

Tuberculomas of the Brain with and without Associated Meningitis: A Cohort of 28 Cases Treated with Anti-Tuberculosis Drugs at a Tertiary Care Centre

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ABSTRACT

Introduction: Tuberculomas are an uncommon and serious form of tuberculosis due to the haematogenous spread of *Mycobacterium Tuberculosis*. The present study describes the clinical presentation, radiological findings and outcome of treatment with anti-tubercular drugs in 28 cases of intracranial tuberculoma from a tertiary care hospital.

Material and Methods: Consecutive adult cases with tuberculomas of brain with or without tubercular meningitis who were admitted at our center from May 2012 to November 2015 were included in the study. The diagnosis was based on clinical and radiological findings, histopathological features and response to anti-tuberculosis therapy.

Results: The study included 28 patients (male; 12, females; 16) with mean age of 37 years. 10 (36%) patients had single tuberculomas and 18 (64%) had multiple tuberculomas. 42.8% patients had associated tubercular meningitis. The commonest presenting features were headache (57%), vomiting (57%), fever (50%), altered sensorium (39.2%), cranial nerve palsies (42.8%), seizures (17.8%), and hemiparesis (25%). Patients with meningitis had higher incidence of fever, headache, papilledema multiple lesions and miliary tuberculomas.

Conclusion: Tuberculomas mainly affect young adults and may present either as an intracranial space occupying lesion or with features of associated tubercular meningitis. Majority of patients show good response to anti-tubercular therapy though the duration of treatment may be prolonged. Patients with persistent lesions beyond 2 years may be followed with periodic contrast imaging only.

Keywords: tuberculoma; intracranial tuberculoma; tubercular meningitis; anti-tubercular therapy.

are predominantly affected while in developed countries tuberculomas are more common in older patients.⁷

Tuberculomas are avascular, granulomatous intracranial space occupying lesions, with diameters ranging from about 0.1 to 10 cm. They can be single or multiple, and may be found anywhere in the brain parenchyma or rarely in the ventricles or along the meninges. The number of identified lesions per patient may range from one to 100 (or more). The brain tissue around the lesions is compressed and shows oedema and gliotic changes. The central areas of tuberculomas may show caseous necrosis.⁸ On computed tomography (CT), tuberculomas are characterized as hypo or hyperdense masses with round or lobulated margins. The lesions show intense homogenous or ring enhancement on contrast studies. The wall of the lesion is irregular with varying thickness. Perilesional edema is often seen.⁹ Magnetic resonance imaging (MRI) helps in differentiating whether tuberculoma is non-caseating, caseating with a solid centre, or caseating with a liquid centre.¹⁰ Tuberculomas are more common in frontal and parietal lobes, usually in parasagittal areas. Once diagnosed, the radiographical response of tuberculoma to therapy can generally be assessed within 4 to 6 weeks.

The CNS tuberculomas can mimic a number of other disease entities, and therefore it is important to be familiar with their clinical and radiologic features for timely and appropriate diagnosis. Clinical presentation and radiological findings are nonspecific, leading sometimes to misdiagnosis. Paradoxical appearance or enlargement of tuberculomas during treatment with antitubercular therapy has also been reported, and is considered to be an immunological phenomenon.¹¹ Anti-tubercular drugs are essential for the successful treatment of cerebral tuberculomas but there is no agreement regarding the duration of therapy. Surgical treatment is required for isolated cases only.¹² Study aimed to describe the clinical presentation, radiological findings and outcome of treatment with anti-tubercular drugs in 28 cases of intracranial tuberculoma from a tertiary care hospital.

MATERIAL AND METHODS

We prospectively studied 28 patients diagnosed with intracranial

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tuberculomas at our center between May 2012 and November 2015. The criteria for inclusion in the study was the presence of one or more contrast enhancing intracranial lesions detected on CT or MRI and the lesions were diagnosed as tuberculomas if one or more of the following criteria was met: 1) clinical and/or radiological response to ATT(n=23); 2) histopathological, microbiologic or radiological evidence of active tuberculosis either pulmonary or systemic (n = 10); 3) histopathologic features of granuloma formation in the biopsied/excised CNS lesion(n=01) and 4) presence of associated tubercular meningitis(n=12). Patients were followed periodically during their course of treatment. Variables studied included patient demographics, clinical features, laboratory investigations, radiologic findings, complications and outcome. MRI was performed on all patients.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software program version 20 with the help of descriptive statistics like mean and percentages.

RESULTS

The study included 28 patients (male; 12, females; 16). The mean age of was 37 years (range 15 to 65 years). Majority of the patients were between 15 and 40 years. About 75% patients had no prior history of tuberculosis or contact with a patient with tuberculosis. The median symptom duration prior to final diagnosis was 15 days. Clinical features and CSF parameters were suggestive of meningeal involvement (concomitant tuberculous meningitis) in 12(42.8%) patients. In 02 patients tuberculomas appeared on treatment of tubercular meningitis while in 02 patients tuberculomas appeared during the initial 2 months of therapy of pulmonary tuberculosis. Headache (62%) Fever (59%), vomiting, were the most common presenting symptoms, while 11(39.2%) patients had altered sensorium at presentation. Neck stiffness (36%), cranial nerve palsies (33%) and papilledema (19%) were the most common clinical signs. Abducens palsy was most commonly involved cranial nerve in 06 patients, 01 patient had optic nerve involvement and 02 had multiple cranial nerve palsies. Facial nerve was involved in 05 patients, however in 03 of them it was upper motor neuron type. 07 patients had associated pulmonary tuberculosis and 2 had disseminated tuberculosis. None of the patients was HIV positive. Laboratory documented anemia occurred in 05 (18%) patients. The erythrocyte sedimentation rate was recorded in only 18 patients and was found to be elevated in 09(50%) subjects.

Cerebrospinal fluid (CSF) analysis was performed in 20 patients, in 3 patients it was avoided due to fear of coning and in 5 patients it was felt unnecessary. 12 patients had CSF pleocytosis (82% with mononuclear predominance and 18% with neutrophilic predominance). Cerebrospinal fluid protein was elevated in 15 (75%) and glucose was low in 13 (65%) patients. PCR of CSF were positive for Mycobacterium tuberculosis in only 07 (41%) out of 17 patients. Histopathologic evaluation was performed in 1 patient in whom a stereotactic biopsy was done. Chest x-rays were performed in all subjects; features of active or healed tuberculosis were identified in 08 (28%) patients.

Ten patients were subjected to computed tomography while all

patients underwent contrast MRI scanning. 10 patients (36%) had a single tuberculoma while 18 had multiple tuberculomas. The location of lesions was supratentorial (70%), infratentorial (15%), or both (15%). Parietal lobe was most commonly involved cerebral lobe (50%), followed in order by frontal (20%), occipital (15%) and temporal lobes (15%). High parietal lobe was single most common site of involvement. None of the patients had a ventricular tuberculoma. The number of tuberculous lesions ranged from 1 to more than 50 and the diameter of the largest tuberculoma was 05 centimeters. 03 patients with associated meningitis had miliary tuberculomas. Associated hydrocephalus was present in two patients, again both had tubercular meningitis.

There were some important differences between the patients of meningitic and non-meningitic classes (Table 1). Higher number of patients in the meningitis group had fever, headache, papilledema, signs of meningeal irritation, multiple tuberculomas and military tuberculomas where as seizures and single tuberculoma were more common in the non-meningitic group.

All patients were given daily regimen of anti-tubercular therapy for a minimum of 12 months with 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol for initial 2 to 3 months, followed by isoniazid and rifampicin for 2 months). Ethambutol however was stopped in 02 patients who developed visual involvement. An initial course of steroids was given in 22(78.6%) patients, who included all patients with meningitis and 10 patients without meningitis who had features of raised intracranial pressure. Long-term follow up of 12 months or more was available for only 24 patients. 2 patients expired after initial improvement and 2 were lost to follow up. 01 patient had enlargement of tuberculoma with clinical worsening while on anti-tubercular therapy and responded to short course of intravenous steroids. A follow up contrast MRI scan was done at 12months in all patients. The lesions completely cleared on anti-tuberculosis treatment in the majority of survivors (20/24). The patients in which lesions persisted were followed with 6 monthly imaging for 30 months. 03 of the 04 patients with persistent lesions had associated meningitis at presentation which resolved on treatment. In 01 patient the lesion cleared after 18 months and in 03, the lesions decreased in size and number but persisted radiologically beyond 24 months on ATT. All these tuberculomas showed some contrast enhancement. ATT was stopped at 24 months and on follow up no worsening was noted up to 30 months. In all these 3 patients the persistent lesions were in the parietal lobe. 01 patient with hydrocephalus was shunted and 01 was managed conservatively. There was no clinical or radiological deterioration in any patient. Most common neurologic sequelae were seizures in 03 patients, hemiparesis in 03patients, unilateral vision loss in 01 patient and unilateral hearing loss 01 patient. A multiple regression analysis identified that the location, size and number of tuberculoma (Odds ratio 1.3, Confidence interval 95%, 0.7-2.1, P=0.15) and concomitant tuberculous meningitis (Odds ratio 1.2, 95 % confidence interval, 0.9-2.2, P=0.14) were not independent predictors of morbidity or mortality.

DISCUSSION

Tuberculomas are the most common infectious cause of central nervous system space-occupying lesions in developing countries

	With meningitis (n=12)	Without meningitis (n=16)	Total (n=28)
Mean age (years)	38	36.5	37
Male	05(41.6%)	07(43.8%)	12(42.8%)
Extra-CNS Tuberculosis	03(25%)	06(37.5%)	09(32%)
Symptoms			
Mean symptom duration (days)	20	12	15
fever	09(75%)	05(31.3%)	14(50%)
headache	10(83.3%)	06(37.5%)	16(57%)
vomiting	08(66.6%)	08(50%)	16(57%)
Altered sensorium	05(41.6%)	06(37.5%)	11(39.2%)
seizures	01(8.3%)	04(25%)	05(17.8%)
Signs			
Neck stiffness	11(91.7%)	01(6.3%)	12(42.8%)
facial nerve palsy	01(8.3%)	04(25%)	05(17.8%)
Ophthalmoparesis	04(33.3%)	02(12.5%)	06(21.4%)
Vision loss	01(8.3%)	-	01(3.6%)
hemiparesis	03(25%)	04(25%)	07(25%)
hemianopia	01(8.3%)	02(12.5%)	03(10.7%)
Papilledema	03(25%)	01(6.3)	04(14.2%)
Radiological Features			
Single tuberculoma	03(25%)	07(43.8%)	10(36%)
Miliary tuberculomas	03(25%)	-	03(10.7%)
Conglomerate tuberculomas	04(33.3%)	05(31.3%)	09(32%)
Hydrocephalus	02(16.6%)	-	02(7.1%)
Persistent lesions	03(25%)	01(6.3%)	04(14.2%)

Table-1: Clinical and radiological features of tuberculoma patients with and without concomitant meningitis.

where tuberculosis is endemic. Due to their nonspecific symptoms and radiological findings, intracranial tuberculomas remain a clinical challenge. Most of our patients were late adolescents and young adults. Tuberculomas like tubercular meningitis is a disease of young adults. Due to very low prevalence of HIV in our population, none of the patients was HIV positive. Fever, headache and neck stiffness was present more frequently in our patients than in previous series.^{13,14} This finding could reflect the higher incidence of concomitant tuberculous meningitis in our patients than others.^{5,15} Cranial nerve involvement was also seen more frequently in our study cohort, possibly due to the higher incidence of meningeal involvement.¹⁶ Also in 03 patients, facial palsy was of upper motor neuron type as part of hemiparesis.

Analysis of the cerebrospinal fluid in patients with cerebral tuberculomas may not always be possible due to presence of raised intracranial pressure which is a contraindication for lumbar puncture. Where spinal taps were performed, the patients displayed characteristic CSF features of lymphocytic pleocytosis, raised protein and hypoglycorrhachia, although 18% of subjects had neutrophilic CSF pleocytosis.¹⁷ Paradoxical appearance of tuberculomas while on antitubercular therapy for central nervous system or pulmonary tuberculosis was found in some cases in our cohort. This particular phenomenon is said to have an immunological basis and many such cases are published in literature.^{18,19}

64.3% patients in our cohort were having multiple CNS tuberculomas whereas according to literary reports, about 15% to

40% cases have more than one lesion.^{5,20} Occurrence of multiple lesions was associated with presence of meningitis which was higher in our series. Supratentorial location of lesions was more common in our series than in previous reports.^{5,21} Parietal and frontal lobes were predominantly involved as is reported most of the studies.²²

The grouping of tuberculomas into ones who have meningitis and those without associated meningitis has clinically both diagnostic and therapeutic significance. In patients with associated meningitis, the clinical presentation was dominated by meningitic features of fever headache and vomiting and neck stiffness ($p=0.042$). Papilledema was only present in the meningitic group. Also miliary tuberculomas were present only in the meningitic group. In patients without meningitis, seizures were more common ($p=0.02$). The presence of associated meningitis makes the evaluation and diagnosis of tuberculoma more reliable. Also the response to treatment can be better assessed in such patients. Conversely all patients with tubercular meningitis should undergo a contrast imaging to look for silent tuberculomas as their presence can modify the length of antitubercular therapy.^{11,18}

Earlier studies have highlighted that majority of the patients having tuberculomas can be effectively treated using drugs alone without surgical intervention.²³⁻²⁵ The recommended duration of anti-tubercular therapy for intracranial tuberculoma is 9 to 18 months; many cases however have received treatment for upto 30 months.²⁶⁻²⁸ In the present study, majority of the patients showed adequate response to one year course of ATT.

An initial course of steroids was added in patients with large lesions, raised intracranial pressure or associated meningitis. However some lesions respond to longer courses of therapy and some respond only partially. The possible explanation could be reduced blood supply in this watershed area which may limit the penetration of drugs at these sites. None of our patients with persistent tuberculomas after 24 months of anti-tubercular therapy worsened on follow up without treatment. Such patients may be followed with periodic imaging only as most such lesions do not show any new activity later although some authors suggest that treatment should be based on radiological response.²⁹ The prognosis of intracranial tuberculomas cannot be predicted from our study due to exclusion of patients who expired without a definitive diagnosis and lack of long-term follow up in few subjects. Mortality was at least 07% and could have been higher. The radiographic outcome of patients with intracranial tuberculomas is variable and does not always appear to correlate with treatment duration or clinical recovery. Tuberculomas may resolve, remain unchanged decrease or rarely increase in size after therapy.³⁰

Our study shows that tuberculomas are still an important type of intracranial space occupying lesions in developing countries like India and we should be well aware of the varied presentations and imaging features of this disease entity. The unpredictable response to drugs may be frustrating at times and the duration of therapy may be prolonged but most patients show good response to treatment.

CONCLUSION

Tuberculomas mainly affect young adults and may present either as an intracranial space occupying lesion or with features of associated tubercular meningitis. Majority of patients show good response to anti-tubercular therapy though the duration of treatment may be prolonged. Patients with persistent lesions beyond 2 years may be followed with periodic contrast imaging only.

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