

Diagnostic and
prognostic *potential* of
NEUROIMAGING and

NEUROTISSUE
markers in

TBM

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Role of Imaging in TBM

Admission imaging

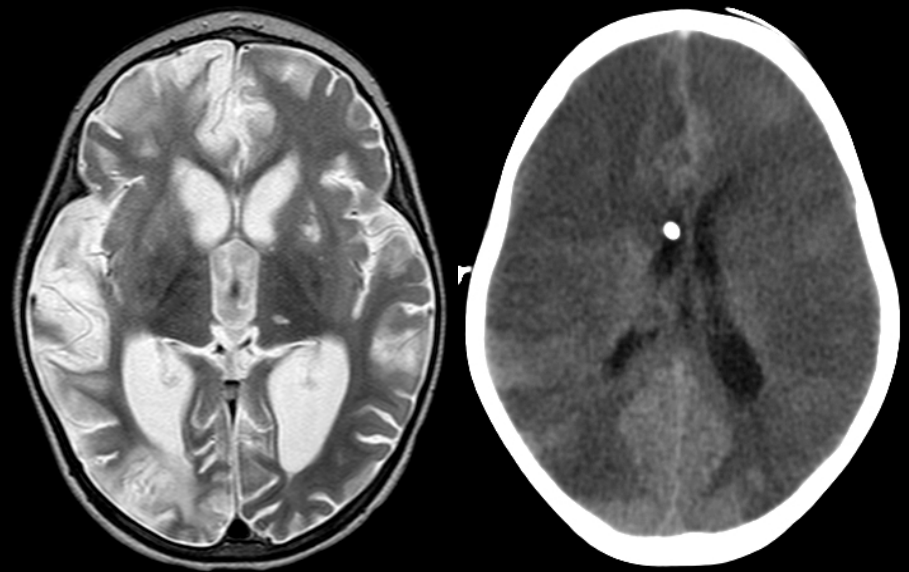
- Diagnosis combined with the history, clinical examination and CSF findings (Marais et al, Tuberculous meningitis: A uniform case definition for use in clinical research. *Lancet Infect Dis.* 2010 Sep 3;10:803-12)

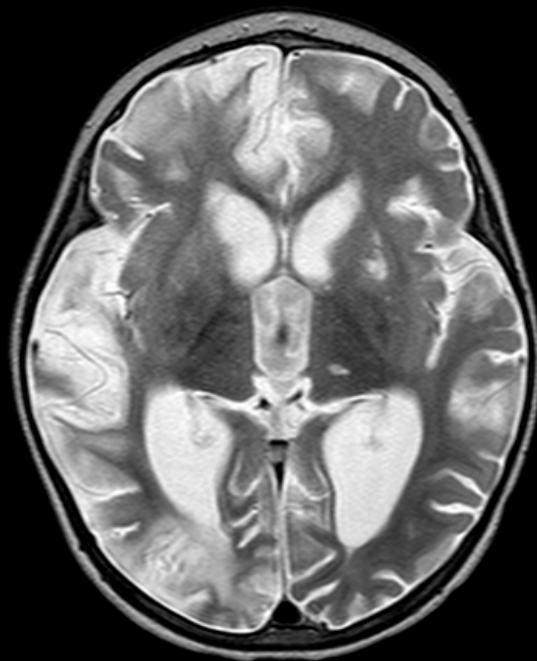
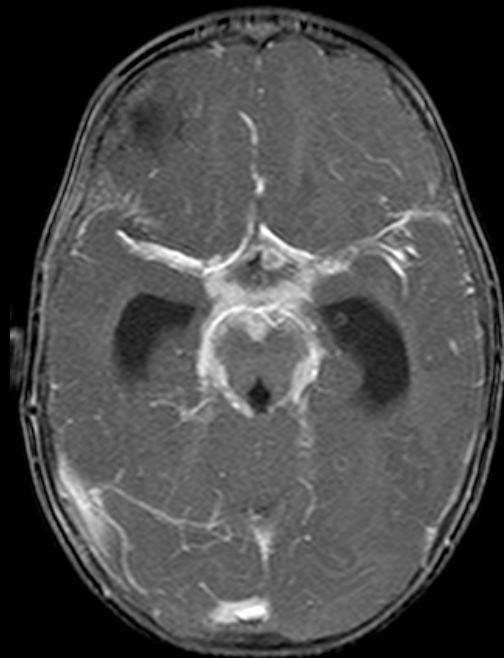
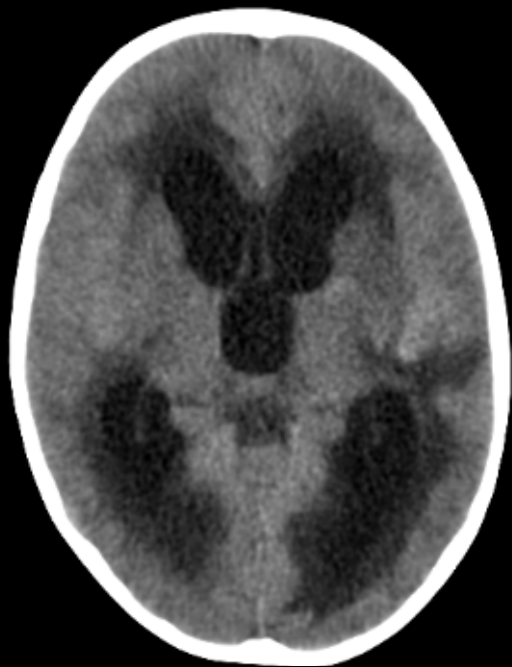
Follow-up imaging

- Guide treatment of ICP
- Insight into disease evolution and predicting outcome

Important considerations

- No uniform guidelines for characterising the severity of radiological features in TBM
- Imaging modality
- Resource limitations





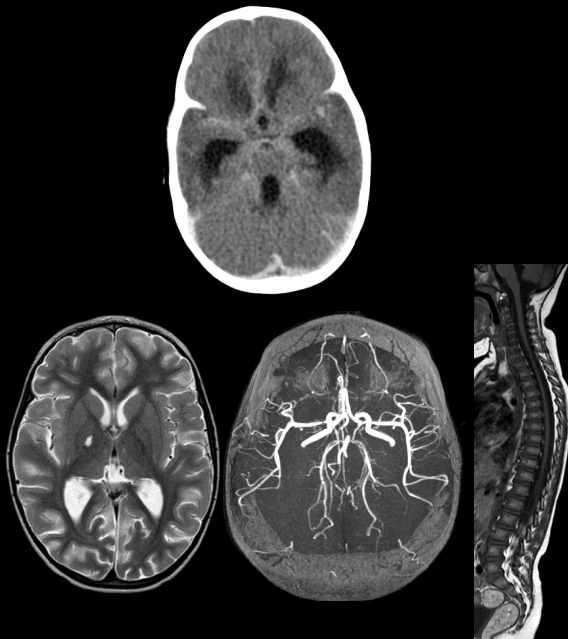
Neuro-markers

S100B, NSE, GFAP

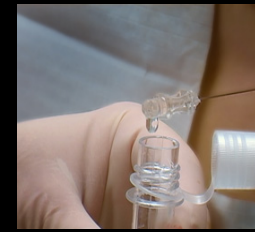
Inflammatory markers

IL-1 β , 1ra, 6, 8, 10, TNF- α , IFN- γ ,
IP-10, MCP-1, GRO, RANTES

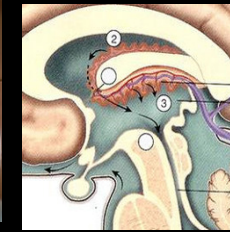
Imaging protocol



blood



cerebrospinal fluid



Admission

Week 1

Week 2

Week 3

Compared to healthy (CSF & blood)
and pulmonary TB controls (blood)



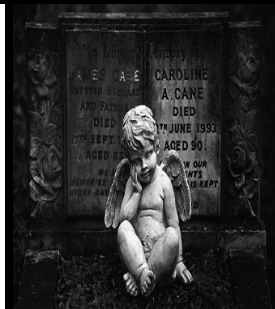
μ Age 4yrs
3 mo – 13
yrs



54%



5%



16%

6 month mortality and clinical outcome

Rohlwink UK et al, *Dev Med Child Neurol*, **2016**; 58(5): 461-8
Rohlwink UK et al, *Pediatr Infect Dis J*, **2016**; 35(10): e301-10

Exudate

93% admission scans

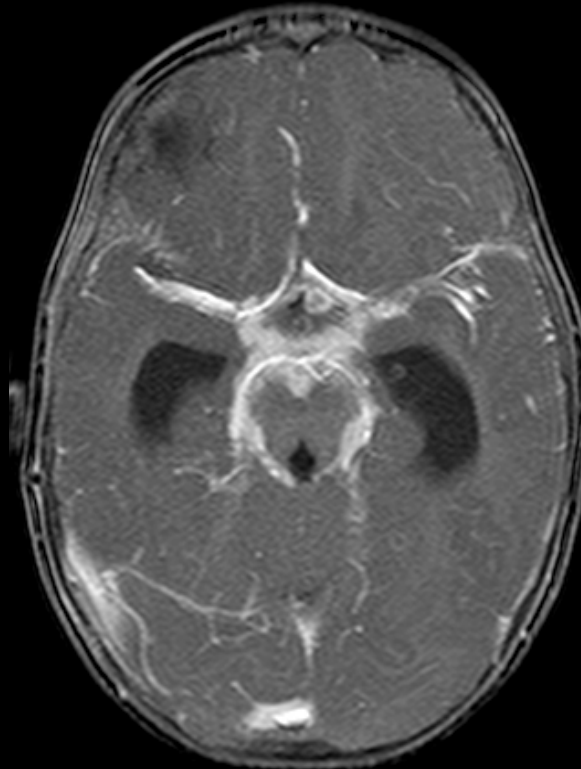
Meningeal inflammation
and enhancing exudate in
subarachnoid space

Contrast-enhanced CT and
T1-weighted MRI

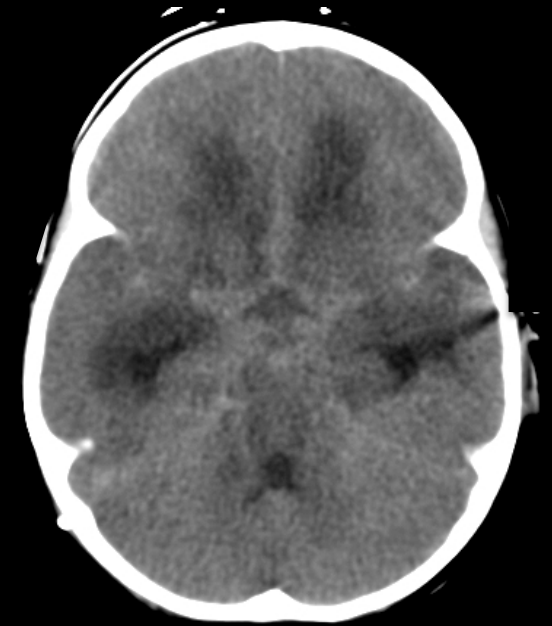
Typical basal pattern

Less pronounced in HIV
co-infected

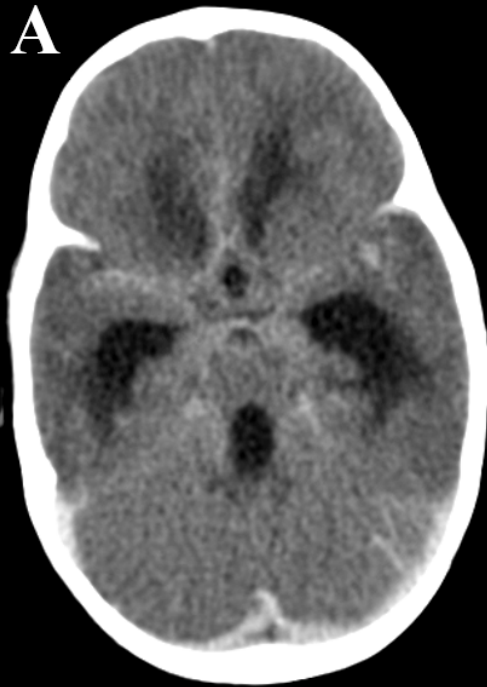
Associated with infarcts
and poor clinical and
cognitive outcome
(moderate-severe)



Pre-contrast
hyperdensity

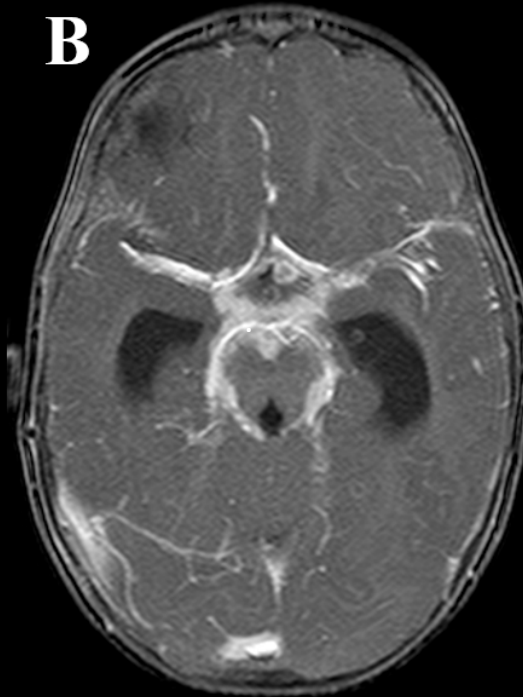


Exudate

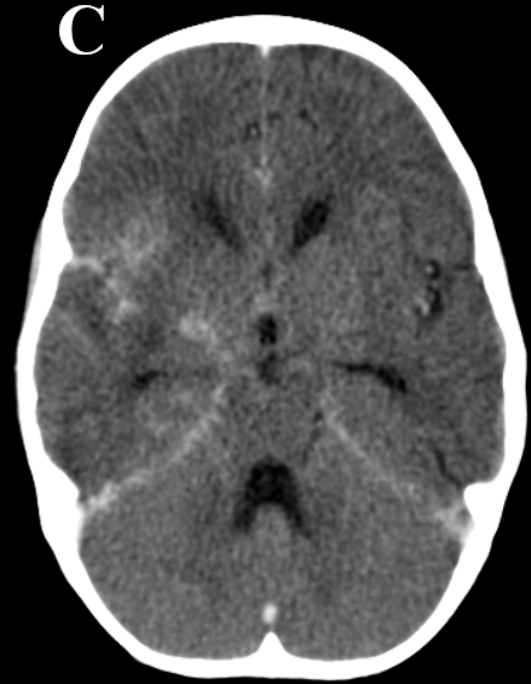


Enhancement 96%

Pre-contrast
hyperdensity in 66%

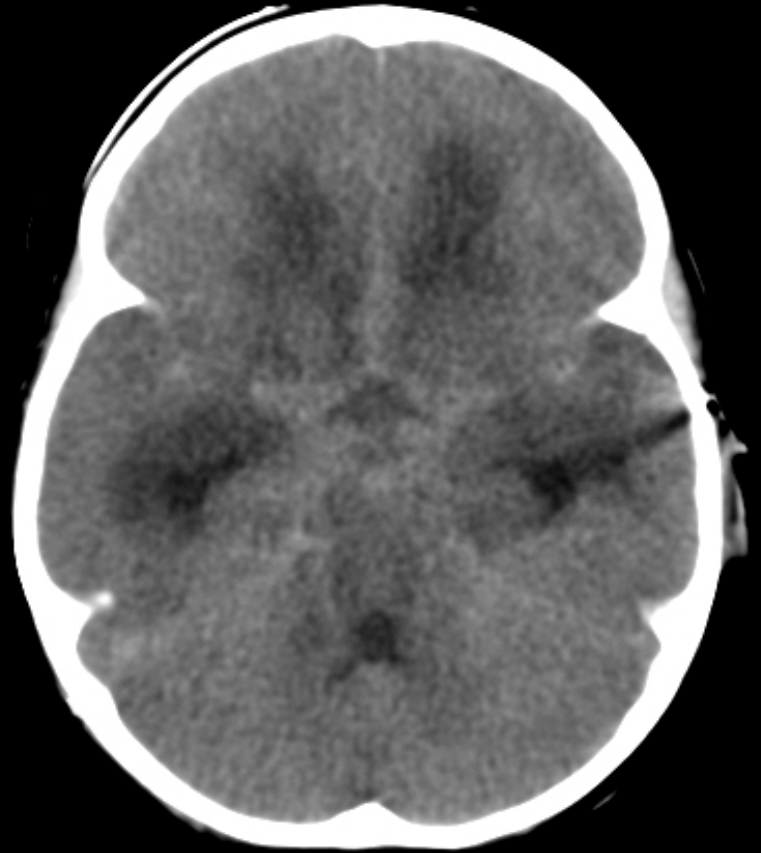
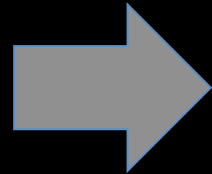


Still visible in all FU scans



Diffuse 95%

Exudate



Exudate and biomarkers

- Association between exudate and inflammatory **cytokines and chemokines** not demonstrated (Thwaites, G.E. 2007; Misra, U.K. 2010)
- Elevated initial ventricular CSF IFN- γ and TNF- α associated with mild enhancement and an absence of infarcts on admission scan - may represent the **early phases** of the inflammatory process.

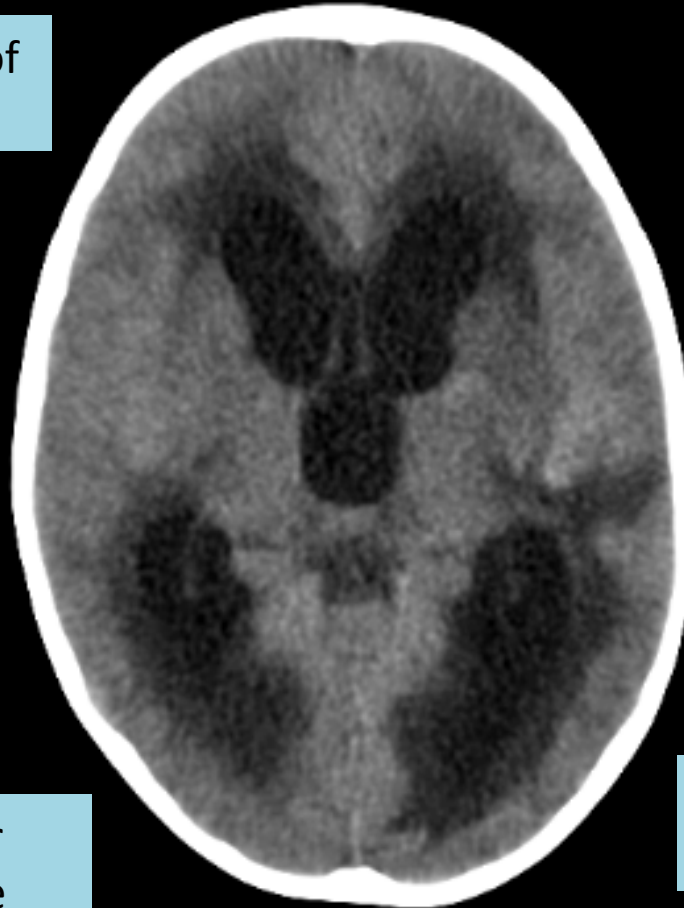
Hydrocephalus

80-90% of cases

Communicating or non-communicating

Progressive: more severe with longer duration symptoms and TBM severity

Periventricular lucency - acute



Medical and surgical treatment: no standard

Contributes to

- high ICP
- low GCS
- visual impairments
- focal neurology

Can't predict ICP from scan

Delay in presentation, severity of hydrocephalus and raised ICP, success of hydrocephalus and ICP treatment, the severity of illness including the concomitant presence of infarcts determine outcome

Hydrocephalus

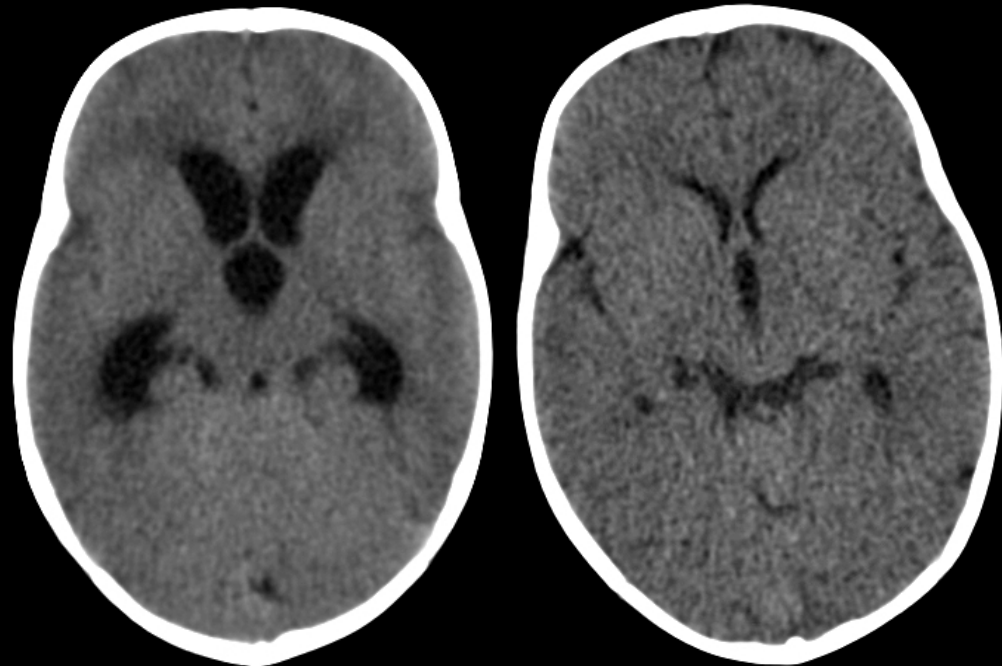
100% in study
(72% overall)

median opening pressure
on admission LP was 24
cmH₂O (1-51 cmH₂O)

80% communicating,
7% non-communicating
uncertain in 7 patients.

Medical treatment
successful in 60% of comm-
hydrocephalus

57% total cohort had VPS
part of early hydrocephalus
treatment/ after failed
medical treatment.



Example of resolution of hydrocephalus with medical
treatment (FU imaging 35 days post admission)

Hydrocephalus and biomarkers

- Markers of inflammation show **mixed** associations with hydrocephalus (Thwaites,G.E. 2007; 1925 Misra,U.K. 2010)
- No association with cytokines
- Associated with highest **S100B and GFAP** -these markers may be sensitive injury due to the mechanical effect of dilating ventricles on the parenchyma

Infarcts

middle cerebral artery
(MCA)

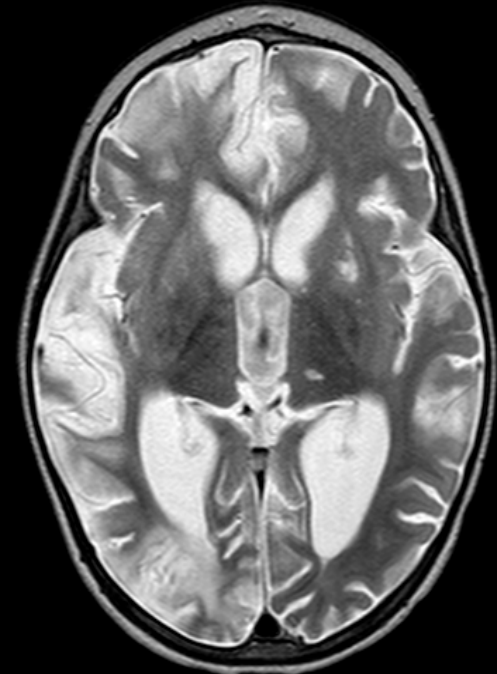
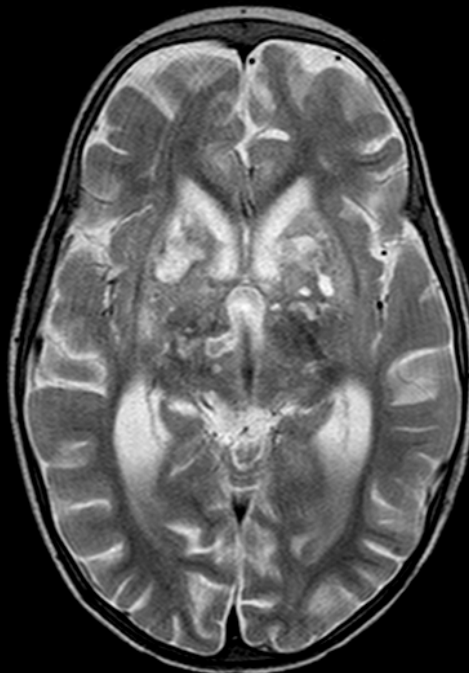
small perforators are
at highest risk

Large vascular territory
distribution

single or multiple,
unilateral or bilateral

Poorly detected on
admission scans

DWI better at detecting
acute infarcts



Infarcts and outcome

Strongly associated
with poor outcome

Mortality

Neurological deficits

Cognitive deficits

Neurodevelopmental
impairment

Regional localisation

Infarct size

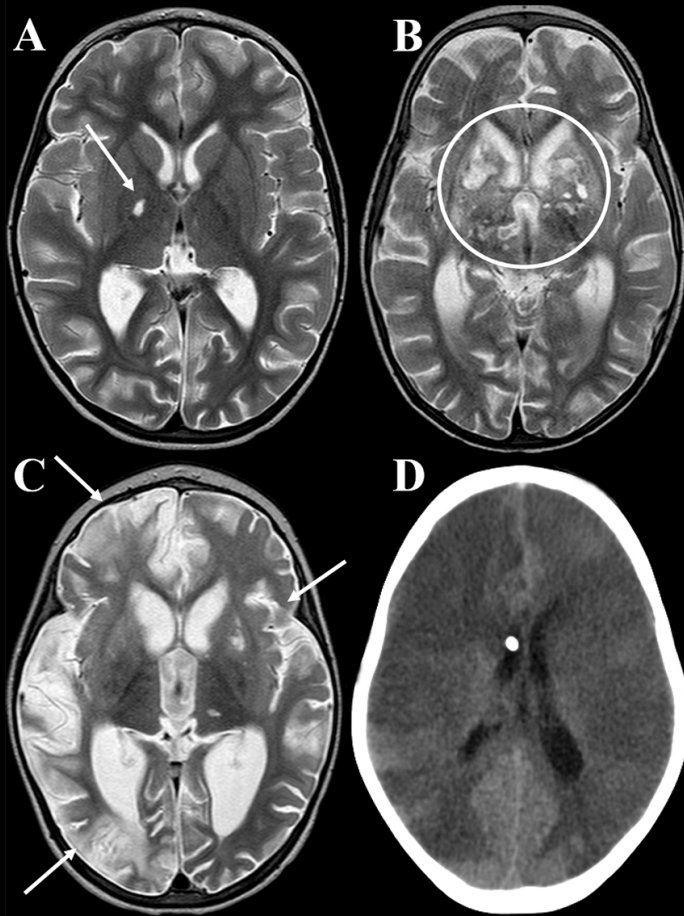
Infarct number

With time

Steroids/aspirin not
associated with
improvement

Koh,S.B. 2007; Ranjan,P. 2003; Andronikou,S. 2006; Leiguarda,R. 1988; Ramzan,A. 2013; van Well,G.T. 2009; Schoeman,J.F. 1997; Shukla,R. 2008; Kalita,J. 2012; Kalita,J. 2009; Springer,P. 2009; Thwaites,G.E. 2007; Misra,U.K. 2010

Infarcts



Infarcts present

- 20% admission scans
- 66% follow-up scans
- 78% MCA
- 33% involved 2 vascular territories
- 33% small/lacunar

Early death (n=4):

- Infarcts were visible in only n=2 admission scans
- FU imaging (mdn 4 (3-11) days: global infarction involving all 7 vascular territories

Outcome overall:

- Multiple, bilateral and large infarcts

Infarcts and biomarkers

- Elevated neuromarkers associated with severe infarction
- Increasing profile suggestive of ischaemia-induced progressive injury
- Increase over time could highlight patients at risk
- Complement imaging

Magnetic resonance angiography

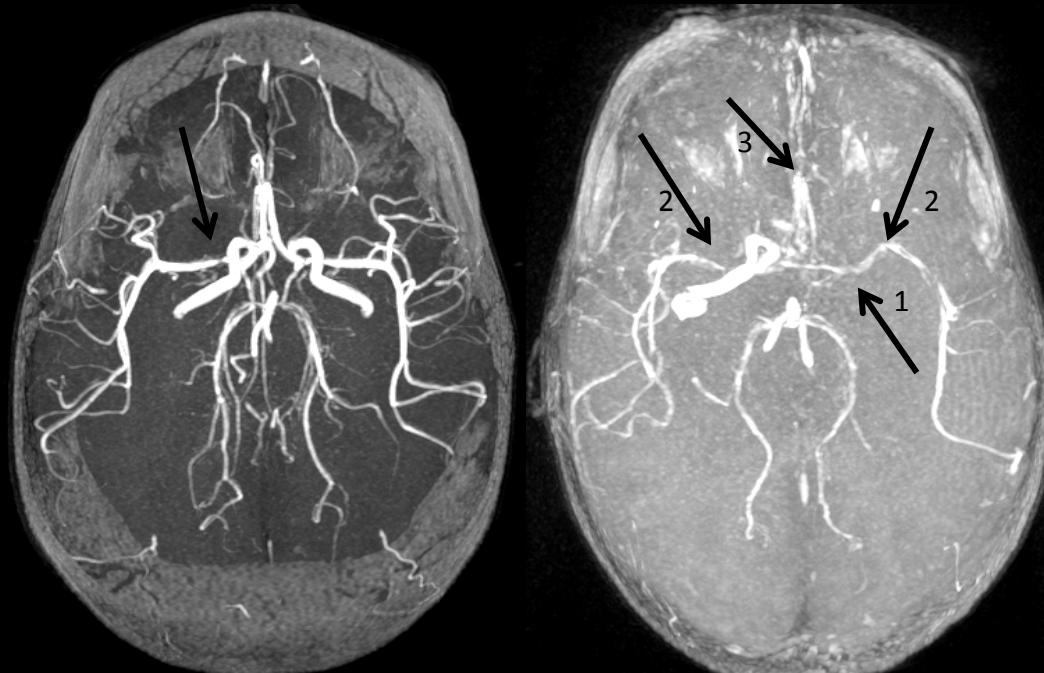
46-70%

Arteritis of
vessel wall

occlusion

thrombosis

vasospasm



Vessel
occlusion

Irregular vessel
calibre

Focal stenosis

55% MRA
abnormalities

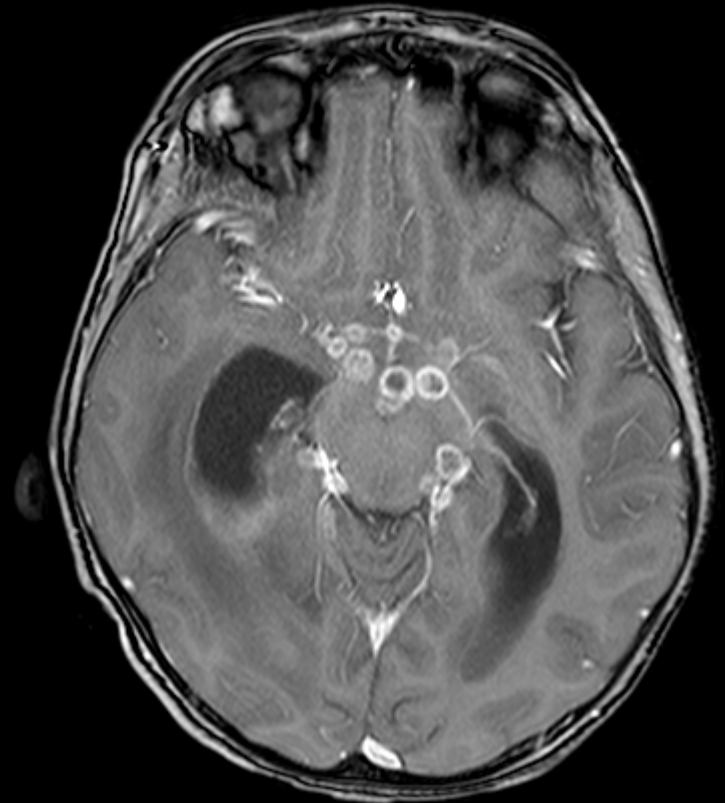
94% MCA

Mdn no vessels =
2 (1-7)

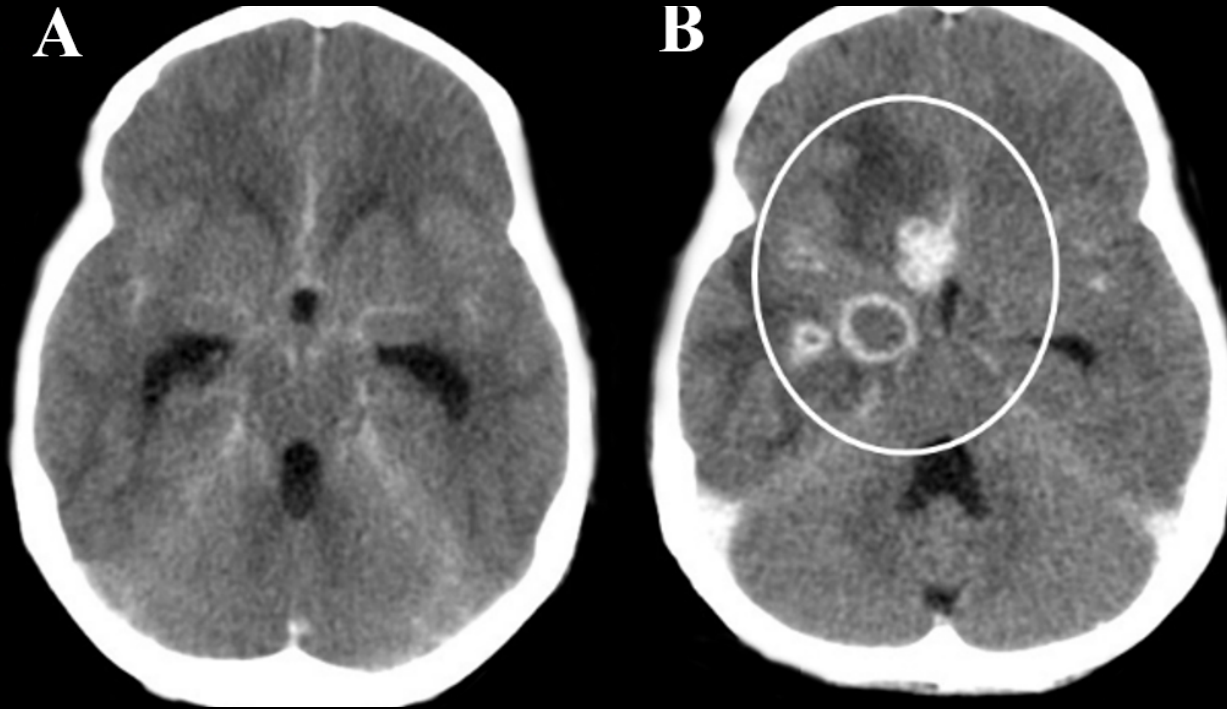
Angiographic
abnormalities \neq
Infarcts

Tuberculomas

- Multiple locations (parenchyma, ependyma, basal cisterns, surrounding the vessels of the Circle of Willis and in the Sylvian fissures)
- Radiological appearance differs depending on whether they are solid, noncaseating or caseating with a solid or liquefied centre - ring enhancement with contrast
- Not uncommon for established tuberculomas to enlarge or new tuberculomas to develop on treatment
- Abscesses are unusual



Tuberculomas



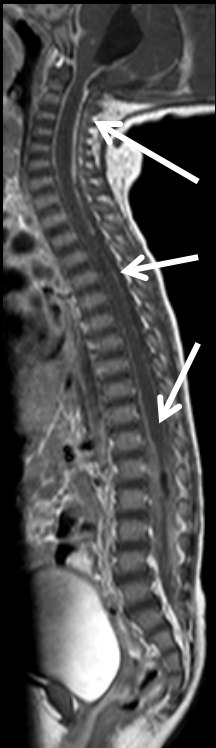
- 59% tuberculomas
- 11% delayed/paradoxical
- 50% cisterns
- median of 78 (47-106) days
- drug sensitive, HIV non-infected
- 50% clinically silent

Spinal disease

Largely
asymptomatic

Occurs in spite of
treatment

- 76% spinal disease
- 92% asymptomatic



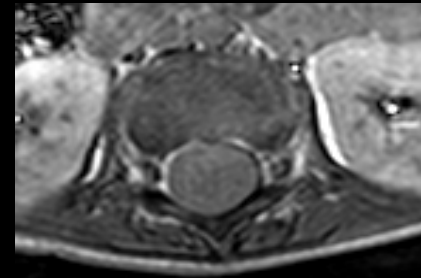
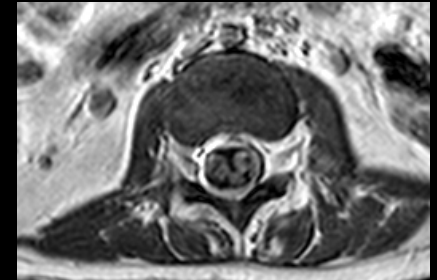
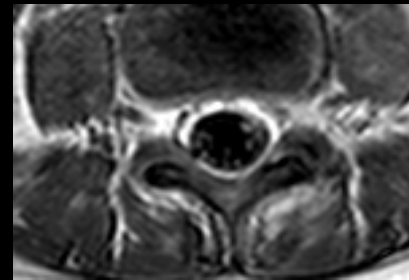
Arachnoiditis



Tuberculomas



Plaques



- More likely dry LP tap
- Higher CSF protein
- ICP deterioration

Conclusion

- Neuro-imaging remains a **critical** part of the diagnosis of TBM
- Features (infarcts) are **prognostic** but irreversible
- Biomarkers of disease progression may offer **early warning signs** and could be a valuable addition to clinical examination, laboratory investigations and imaging in management of TBM

Acknowledgements

- Anthony Figaji
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