Stroke in TB meningitis: Pathophysiology , Clinical & Management issues

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Plan of presentation

- Introduction
  - Stroke & infection
  - Stroke in non CNS TB & TBM
- Pathophysiology
- Prevention
- Hyponatremia

Stroke global burden

- 2nd commonest cause of mortality
- 3rd leading cause of disability *(WHO 2012)*
- In the developing countries
  - Burden of Stroke 70 %
  - Death & disability adjusted life years 87% *(WHO 2012)*
  - Infections important etiology

Tuberculosis and the Risk of Ischemic Stroke

A 3-Year Follow-Up Study

Stroke 2010, 41,244

Jau-Jiuan Sheu, MD, MPH; Hung-Yi Chiou, PhD; Jiunn-Horng Kang, MD, MSc;
Yi-Hua Chen, PhD; Herng-Ching Lin, PhD

- Population based study 2000-2003 pts Rx for TB without CSN TB (N 2283) Control (N 6849)
- IS in TB :136(6%) Vs control 256(3.7%)
  - Controlling age , gender, DM.lipids, CA, CAD HR for IS 1.52(95% CI 1.21-1.91P<0.001)
- TB is a risk factor for IS and not ICH

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Journal of the Neurological Sciences

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Experience of pediatric stroke from a tertiary medical center in North India

Jayantee Kalita, Gourav Goyal, Usha Kant Misra *

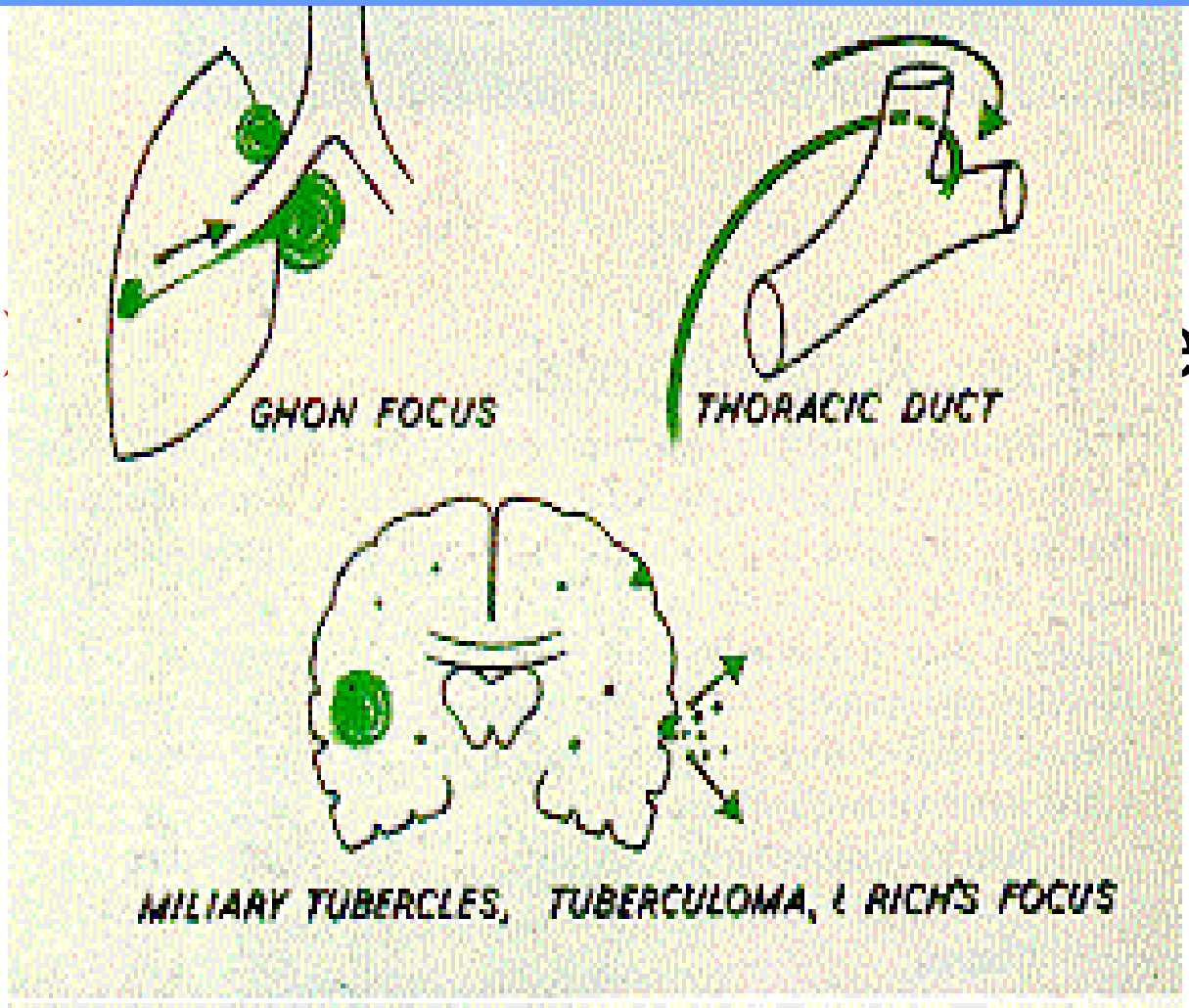
- 10 y 2001-2011 follow up 79 pts (1 mo-18 Y)
- IS 62(78.5%), ICH 10 (12.7%) CVST 8.9%)
  - *Neuroinfection 25 (31.6%)*
    - *(TBM 21 , Fungal 2, NCC1, HepC1)*
  - Cardioembolic 9
  - Prothrombotic 5
  - Arteritis/dissection 4/3
  - Mitochondrial 1
  - Cryptogenic 13

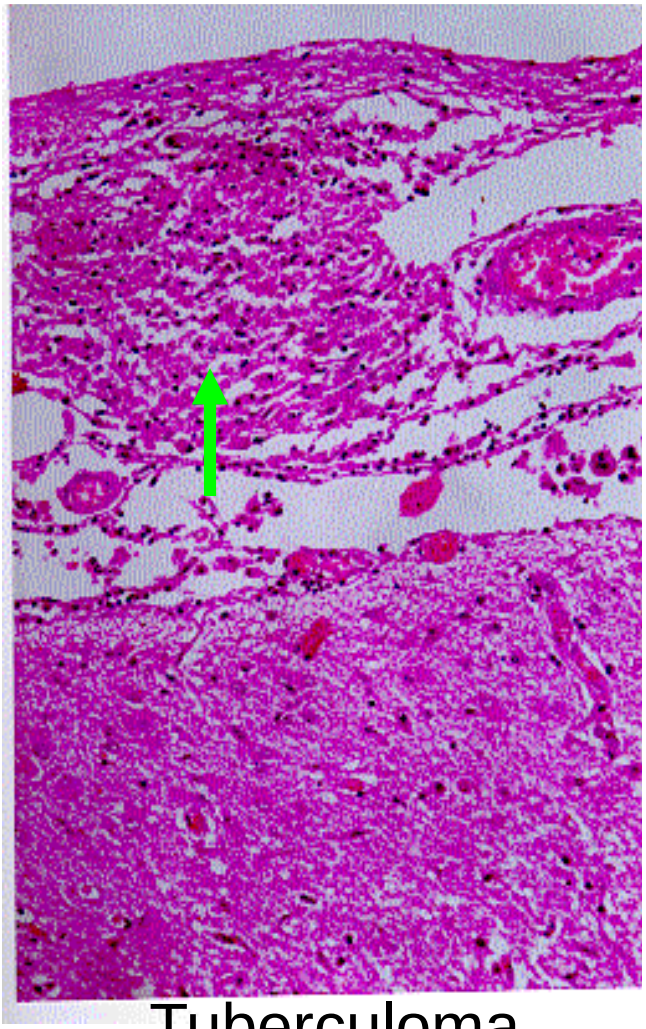
Stroke in TBM (Rev)

- Stroke in young due to TB vasculitis
  - 8% *(Dalal et al1979)*
  - 19% *(Thomas et al 1977)*
- Stroke usually insidious in onset in the background of TBM
- TIA/RIND rare
- Aphasia, agnosia, apraxia & VBI rare
- Stroke associated with x 3 worse outcome *(Kalita et al 2009, Chan et al 2004)*

Pathology

TBM: pathogenesis



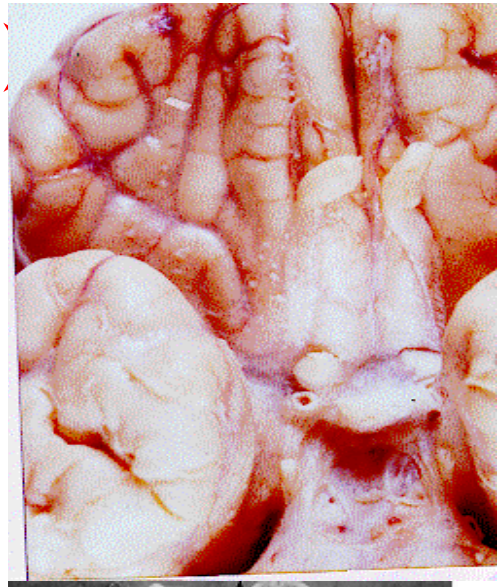


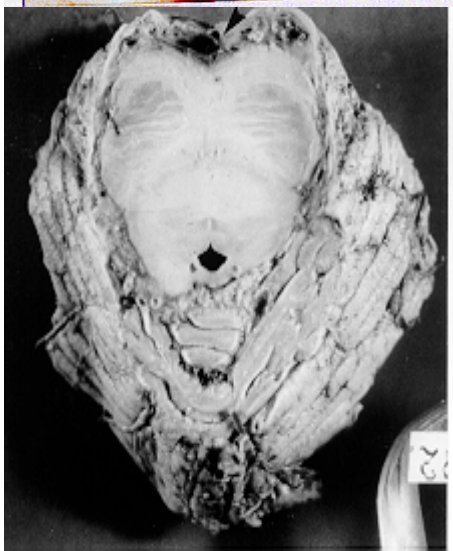
Tuberculoma

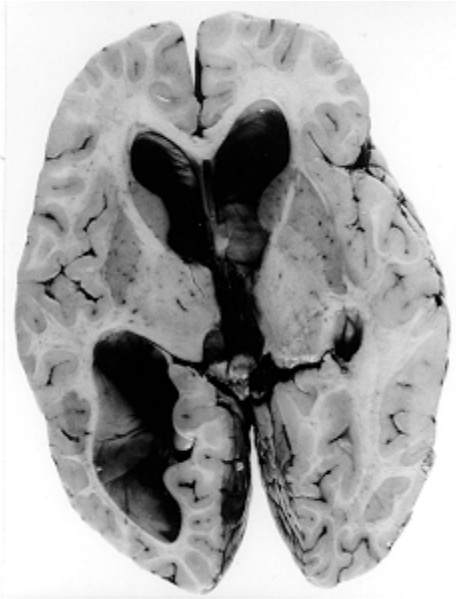
10% primary complex → pneumonia → Miliary TB

Pathology of TBM

Exudate

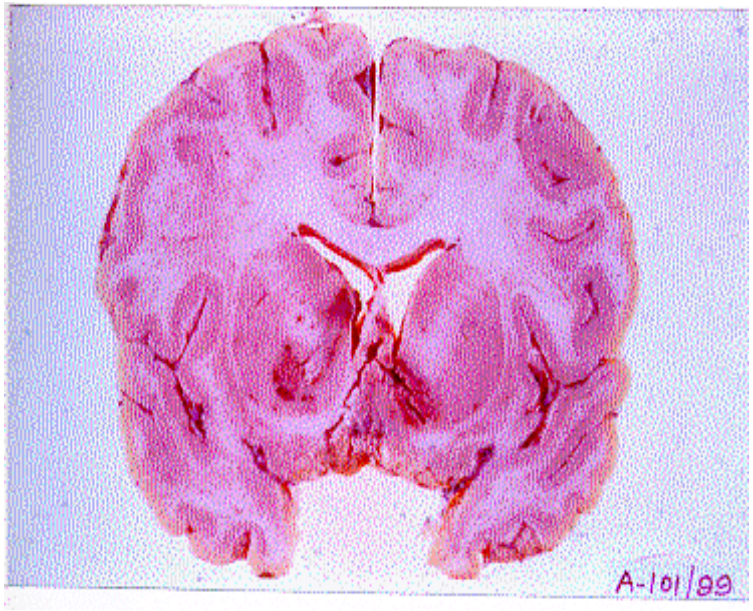


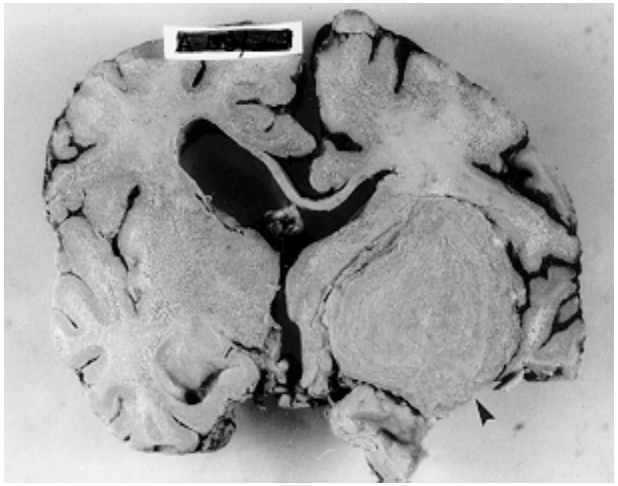




Hydrocephalus

Infarct

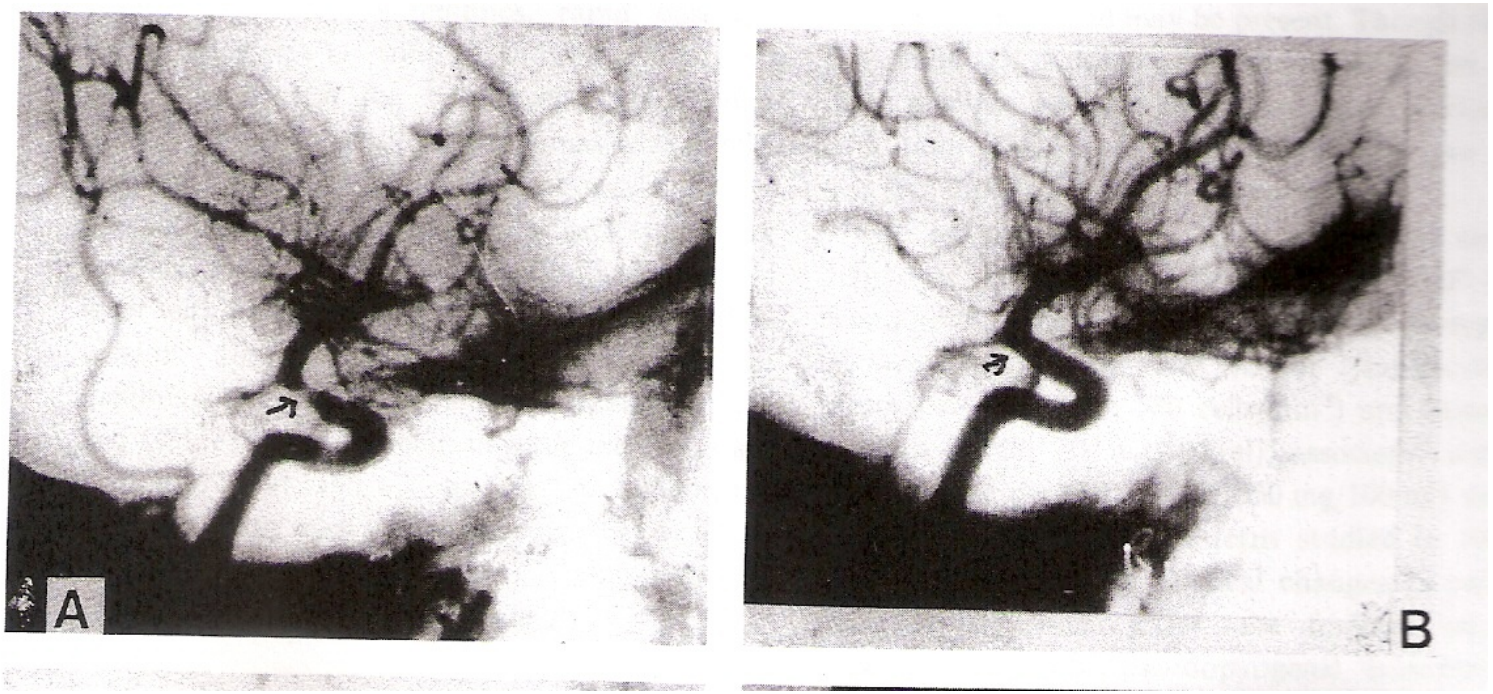




Tuberculoma

Stroke in TBM

- Tubercle along pial vessels
- Restriction of tubercular pathology in an arterial territory with a caseous mass in body ? Embolic
- Vasculits → Thrombosis
- Hemodynamic changes



Vasculitis in TBM

- Small & medium size vessels → infarction
- Incidence of vasculitis :

  Autopsy: 41%

  Angiogram : narrowing 14%,
  Hydrocephalus 29% (*Dalal1979*)
- CT scan 17-63%
- MRI:54%

TB vasculitis :pathology

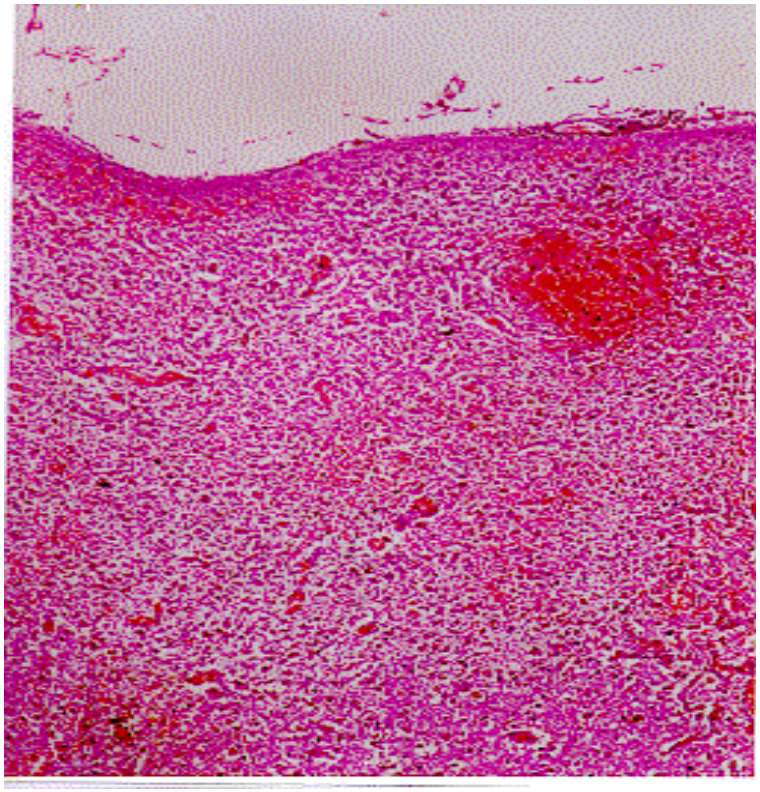
- Tuberculoma in vessel wall rare
- Streptomycin: vasculitis → Fibrous endarteritis with narrowing of lumen
- Exudates α arteritis *(Tandon & Pathak 1973*)

  ↑caseation in SM Rx cases may contribute
- Reversible narrowing of vessels
- Poor clinical correlation
  (Wadia and Singhal 1967)
- Stroke from TB vasculitis without meningitis:

(Dalal & Dalal 1989)

Pathology and pathogenesis

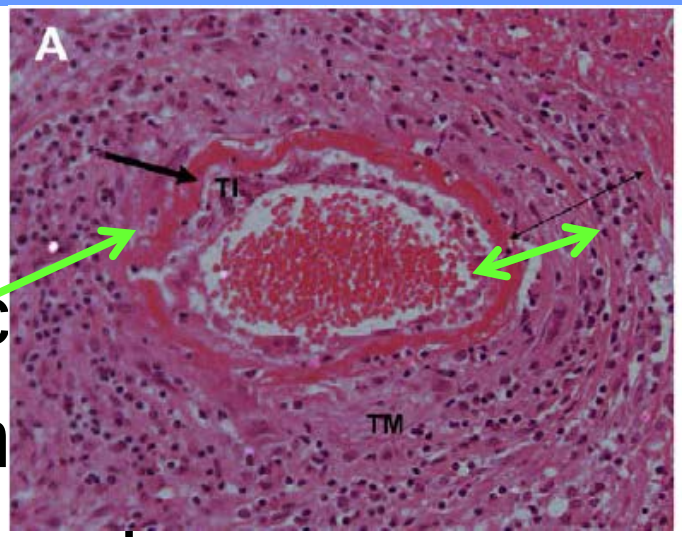
- Inflammatory infiltration
- Subendothelial protrusion with or without tubercle
- Uniform concentric subintimal proliferation with narrowing of lumen

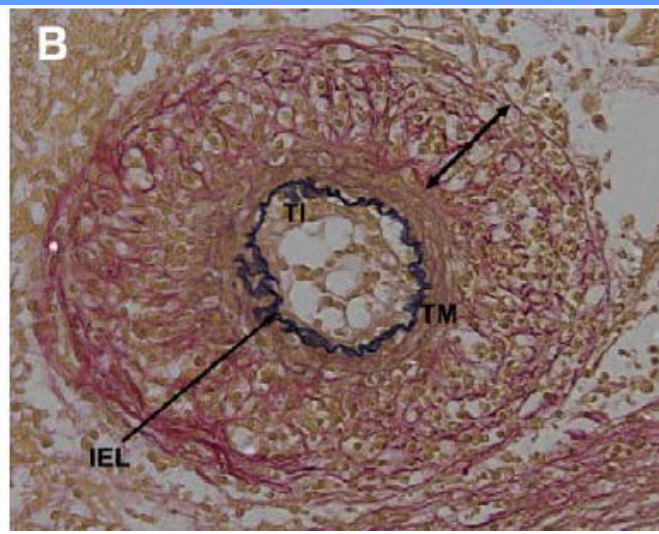


- Intimal fibrinoid degeneration : leakage of blood in parenchyma

Infiltration in vessels in TBM
(Lammie et al 2009)

- Media & Advent infilt.
- Fibrinoid nec
- Artery & vein Equally involved
- Media resistant
- Response to AFB
- Tuberculoma in adventiaia > media or intima

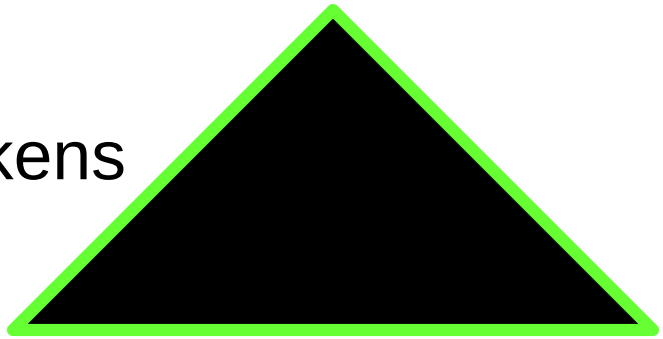




Vascular pathology a function of duration of Rx

- Single or combination
- Duration of illness / Rx determines frquency of changes

Infiltration 2-3 wk



As exudates thickens

Proliferation

SM cells in intima 11d

Collagen 45-60 d

Elastic fibers 16 wk

Necrosis

- Infarcts in TBM : hemodynamic
  - Vasospasm, Intimal proliferation
  - Thrombosis
  - Stretch
  - Strangulation

Poor clinical correlation with angiographic abnormality

- Arterial narrowing without corresponding brain pathology
- Uncommon: organizing thrombus in vascular territory that matches the age of infarct: consider other possibilities e.g. syphilis

"We were impressed by the absence of thrombosis as a factor producing arterial occlusion in TBM " (*Dastur and Lalitha 1973*)

Coagulant and fibrinolytic activity in TBM

(Schoeman et al Pediatr Infect Dis J 2007 , 26:428)

- *Prothrombotic state in pul TB→ DVT (Robson et al 1997)*
- 16 TBM children II-III evaluated
  - Anticoagulant (Prot C, Prot S antithrombin)
  - Pro coagulant: Factor VIII,
    Plasminogen activator inhibitor(PAI)
    Anticardiolippin antibodies tPA
- Prothrombotic profile
  - ↓Anticoagulant : ↓ Prot S
  - ↑Procoagulant : ↑Factor VIII, PAI,
  - N TPA : ↓ Fibrinolysis activity
  - ↑Platelet count ↑ during Rx (← IL6)
- More marked in stage III than Stage II
- Normalized in 1 st mo of ATT

- Pathology and pathogenesis
- Clinical features
- Radiology
- Prevention
- Conclusion

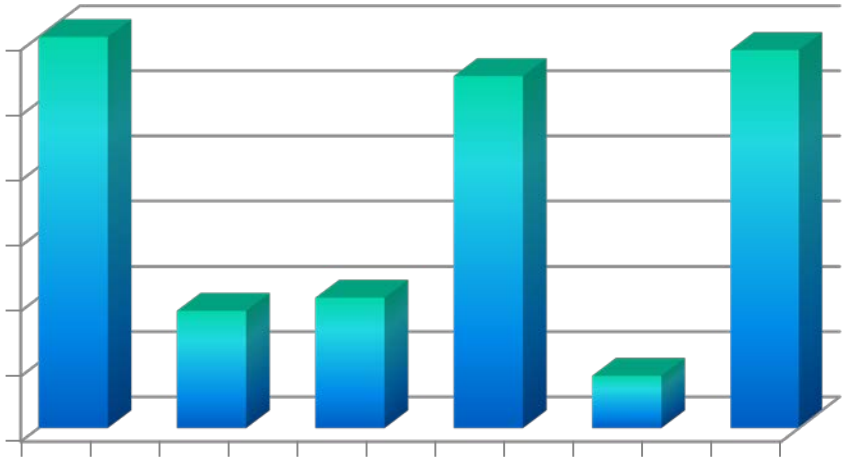
Plan of presentation

- Pathology and pathogenesis
- Clinical features
- Radiology
- Prevention
- Conclusion

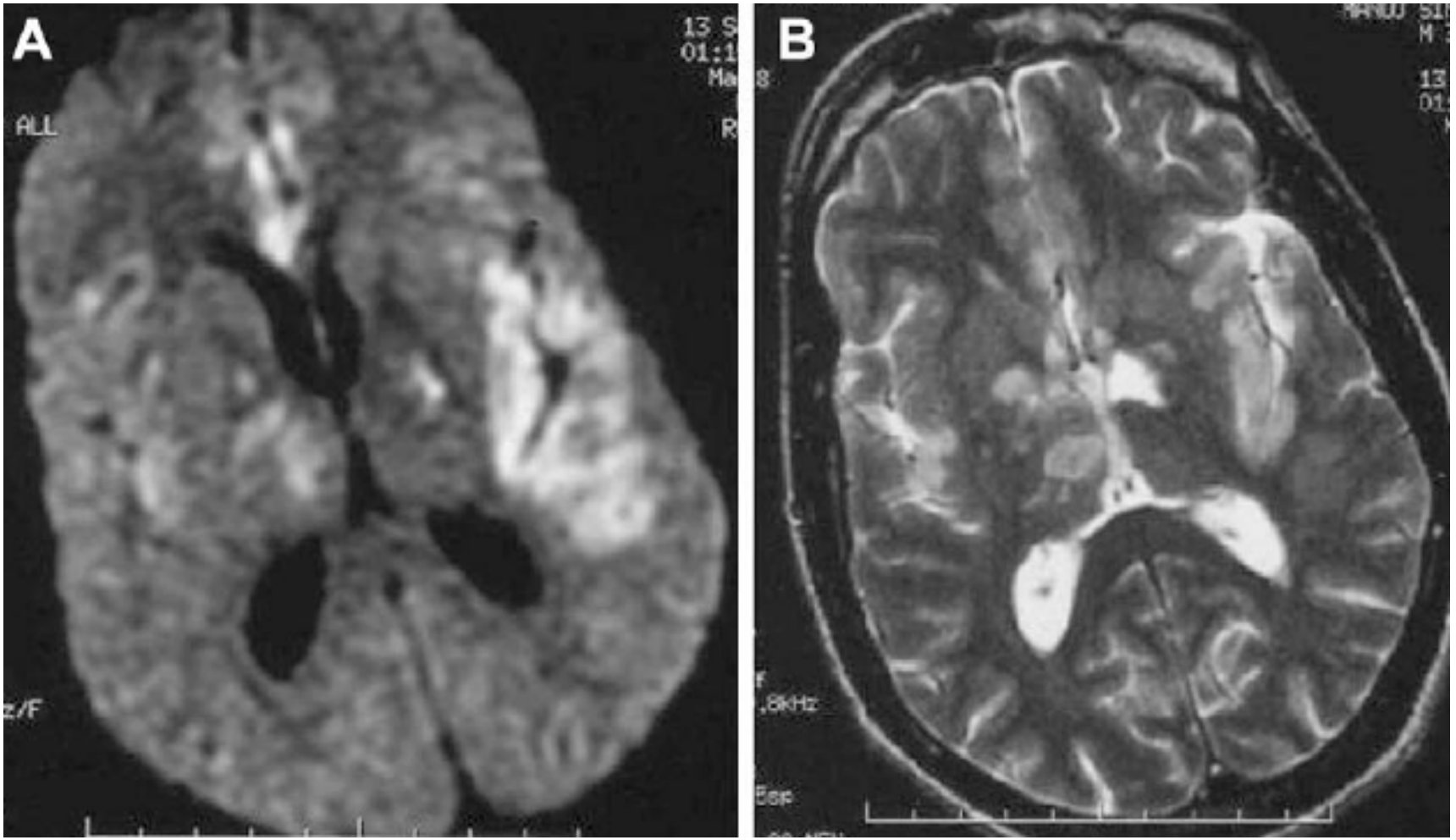
Frequency & type of stroke in TBM

- 55/122 (54%) TBM patients had infarction.
  - On admission: 42
  - By 3 months:13
- Stroke type
  - Ischemic 54
  - Hemorrhagic tr 7
  - Hemorrhage1

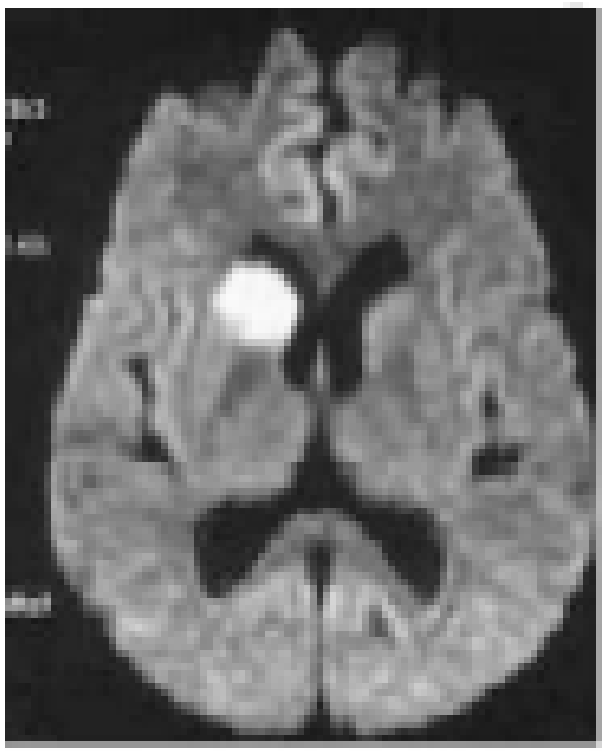
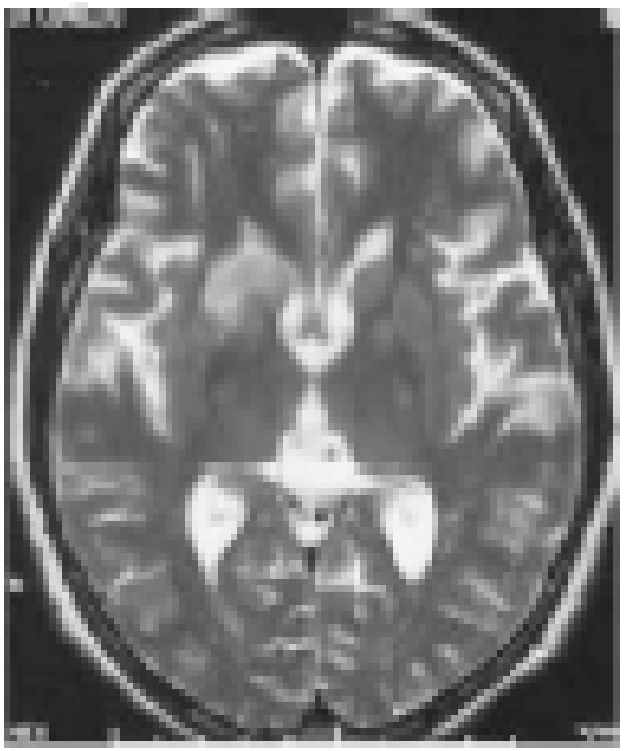
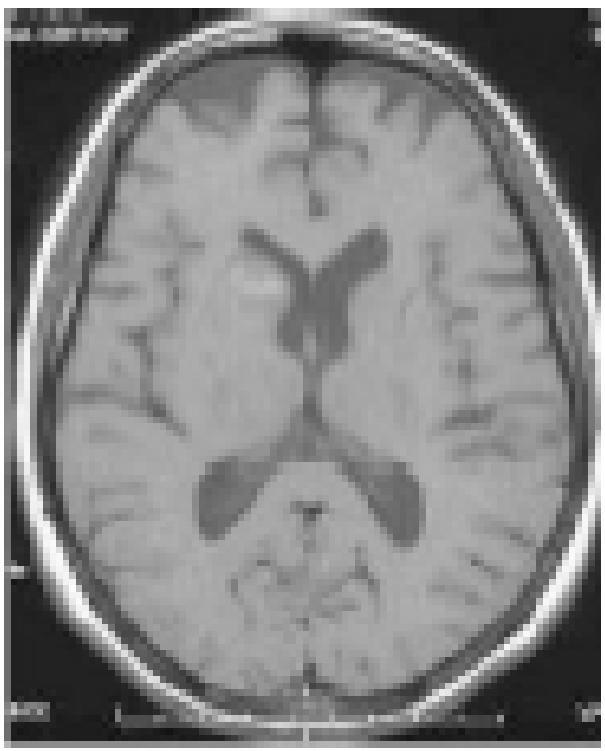
  (Kalita et al 2009)



Cortical & subcotical infarcts in TBM



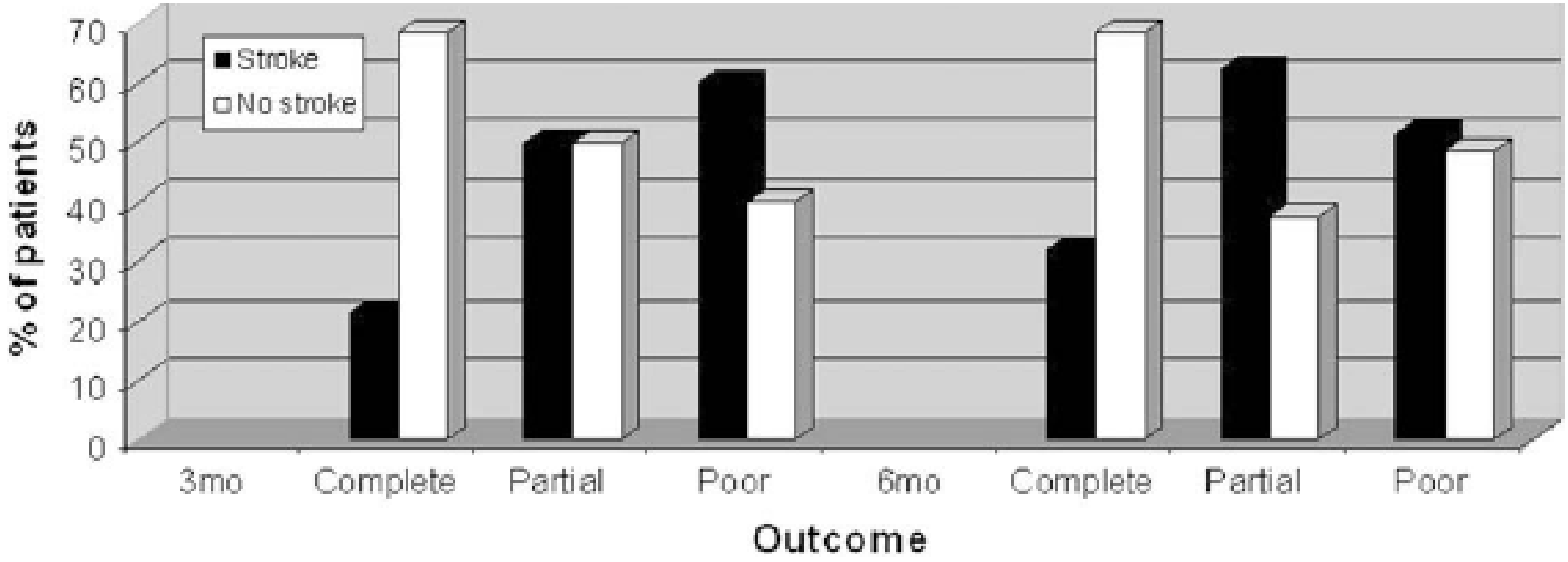
Hemorrhagic infarcts in TBM

Predictors of stroke in TBM

Variable	Stroke	No stroke	P
↑BP +	6	0	
-	49	67	0.007
Stage I	9	31	
II	37	3	0.001
III	9	51	
Hydrocephalus	30	17	0.001
Exudate	21	11	0.008
Prog: Complete	7	29	
Partial	11	13	0.02
Poor	23	15	

Infarcts in TBM associated with poor outcome at 3 mo but not at 6



Lacuens in TBM & ischemic stroke

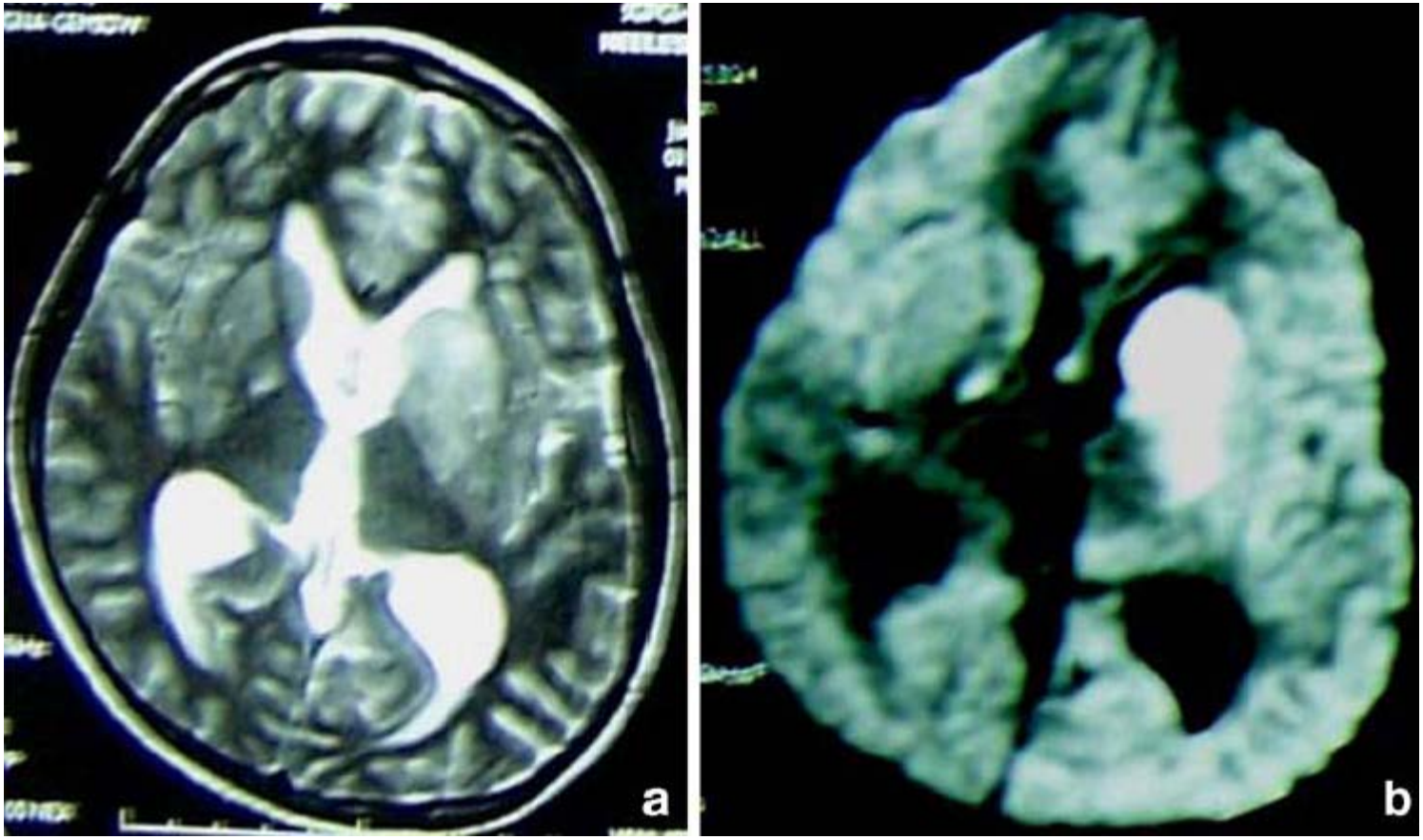
Demographic variables	TBM (n=24)	Ischemic stroke (n=24)	p value
Sex ♂ ♀	13 11	20 4	0.06
Age (y)	32.62±19.09	54.0±15.64	<0.0001
Hypertension	3	11	0.03
Diabetes mellitus	2	6	0.25

(Nair et al Neuroradiol 2009)

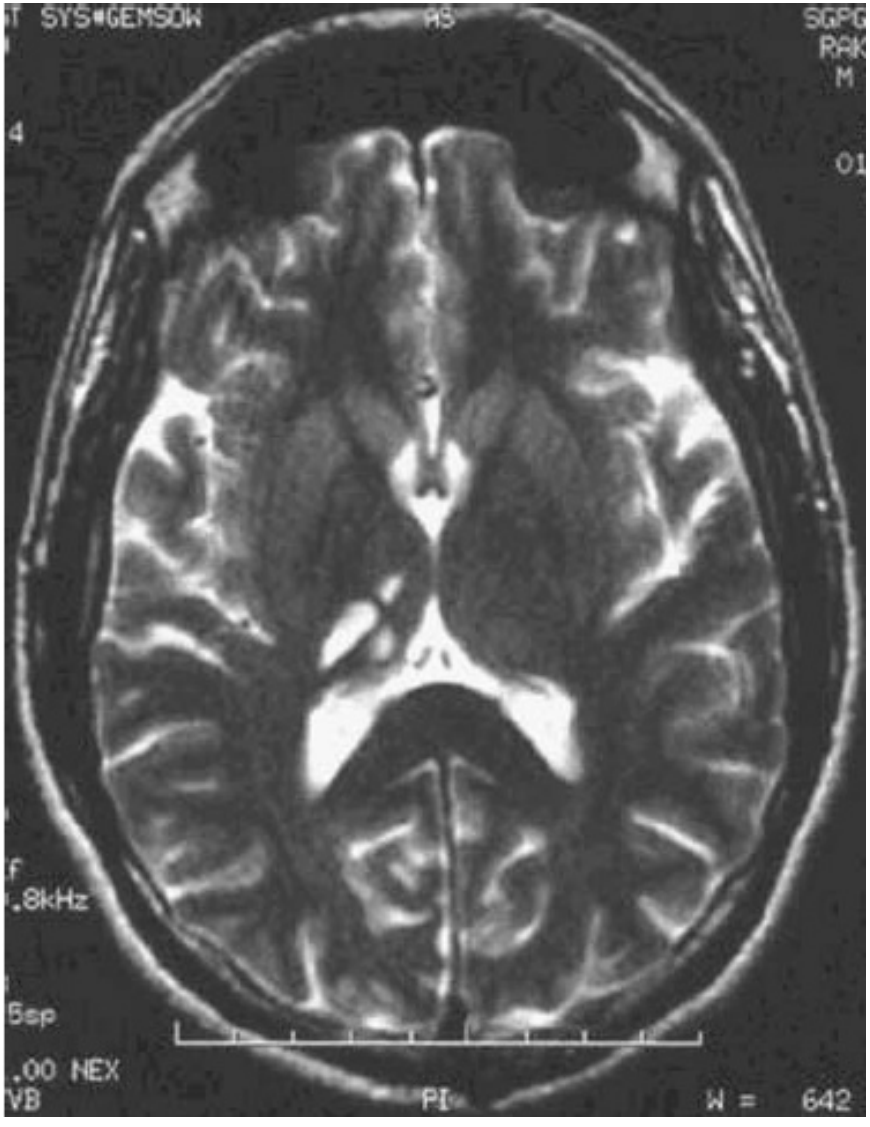
Distribution of lacunes in TBM & IS

Region involved	TBM (n=24)	Isch stroke (n=24)	p
Caudate nu	9 (37.5)	2 (8.32)	0.04
Lentiform nu	15 (62.4)	13 (54.16)	0.77
IC Ant limb	5 (20.8)	2 (8.32)	0.42
IC Post limb	5 (20.8)	7 (29.16)	0.74
IC Genu	6 (25)	1 (4.16)	0.1
Ant thalamus	8 (33.3)	3 (12.48)	0.17
Post thalamus	5 (20.8)	9 (37.5)	0.34

Caudate infarct in TBM



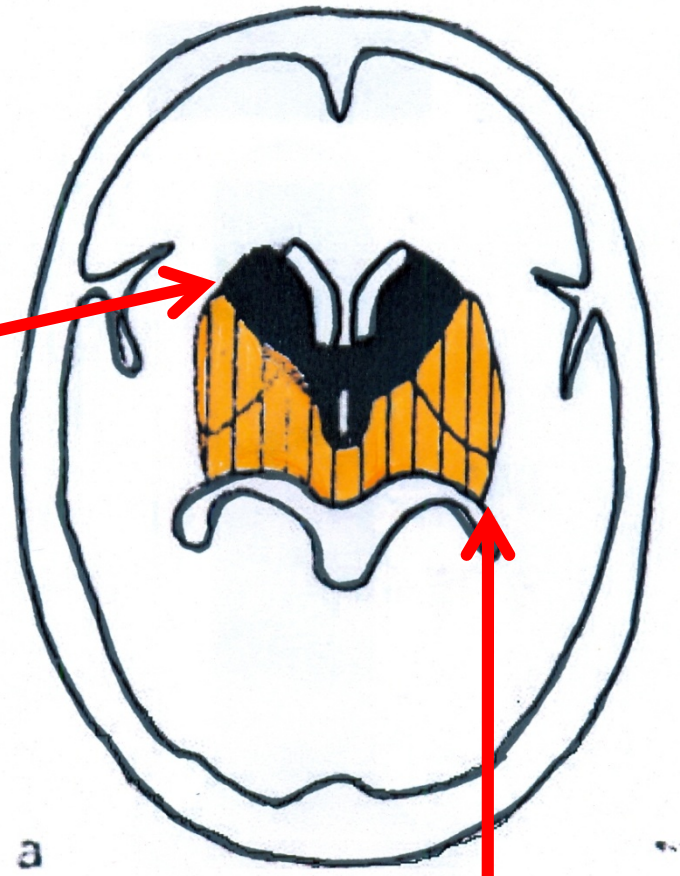
Infarction in ischemic stroke : thalamus & post limb of internal capsule



Location of basal ganglia infarct in TBM & ischemic stroke *(Hsieh et al 1992)*

- Lacunes
  - Anterior in TBM in 70.8%
  - Posterior in IS 91.6%
- TBM:
  - Medial str.
  - Thalamotuberal
  - Thalamoperforate
- IS:Lateral striate vessels
- Posterior location in TBM may be due to coexistence of IS risk factors

(Nair et al, Neuroradiology 2006)

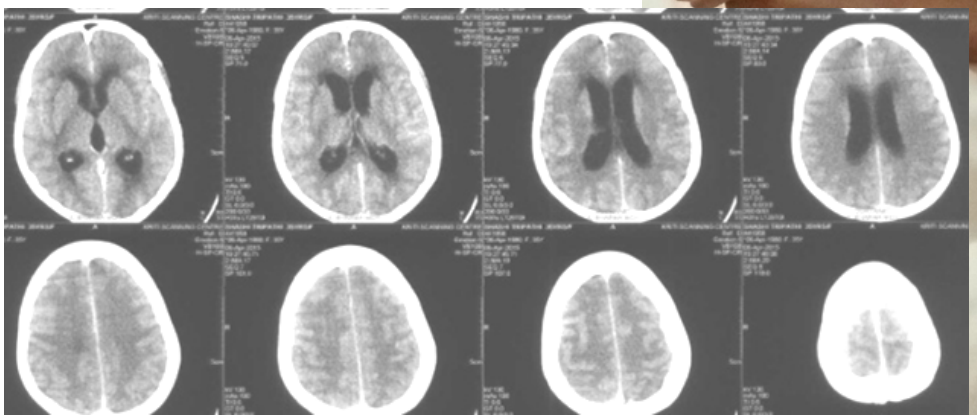


TB Zone:
caudate, genu
Ant lat
thalamus

Ischemic Zone:
Post limb,
lentiform
PL thalamus

Hemorrhagic lesion in TBM

- 32 F Fever, headache 4 mo
- Alt sensorium 1mo
- LL weak 1 wk
- Pupils sluggish
- Ppapilloedema
- LL power 2/3



Case report

- CSF

Cells= 400 (P-60%,ly-40%)

Protein= 495 mg/dl

Sugar = 21 mg/dl (80 mg/dl RBS)

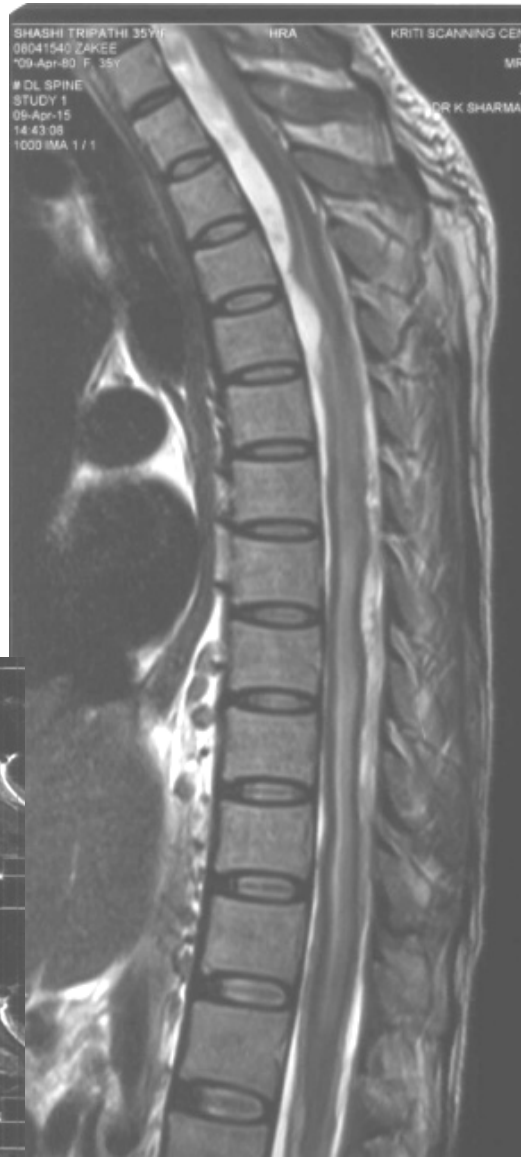
RHZE

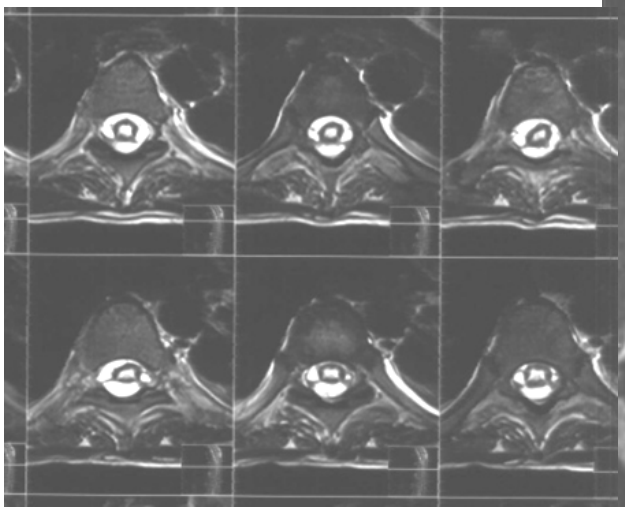
- 2 mo sudden worseni

  ? Hydrocephalus

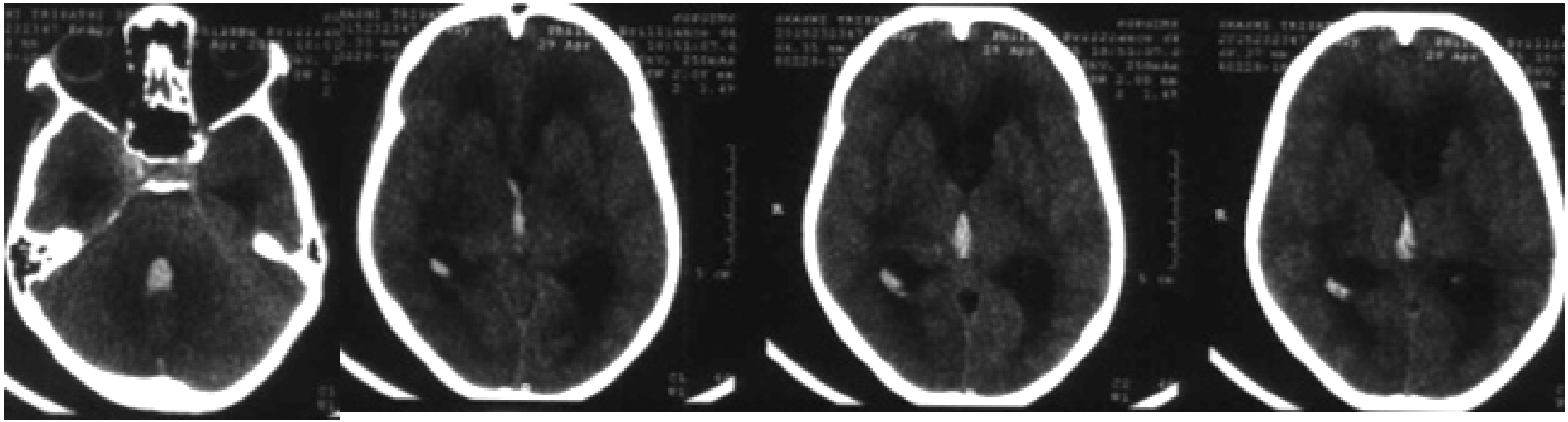
  ? Stroke

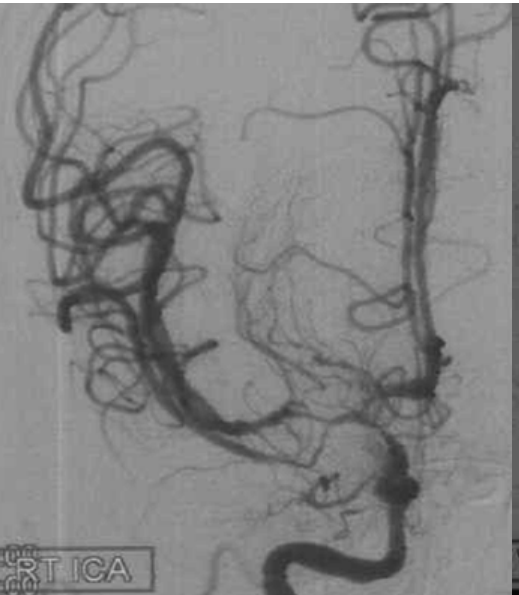
  Stroke

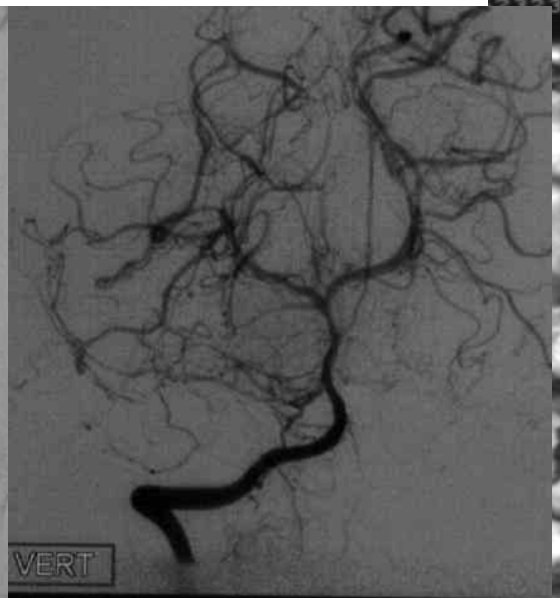


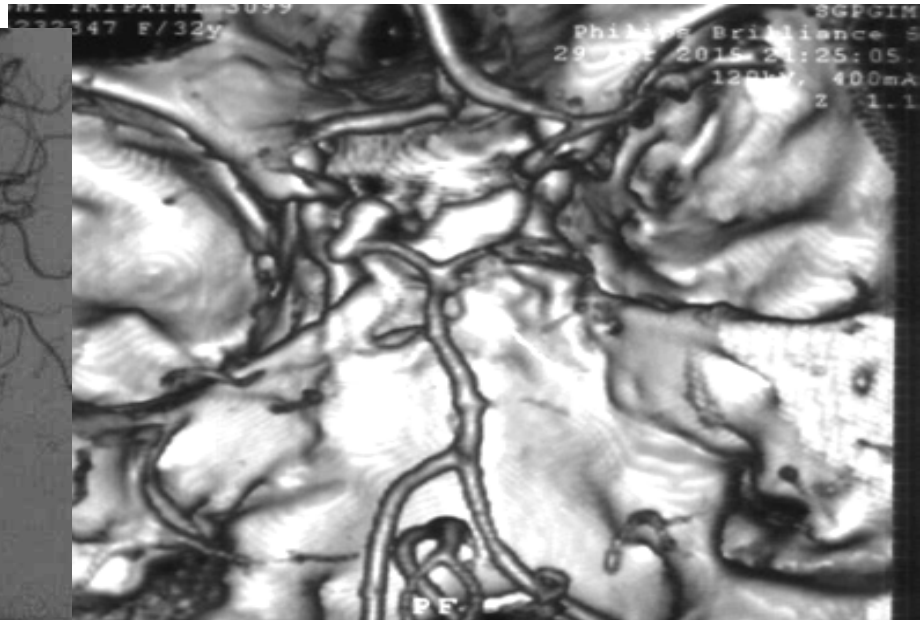


TBM with hydrocephalus , arachnoidits & ICH









Aneurysm or hemorrhage in TBM

Author yr	Age /sex	Site aneurysm	ICH	Casue
Brwon 1951	??	??	-	Clsoe TBculoma
Suwanweb 1972	22F	BL ACA, R MCA, L PCA	=	Ca, infl exudate
Whelan 1981	??	L MCA rrifurcation	-	Clsoe Tbculoma
Leguarda 1988	<14	MCA horizontal part	-	Infl exudate
Gupta 1994	24 M	MCA	-	Infl exudate
Griffith 2000	9 M	PCA	SAH, IVH	Ifl exudate
Tsuboi 2000	55F	MCA	SAH, IVJ	

MR angiography in tuberculous meningitis

Acta Radiol 2012 , 53 : 324

Jayantee Kalita[1], Sreeram Prasad[1], Pradeep K Maurya[1], Sunil Kumar[2] and Usha K Misra[1]

- N67 age 34 (3-75): Abn 61(91%)
- MRA abnormal in 34(50%)
  - MCA 21, PCA 14, ICA 8, ACA 8, Basilar 5, vertebral & sup cerebellar 1 each
  - Corresponding infarct 61.8%
  - Abn both ant & posterior territoreis 25%
  - MRA abnromality related to Hydrocephalus & infarct
- Infarction at 3 mo : abn MRA 47%

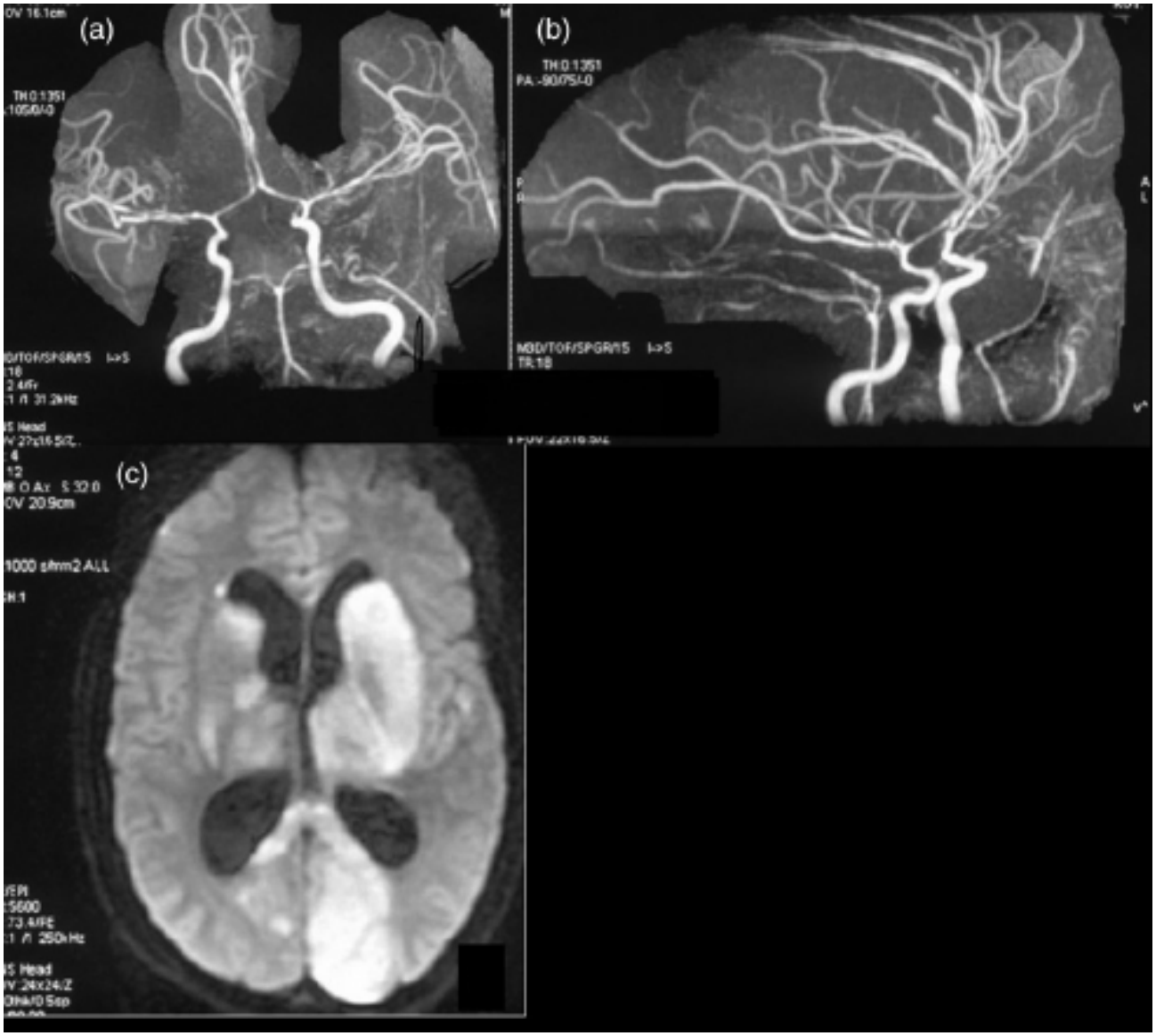
TBM MRA clinical correlation

- 21y M TBM
- Narrow

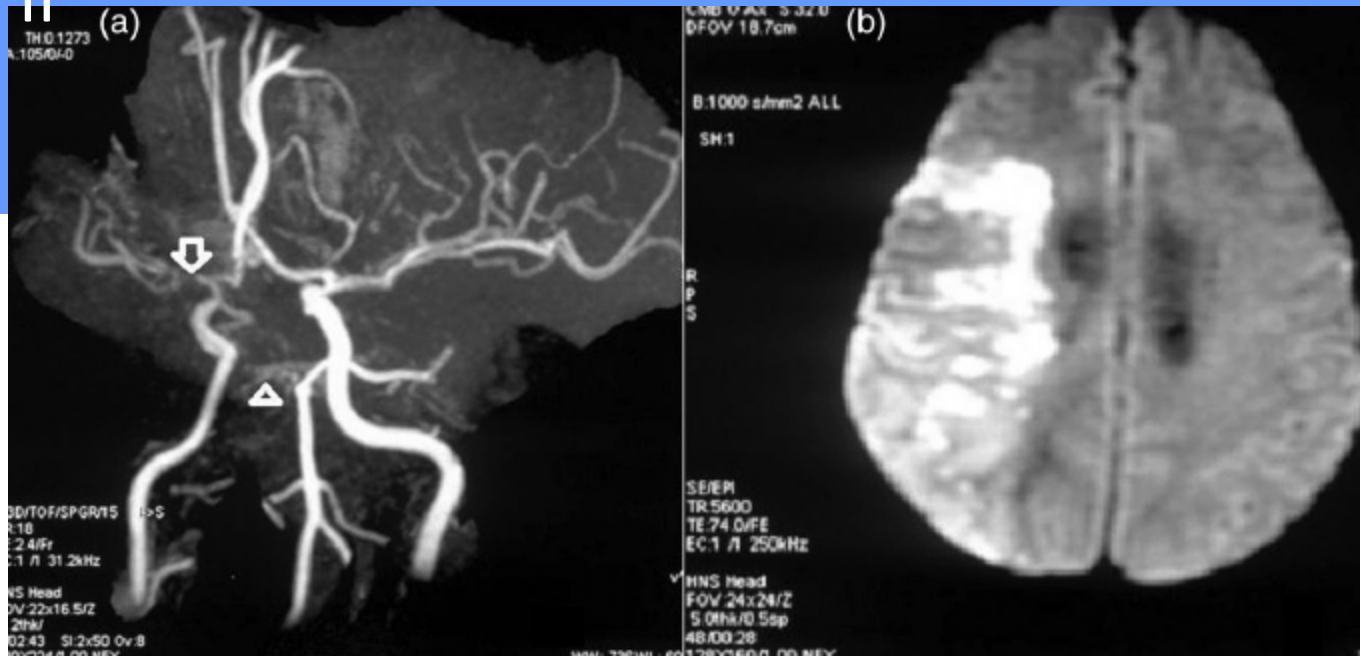
PCA, MCA

ACA

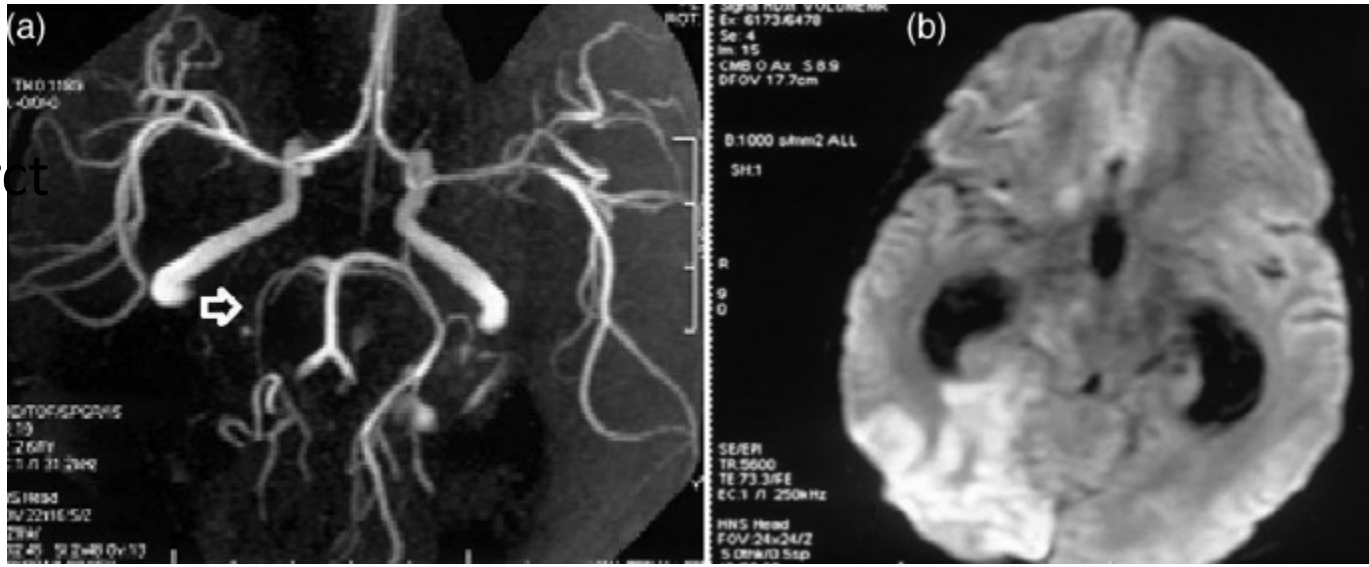
- Infarct OCC
- BG BL



36 y M TBM stage II
R MCA narrowing
R PCA occlusion
Coresponding infa



14y M TBM stage III
R PCA occlusion
Parito occipital Infarct
& R frontal
Pt died at 5 mo

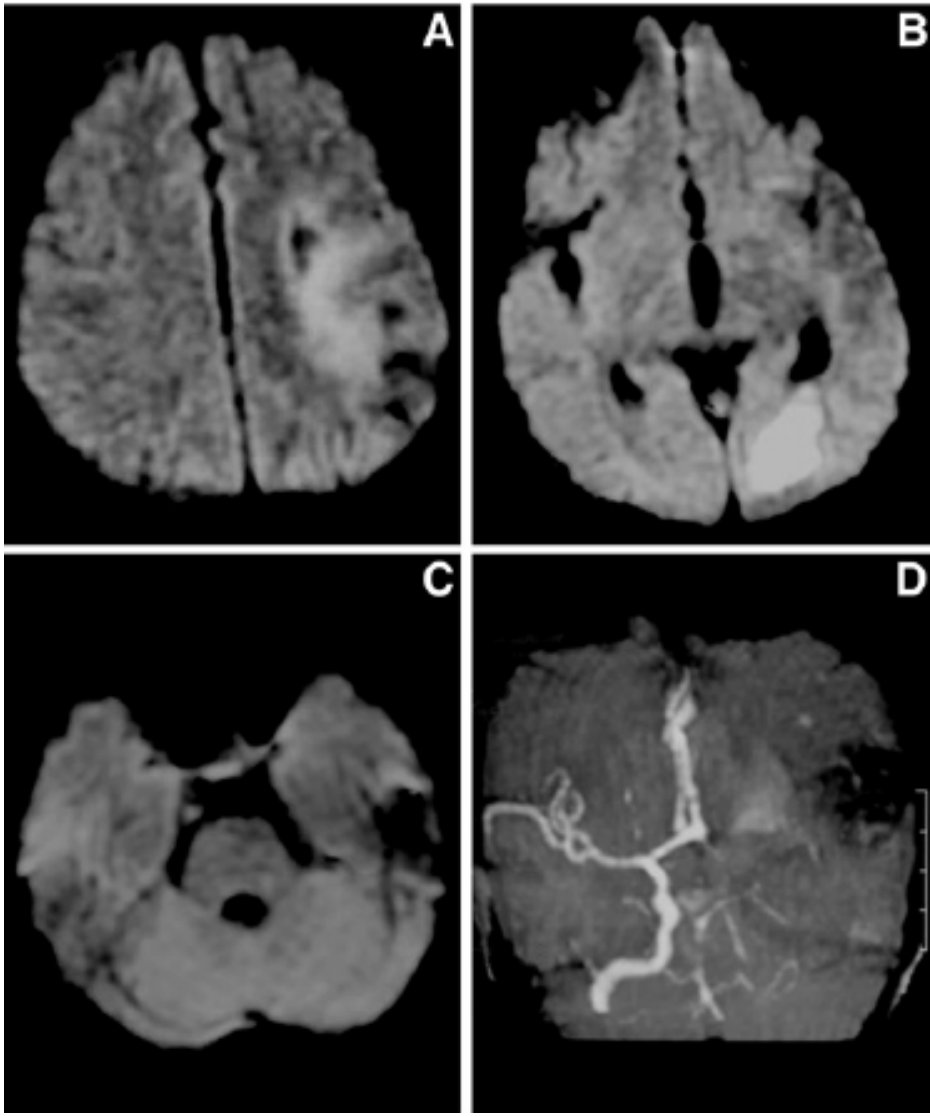


Case report

- 22y ♀ TBM stage II
- RICA,PCA, ACA bloc
- Infarction in

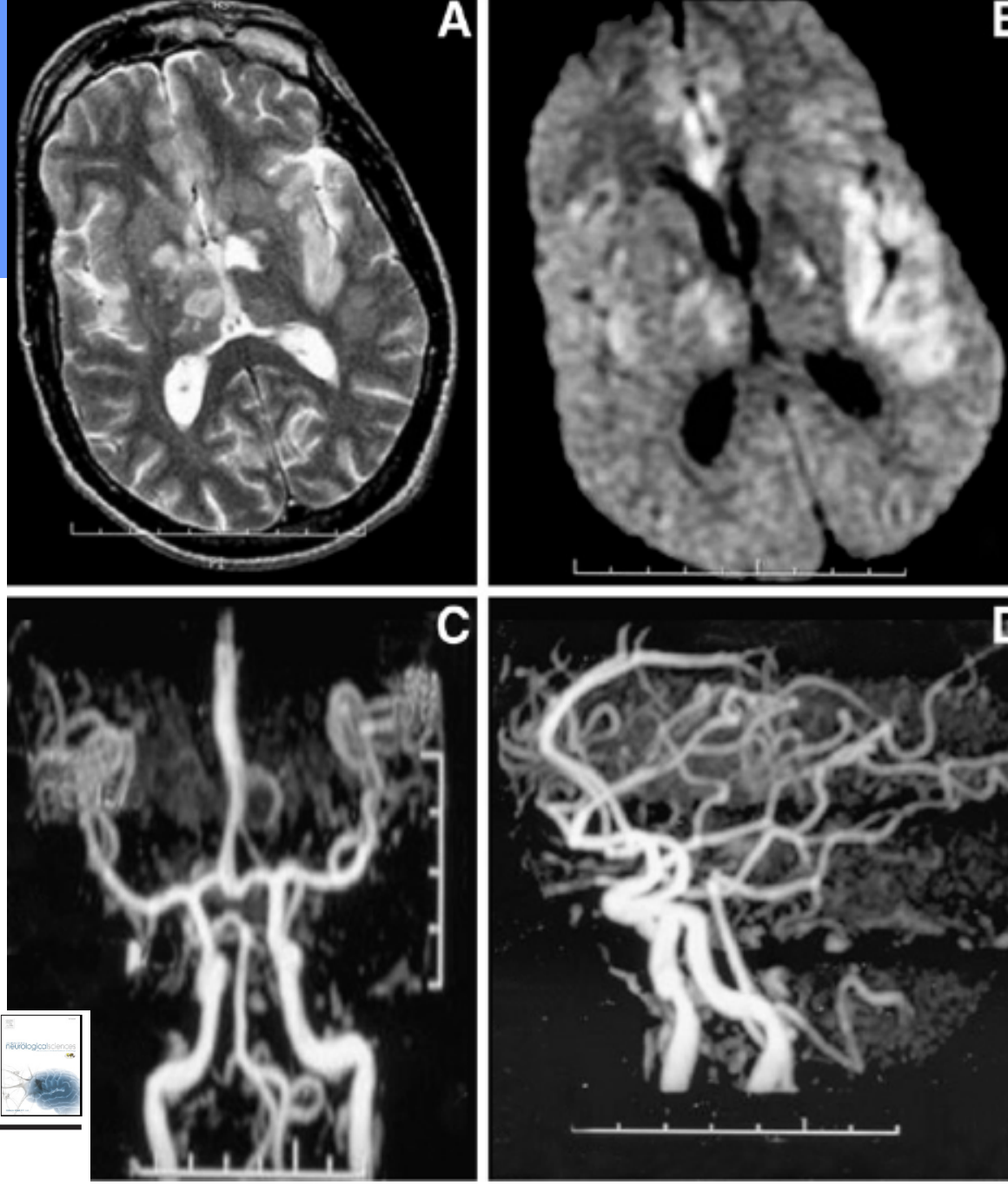
  Parito occipital

  & cerebellar



Clinical &MRA correlation

- 30Y♂ Stage III TBM
- Cortical & BG infarct in MCA territory
- MRA normal



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Stroke in tuberculous meningitis

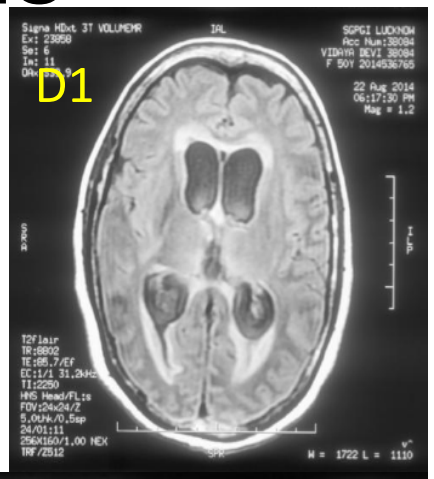
Usha Kant Misra*, Jayantee Kalita, Pradeep Kumar Maurya

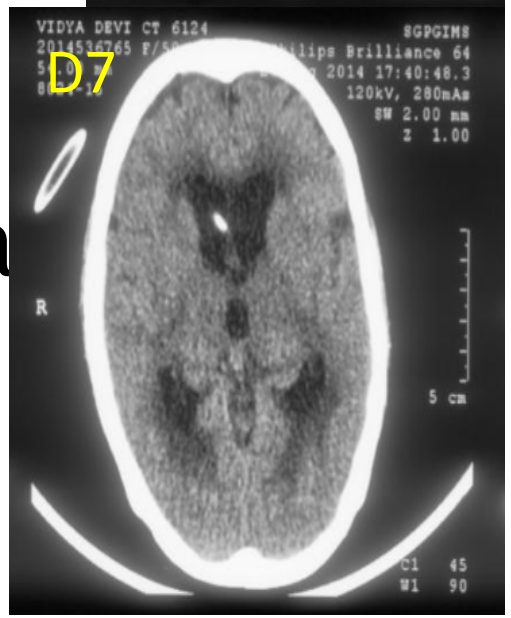
Angiographic findings in TBM

Author	Rojas Echeveri 96	Gupta 94	Gupta 79	Leeds 71	Airon 91	Kalita 13
Vessels narrow/occluded	46	50	48	100	93	110
ICA	8%	50%	4%	40%	93%	23.5%
MCA	42%	40%	44%	60%		62%
ACA	33%	15%				15%
PCA	13%	50%				41%
Modality	DSA	MRA	X-angio	X-angio	X-angio	MRA
Pts N0	24	20	50	5	14	67

Case report
50y♀:fever 1mo, drowzy paraplegia 15 d

- CSF: protein 495mg%, 100l/mm3 sugar 30(121) mg/dl
- D2: RHZE
- D5 :Asymmetric pupil :herniation
- D6/D 7 : EVD → revised
- D8 Mechanical ventialtion
- D10 :Ext posturing deep coma
- D30: GI bleed , DIC & VAP
- D41 VP Shunt





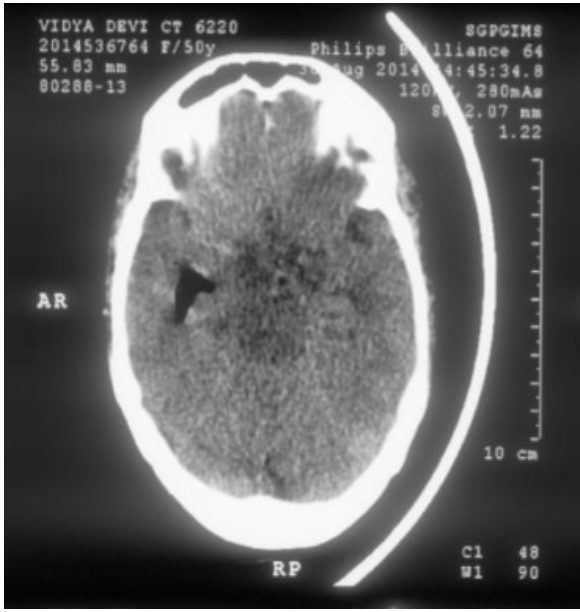
Worsening after shunt

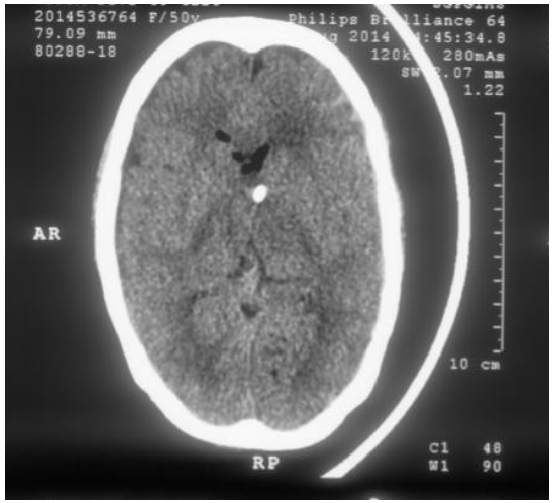
- CSF over drainage :
  - ICH / SDH ↓CSF buyoncy →
  - Traction on vessels

    Hemispheric shift & infarct

    Due to CSF overdrainage
- EVD over drainage ↑Lumbar pressure upward herniation

  (Adams et al 2007)

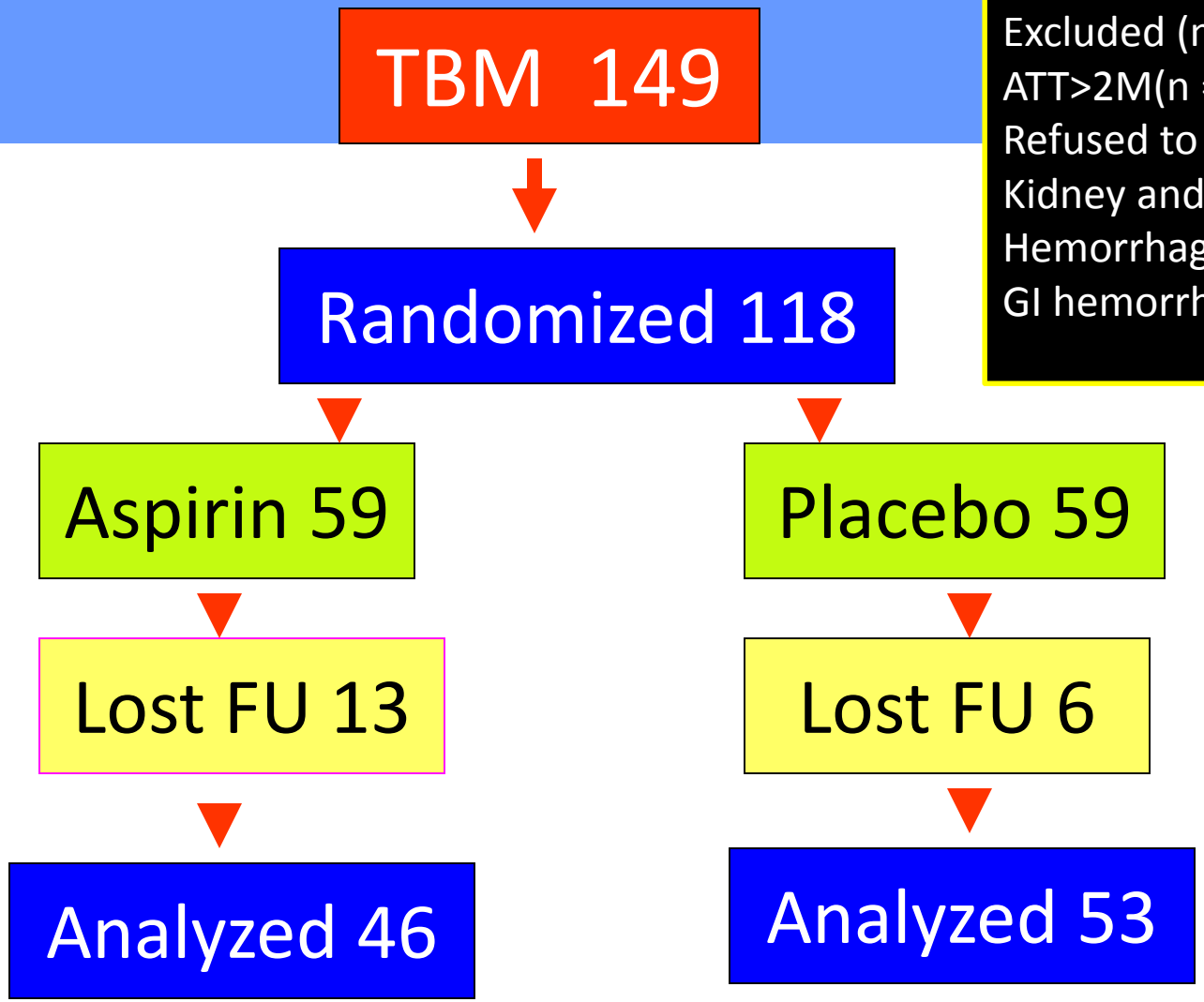




Preventing stroke in TBM

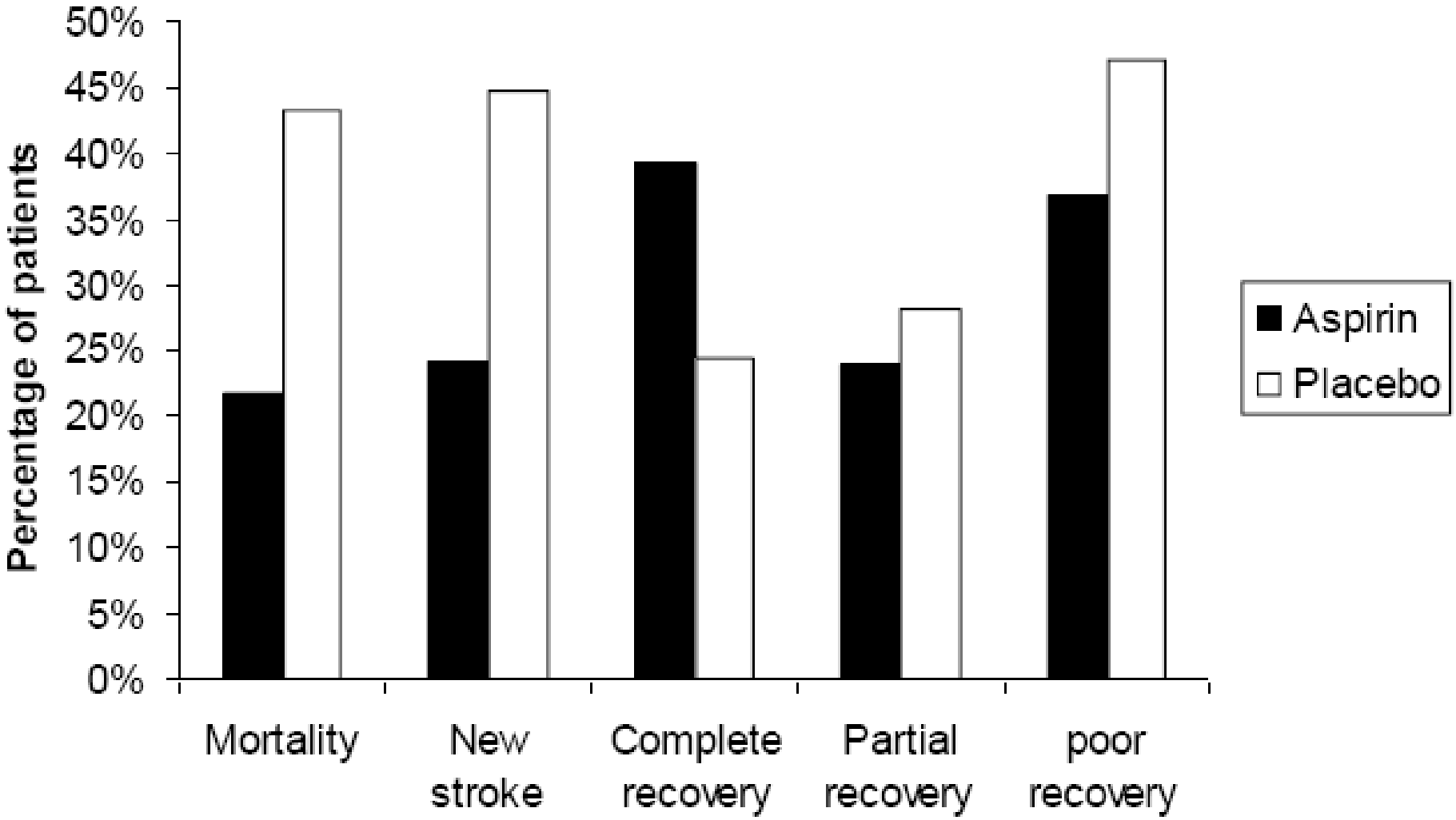
- Corticosteroids
  - ↓ mortality & ↑outcome
  - But not the frequency of stroke/hemiplegia
- Aspirin
  - Anti inflammatory
  - Antiplatelet
  - Antioxidant
  - Used for stroke prevention
- Aim

To evaluate the role of aspirin in preventing stroke in TBM



Role of aspirin in TBM

Effect of aspirin, mortality & outcome in TBM at 3 mo



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Role of aspirin in tuberculous meningitis: A randomized open label placebo controlled trial

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Hyponatremia in TBM (N=76)

- Occurred in 34(45%) pts
  - Mild (134-130 Meq/L) 3
  - Moderate (129-120 Meq/L) 32
  - Severe (<120 Meq /L) 8
  - Related to
    - GCS, TBM severity
    - MV
    - Co-morbidity

CSW 17
SIADH 3
Miscellaneous 14

- CSW related to severity of TBM

(Misra et al J NS 2016)

Cerebral salt wasting in TBM

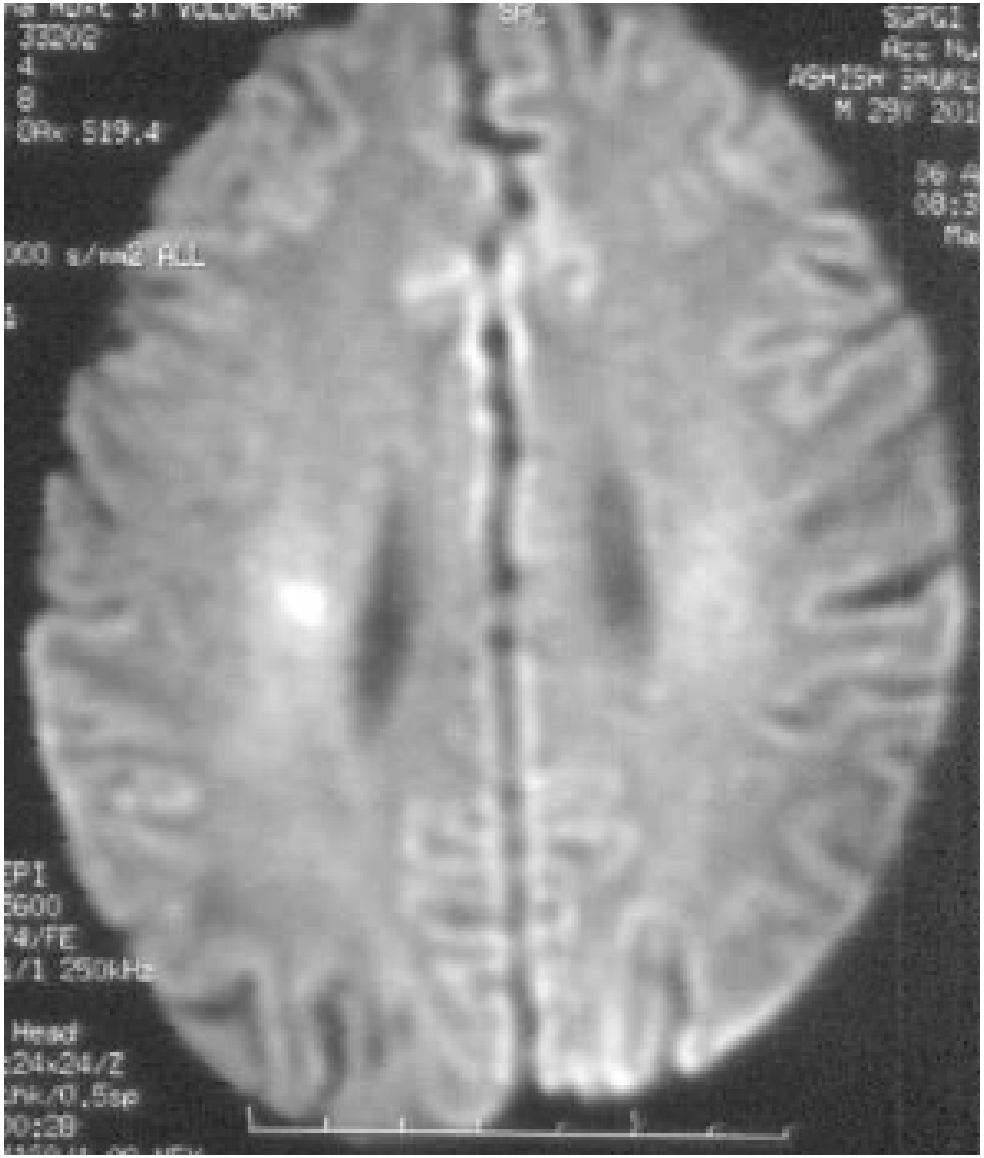
Parameter	CSW(N34)	No CSW (N 47)	P
Corona radiata inf	10 (67.5%)	3 (19%)	0 .01
Hydrocephalus	7 (9.4%)	10 (42%)	0.001
Exudate	28 (82.4%)	26(60.5%)	0.04
mRS >2	21(64%)	10(26%)	0.01

Infarction in TBM with CSW

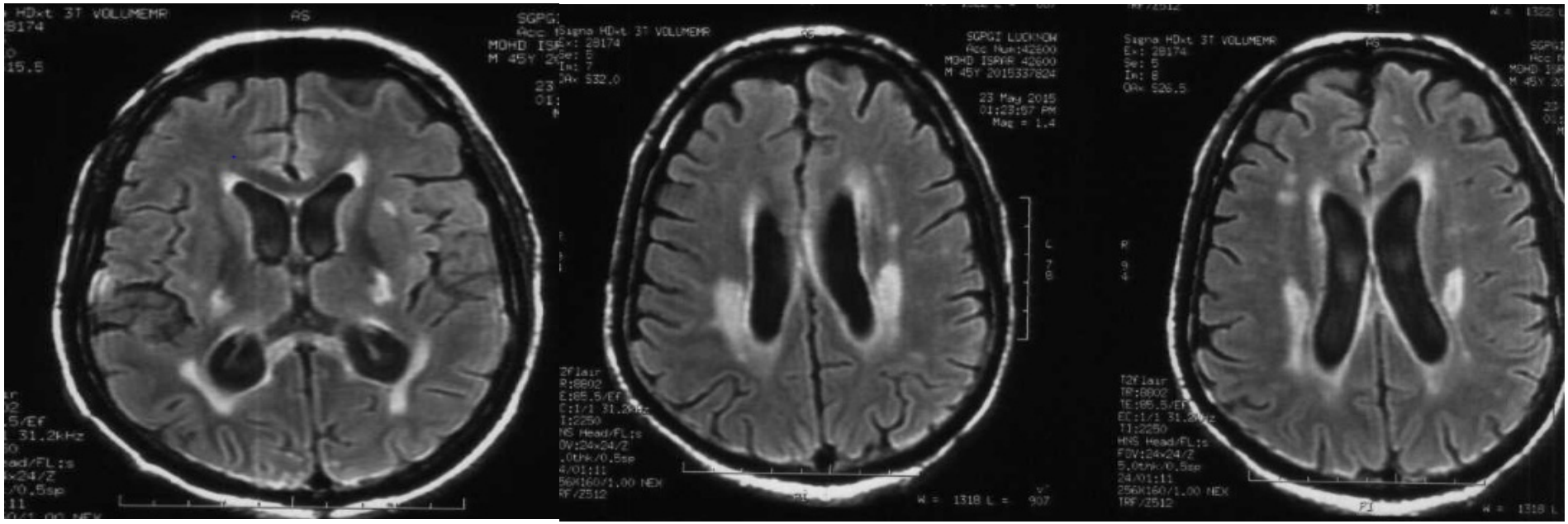
- 15 y M TBM stage III
- Periventricular

Int border zone infarct

- CSW Dx D1



Internal borderzone infarct in TBM with CSW



45 y M TBM stage III ,DM2 , Hypt

CSW d 40 , stroke 68

↓Na corrected after 12 d polyurea after 68 d

Conclusions

- Stroke in TBM is different
  - No TIA, RIND , more subtle
  - TB zone no stroke risk factor, Ischemic zone pts are older and have DM2, Hypt ↑ lipid
  - Mainly subcortical :tubercular / internal border zone
  - Asymptomatic 2/3 , symptomatic1/3
  - Occurs at any stage of TBM
  - Multi-factorial

Conclusions

- Cause of stroke
  - Vasculitis
  - Prothrombotic state
  - Hemodynamic factors, CSW / hypovolemia,? Hypotension hypo-perfusion
  - Co-morbidities
- Multipronged approach to stroke prevention in TBM

Possible mechanism of infarction in TBM

- Haemorrhoelogy
- Change in micro vascular bed
- Response of vessels to neural or neurochemical factors
- Immunogenic phenomena Localize TB antigens in the vessel wall: endothelial, sub endothelial or smooth muscles

(*Shankar et al 1989*)