A clinical study of CNS Tuberculomas

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Abstract
Thirty cases of CNS Tuberculomas were studied as suggested by the CT Scan Brain (Plain and Contrast) from 2007 to 2009, at Gandhi Medical College, Hyderabad, India. It was most common in second and third decade of life. The most common clinical presentation was convulsions. Routine investigations did not yield the diagnosis of tuberculosis. All patients were treated with Anti Tuberculous Treatment (ATT), for 6 months and oral steroids. ATT consisted of 2 months of intensive phase of HRZE and 4 months of continuation phase of HR. No surgical intervention was done. After completion of chemotherapy, they were followed up for 6 months. Repeat CT Scans were done, which showed clearance of all tuberculomas.

Key words
CNS Tuberculoma, ATT, Steroids.

Introduction
Tuberculosis, which is one of the oldest diseases known to affect humans, and is likely to have existed in prehominids, is a major cause of death worldwide. This disease is caused by acid fast bacilli belonging to mycobacterium tuberculosis [1]. The disease usually affects the lungs and in up to one-third of cases other organs are also involved. Central nervous system (CNS) tuberculosis presents mainly as tuberculosis meningitis, tuberculoma and rarely as tubercular brain abscess. Tuberculosis of the CNS is the most severe and life threatening form of the disease, especially in children. Thus early diagnosis and prompt anti-tubercular therapy (ATT) is important for optimal outcome.

Epidemiology
In places where tuberculosis is endemic like in India, intracranial tuberculomata comprise as many as 10 – 35% of intracranial space...
occupying lesions. But, in western countries this accounts for 0.2% only [2]. In many of the older series, tuberculomas were common in males, but in more recent series females have outnumbered males. Although tuberculomas can occur at any age, 86% of patients with intracranial tuberculoma are below the age of 25 years [2].

**Pathogenesis**
Intracranial tuberculoma is the result of haematogenous spread from a primary focus which is characteristically the lung. The focus may be quite small and therefore may not be visible on routine chest radiographs [3].

**Gross features**
Tuberculoma is a well circumscribed intraparenchymal mass that may be up to several centimeters (ranging from a few mm to 3-4 cm) in diameter causing significant mass effect. They are solitary or multiple, the ratio being 4:1.

They are hard, nodular, avascular and easy to shell out. There may be a connection to the adjacent dura, surrounding brain tissue is usually more oedematous. Oedema is occasionally so extensive and out of proportion to the size of tuberculoma itself, that it has been to constitute tuberculous oedematous encephalopathy.

**Microscopic features**
Tuberculoma of the brain, like a tuberculous granuloma occurring elsewhere in the body, is a product of mesodermal tissues – the meninges, vascular tree and microglia. Tuberculoma is a mass of granulation tissue made up of conglomerate of microscopic tubercles which consist of central zone of caseous necrosis surrounded by tuberculous granulation tissue consisting of numerous follicles made up of epitheloid cells (derived from altered mononuclear phagocytes), langhans cells and some lymphocytes.

Tubercles originate during episodes of bacillemia which are known to occur in chronic tuberculous infection, but the extent and rate of progression of this initial foci in tuberculomas is extremely variable and depend upon complex and incompletely understood factors of resistance [4].

**Anatomical distribution**
Tuberculoma may occur at any site within the cranium. It is usually located in the cerebellum and cerebral hemispheres, particularly in the frontoparietal region and basal ganglia and rarely in the corpus callosum, quadrigeminal system, cerebello-pontine angle and retro-orbital and supra-orbital region [5]. The ventricles of the brain have a special immunity against all kinds of infections and thus tuberculomas in these areas are extremely rare [6]. Supratentorial masses are said to occur more frequently in adults. And infratentorial masses are more frequent in children, but, the lesion can appear at any site [7-9].

**Clinical features**
In tuberculomas, one third of patients have evidence of tuberculosis elsewhere, a third of patients have history of previous tuberculosis or tuberculous contact and in one third it is completely unexpected [4]. Thus, a past history of tuberculosis is common and is of great value in differential diagnosis, absence does not exclude the diagnosis [2].

The clinical Manifestations are pleomorphic. The pleomorphism is mainly related to individual differences in size and topography of lesion. Symptoms and signs of raised intracranial tension (ICT) are usual features and constitute; Headache, Vomiting, Convulsions, Blurring of Vision, and Papilloedema.

The other clinical features depend on the site of tuberculoma. Somnolence occurs due to the periorbital oedema. Lateralising signs do occur when the lesion is in cerebrum or cerebellum. Convulsions are the most common clinical manifestation of intracranial tuberculoma.

Intracranial tuberculomas may already be present, even weeks or months before the clinical manifestations appear [2]. Tuberculoma at times (<10%) may be associated with tuberculous
meningitis. The signs and symptoms of meningitis may be present i.e., neck stiffness and fever.

In tuberculous meningitis, the appearance of new neurological signs and symptoms may indicate the development of cerebral tuberculoma which may occur in first two months of successful treatment. This is generally recognised as paradoxical response to therapy. The exact mechanism for this may be complex host-organism interactions [2].

**Diagnosis of CNS Tuberculoma**

**ESR:** There may be raised ESR.

**Tuberculin test** [10]: Tuberculin test is the means of estimating the prevalence of infection in a population, tuberculin sensitivity slowly wanes with time. The validity of tuberculin test, like all medical tests, is subject to variability. It may be useful in regions where tuberculosis is not endemic, but is not reliable indicator of active disease in developing countries, because of high incidence of positive results.

**Chest radiograph:** Only in one third of patients there may be evidence of pulmonary infection. The focus may be quite small, that at certain times, it may not be visible on radiographs [4].

**Sputum for AFB and sputum culture:** They are positive wherever there is associated active pulmonary tuberculosis.

**CSF analysis:** CSF examination has no role in diagnosing CNS tuberculosis. Isolated protein elevation was the most common abnormality. Smear for acid fast bacilli are not very sensitive and negative smears should not be taken as proof against diagnosis. PCR of CSF is relatively a new technique used for diagnosis of tuberculosis. The sensitivity of PCR is variable ranges from very low to high.

**CT scan brain:** Intense nodular or uniformly enhancing mass lesions may be seen

**MRI Brain:** CNS tuberculomas is seen as low intensity signal on T2 weighted MRI. Gadolinium enhanced T1weighted MRI showed rim enhancement.

**Histopathology:** When sufficient clinical data is present no histological confirmation is needed especially in developing countries like India.

**Differential diagnosis**

The differential diagnosis includes Neurocysticercosis, Brain Abscess, Syphilitic Gumma, Nocardiosis, Actinomycesis, Toxoplasmosis, Crypto Coccus Neoformans, Candida Albicans, Primary Brain Tumours, Metastatic Tumors.

**HIV and Tuberculosis**

Mycobacterium tuberculosis infection elicits the production of proinflammatory cytokines (INF-g) which upregulates the HIV infection. The HIV viremia is increased, which causes further decrease in CD4 counts leading to progression of HIV disease.

Extra pulmonary tuberculosis occurs when CD4 counts is < 300/mm³. CNS tuberculoma is one among the various CNS manifestations leading to seizures in HIV patients (in about 13.04%).

**Management**

Medical treatment of CNS Tuberculomas i.e. anti-tubercular treatment along with steroids is superior to any other treatment modalities. Treatment should be given for 6 months. Surgery is not recommended.

**Anti tubercular treatment**

ATT-consists of 4 drugs (INH- 5 mg/kg bodyweight, Rifampicin- 10 mg/kg body weight, Pyrazinamide-15-30 mg/kg bodyweight and Ethambutol- 15-25 mg/kg bodyweight) for first 2 months, followed by 2 drugs (INH- 5 mg/kg body weight, Rifampicin – 10 mg/kg bodyweight) for 4 months. The signs and symptoms will improve within one month. Treatment should be lengthened to 18 months, if
the patient does not receive pyrazinamide during the first two months therapy OR if cultures remain positive for extended periods OR signs and symptoms respond slowly. If the patient has multidrug resistance strain, therapy should be prolonged for 24 months. Patients with HIV also may need longer courses of therapy.

Role of steroids
Steroids improve symptom and seizure control and reduce Tuberculoma size and peri-lesional oedema. Eliminates paradoxical response. Dexamethasone-6-12 mg/d or Predinisone 60 – 80 mg/d for 3 months then tapered over 4 to 8 weeks. Symptoms recur if the steroids are tapered too soon or too fast.

The anti inflammatory properties of steroids are well known. It controls the systemic effects of TNF, IFN and other immune mediators. It reduces immune mediated tissue edema that occurs before and with treatment. It suppresses the clinical manifestations of hypersensitivity of tubercular proteins. It reduces the extent of fibrosis associated with healing process induced by ATT.

Seizures are commonly associated with CNS tuberculomas and resolve after treatment with ATT along with steroids. There is no role of antiepileptic drugs.

Prognosis
Almost all patients are cured. The outcome is improves when therapy is started early in the disease course. However regular follow up and strict compliance are very important.

Materials and methods
Thirty patients of CNS tuberculomas (CT scan proved) were included in the study, from 2007 to 2009, at Gandhi Medical College, Hyderabad, India.

Diagnostic criteria
Consistent signs and symptoms, and CT scan showing round single or multiple uniform hyper dense lesions, with ring enhancement on contrast study, with or without surrounding oedema and one of the following.

- History of tuberculosis in the family
- Chest x-ray consistent with tuberculous infection of the lungs.
- Mycobacterium tuberculosis detected on PCR, or isolation of Mycobacterium tuberculosis from CSF, or gastric aspirate on acid fast stain or culture.

A detailed history was taken from the patient, and from the patient’s relatives if the patient is not cooperative or in altered sensorium. History included the age, occupation, address and patient’s symptoms. History of the past or present pulmonary or extra pulmonary infections is enquired. History of any head injury is also obtained. History of tuberculosis in the family and any history of exposure is also obtained. History of BCG vaccination and of any drug allergy is obtained.

A detailed CNS examination was done. Other systems examination, especially of the respiratory system was done to find out the primary focus of infection. All patients were subjected to routine biochemical investigations and liver function tests, renal function tests, HIV I and HIV II, sputum for AFB, X-ray chest, CT Scan of the Brain, Fundus Examination, CSF for biochemical analysis, microbiological analysis, cytology, and PCR for mycobacterium tuberculosis.

All patients were kept on anti tuberculosis treatment for 6 months and oral steroids i.e., Prednisolone dose adjusted according to body weight. Along with the specific treatment, symptomatic treatment was also given wherever it necessitated. No surgical procedures were done. Repeat CT Scans were done on completion of treatment.

Results
In the present series diagnosis was based on clinical and CT imaging criteria. In the presence
of consistent clinical and CT imaging, the clinical history is obtained. Family history of tuberculosis is sought, but seldom was positive in any of the patients. An effort was made to exclude other lesions which can mimic CNS tuberculoma.

30 patients satisfying the diagnostic criteria and clinical presentation were studied. It was more common in the age group of 21-40 years group. Male to female ratio was 19:11.

Symptomology
Of the 30 patients, 20 patients presented with convulsions, among whom 7 presented with generalised tonic clonic seizures. 12 patients had associated features of raised ICT like headache and vomiting. There were no focal neurological deficits on clinical examination, except one, who had neck stiffness. 2 patients had altered sensorium of whom one patient was HIV positive. 7 patients had convulsions and hemiparesis. 1 patient presented with only hemiparesis without any associated convulsions or other features. 1 patient presented with headache and vomiting, 1 patient presented with only headache. Among the 30, 2 patients had associated signs of meningeal irritation like neck stiffness. The most common clinical presentation was convulsions associated with other features of raised ICT followed by hemiparesis followed by headache.

Four patients had a past history of pulmonary tuberculosis. One patient had active pulmonary tuberculosis. BCG vaccination history and scar is present in 21 patients only. Occurrence of tuberculoma in them also suggests that the protective value of BCG wanes with duration. ESR was raised in patients, of whom 1 had active pulmonary tuberculosis and other had associated tuberculous meningitis.

Retroviral disease (HIV positive) is present in 2 patients. Sputum for AFB was positive in only one patient i.e., who had active pulmonary tuberculosis, rest of them were all negative for AFB.

X-ray chest was normal in all except in 3 patients. Of these 1 with active pulmonary tuberculosis had patchy consolidation, 1 had fibrosis left upper zone and 1 had calcific lesions in the upper zone.

In the present series CSF analysis is done in all except 2 patients who had mild papilloedema. CSF analysis of two patients showed increase in cell count with predominant lymphocytes and marked protein elevation. They are the patients with associated TB meningitis. Rest of the individuals had normal CSF biochemical analysis, except for mild protein elevation in 3 patients. All had normal cell count.

PCR for mycobacterium tuberculosis, a relatively new technique for rapid diagnosis of tuberculosis is done in 6 patients and among them only 1 patient is positive for mycobacterium tuberculosis implying that the sensitivity of it is variable ranging from low to high.

CT scan
28 patients showed single ring enhancing lesions with perilesional oedema. 2 had multiple tuberculomas.

All patients were treated with ATT - 2 months of intensive phase consisting of HRZE and 4 months of HR. Prednisolone at a dose of 1 mg/kg body weight is given for 3 months and then tapered over next 4 - 8 weeks. They were followed up for 6 months.

Two patients died. One patient was HIV positive, and he died within 15 days of hospital admission. Other patient died of subdural hematoma, due to head injury.

All patients improved within 1 month of starting of treatment as assessed by the pre and post treatment disability level, suggesting that CNS tuberculoma do not require surgery and respond well to anti-tuberculous therapy and steroids. If diagnosed early and treated promptly all of them are curable.
Conclusion
CNS Tuberculoma is common in young adults. Most of them present with convulsions. Only very few have past history of Pulmonary Tuberculosis. CSF analysis and PCR are not conclusive for CNS Tuberculoma. CT scan is the most important neuroimaging technique for diagnosing CNS Tuberculoma. Standard short term regime of ATT with 2HRZE + 4HR with steroids has proven effective.

References