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Review Article

Dilemmas in the diagnosis and treatment of intracranial tuberculomas

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ABSTRACT

Tuberculosis (TB) remains a major public health problem across the globe. A common form of extrapulmonary TB (EPTB) with high mortality and morbidity is neuro TB or tuberculosis of the nervous system. The management of brain TB remains a big challenge due to the lack of specific diagnostic tools and appropriate treatment guidelines. In this context, this manuscript discusses clinical, diagnostic and treatment dilemmas in the management of intracranial tuberculomas. Brain tuberculoma may occur at any site within the cranium, no part of the brain substance or ventricular surface being exempt. The diagnosis of tuberculoma is often based on imaging techniques such as CT brain and MRI/MRS, even though, no radiological feature is confirmative or specific for tuberculoma. In this regard, a promising development is a new MRS marker that is currently being assessed. Based on a single peak at 3.8 ppm, it may differentiate tuberculoma from tumors. This lack of diagnostic tools results in an increased cost to patient on average three times that for pulmonary TB. The increase in cost stems from multiple laboratory tests with diagnosis often achieved only after biopsy. As for treatment, the choice of drugs for treatment and the duration for treatment is also not clearly understood. The recent increase in drug resistant TB adds to the problem. The possible pitfalls during treatment include paradoxical response, hyponatremia, and development of hydrocephalus. These and other treatment related complications require follow-up and monitoring. A fraction of patients may even require emergency surgery due to increased intracranial tension. This can further increase cost to the patient and family. Overall, there is a need for continued efforts to develop new diagnostic tools for brain TB. Until such tools are available, high degree of awareness among treatment providers is necessary to avoid delays in diagnosis and increased costs.

1. Introduction

Tuberculosis (TB) remains a significant infectious disease with an estimated 10.4 million new cases and 1.8 million deaths in 2016 globally [1]. Neuro tuberculosis or tuberculosis of the nervous system is one of the common forms of extrapulmonary TB associated with a high mortality and morbidity [2]. The commonest presentation of neuro tuberculosis is tuberculous meningitis (TBM). The other forms are tuberculoma of the brain, encephalopathy, brain abscess, Pott's paraplegia, meningoencephalitis, arteritis, and arachnoiditis [3]. Neuro TB, a disease caused by Mycobacterium TB is highly devastating, and accounts for approximately 1% of all cases of TB and has a deadly link with AIDS [2,4]. People infected with both HIV and the tubercle bacilli have a 25 fold increased risk of developing potentially fatal disease. There are no clear cut guidelines in the diagnosis and treatment of this severe form of tuberculosis.

The diagnostic dilemma includes non-specific vague clinical picture such as altered sensorium, Seizures, headache and focal neurological deficits. The diagnosis of tuberculoma is often with the help of imaging techniques such as CT brain and MRI, even though no radiological picture is confirmative or specific for tuberculoma. Tuberculoma may occur at any site within the cranium, no part of the brain substance or ventricular surface being exempt. The tuberculomas are more common infratentorially in children and supratentorially in adults. The lesions are usually located in the subcortical region but occasionally present on the surface of the brain. The ratio of supratentorial to infratentorial tuberculoma was 3:4. Patients in whom TBM preceded the formation of a tuberculoma often had cerebellar lesion, or multiple deep-seated lesions in the basal ganglia and brainstem, suggestive of severe form of miliary spread.

The treatment dilemma includes selection and usage of appropriate Anti TB drugs, diagnosis and management of paradoxical reactions including IRIS, management of Brain Oedema, hydrocephalus, Seizures, Psychosis and Vasculitis. The recent increase in drug resistant TB adds

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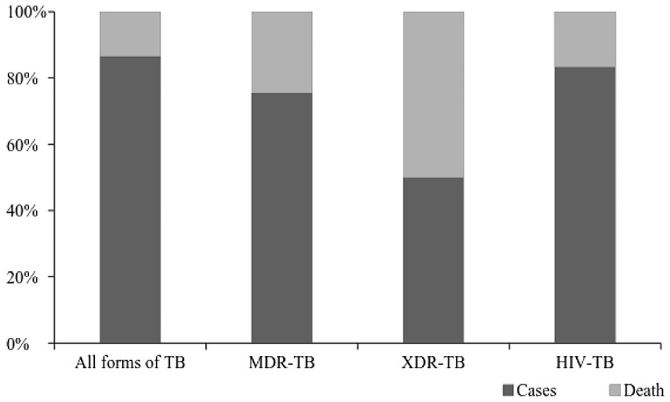

Fig. 1. The estimates of various forms of TB globally for the year 2016.

to the problem of selection of anti TB drugs. This paper discusses the clinical, diagnostic and treatment dilemmas in the management of Intracranial Tuberculomas.

2. Epidemiology of tuberculosis

Tuberculosis is one of the world's top health challenges. More than 2.4 billion people equal to a one third of the world's population are infected with TB. It was estimated that each day, 26,000 new cases occur globally and > 4000 die of TB. Despite the best efforts to diagnose and treat TB, epidemiologically there is an unacceptable low rate of decline in incidence each year. Fig. 1 describes the estimates of global TB for the year 2016 including drug resistant TB and HIV associated TB [1]. India has the highest TB burden globally accounting for one fourth of the global incidence [1]. TB is a multisystem disease with myriad presentations and manifestations which can affect any organ or tissue. Extra-pulmonary tuberculosis (EPTB) is relatively neglected and increasing in incidence, in comparison to pulmonary tuberculosis (PTB) in low-burden settings and poses specific diagnostic and management challenges. Neuro TB accounts for approximately 1% of all cases of TB [2].

3. Neuro TB: clinical dilemmas

Neuro TB is essentially a pauci-bacillary condition, occurring in all age groups with protean clinical manifestations that mimics other inflammatory and neoplastic conditions. The clinical manifestations depend on the host immunity and the site of involvement. The clinical presentations vary according to the geographic location of the tuberculoma(s), population groups and a wide variety of host factors [5]. Neuro TB may manifest as single or multiple granuloma (tuberculoma), leptomeningitis, cranial nerve palsies including optochiasmatic involvement, hydrocephalus, vasculitis leading to infarcts of deep gray nuclei and deep white matter, and focal abscesses and hypopituitarism.

Associated TB meningitis or pulmonary TB or lymph node TB may help in the diagnosis of brain tuberculoma. Tuberculoma simulates a tumor (Space Occupying Lesion) in the brain and thus the symptomatology of a tuberculoma varies with its anatomical location. The commonest location is frontal or parietal. There are no specific signs or symptoms which will indicate that the patient has a tuberculoma. It generally presents as a slow growing intracranial space occupying lesion (SOL). Headache vomiting convulsions, focal neurological deficit and poor vision are the main presenting symptoms and on examination, these cases may present only with signs of increased intracranial tension (ICT) with or without neurological deficit. The constitutional symptoms and signs of inflammatory lesions are uncommon. Unlike patients with TBM those with tuberculoma often look clinically well preserved. A history of fever is recorded in no more than 10–20% of cases. Concomitant or coexisting tuberculosis elsewhere in the body helps in the diagnosis.

Focal seizures are frequently the first symptom to appear. Symptoms and signs of ICT are seen in large and multiple tuberculomata. Focal neurological deficit depending on the site of lesion is observed in 50% of cases. False localising signs were observed in cerebellar tuberculoma.

4. Diagnostic dilemma

Following clinical diagnosis, cerebrospinal fluid examination is often normal and a biopsy from the lesion though the diagnosis of choice, is technically too demanding and not feasible in most of the times. So the clinicians are in a great dilemma as regard to a confidant diagnosis of tuberculoma of the brain.

4.1. Role of imaging

4.1.1. Computed tomography scan (CT scan)

In the early 1980s imaging techniques like CT scan and MRI brought a breakthrough in the early diagnosis and treatment of brain tuberculoma. Many a surgical procedures have been avoided due to timely diagnosis by these two techniques. Serial CT scans have also been found to be valuable in the follow-up of patients. CT and MRI can demonstrate tuberculomas and signs of meningeal enhancement as well as complications of TBM such as hydrocephalus and infarction. Tuberculomas typically appear as contrast enhancing ring lesions, solitary or multiple with surrounding oedema [6]. Tuberculomas also presents as lesions with hypoattenuation, with little or no enhancement; homogeneously enhancing lesions (non caseating granulomas), or with a central calcific focus, that form a target like lesion, and miliary pattern with multiple tiny nodules scattered throughout the brain. All these lesions are surrounded by hypoattenuating edema. The morphology of the CT scan lesion appears to depend on the stage of evolution of the disease and the patient's immunological status.

However none of these CT scan appearances are specific for diagnosis of tuberculoma. Even though CT scan of brain is the primary investigation of choice and is very sensitive (100%) in detecting ring-enhancing lesions, it lacks specificity and has got a pretty low negative predictive value (31%) [7,8]. This clearly emphasizes the limitation of CT scan of the brain with contrast as the sole diagnostic modality of intracranial tuberculoma. It is important to note that cryptococcal meningitis, viral encephalitis, sarcoidosis, meningieal metastasis and lymphoma may also have similar radiological findings. CT and MRI cannot reliably differentiate tuberculoma from other causes of ring enhancing lesions [9,10]. Thus CT imaging alone is inadequate and other methods are needed to confirm the diagnosis [11]. Fig. 2 shows the various CT appearances of brain tuberculoma.

The CT criteria for diagnosing tuberculoma based only on CT morphology is not uniform and there is no uniform policy or consensus of opinion. With these limitations one may state that the incidence of probable tuberculomas proved by CT has been on the increase.

4.1.2. Magnetic resonance imaging (MRI)

MRI with gadolinium enhancement is the preferred method of initial investigation (Fig. 3). It is considered as most sensitive test for detecting the extent of leptomeningeal disease and in detecting parenchymal abnormalities and hydrocephalus. However MRI may miss early meningitis and early infarcts. Like CT imaging no MRI findings are pathognomonic for brain tuberculoma. There is no radiation burden when MRI is used for imaging, in contrast to CT imaging. MRI image quality is superior to CT images. Tuberculomas frequently show varied types of enhancement, including irregular shapes, ring-like shapes, open rings and lobular patterns. By MRI a non-caseating tuberculoma may appear hyperintense on T2-weighted and slightly hypointense on T1-weighted images. A caseating tuberculoma appears iso- to hypointense on both T1-weighted and T2-weighted images, with an iso- to hyperintense rim on T2-weighted images. The diameter of the ring