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

Imaging protocol

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

6 month mortality and clinical outcome

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)

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

Progressive: more severe with longer duration symptoms and TBM severity

Communicating or non-communicating

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 communicating 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

- 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

Associated with:
- Regional localisation
- Infarct size
- Infarct number
- With time
- Steroids/ aspirin not associated with improvement

References:
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% MRA abnormalities
- 94% MCA
- 55% MRA abnormalities
- Median no vessels = 2 (1-7)

- Arteritis of vessel wall
- Occlusion
- Thrombosis
- Vasospasm

- Vessel occlusion
- Irregular vessel calibre
- Focal stenosis

Angiographic abnormalities ≠ 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
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