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Infarction Patterns among Patients with Tuberculous Meningitis: An Entity with Diversity in Itself

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Introduction

Tuberculosis (TB) is one of the most common infectious diseases of developing countries. As per World Health Organisation (WHO) Global TB report 2022, the incidence of TB increased. The number had increased to 10.6 million people worldwide with a total mortality of approximately 1.6 million (~15.1%)[1]. Tuberculosis is caused by *Mycobacterium tuberculosis*, an acid-fast bacillus producing granulomatous lesions. Primary infection evokes protective response in the human body whereas Post-primary TB evokes destructive response. When the host has insufficient immunity as seen in children, elderly, immunocompromised (primary or secondary) or immunosuppressed persons, primary TB occurs where granulomas are formed. There can occur dissemination to other organs via lymphatics or blood which produces a whole clinical spectrum of disseminated TB leading to meningitis, miliary tuberculosis, renal and adrenal TB, third space effusions, abscesses etc[2]. Amongst all the systemic manifestations, Central nervous system Tuberculosis (CNS TB) accounts for approximately 1 - 2% of cases but with high morbidity and mortality burden. In CNS TB, small mycobacteria rich foci form in one of the three sites namely brain, spinal cord, or meninges. Most common presentation of CNS TB is tuberculous meningitis (TBM), whereas encephalitis, tuberculoma/s, vasculitis, ventriculitis, myelitis or tuberculous abscess can also be seen[3]. Infarcts are not uncommon in patients with TBM. Back in 1992, Hsieh and colleagues observed that amongst all the infarctions which occur in TBM, 75% involved what is known as tubercular zone. This Tubercular zone (also known as TB zone) is the area which is supplied by the medial lenticulostriate and thalamo-perforating arteries. In contrast to this, the ischaemic zone is the area which is supplied by the lateral lenticulostriate, anterior choroidal and thalamo-geniculate arteries. As described classically by Hsieh *et al*, the "TB zone" involves (1) Head of caudate nucleus, (2) Genu of internal capsule (3) Anterior limb of internal capsule and (4) Anteromedial Segment of thalamus whereas lentiform nucleus, posterior limb of internal capsule, posterolateral segment of thalamus contribute to the "Ischaemic zone"[4]. Recent case reports also show these two classical patterns and outcome of infarctions in tuberculous meningitis[5,6].

Material and Methods

This was a retrospective study conducted in the Department of Neurology and General Medicine from a period of March 2019 till March 2024. Only patients with TBM having infarction were included in this series. Clinico-demographic profile and Magnetic Resonance Imaging (MRI) findings were studied. CSF study was conducted on the day of the admission and MRI was carried-out within 48 hours of hospital admission. Co-morbidities and risk factors contributing to ischaemia were not excluded from the study. Patients with ischaemic stroke prior to onset of TBM were excluded from the study. The outcome and disability at the time of discharge were studied. Since this was a retrospective study, waiver of consent and institutional ethics committee was taken.

Results

Amongst all 20 (100%) total patients studied, there were 13 (65%) males and 7 (35%) females. The average age was found to be 47.6 years. Major co-morbidities in these patients were hypertension, diabetes mellitus and hypothyroidism. 6 (30%) patients had pulmonary TB. Most common site involvement other than CNS was abdominal. Mean duration of illness was 21.95 days. 6 (30%) patients had history of contact with TB patient. None of the patients had immunocompromised status in the form of HIV seropositivity. Five (25%) patients had modified Rankin Scale (mRS) of 2, five (25%) had mRS of 3, two (10%) had mRS of 4, four (20%) patients had mRS of 5 and three (15%) had mRS of 6 indicating death. All the patients received antitubercular treatment as per National guidelines along with corticosteroids and antiplatelets. 6 patients had seizures warranting the addition of antiseizure medications. Ventriculoperitoneal shunt was required in 1 patient and 2 patients needed decompressive craniotomy due to mass effect of the lesion. Table I. Shows the clinico-demographic

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profile of patients with TBM with infarction.

The Magnetic Resonance Imaging (MRI) Brain findings of these patients along with CSF findings are depicted in Table II. Fig. 1 and Fig. 2 show the various infarction patterns that were found in these patients. Eleven out of 20 patients had multiple infarctions and 17 out of 20 were supratentorial (Table III). 10 patients had TBM grade III according to Palur grading whereas 7 had Palur grade IV and only 3 had Palur grade II (Table IV).

Table I: Showing the clinico-demographic profile of patients of CNS tuberculosis.

S. No.	Age	Sex	Co-morbidities	History of Pulmonary Tuberculosis	Extra-pulmonary involvement besides CNS	Duration of illness	Treatment for tuberculosis taken or not before arrival to hospital	Treatment (duration)	Contact with patients with tuberculosis	HIV Status	Back-ground	Treatment Received	mRS at discharge	Outcome
1.	62	Male	Coronary artery disease	Yes	Abdominal lymphade-nopathy	3 months	Yes (1 month)	HRZE	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid	5	Alive
2.	69	Male	Hypertension, diabetes mellitus	No	No	15 days	No	No	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid Antiseizure medication	5	Alive
3.	29	Female	None	No	No	20 days	No	No	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid	2	Alive
4.	25	Female	Hypothyroidism	No	No	20 days	No	No	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid Antiseizure medication	2	Alive
5.	52	Male	None	Yes	No	5 days	No	No	No	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid Antiedema measures Ventriculoperitoneal shunt	5	Alive
6.	60	Female	Diabetes mellitus, Hypertension, COPD, DCMP	Yes	No	7 days	No	No	No	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid Diuretics Antiseizure medication	5	Alive
7.	34	Female	None	No	No	10 days	No	No	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid	3	Alive
8.	22	Female	None	No	No	15 days	No	No	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid	6	Death
9.	47	Male	Diabetes mellitus	No	No	27 days	No	No	Yes	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid	3	Alive
10.	38	Female	None	No	No	21 days	No	No	Yes	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid	3	Alive
11.	55	Male	None	No	No	60 days	No	No	No	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid	3	Alive
12.	54	Male	Hypertension, Hypothyroidism, Diabetes Mellitus	No	No	18 days	No	No	Yes	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid	2	Alive
13.	65	Male	Diabetes Mellitus	Yes	Abdominal	7 days	No	No	Yes	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid Antiseizure medication Decompressive craniotomy	6	Death
14.	39	Male	None	No	No	10 days	No	No	No	Negative	Urban	Antitubercular treatment	2	Alive

											Antiplatelets Corticosteroid		
15.	27	Female	None	No	No	24 days	No	No	No	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid	4	Alive
16.	30	Male	None	No	No	15 days	No	No	No	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid	3	Alive
17.	44	Male	None	Yes	No	15 days	No	No	No	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid	2	Alive
18.	67	Male	None	Yes	No	23 days	No	No	Yes	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid Antiseizure medication Decompressive craniotomy	6	Death
19.	81	Male	Hypertension, Diabetes Mellitus	No	No	7 days	No	No	Yes	Negative	Rural	Antitubercular treatment Antiplatelets Corticosteroid Antiseizure medication	4	Alive
20.	52	Male	Hypertension	No	No	30 days	No	No	No	Negative	Urban	Antitubercular treatment Antiplatelets Corticosteroid	2	Alive

Table II: Showing the Radiological (MRI Brain) and CSF findings profile of patients of CNS tuberculosis.

S. No.	MRI Brain Findings	CSF Glucose	Blood Sugar	CSF Protein	CSF Cbnaat for MTB	Rifampicin Resistance	ZN Stain	Gram Stain	Cytology
1.	Acute infarct in left pons	73	104	12	Detected	Not Detected	NEG	NEG	N30L70
2.	Acute infarct in right cerebellar hemisphere, left basal ganglia and right medial temporal lobe	56	96	41	Detected	Not Detected	NEG	NEG	N10L90
3.	Acute infarcts left capsuloganglionic region and left gyrus rectus and basifrontal areas.	70	82	112	Detected	Not Detected	NEG	NEG	N40L60
4.	Acute infarcts in bilateral capsuloganglionic regions, right corona radiata, bilateral basifrontal and right temporal lobe	61	112	101	Detected	Not Detected	NEG	NEG	N30L70
5.	Acute infarct left anteromedial thalamus	79	105	102	Not Detected	Not Detected	NEG	NEG	N60 L40
6.	Acute infarcts in the right thalamus, thalamocapsular region, right medial temporal lobe, right cerebral peduncle and left cerebellar peduncle	56	89	112	Detected	Not Detected	NEG	NEG	N30L70
7.	Acute infarcts in bilateral anteromedial thalamus (Right> Left)	78	100	100	Detected	Not Detected	NEG	NEG	N30L70
8.	Acute infarct in left dorsal pons	59	115	46	Detected	Not Detected	NEG	NEG	N10L90
9.	Areas of diffusion restriction in splenium of corpus callosum suggestive of acute infarct	155	88	48	Detected	Not Detected	NEG	NEG	N10L90
10.	Left Cerebellar infarct	114	98	90	Not Detected	Not Detected	NEG	NEG	N30L70
11.	Acute Vasculitic infarct in basal ganglia	39	120	59	Not Detected	Not Detected	NEG	NEG	N40L60
12.	Brainstem infarcts	47	126	66	Detected	Not Detected	NEG	NEG	N30L70
13.	Large Right MCA territory infarct with haemorrhagic transformation	46	188	81	Detected	Not Detected	NEG	NEG	N10L90
14.	Acute Vasculitic infarct in basal ganglia	113	156	10	Not Detected	Not Detected	NEG	NEG	N10L90
15.	Acute Vasculitic infarct in basal ganglia	30	106	271	Not Detected	Not Detected	NEG	NEG	N10L90
16.	Acute infarct in posterior limb of internal capsule	34	98	32	Detected	Not Detected	NEG	NEG	N30L70
17.	Acute infarct in posterior limb of internal capsule	89	130	66	Detected	Not Detected	NEG	NEG	N30L70
18.	Large right MCA territory infarct	58	90	25	Detected	Not Detected	NEG	NEG	N10L90
19.	Right frontal infarct	206	450	84	Not Detected	Not Detected	NEG	NEG	N10L90
20.	Acute infarcts in bilateral anteromedial thalamus and anterior limb of internal capsule	67	103	78	Not Detected	Not Detected	NEG	NEG	N40L60

Table III: Distribution of infarctions

Number of infarctions	Single infarction	9
	Multiple infarctions	11
Distribution of infarctions	Supratentorial	17
	Infratentorial	3
Duration	Acute	20
	Chronic	0

Table IV: TBM Palur grade

Palur grade	Clinical features	GCS Score	Number of patients
I	No neurological deficit	15	0
II	Neurological deficit	15	3
III	Altered sensorium, easily arousable	9-14	10
IV	Deeply comatose	3-8	7

Discussion

The prevalence of stroke in TBM ranges from 15% to 67%, and when it does occur, it is typically linked to unfavourable outcomes[7]. Infarction patterns associated with TBM have been previously documented. Infarcts in the TB zone have been the subject of numerous research and case studies as a poor prognostic indicator. In our study, a worse prognosis was indicated by the subcortical location of infarcts in the tubercular zone. Hsieh and colleagues (1992) examined the location of infarcts in patients with TBM, as was previously mentioned. According to their observations, of 14 patients, 75% had an infarction in the "TB zone" and only 11% in the "Ischaemic zone." They observed that TB zone infarctions that were bilaterally symmetrical were more common in TBM (71%)[4]. A different study conducted in 2016 by Tai MLS *et al* found that 34 patients, or 67% of the 51 patients examined, had cerebral infarction. Using Hsieh's patterns to categorise the infarctions, 20 out of 34 patients (or 59%), had infarcts in both the "TB zone" and the "ischaemic zone." Conversely, infarcts in the "ischaemic zone" and "TB zone" were seen in 12 patients (35%) and 2 patients (6%), respectively[8]. In 2019, Soni *et al* examined 90 TBM patients. They discovered that cerebral infarcts occurred in 57.7% of the participants in the study. There were 35%, 13%, and 15% of these infarctions in the ischaemic, tubercular, and both zones, respectively. In TBM, there can be microscopic or macroscopic vascular involvement. Subcortical lacunar infarcts, large blood vessels occlusions, and various other presentations might result from the involvement of small, medium, and large vessels. It has been observed that MTB-induced direct vessel wall

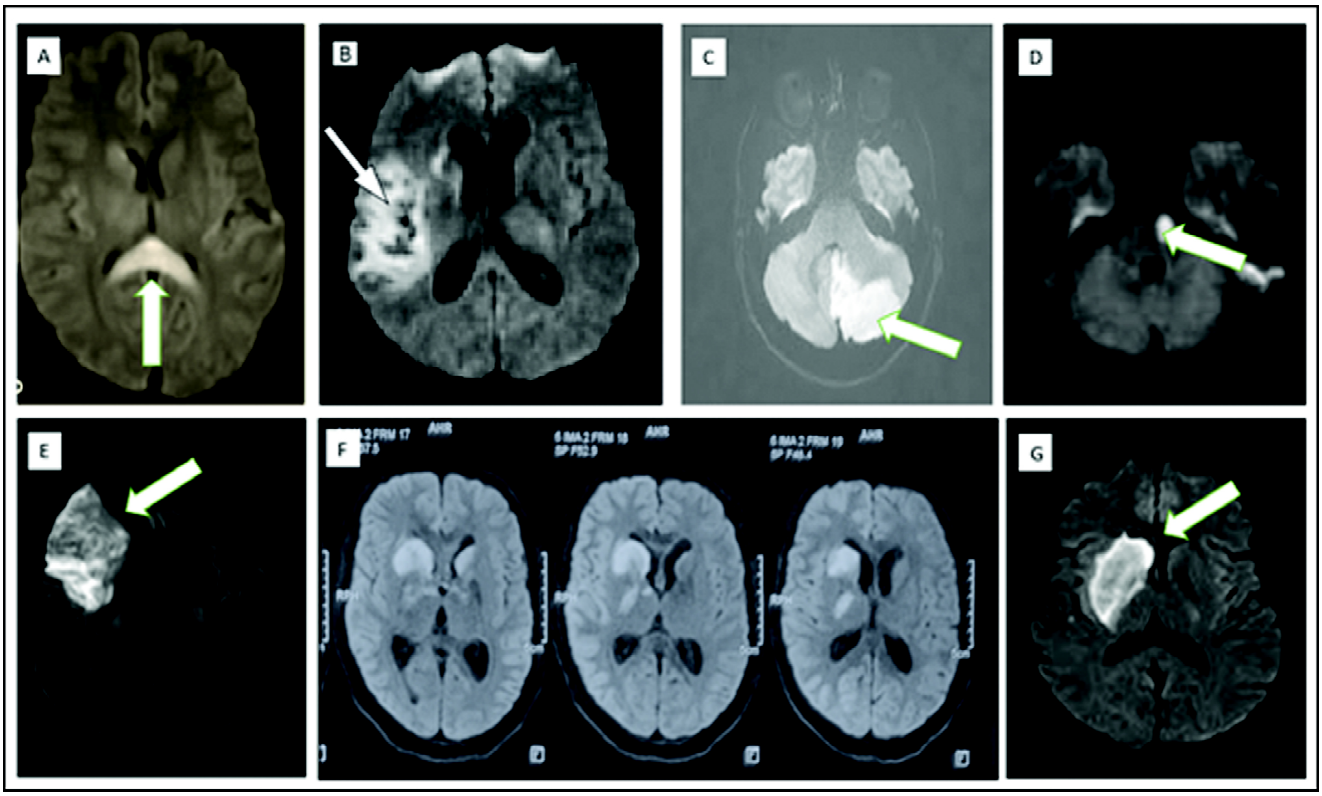

Fig. 1: *A. Splenium Infarct B. Right MCA Infarct with haemorrhagic transformation C. Left Cerebellar Infarct D. Left Pontine Infarct E. Right MCA Infarct F. Multiple Thalamoganglionic Infarcts G. Right Caudate and Putamen Infarcts.*

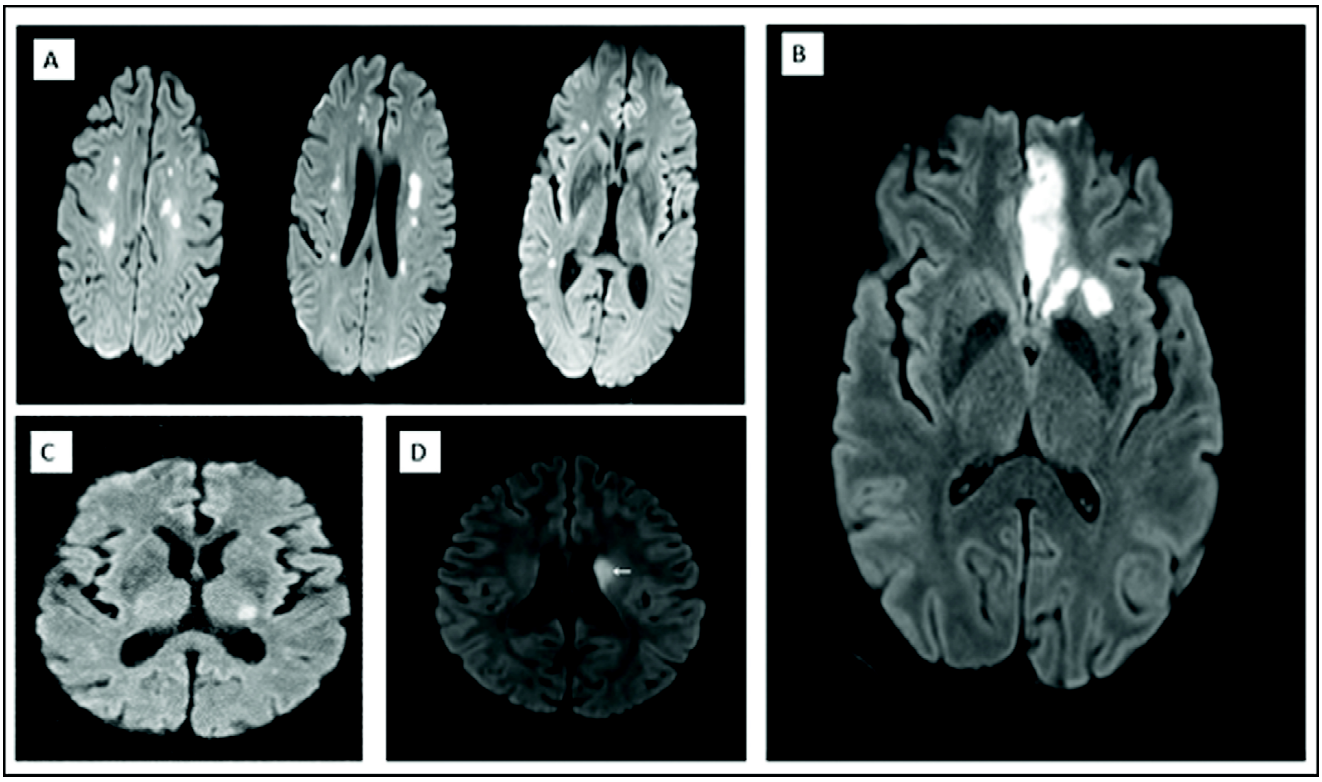

Fig. 2: *A. Multiple Infarcts in cortical and subcortical regions B. Infarcts in Left Basi-frontal and Basal Ganglia region C. Acute Infarct in Posterior Limb of Internal Capsule D. Acute Infarct in left Corona Radiata.*

damage, immunological vessel wall destruction in vasculitis, accelerated atherosclerosis, and finally thrombogenesis, can all play a role in the development of stroke in TBM patients. The same study found a negative correlation between the load of cerebral infarctions, grade of TBM, association with stroke, and overall severity of illness[9]. The most recent systematic review, which was done in 2022, included 71 studies totalling 2194 TBM patients who experienced a stroke. It was discovered that the expected probability of stroke in TBM was 0.30 (95% CI, 0.26 - 0.33). According to their analysis, the pooled proportions of poor outcomes and death were 0.51 and 0.22, respectively[10]. In our study, the subcortical location of infarcts in tubercular zone heralded poorer prognosis, Amongst 20 cases, 13 (43%) were subcortical, 3 out of 20 (15%) were cortical and 4 out of 20 (2%) were brainstem infarcts. Among those 10 out of 20 (50%) were in tubercular zone, 3 out of 20 (15%) were in ischemic zone and 14 out of 20 (70%) were in other areas. In another study on 40 patients with TBM, two-thirds of patients complicated by cerebral infarct had poor outcome despite adjunct dexamethasone therapy. Stroke was associated with poor outcome at 3 months of treatment but not at 6 months. This may be due to the high frequency of basal ganglia lacunar stroke which have better outcome compared to those with larger stroke[11]. In another study, like many other studies, the most frequent locations of infarction were internal capsule and basal ganglia. Stroke, especially the middle cerebral artery territory infarct, was associated with poor prognosis at 6 months. However, outcome of TBM was also found to be associated with many other factors such as cranial nerve and focal neurologic deficits, vision impairment, meningeal enhancement, advanced stage of TBM, low Glasgow coma scale score, baseline modified Rankin scale and high protein content of CSF[12]. In another study significant poor prognostic indicators (for patients who either deteriorated or died) among patients having stroke were presence of cranial nerve deficit, internal capsule infarct, centrum semiovale and brainstem infarcts. Infarcts in posterior cerebral circulation had poor prognosis[13]. There are no specific guidelines but various studies in the existing literature are in favour of antiplatelet agents as repurposing drug in infection-related ischaemia, cancer-related strokes etc. Asian studies also found efficacy and relative safety of antiplatelet agents in TBM related infarctions[14-18]. Efficacy of use of antiplatelet agents for mortality benefit cannot be completely estimated in the present study due to very small sample size, different infarction patterns and coexisting comorbidities. Although hypertension, diabetes mellitus, cardiomyopathies, etc., predispose individuals to ischaemic stroke, it is impossible to rule-out the confounding effect of these co-morbidities in onset of ischaemic cerebrovascular ischaemic events in

patients with TBM. However, this adds to the limitation of the present study.

Conclusion

The pattern of infarction in TBM can assist in forecasting outcomes. The variables which also add-in include immune status of patient (HIV reactive), TBM clinical grade, rapid deterioration, response to antitubercular treatment including resistance patterns as well as CSF findings. Large infarctions as well as multiple infarctions carry a poorer prognosis.

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