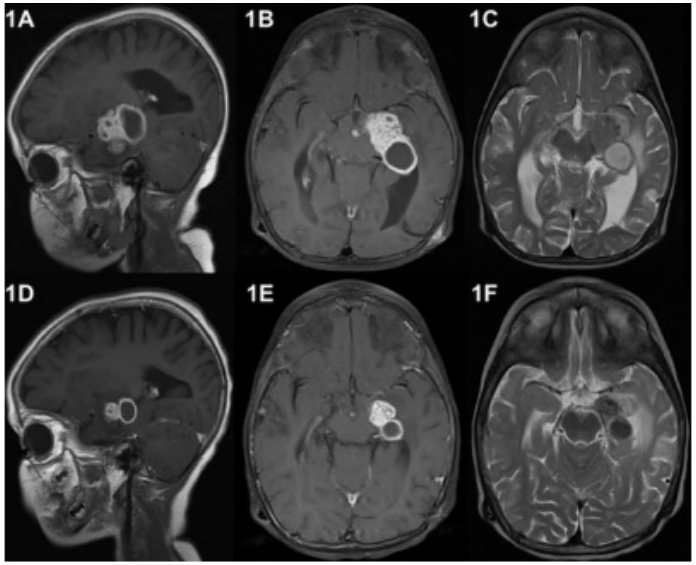
Thalidomide Use for Complicated Central Nervous System Tuberculosis in Children: Insights From an Observational Cohort

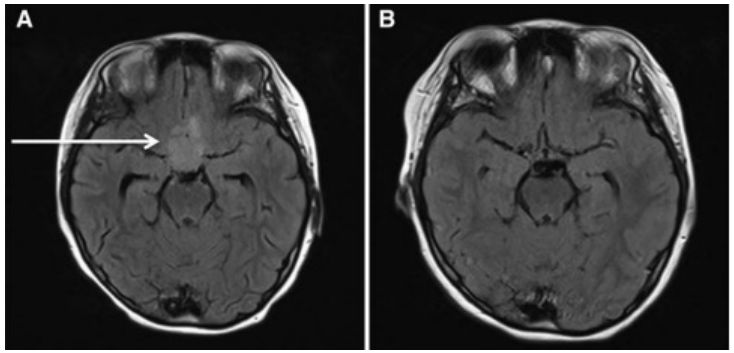
Ronald van Toorn,[1] Regan S. Solomons,[1,©] James A. Seddon,[2,3] and Johan F. Schoeman[1]

SUCCESSFUL TREATMENT OF A SEVERE VISION-THREATENING PARADOXICAL TUBERCULOUS REACTION WITH INFLIXIMAB

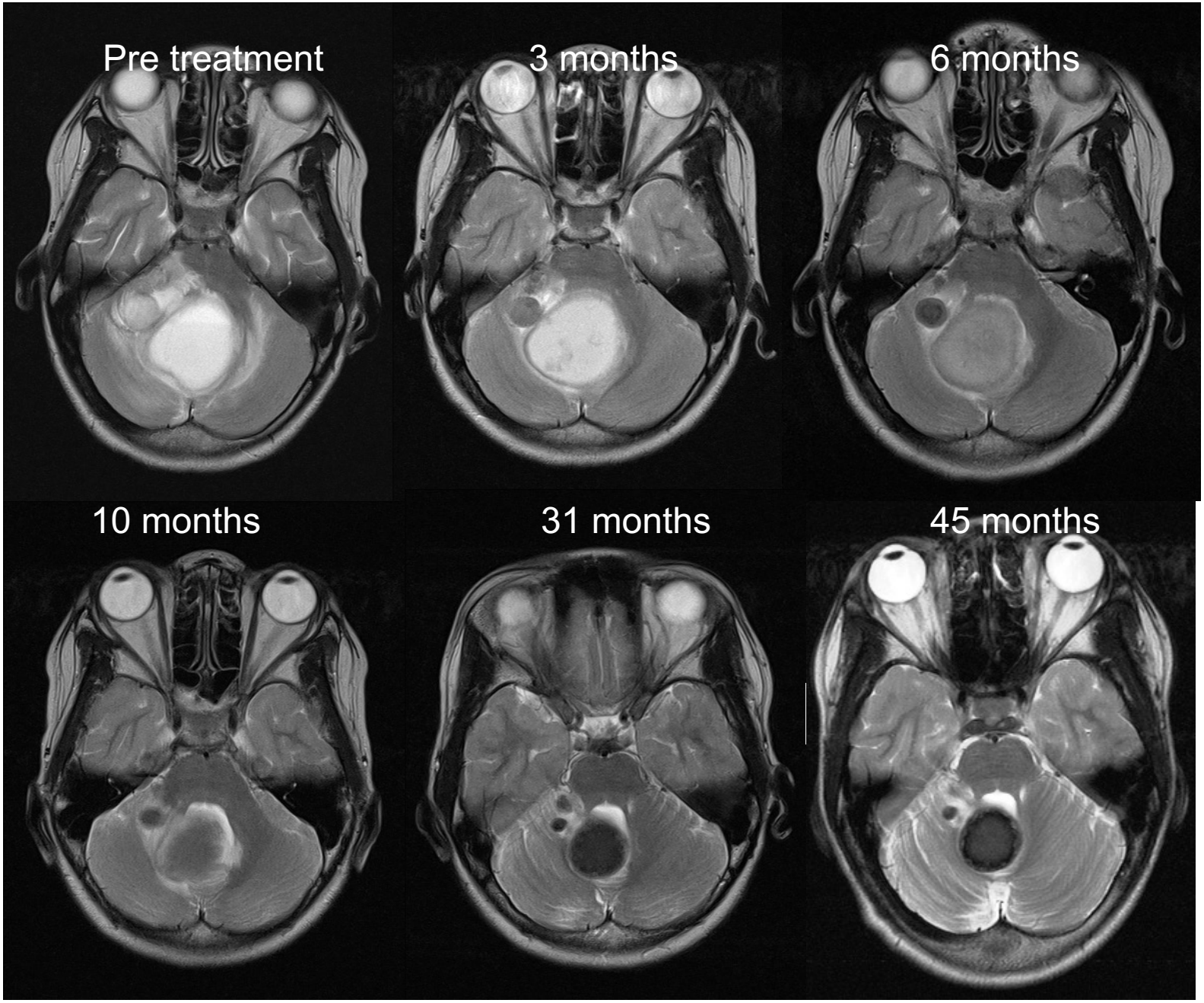
FIRST PEDIATRIC USE

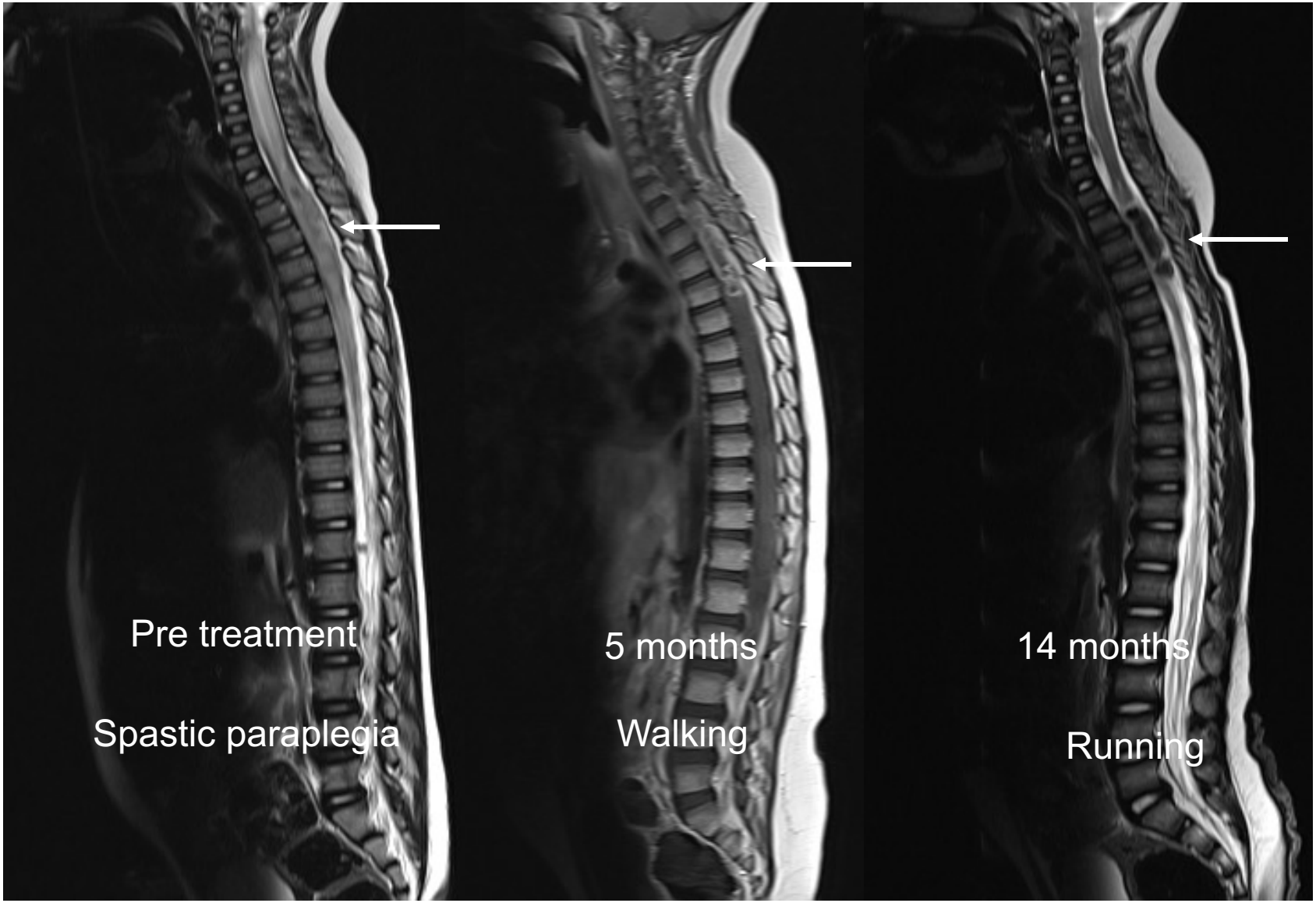
Yara-Natalie Abo, MBBS, Nigel Curtis, PhD,*†‡ Coen Butters, BMed,* Thomas H. Rozen, MBBS,*†‡ Ben J. Marais, PhD,§¶ and Amanda Gwee, PhD*†‡*





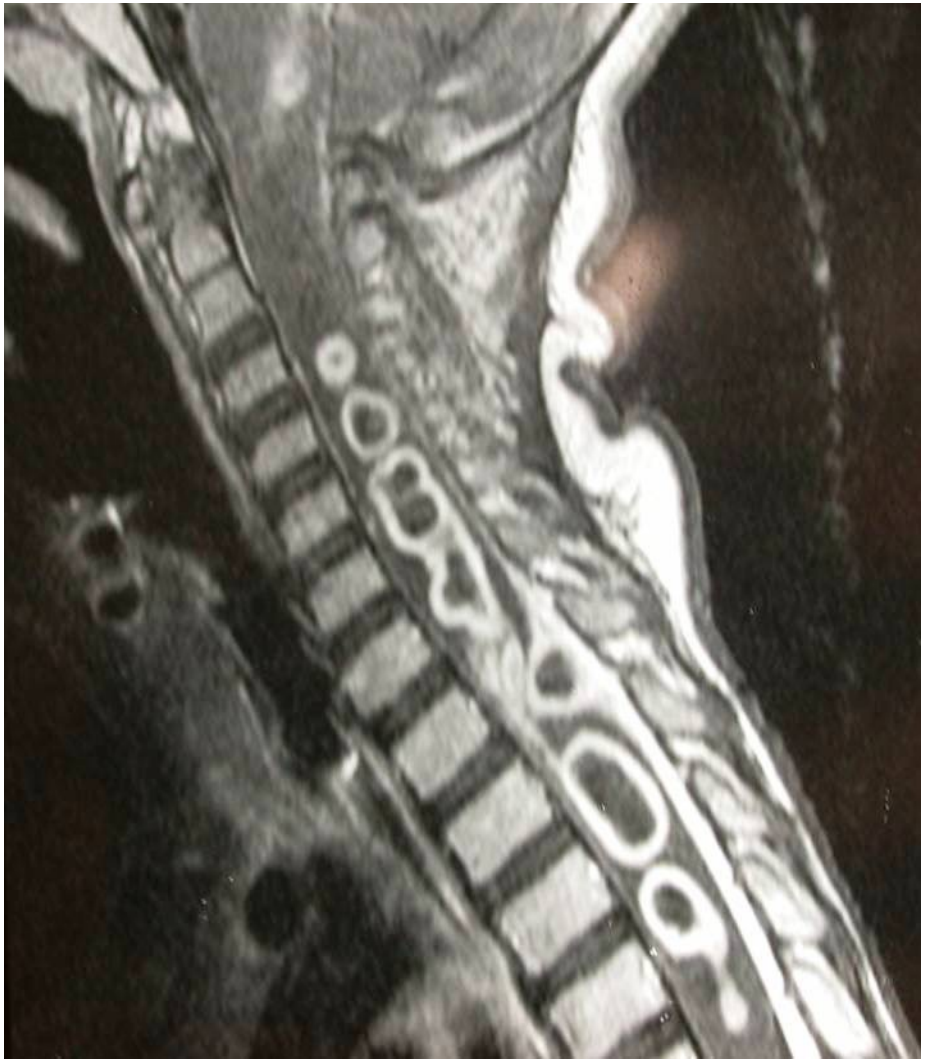
Van Toorn et al. Clin Infect Dis 2021; 72: e136-e145


Pre treatment
3 months
6 months
10 months
31 months
45 months

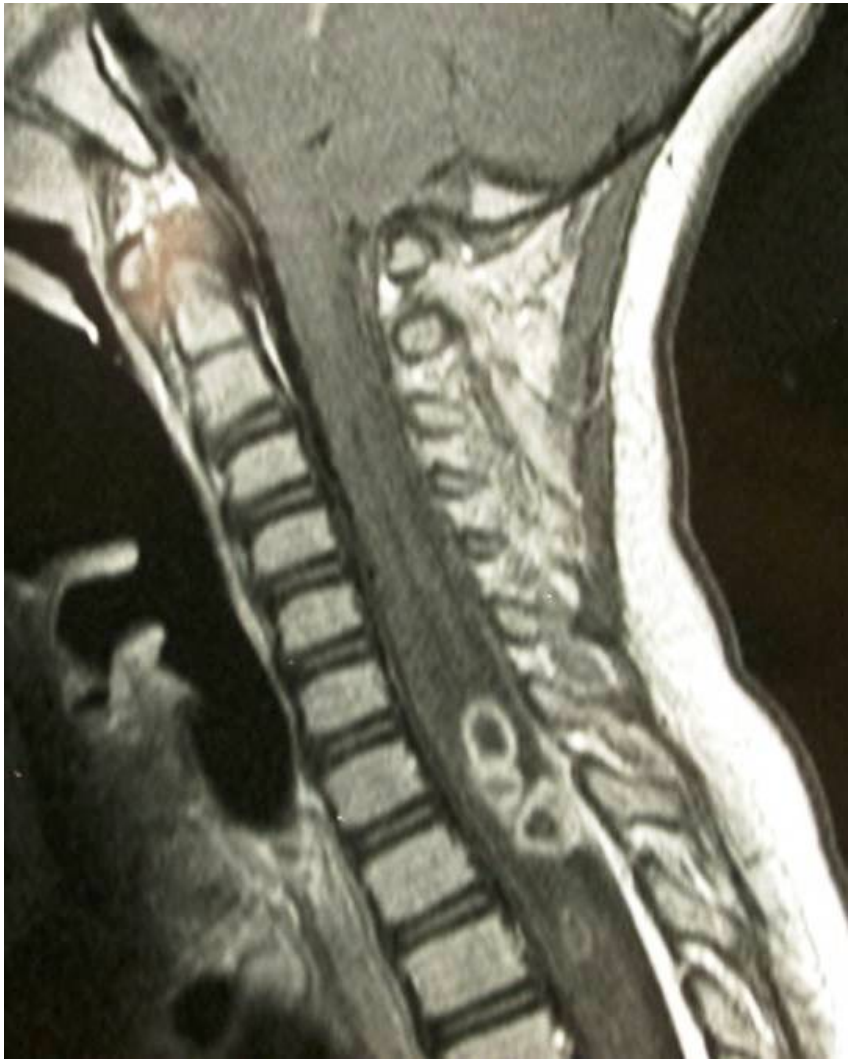


Van Toorn R et al. Clinico-radiological response to neurological tuberculous mass lesions in children treated with Thalidomide. PIDJ 2014

Pre

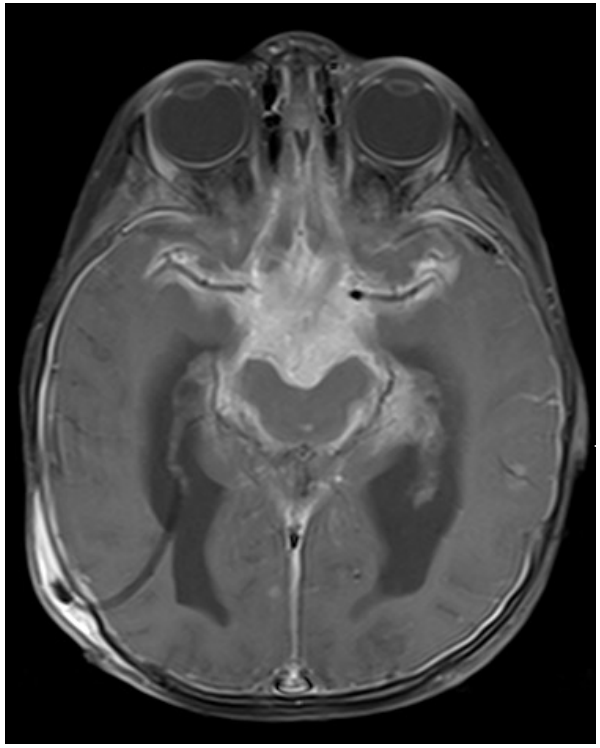


Post

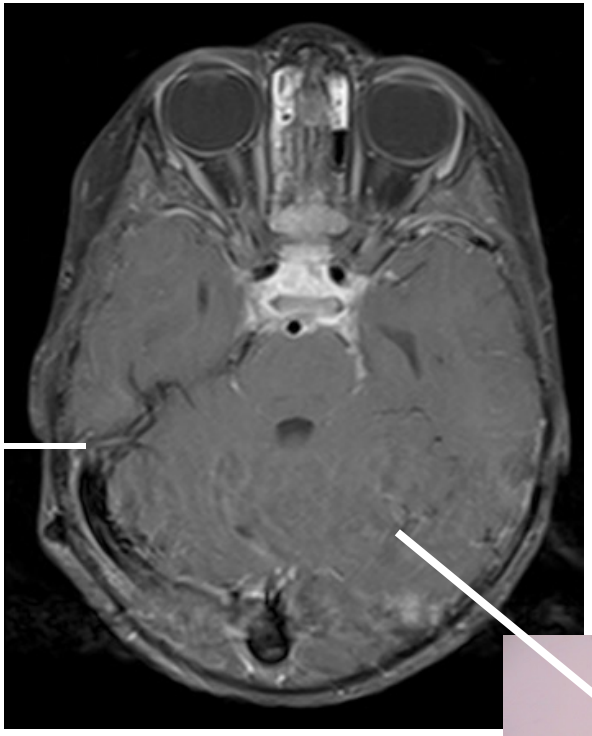


Optochiasmic arachnoiditis

Pre Thalidomide



Post Thalidomide

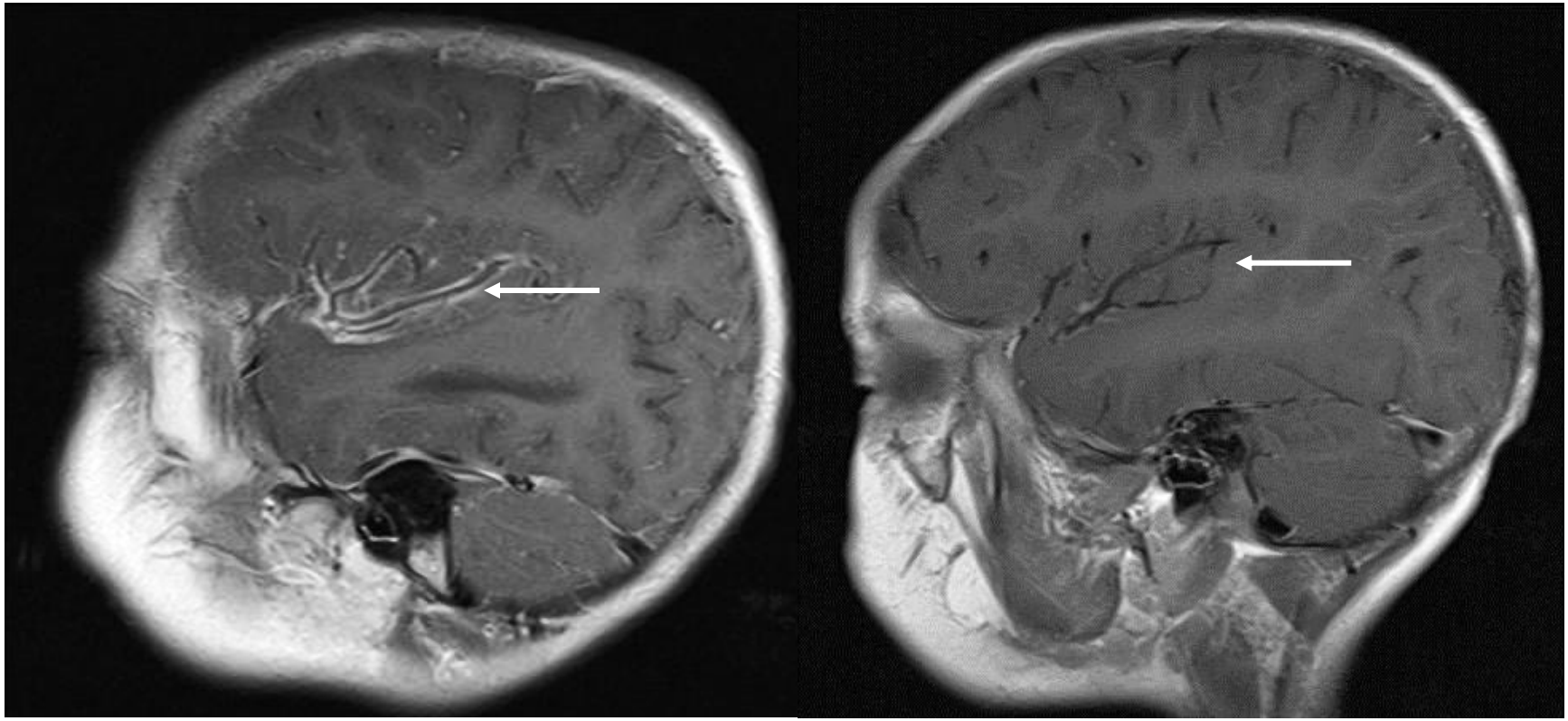


Full recovery of vision

TBM related vasculitis

Pre Thalidomide

Post Thalidomide



Fluid management in TBM

Hyponatremia occurs in up to 85% of children with TBM
SIADH or Cerebral salt wasting implicated
Avoid fluid restriction

Rx of hyponatremia in TBM

Classification of hyponatremia/low serum sodium	Definition mmol/L	Action
Normal	135 – 145	None needed – continue normal fluid intake
Mild	130-134	Review hydration status carefully consider repeating after 24 hours if remains clinically stable
Moderate	120-129	Intravenous correction is usually needed: correction at 4 mmol/L over 24 hours. If neurological symptoms associated with the low sodium occur, an initial bolus of 3 ml/kg over 1 hour of 3% saline can be considered. If chronic hyponatremia, oral correction can be considered provided there are no symptoms of hyponatremia.
Severe	<120	Intravenous correction is usually needed: correction at 4 mmol/L hour over 24 hours with a maximum correction of 8 mmol/L for 24 hours. An initial bolus of 3-5 ml/kg of 3% saline over 1 hour can be consider.

- **Sodium deficit: Weight in kg x 0.6 (135- current serum sodium)**
- **Volume of 0.9% NaCl required to address the sodium deficit: = sodium deficit / 0.154**
- **Calculating the time needed to correct the deficit: Time(hrs) = 2 x (140-serum sodium**)**
- **DO NOT CORRECT TOO FAST. Serum sodium should not increase >8 mmol/L in 24hrs. Stop additional sodium replacement when it reaches 135 mmol/L**

Staging in TBM

Modified MRC staging

Stage 1	GCS 15 without neurological deficit
Stage 2	GCS 15 with neurological deficit. GCS 10-14 with or without neurological deficit
Stage 3	GCS < 10 with or without neurological deficit.

Refined MRC staging

Stage 2a	GCS 15 with neurological deficit GCS 13-14 with or without neurological deficit.
Stage 2b	GCS 10-12 with or without neurological deficit.

Motor and cognitive outcome

Table 1 Motor outcome after 6 months using the refined MRC scale after 1 week (n = 483)

	n	Stage 1 %	Stage 2a %	Stage 2b %	Stage 3 %
Normal	243	39.1	26.7	24.7	9.5
Left hemiparesis	71	1.4	33.8	33.8	31.0
Right hemiparesis	58	0	34.5	41.3	24.1
Quadriparesis	60	0	3.3	23.3	73.3
Death	51	0	1.9	1.9	96.0

MRC = British Medical Research Council.

Table 2 Mean developmental quotient of children (*n* = 353) using refined MRC staging after 1 week

	Mean DQ	95%CI
Stage 1	78.6	75.8–81.3
Stage 2a	68.3	65.0–71.4
Stage 2b	58.9	54.5–63.6
Stage 3	44.3	38.0–50.4

MRC = British Medical Research Council; DQ = development quotient; CI = confidence interval.

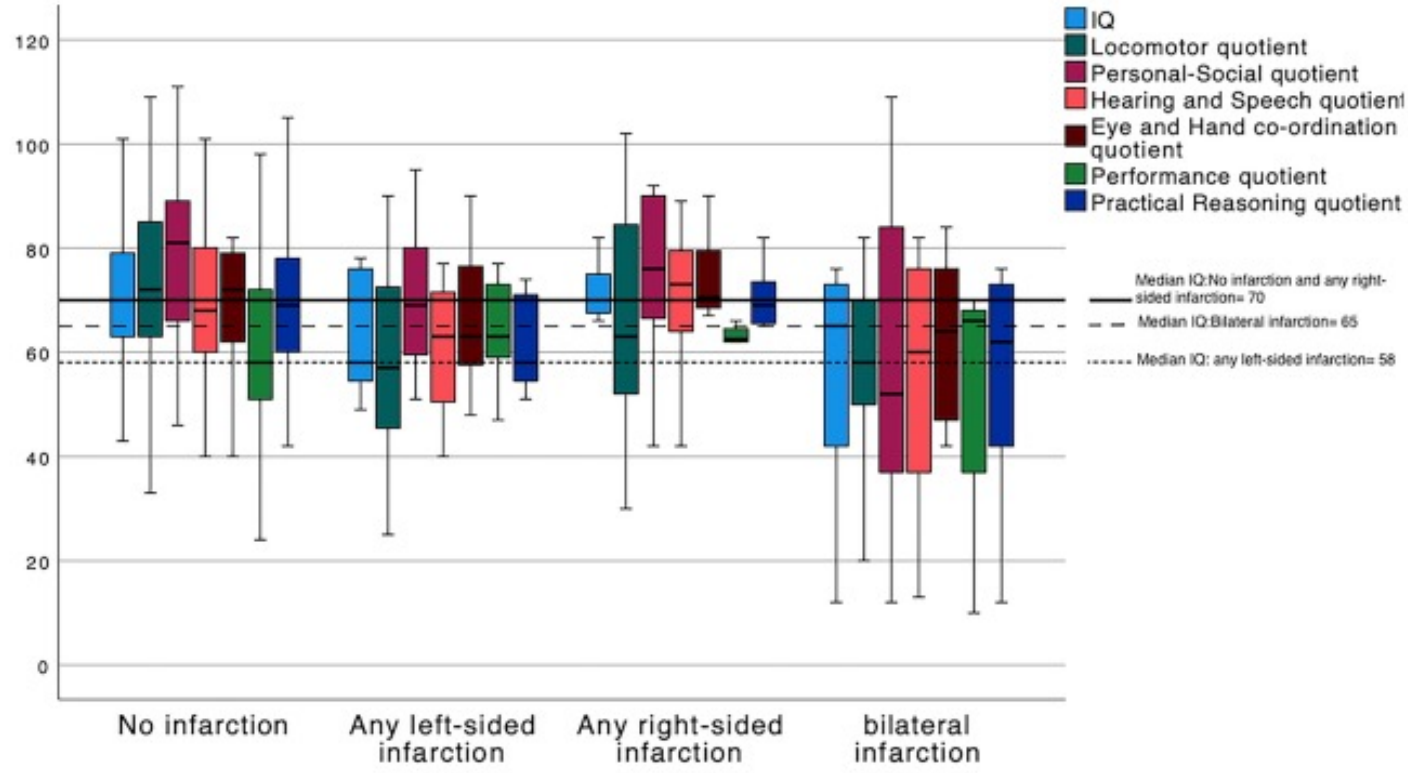


Fig. 3 Boxplots of Griffiths total IQ and sub-quotients compared to presence and site of radiological infarction

Management of post TBM disease

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CLINICAL STATEMENT

Post-TB health and wellbeing

SUMMARY

TB affects around 10.6 million people each year and there are now around 155 million TB survivors. TB and its treatments can lead to permanently impaired health and wellbeing. In 2019, representatives of TB affected communities attending the '1st International Post-Tuberculosis Symposium' called for the development of clinical guidance on these issues. This clinical statement on post-TB health and wellbeing responds to this call and builds on the work of the symposium, which brought together TB survivors, healthcare professionals and researchers. Our document offers expert opinion and, where possible, evidence-based guidance to aid clinicians in the diagnosis and management of post-TB conditions and research in this field. It covers all aspects of post-TB, including economic, social and psychological wellbeing, post TB lung disease (PTLD), cardiovascular and pericardial disease, neurological disability, effects in adolescents and children, and future research needs.

KEY WORDS: quality of life; post-tuberculosis lung disease; tuberculous neuropathy; tuberculous pericarditis; post-TB socio-economic burden

Conclusions

The best way to improve survival is through early diagnosis and treatment.

Many of the sequelae of TBM can be attributed to a dysregulated host immune response. Effective HDT are therefore likely to be critical in improving survival and clinical outcomes.

After years of neglect, substantial research into childhood TBM is underway. Despite these advances, TBM remains a devastating condition and much remains unknown in the field of TBM therapy.