CNS tuberculosis diagnosis and management

Moderators – Dr MMS
Dr SS

Introduction

- As old as history of mankind .
- Odier, Ford described meningeal TB 1790 .
- Sir William McEwen performed first surgery for intracranial tuberculoma in 1983 .
- Caused by Mycobacterium tuberculosis (Acid fast bacillus , obligate aerobe)

- CNS TB complicate 10% of all tuberculosis
- Always secondary to primary focus elsewhere in body (pulmonary , GIT etc)
- Route of dissemination - haematogenous or contagious spread
- Incidence has increased with emergence of HIV infection

CNS tuberculosis

- Intracranial
  - Parenchymal
  - Meningeal
  - Osseous
- Spinal
  - Parenchymal
  - Meninges
  - Arachnoiditis
  - Osseous

Parenchymal lesion

- Abscess
- Tuberculoma (Micro)
  - Tuberculoma en plaque
  - Tuberculous abscess
  - Cystic tuberculoma
  - Multiple grape like tuberculoma
  - Microtuberculoma
  - Calcified tuberculoma
  - Tubercular encephalopathy

- Meningeal - meningitis + HCP
- Calvarial – osteomyelitis
- Spinal - parenchymal – tuberculoma
  meningeal - arachnoditis
  vertebral – pott's spine

Diagnosis

- Hb/ ESR
- CXR
- Mantoux test
- ELISA
- CSF
- PCR
- Imaging
- Biopsy

Tubercular Meningitis

- Most common manifestation of CNS TB.
- Considered disease of childhood , however in India all age groups susceptible .
- Acute , chronic phase & its sequelae .
- Of neurosurgery interest are sequelae – HCP , tuberculoma or chiasmal arachnoiditis.
- Other sequelae - vasculitis , infarcts.

  TBM with HCP
- Invariably occurs after 4-6 weeks .
- Communicating (mostly) or obstructive .

Diagnosis of TBM

- Diagnosis of TBM still pose considerable difficulties.

- Supportive - H/O tuberculosis
  Hgm /ESR
  CXR
  Mantoux test

- CSF analysis – Sugar - low
  Protein – high
  Cells - lymphocytosis

- Bacteriological test (CSF)

Method	Sensitivity	Specificity
Z-N stain	25%	
Culture	18-83%	100%

- Limitations – CSF should examined before or just after start of ATT
- Time for growth – 2-4 weeks.

Molecular and Biochemical assay

Test	Sensitivity	Specificity
PCR	56%	98%
ELISA (Antigen)	52-93%	58-98%
ELISA (Antibody)	38-94%	95-100%

- Rapid and positive after starting treatment.
- Drawback – can't differentiate acute or chronic infection,
  cross - reactivity
  often poor sensitive and specific

- CSF ADA level - >5-15 iu/L

Sensitivity	Specificity
44-100%	10-100%

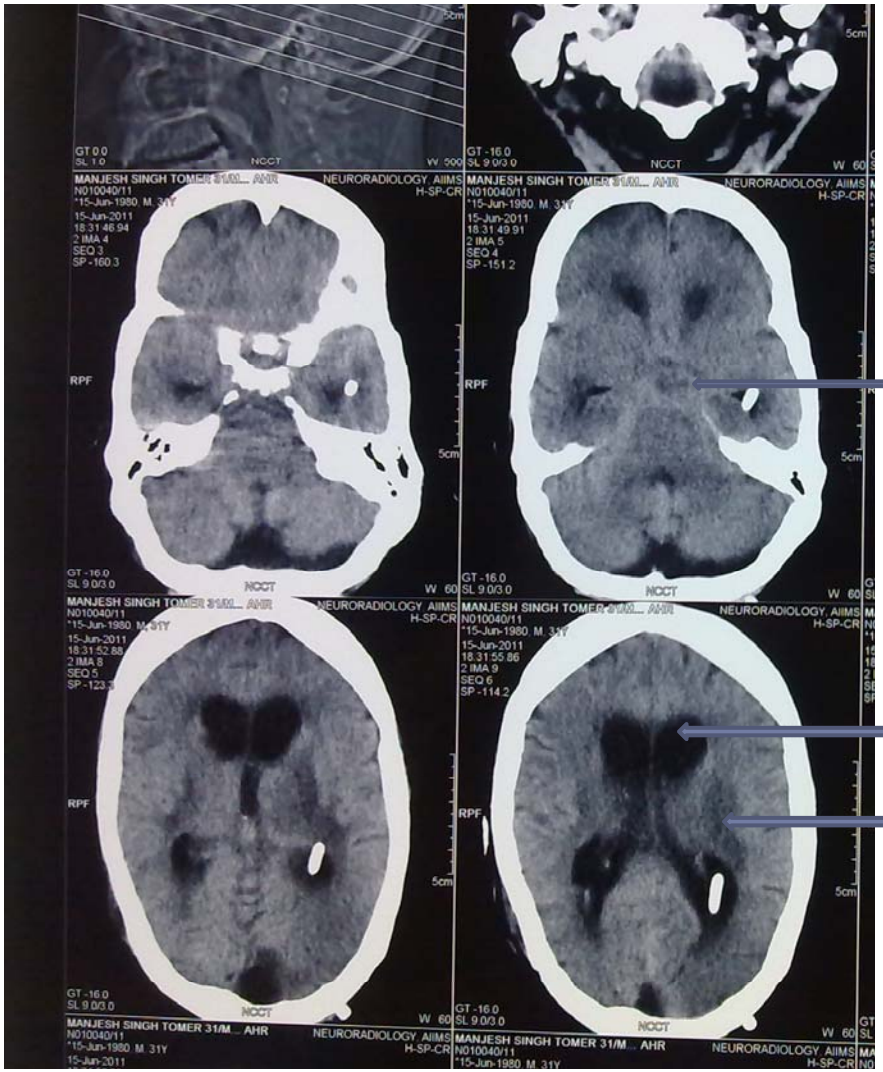
- High CSF ADA levels- malaria , lymphoma , pyogenic & cryptococcal meningitis , brucellosis .
- Not recommended as routine diagnostic test

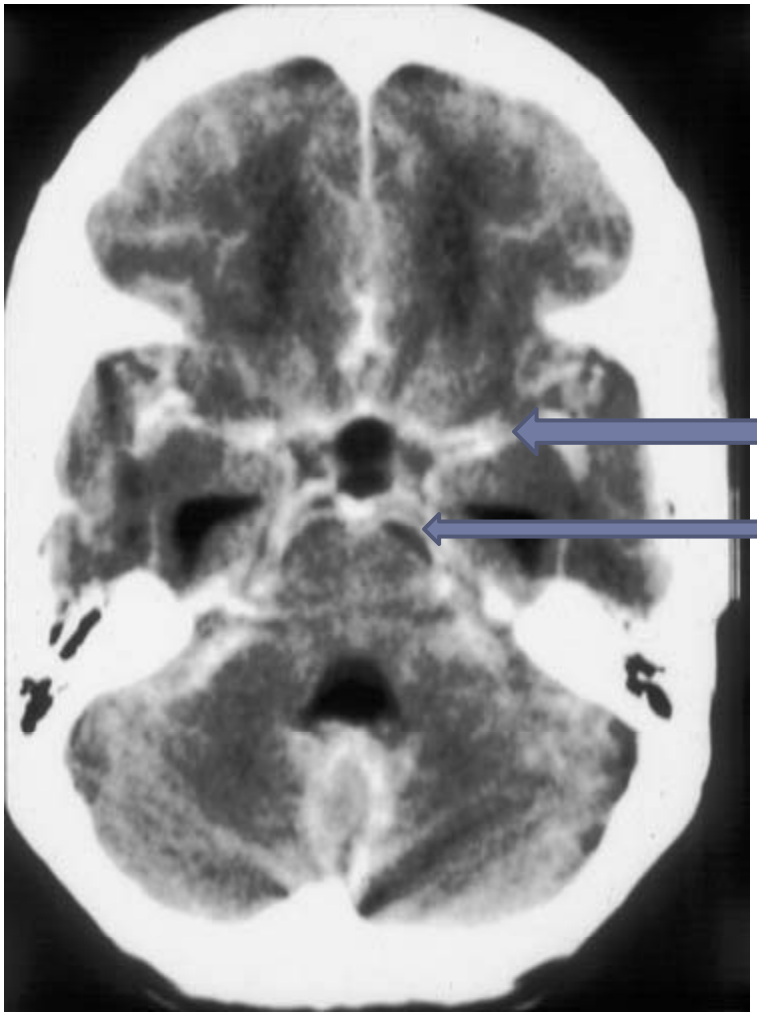
Rock RB, Olin M, Baker CA, Molitor TW, Peterson P K . Central nervous system tuberculosi :African Health Sciences Vol 11 No 1 March 2011 1 2 7pathogenesis and clinical aspects. Clin Microbiol Rev. 2008 ;21:243-6

Imaging

- NCCT:
  - scans may be normal
  - Obliteration of basal cisterns by hypo/ iso dense exudate
  - en plaque dural thickening
  - Popcorn calcification
  - Hydrocephalus
  - Sequelae of chronic meningitis
    - Infarcts
- CECT:
  - Abnormal meningeal enhancement
  - Leptomeningeal enhancemant sylvian fissures, tentorium
  - Granulomas in the basal meninges
  - Ependymitis

Imaging





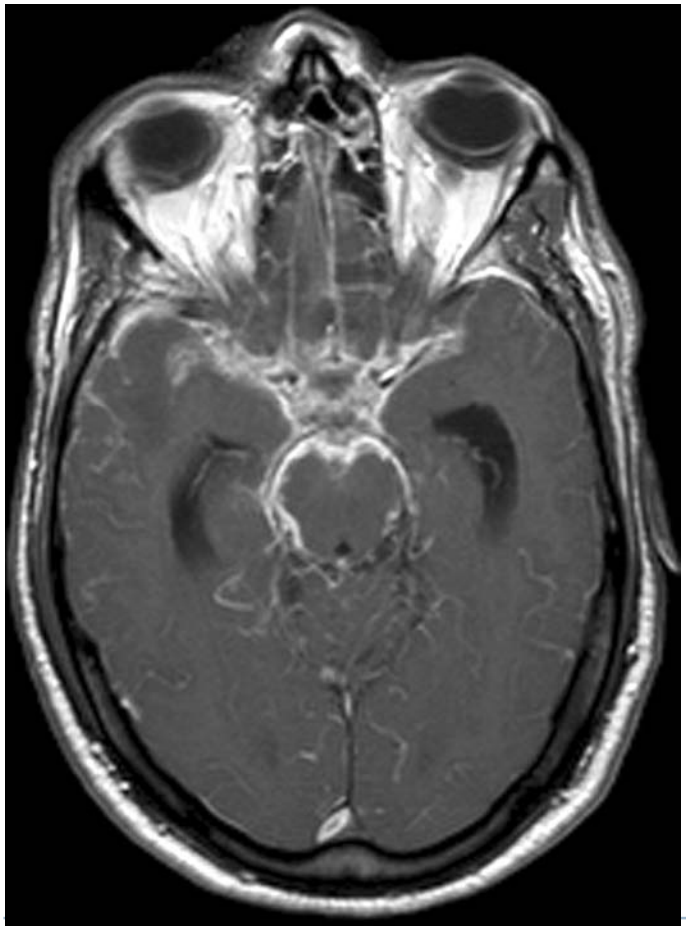
Exudates along sylvian fissure

Basal exudates enhancement

- Periventricular lucency indicates transependymal flow of CSF –sign of raised ICP however in TBM it could be spread of inflammatory process making unreliable sign of raised intraventricular pressure.

- **R Patir, R Bhatia, Tandon PN. Surgical management of tuberculous infections of the nervous system. Schmidek and Sweet operative neurosurgical techniques 5th edition; 1617-1631**

MRI



Tuberculous meningitis. Axial contrast-enhanced T1-weighted magnetic resonance (MR) image shows florid meningeal enhancement that is most pronounced within the basal cisterns

- Ahuja and colleague set criteria for clinical diagnosis of diagnosis of TBM based on

  Clinical feature

  CSF

  CT scan

  Presence of extra neural tuberculosis .

- Definite, Highly probable, Probable and Possible TBM .
- 91% of highly probable & 66%of probable group improved with ATT .

- Diagnostic criteria for tuberculos meningitis and their validation , Tuber lung dis Vol – 75 , 149-152, 1994 .

Treatment for TBM

- ATT
- Anti convulsant
- Steroids

- Role of surgery - V-P shunt or ETV
- Optico –chiasmatic decompression for arachnoidits

ATT

Intensive phase treatment	Continuation phase
2 months of HRZE[a]	4 months of HR

[a] WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative PTB or EPTB who are known to be HIV-negative. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin

WHO Treatment of tuberculosis: guidelines – 4th ed.

Duration of Anti –Tubercular treatment

- Pulmonary and extra pulmonary disease should be treated with the same regimens. Note that some experts recommend 9–12 months of treatment for TB meningitis *given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints because of the difficulties of assessing treatment response. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In tuberculous meningitis, ethambutol should be replaced by streptomycin*

WHO Treatment of tuberculosis: guidelines – 4th ed.

- British infection society recommendation 2009 –

  12 months

- Indian academy of pediatrics 2010 recommendation –

  In patient with TBM on category I Tt, 4 drugs can be used either HRZE or HRZS , continuation phase of TBM Tt should extend for 6-7 months , extending total duration of treatment for 8-9 months.

American thoracic society and centre for disease control (2003)recommendation

TBM and tuberculoma is for 12 months if bacterial strain sensitive .

For MDR TB – 24 months .

For patients who do not receive pyrizinamide in first 2 months extend Tt for 18months .

- Steroids – Dexamethasone should be given to all irrespective of age and stage .

Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008;1:CD002244.

- Role of steroids –

  Improve survival and intellectual outcome

  Enhance rate of resolution of basal exudate.

- Kumar Velu and assoc Randomised control trial of dexamethasone in TBM , Tuber Lung Dis , 5 page 203-207 .

- No change in incidence of basal ganglia infarction , ICP .
- Age >14 - Dexamethasone for 4-6 weeks .
- Age <14 – Prednisolone for 8 weeks .

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British MRC grading for TBM

Stage	
1	Fully conscious, no paresis
2	Decreased level of consciousness, localizing pain
3	Deeply comatose ± gross paresis

Role of surgery

TBM with HCP

- V-P shunt OR ETV

Role of ETV

- Success rate of ETV is 77% in 35 patient with 60% had early and 17% delayed recovery .

Minim Invasive Neurosurg. 2005 Feb;48(1):47-52.**Endoscopic third ventriculostomy in post-tubercular meningitic hydrocephalus: a preliminary report.** Singh D, Sachdev V, Singh AK, Sinha S.

- 68% benefited from ETV

Hussain et al ,neurosurgery review 2005 , role of neuroendoscopy in management of patient with TBM

- Success rate for ETV 73.1 %

J. Neurosurg.: Pediatrics / Volume 3 / May 2009

- **Success rate of ETV depend upon –**
  - **Stage of disease (I & II)**
  - **Presence of cisternal exudates**
  - **Duration of pre-op ATT (4 weeks)**

- *Surgical outcome of tuberculous meningitis hydrocephalus treated by endoscopic third ventriculostomy: prognostic factors and postoperative neuroimaging for functional assessment of ventriculostomy J. Neurosurg.: Pediatrics / Volume 3 / May 2009*

Prognosis of TBM

- Based on Palur et al (mean follow up 45.6 months)

Grade	Mortality
I	20%
II	34.7%
III	51.9%
IV	100%

- Grade of TBM at time of admission is most significant factor determine outcome .

CNS Tuberculoma

- Mostly cortical and subcortical
- In children mostly posterior fossa in involved , while in adult supratentorial compartment is common
- Can occur at brainstem , thalamus , pitutary gland

Tuberculoma

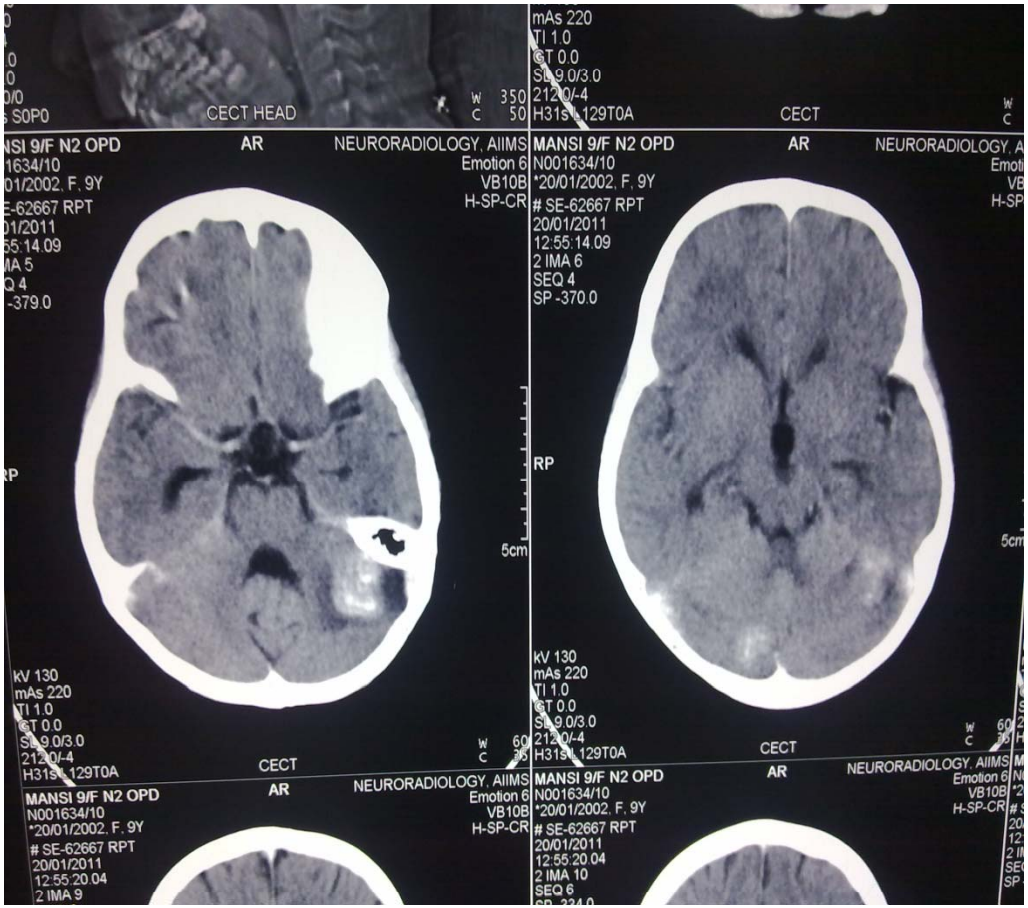
SUPRATENTORIAL	78
PARIETAL	28
FRONTAL	26
TEMPORAL	15
BG / THALAMUS	4
SELAR/SUPRASELLAR	4
ORBITAL FISSURE	1
INFRATENTORIAL	**50**
CEREBELLUM	44
CP ANGLE	3
TENTORIUM	1
BRAINSTEM	2

R Patir, R Bhatia, Tandon PN. Surgical management of tuberculous infections of the nervous system. Schmidek and Sweet operative neurosurgical techniques 5th edition; 1617-1631

CT appearance of tuberculoma

- Cerebritis stage – hypodense lesion with out of proportion edema.

Posterior fossa lesion



Mature tuberculoma

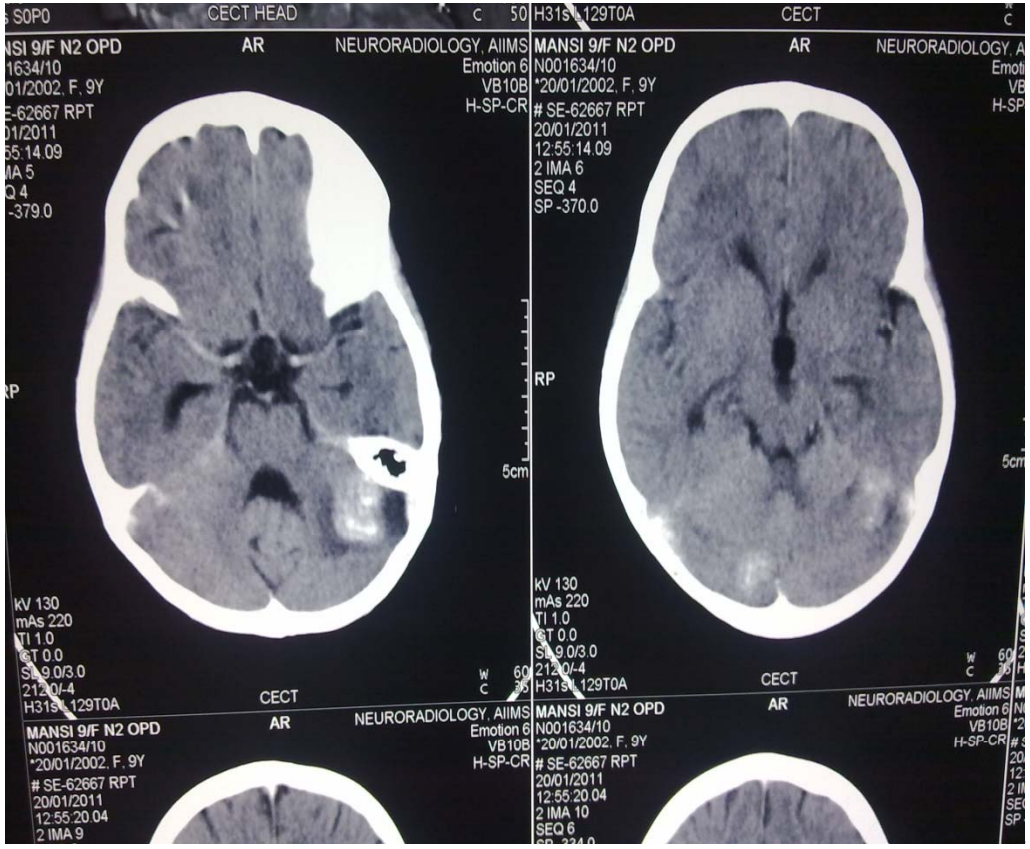
- Immature Tuberculoma -

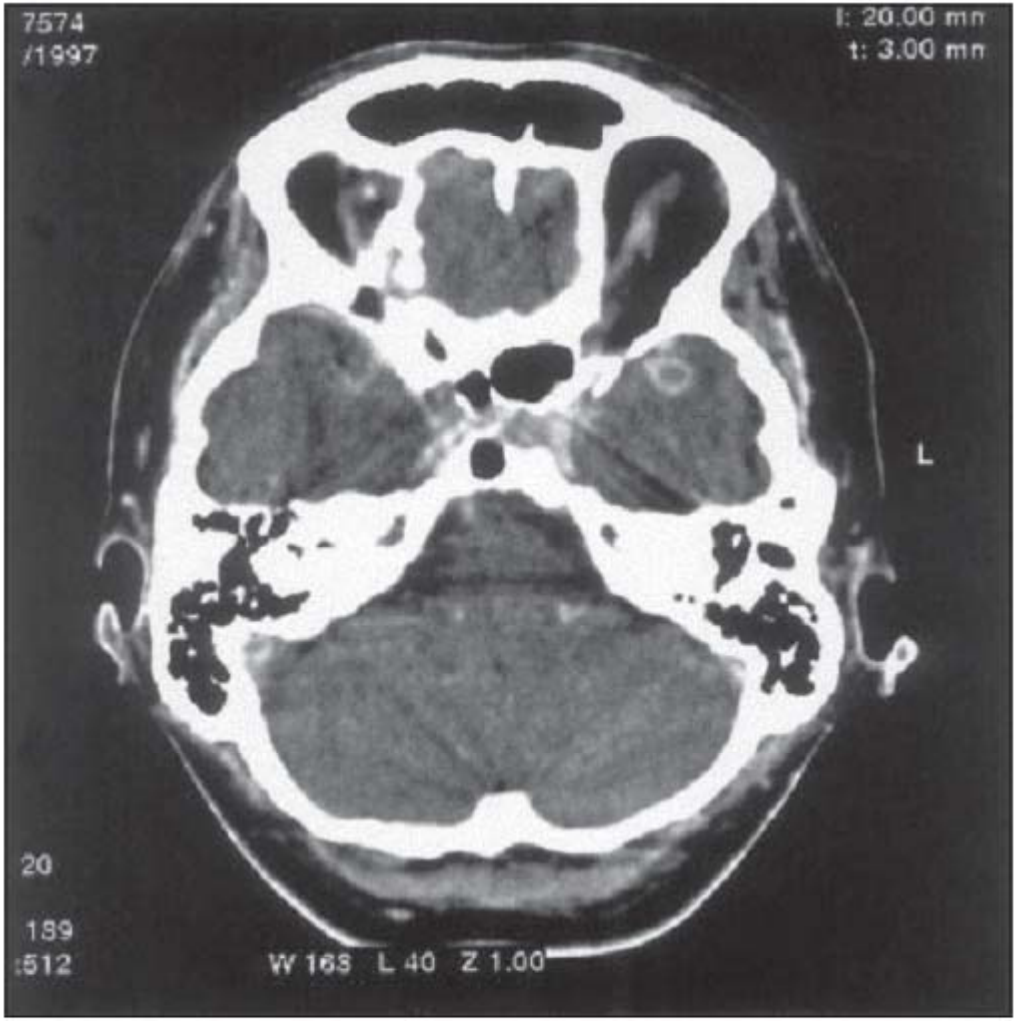
  with out contrast – iso to hyper dense area , with edema

  With contrast – either ring or nodular or irregular enhancement

- Mature tuberculoma – well enhancing ring or disc shape lesion with perilesional edema , target sign , calcification seen often .

- Sensitivity of CT – 100% , specificity – 85.7% and positive predictive value - 33%.



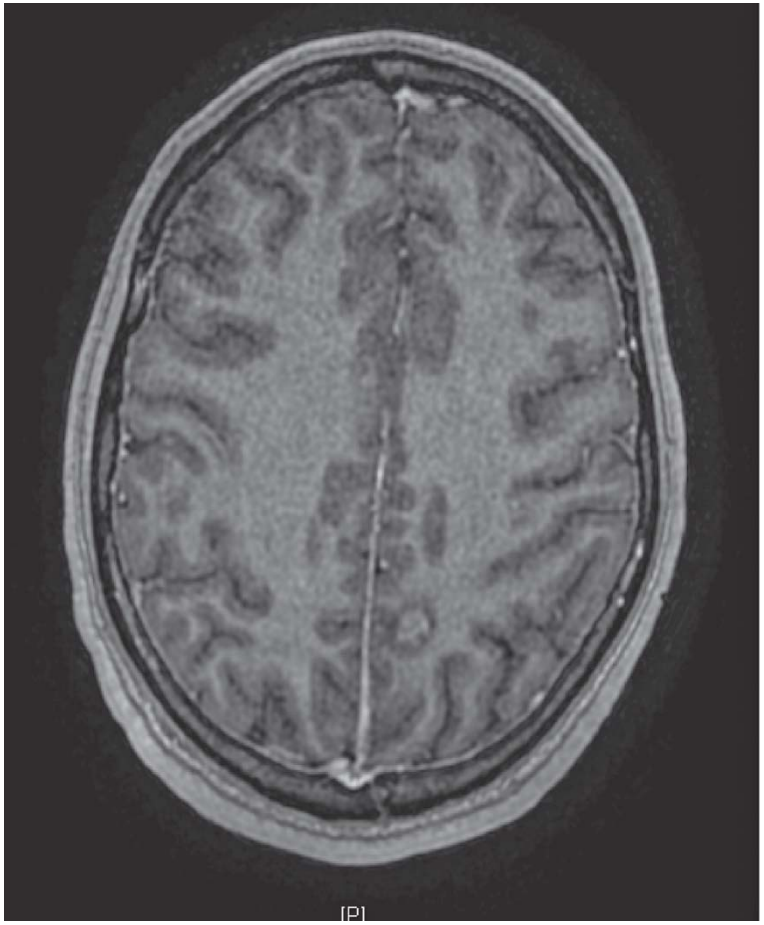


Caseating tuberculosis granuloma involving the left temporal lobe. CECT shows a rim-enhancing lesion in the left temporal lobe consistent with a caseating tuberculosis granuloma

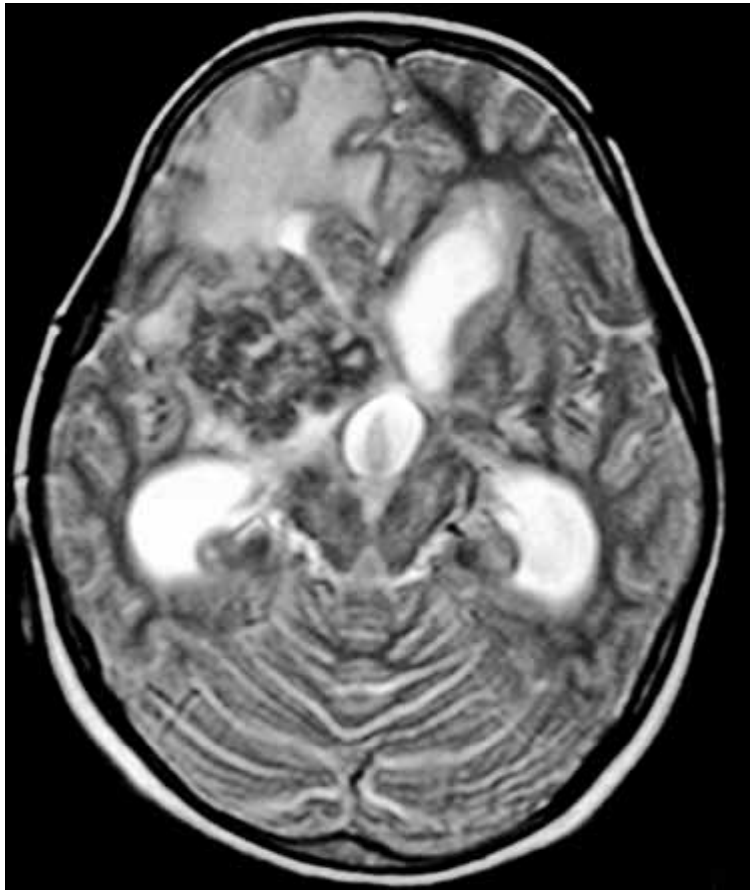
Imaging (MRI tuberculoma)

- T1 : isointense
- T2: central hyper with hypo ring
- Marked thin rim enhancement
- Hypo on T2: fibrosis, gliosis, macrophage infiltration

MRI appearances

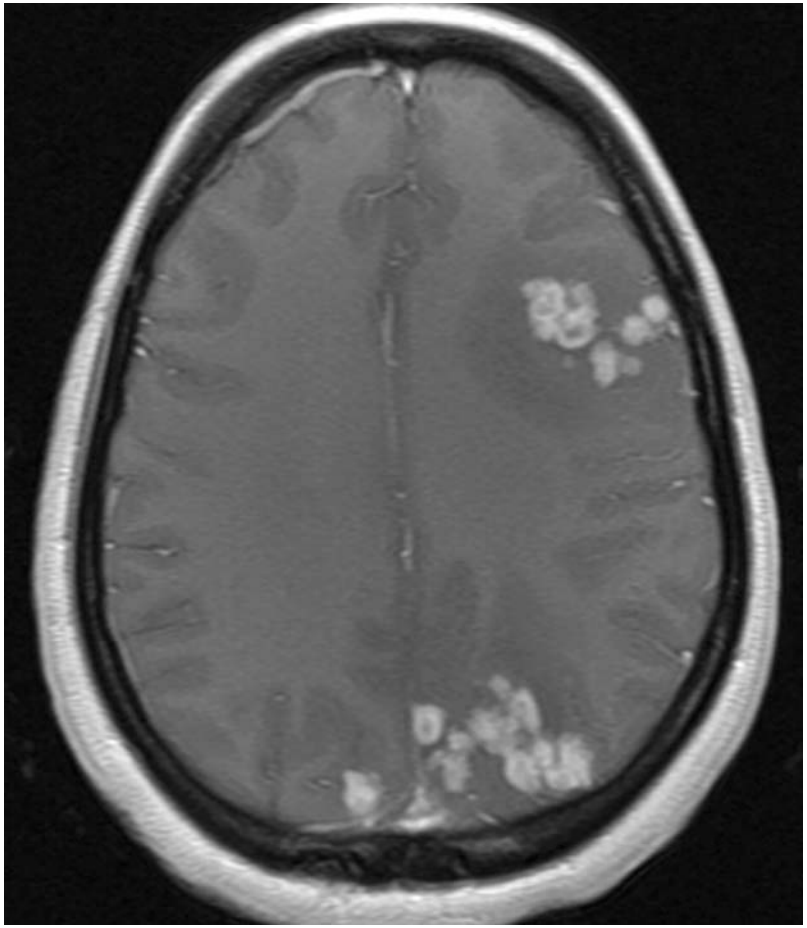


T1 MRI – isointense lesion in Left parietal area

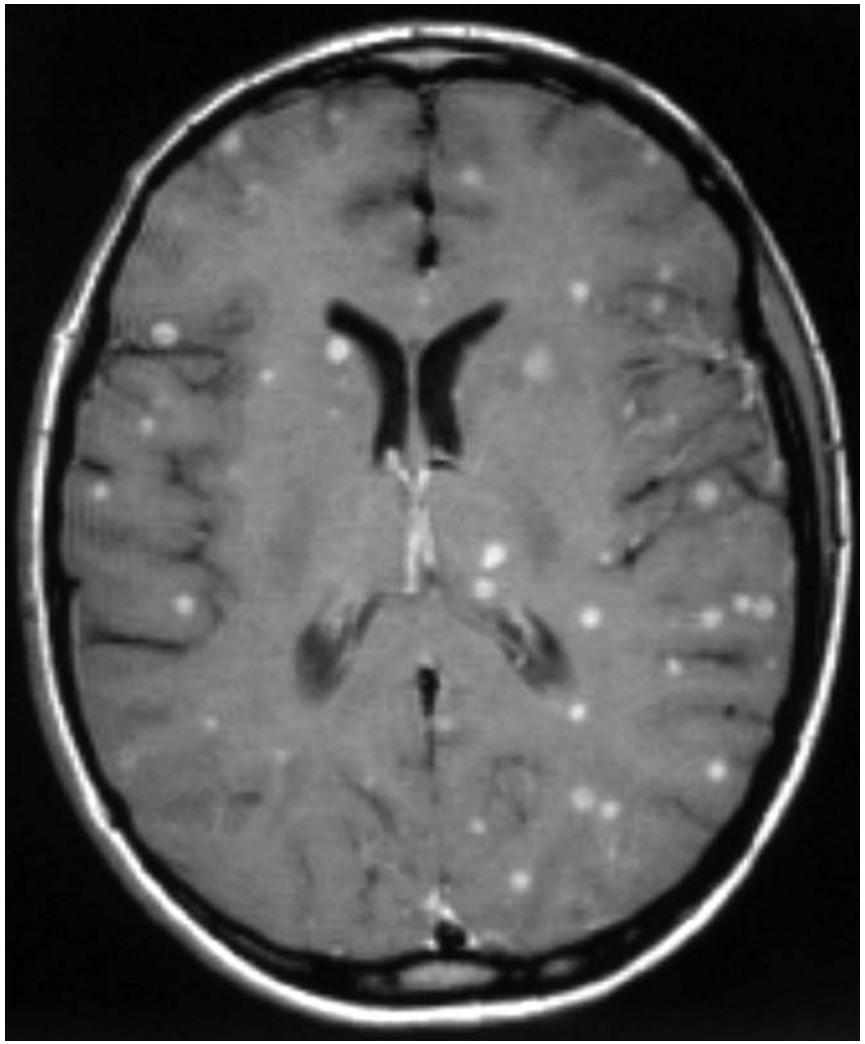


hypointense lesions in the bilateral gangliathalamic regions

centrally hyperintense granuloma with a peripheral hypointense rim.



Parrenchymal tuberculosis. contrast-enhanced T1-weighted MR image demonstrates multiple enhancing caseating and non-caseating tuberculomas, predominantly within the left frontal and parietal lobes



Milliary CNS tuberculosis. Axial contrast-enhanced T1-weighted MR image shows multiple small high-signal-intensity foci within both cerebral hemispheres

Tubercular abscess

- 4-8% of all patient with CNS TB , and 20 % of all patient with HIV infection.

- MRS for TB abscess – lipid and phosphoserine
- Pyogenic abscess - lactate

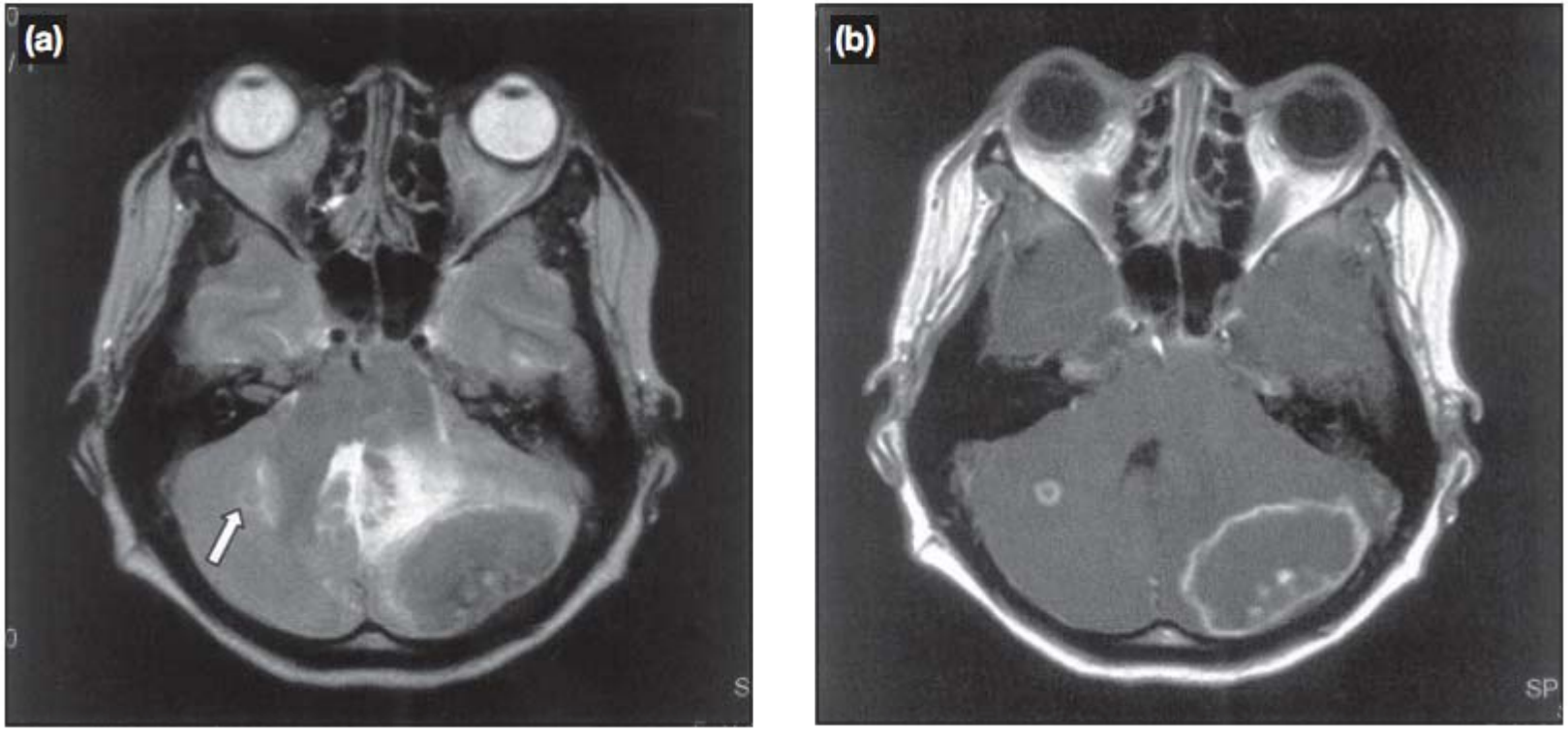


Figure 15. Tuberculosis abscess and granulomas in a 21-year-old woman. (a) Axial T2-weighted magnetic resonance imaging reveals a large hypointense left cerebellar lesion with associated oedema. Another small low-signal lesion containing a central dot-like high signal is noted in the right cerebellar hemisphere (arrow), also with surrounding hyperintense oedema. (b) Axial T1-weighted magnetic resonance imaging after intravenous gadolinium injection reveals a uniformly thin smooth wall of enhancement surrounding the large left cerebellar lesion consistent with a tuberculosis abscess, and solid nodular enhancement of several contiguous tuberculosis granulomas. The tiny right cerebellar lesion shows rim enhancement and is consistent with a caseating soft tuberculous granuloma.

Treatment of tuberculoma

- Medical therapy –

  ATT

  Anti epileptics

  Steroids

- Role of Surgery-
  - Vision or life threatened by mass effect
  - Failure of response to medical therapy
  - Paradoxical increase in lesion size with therapy
  - Diagnosis in doubt

Anti Tubercular Treatment

- Intensive phase - HRZE (3-4 months)
- continuation phase - HR (12-16months)
- Pyridoxine

Duration of treatment

6 months

van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: Is a 6-month treatment regimen sufficient? Int J Tuberc Lung Dis 2001;5:128-35.

12 months

Thwaites GE, Hein TT. Tuberculous meningitis: Many questions, too few answers. Lancet Neurol 2005;4:160-70

18 months or Longer

Santosh Isac Poonnoose, Vedantam Rajashekhar: Rate of Resolution of histologically verified intracranial tuderculomas. Neurosurgery 53:873–879, 2003

Rate of radiological resolution of intracranial tuberculoma

Series	duration of ATT	residual lesions %
Wang 1996 (16)	6	20
Rajeshwari 1995 (6)	9	12
Awada 1998 (2)	12	0

- In all above studies diagnosis is based on imaging .

- Poonnoose et al , Neurosurgery VOLUME 53 | NUMBER 4 | OCTOBER 2003

- Rate of resolution of histopathologically proven tuberculoma with ATT

- Duration of ATT – 9 months - 18.2 % complete resolution
  18 months - 69.2% residual lesion
  24 months - 54% complete resolution

- Duration of ATT must be tailored to radiological response of lesion to therapy , pt's clinical status should not govern the discontinuation of drugs .
- The radiological findings should dictate the continuation or termination of ATT or the administration of alternative drugs

- Size of lesion (4 cms) and extent of surgical resection can affect duration of treatment .

Santosh Isac Poonnoose, Vedantam Rajashekhar: Rate of Resolution of histologically verified intracranial tuderculomas. Neurosurgery 53:873–879, 2003

Drugs

Drugs	Contraindication	Side effects
INH	Drug induced liver disease	Hepatotoxicity , peripheral neuritis , optic neuritis, convulsion , lupus syndrome
Rifampicin	Jaundice ,pregnancy	Liver toxicity , GI distrubances
Ethambutol	Optic neuritis	Optic neuritis, color blindness , peripheral neuritis
Pyrizinamide		Hepatitis
Streptomycin	Pregnancy	Ototoxicity , renal damage

Second line drugs

Group	Drugs (abbreviations)
Group 1: First-line oral agents	• pyrazinamide (Z) • ethambutol (E) • rifabutin (Rfb)
Group 2: Injectable agents	• kanamycin (Km) • amikacin (Am) • capreomycin (Cm) • streptomycin (S)
Group 3: Fluoroquinolones	• levofloxacin (Lfx) • moxifloxacin (Mfx) • ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	• para-aminosalicylic acid (PAS) • cycloserine (Cs) • terizidone (Trd) • ethionamide (Eto) • protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• clofazimine (Cfz) • linezolid (Lzd) • amoxicillin/clavulanate (Amx/Clv) • thioacetazone (Thz) • imipenem/cilastatin (Ipm/Cln) • high-dose isoniazid (high-dose H)[b] • clarithromycin (Clr)

- Use any of the first-line oral agents (Group 1) that are likely to be effective.
- Use an effective aminoglycoside or polypeptide by injection (Group 2).[b]
- Use a fluoroquinolone (Group 3).
- Use the remaining Group 4 drugs to complete a regimen of at least four effective drugs.
- For regimens with fewer than four effective drugs, consider adding two Group 5 drugs. The total number of drugs will depend on the degree of uncertainty, and regimens often contain five to seven.

Use at least 4 drugs

Role of surgery

- Life threatening edema
- Risk of vision loss
- Diagnosis is in doubt
- No response to drugs clinically and radiologically
- Obstructive HCP

Principles of surgery

- Non eloquent areas total excision (small lesion)
- Subtotal/ partial excision (eloquent cortex)
- Conservative excision around vital structures
- Evacuation of central liquifactive portion in deep seated lesions .

Thank you