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Changes in the diagnosis and neurosurgical management of brain tuberculosis since 1982: Documenting a personal experience

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Vedantam Rajshekhar

Senior Consultant Neurosurgeon, CMC Chittoor Campus, Chittoor, Andhra Pradesh, India

Introduction

There have been tremendous changes in the practice of neurosurgery since the author began his neurosurgery journey in 1982. These include transformational changes such as the introduction of computerized tomography (CT) and magnetic resonance imaging (MRI) and the widespread use of the operating microscope. During the same period of over 40 years, a neurosurgeon practicing in India would have also witnessed several changes in the diagnosis and management of patients with tuberculosis affecting the brain (brain tuberculosis). Some of these changes were consequent to the advances in neuro-imaging (CT/MRI) and neurosurgical techniques such as stereotactic instrumentation while others can be attributed to advances in other scientific disciplines such as immuno-diagnostics and therapeutics.

This chapter is aimed at documenting these changes from the author's perspective. It is essentially a narration of personal observations backed by the author's peer-reviewed publications in the field of brain tuberculosis. The author admits that a major limitation of this exercise is that this chapter is not a comprehensive review of the advances in the diagnosis and management of patients with brain tuberculosis over the last forty years. Consequently, several major publications in the field might not be cited in the chapter. Finally, the focus of the author's work, understandably, is on aspects of brain tuberculosis which engage a neurosurgeon such as brain tuberculomas and tuberculous meningitis (TBM) with hydrocephalus (TBMH).

Empiric therapy versus histological verification for brain tuberculomas

Brain tuberculosis (TBM and tuberculoma) was a very common disease in Indian patients in the 1960s and 1970s and some large surgical series reported that nearly a quarter of all pathologically verified brain masses were tuberculomas. [1] A pre-operative diagnosis of tuberculoma was challenging in the pre-CT era. Empirical anti-tuberculous therapy (ATT) for a few weeks or months for any relatively avascular brain mass on cerebral angiography which did not need early surgery for raised intracranial pressure (ICP), was standard practice amongst Indian neurosurgeons. This practice continued even after the CT scan became available in India in 1981. This strategy was especially common for contrast enhancing small masses in eloquent regions such as the sensori-motor cortex ("microtuberculomas" [2]) and relatively inaccessible deep seated masses (both contrast enhancing and non-enhancing).

The introduction of a CT guided stereotactic system in the author's department, in 1986, allowed safe and minimally invasive access (most often under local analgesia and therefore feasible even in patients unfit for general anesthesia) and histological verification of masses located in eloquent regions and deep seated masses.[3]

One of the major discoveries made with the help of stereotactic guidance and histological study of small enhancing masses located in the sensori-motor cortical regions was that of the Solitary Cysticercus Granuloma (SCG). [4] These lesions were initially treated with empiric ATT in the belief that these were "microtuberculomas". They were later serendipitously found to resolve spontaneously without ATT. [5] This discovery resulted in the enigma of "disappearing CT lesions", whose etiology confounded clinicians and radiologists in India and elsewhere. Once we documented that most of these lesions were SCG, we evolved diagnostic criteria for SCG which helped in distinguishing SCG from small brain tuberculomas in patients presenting with seizures. [6] These diagnostic criteria have been shown in a prospective study to have high sensitivity, specificity, positive and negative predictive values. [7]

Not only the "microtuberculomas" but several other "tuberculomas" suspected on CT and being treated unsuccessfully with empiric ATT, were later shown through histological verification to be tumours such as lymphomas, gliomas, metastases and even meningiomas. [3] We advocated histological verification before initiating ATT even for suspected tuberculomas in hitherto "surgically inaccessible" regions such as the brain stem.

In a prospective study we documented that a CT based diagnosis of brain tuberculoma had a poor positive predictive value of 33.3%. [8] A point often ignored is that the positive

predictive value of a diagnostic test is dependent on the pre-test probability of the disease for which the test is being done. The pre-test probability is nothing but the prevalence of the disease. So with the prevalence of brain tuberculomas coming down significantly from around 25% to less than 5% of all brain masses by the 1990s, the positive predictive value of CT scan in correctly diagnosing a brain tuberculoma is understandably very low. Our study showed that if "tuberculoma" is considered in the top two differential diagnoses for a brain mass seen on a contrast CT scan, the likelihood of that diagnosis being accurate is only 1 in 3. In other words, for every 3 patients diagnosed to have a "tuberculoma" on a CT scan, only in 1 will it be correct and in 2 it will be erroneous.

The introduction of the MRI in the early 1990s improved the ability to accurately predict the diagnosis of brain tuberculomas. There are some radiologists who believe that MR based diagnosis of a tuberculoma is almost always accurate. But even with advanced MR techniques such as magnetic resonance spectroscopy (MRS) the author and several other Indian neurosurgeons have experienced many patients in whom a brain neoplasm has been mis-diagnosed as a tuberculoma or vice versa where a tuberculoma has been mis-diagnosed as a neoplasm.

So, is there a role for empiric therapy for a "brain tuberculoma" diagnosed on MR imaging? While in general empiric ATT should be avoided, selected cases have been managed successfully by the author using empiric ATT. These patients have had masses which had the characteristic features of a tuberculoma on MR imaging and were not causing severe raised ICP. Most importantly, the patients were assessed for their ability (financial and logistical) to come for a review within 6 weeks of initiation of ATT to look for a clinical and imaging response.

Limitations of stereotactic biopsy for tuberculomas

Although, stereotactic biopsy can exclude a neoplasm in a patient with tuberculoma, a definitive diagnosis of tuberculoma may be elusive in several patients. Most often, the pathologist is only able to provide a diagnosis of "chronic inflammation and gliosis". The biopsied tissue is unlikely to reveal "necrotizing granulomatous inflammation" and "Langhan's giant cells" which are the hallmarks of a tuberculoma. In a series of 7 patients with tuberculoma in whom we did a stereotactic biopsy, only in 2 (28.6%) was a definite diagnosis confirmed. One of these patients had AFB in the tissue. [9] Other authors had a better success rate of nearly 85% in making a definitive diagnosis of tuberculomas on stereotactic biopsy samples. [10] The main reason for the inability to provide a definitie diagnosis is the tiny amount of tissues obtained through a stereotactic biopsy. Another reason is that the lesion is the firm to hard consistency of tuberculoma which prevents the blunt stereotactic probes from penetrating the outer thick "capsule" of the tuberculoma. The tissue that is retrieved is therefore usually from the periphery of the tuberculoma or the brain matter just adjacent to the tuberculoma which is likely to only show features of inflammation and not the granulomatous inflammation and necrosis typical of a tuberculoma.

Cultures of the biopsied tissue for acid fast bacilli (AFB) are also unlikely to have a positive yield due to two reasons. One reason is that a brain tuberculoma is a pauci-bacillary disease with a positive culture noted in <35% even when a tuberculoma is excised and large pieces of it are subject to culture. [11] The second reason is again the fact that in most cases, the biopsied tissue is from the periphery of the tuberculoma whereas the bacilli are more likely to be at the centre of the tuberculoma with the periphery being composed of the fibrosis and other inflammatory reaction from the host.

Surgery for brain tuberculomas

Surgery for brain tuberculomas is considered for any one or more of the following reasons: i. to obtain a definite diagnosis or tissue for culture studies in a case strongly suspected to be a tuberculoma but which is not responding to conventional ATT (? multi-drug resistant; MDR TB); ii. to reduce raised ICP which threatens life or vision; and, iii. for an unsuspected tuberculoma (misdiagnosed on imaging as a neoplasm). [12]

While stereotactic biopsy may suffice to obtain a diagnosis, for other indications including when culture studies are desired, a craniotomy is necessary. With a craniotomy, varying degrees of resection (biopsy, partial or gross total) of a suspected tuberculoma can be

Table 1: Take home messages

Diagnosing brain tuberculomas

- CT or MRI based diagnosis of brain tuberculoma can be erroneous. Therefore, ideally histological verification should be sought for all brain masses either through microsurgical excision or through stereotactic biopsy.
- For small enhancing lesions in patients presenting with seizures, application of the diagnostic criteria for SCG can distinguish patients with SCG from those with tuberculomas, although a follow up imaging is mandatory to confirm the diagnosis of SCG.
- Empiric therapy should be restricted to selected patients with typical features of a tuberculoma on MR imaging and MRS, who are likely to be compliant with follow up. Early clinical and imaging follow up should be performed by 6 to 8 weeks after initiation of empiric therapy.

Stereotactic biopsy for brain tuberculomas

- Stereotactic biopsies may not yield a definitive diagnosis of tuberculoma in an substantial proportion of definite cases; in the rest only a diagnosis of “inflammatory” lesion is obtained.
- The decision to start ATT, following a stereotactic biopsy in patients without a definite diagnosis of tuberculoma, is made when the clinical and imaging features are strongly suggestive of a tuberculoma.

Surgery for brain tuberculomas

- Surgery for a brain tuberculoma is done for different indications.
- While a safe gross total resection of a tuberculoma is desirable especially if the indication for surgery is to relieve raised ICP, leaving a small or large residue is generally inconsequential as this can be safely and effectively treated with adjunct ATT.

Prognosis for brain tuberculomas

- Mortality rates for patients with brain tuberculomas have reduced dramatically and surgery for them is very safe with very low mortality rates of <1%.
- Morbidity rates in the form of residual deficits and seizures may be seen in nearly 20% of patients.

Surgery for tuberculous meningitis with hydrocephalus (TBMH)

- Vellore grading at the time of surgery is a reliable predictor of outcome following shunt surgery or ETV in patients with TBMH.
- Patients in Vellore grades 1 to 4a can undergo shunt surgery/ETV at the earliest.
- Shunt surgery/ETV in patients in Vellore grade 4b should be considered only in those who respond to a period of EVD (72 hours); outcome of surgery in those who do not respond to EVD is likely to be very poor.
- ETV should performed by experienced surgeons and is likely to be more successful in those who have received ATT for 4 weeks rather than in those with acute TBM of <4 weeks duration. ETV has not been shown to be more successful than VP shunt in randomized controlled trials.
- Long-term follow up is needed to determine the outcome of VP shunt or ETV in patients with TBMH as several patients succumb to the disease many months or years after the surgery. Overall nearly 40% of patients undergoing surgery may die on long-term follow up.

Unusual presentations of brain tuberculosis

- Tuberculosis should continue to be considered as one of the differential diagnosis for brain and skull base masses even when the location seems unusual for a tuberculoma.

Trends in brain and spine tuberculosis

- The prevalence of brain tuberculosis seems to be decreasing.
- However, spine TB seems to be becoming more prevalent.
- MDR TB also seems to be increasing.

Duration of anti-tuberculous therapy (ATT) for brain tuberculosis

- There is no consensus on the duration of ATT that is appropriate for patients with TBM and brain tuberculomas.
- A minimum of 12 months of ATT is recommended for patients with TBM.
- For patients with brain tuberculomas with residual disease after surgical intervention or being treated empirically, the minimum duration should be 12 months.
- The duration of ATT in patients with brain tuberculoma/s should be guided by the findings on neuro-imaging studies. Small contrast enhancing residues of 1 cm or less can be left alone without treatment but need follow up with repeat imaging 6 months later.
- There may be a case for stopping ATT at around 9 months in patients in whom a solitary brain tuberculoma has been totally excised (documented by early postoperative imaging) and if there is no recurrence on neuro-imaging done at 9 months.
- For MDR/XDR TB the duration of ATT and the composition of drugs used for the ATT will need modification.

done. Ideally, a total but safe resection of a tuberculoma should be done especially if the aim of surgery is to relieve raised ICP. But in most patients with a tuberculoma the extent of resection is not a determinant of outcome (unlike for a brain tumour) since ATT is available as an effective adjunct therapy after the surgical resection. Obviously, a total resection should only be considered for tuberculomas which are in non-eloquent regions. A major advantage of a total resection is that there is no residue left for recurrence and possibly the duration of adjuvant therapy may be reduced. This will be dealt with in a later section. However, even a remote possibility of causing neurological morbidity should deter one from aggressively seeking a total resection.

Outcomes in patients with brain tuberculomas

By the early 1980s the outcomes for patients with brain tuberculomas was generally good. Surgical mortality was greatly reduced and close to <5%. But Mathai and Chandy [1] reported in 1966, that the mortality in these patients was 27% prior to 1960 which had dropped to 16% after 1960. One of the reasons for the high mortality, besides the overall high surgical mortality in that era, was the lack of effective ATT. Some of these patients possibly developed fulminant TBM after the surgery due to dissemination of the disease through the CSF during surgery. But with the availability of isoniazid which readily crosses the blood brain barrier, this is not a major concern anymore. The author from his experience of managing several hundred patients with brain tuberculomas will guess that the mortality rate for patients with brain tuberculomas is <1%. However, those with tuberculomas with MDR or extremely drug resistant (XDR) bacilli might have higher mortality rates.

An estimated 20% of patients with brain tuberculomas might have residual deficits or chronic epilepsy even after the tuberculoma has resolved. [12]

TBM with hydrocephalus (TBMH)

Shunt surgery

Bhagwati proposed the use of ventriculo-atrial (VA) shunt for TBMH in 1971.[13] VA shunts were routinely being used in the author's department till around 1985 when VA shunts were replaced with ventriculo-peritoneal (VP) shunts. The shift from VA to VP shunts was for shunts in general and not specifically for shunts done for TBMH. The two main reasons for this change were the risk of shunt nephritis which is a unique complication associated with VA shunt and the higher risk of bacteremia with VA shunt compared to VP shunt as the shunt tube is directly in contact with the blood stream.

By the mid-1980s it was evident that the results of shunt surgery were varied with some patients achieving very good results while others, especially the sicker patients, having a poor outcome with high rates of mortality and morbidity. We also noticed that several sick children with altered sensorium who we shunted ended up having shunt infection, multiple shunt revisions and skin erosions over the shunt components and ultimately had to have their shunts removed. We wondered about the futility of performing shunt surgery in this category of patients. There was also no literature on the long term results of shunt surgery in patients with TBMH.

In an effort to identify risk factors for poor long-term outcome in patients who underwent shunt surgery for TBMH, we embarked on a retrospective study. [14] Our retrospective study in a large cohort of 114 patients with TBMH who had shunt surgery between 1975 and 1986, showed that at a follow up ranging from 6 months to 13 years (mean, 45.6 months), 48 (42.1%) patients had died. Several patients died many months to years after the surgery. This study established the fact that the long-term outcome can be poor even if the patient is discharged in a good condition following the shunt surgery. Indeed, 33.8% of patients who had a normal sensorium before surgery died on long-term follow up. [14]

The second and most important finding of this study was that of several predictors of outcome (age, CSF cells, CSF protein, number of shunt revisions, need for bilateral shunts, duration of altered sensorium and admission grade) only the grade at admission (1 to 4, 1 and 2 had normal sensorium, 3 and 4 had altered sensorium) was significantly associated with final outcome determined on the Glasgow Outcome Scale. Patients in the worst grade (grade 4) had a dismal outcome with all 7 patients succumbing (100% mortality).

Based on the findings of our study, we proposed that all patients in Vellore grades 1 and 2 should undergo shunt surgery at the earliest. We suggested the use of the response to external ventricular drainage (EVD) for 72 hours to decide on whether to proceed with shunt surgery or not in grade 3 and 4 patients. Those who did not improve were recommended best medical therapy. For grade 3 patients we were not too dogmatic about not performing shunt surgery if they did not improve with EVD, as nearly 50% of patients who had undergone shunt surgery, without any selection, had good outcome on long-term follow up. [14,15]

The main reason for not advocating shunt surgery in those who do not respond to EVD is the rationale that the altered sensorium in these patients (all patients in grade 4 are in coma; GCS <8) is not due to the raised ICP caused by the hydrocephalus but is due to the diffuse encephalitis and arteritis causing ischemia of ganglionic and brain stem structures.

Prognosticating outcome using the Vellore grade

We used the Glasgow Coma Score to grade patients with TBMH into 4 grades in a modification of the grading system used in the retrospective study discussed above. [16] Using the modified Vellore grading system, we performed a prospective study wherein we used the response to EVD for 72 hours to choose patients in grades 3 and 4 for shunt surgery. [16] We found that Vellore grade at surgery was a good predictor of outcome at a mean follow up of 23.1 months. The important finding of this study was that response to EVD does not predict long-term outcome in grade 3 patients. Therefore, we recommended that shunt surgery should be offered to all grade 3 patients. All but one of 13 grade 4 patients did not improve with EVD and died. Hence, we recommended that for grade 4 patients, response to EVD should determine the need for shunt surgery.

The modified Vellore grading has been validated by several authors who have shown a good correlation between the Vellore grade at surgery and the outcome of either VP shunt or ETV. [17-26]

Sub-categorization of Vellore grade 4

Evidence of good outcomes following shunt surgery in a small but significant subset of Vellore grade 4 patients, suggested that there was a need for sub-classifying these patients. [23,27] The presence of infarcts in the basal ganglia or brain stem on MR imaging were predictors of poor outcome and hence were used in addition to the GCS to distinguish the two sub-grades.[27,28] Hence, grade 4 was sub-categorized as 4a (GCS 7 or 8) and 4b (GCS 3-6 or 7 or 8 with brain stem or basal ganglia infarcts). [29] It is suggested that patients in grade 4a may be offered shunt surgery directly without a trial of EVD but those in grade 4b should undergo a trial of EVD and only if those with a good response, be considered for shunt surgery. [18] The sub-categorization and its significance need validation in future studies.

Role of ETV

By the late 1990s, ETV was being increasingly used to replace shunt surgery in patients with hydrocephalus. Given the high rate of shunt revisions for block and infection (nearly 30%), in patients with TBMH [12,17,20], it was felt that ETV was a good alternative to avoid implantation of a foreign body. There was, however, a concern that TBMH which is most often of the communicating type (80%) rather than the obstructive type might not be an ideal setting for an ETV. [30] We had success in using ETV in patients with "burnt out" TBM who required multiple shunt revisions for TBMH. [31] Further experience from different centres showed that ETV was successful in about 60% of patients who had received at least 4 weeks of ATT. It was not only difficult to perform during the acute stage of TBM (<4 weeks) due to murky CSF and thickened and vascular third ventricular floor but was also not likely to function due to the thick exudates in the basal cisterns. [21,24,25] Two randomized controlled trials in children have, however, not shown ETV to be superior to VP shunt in treating TBMH. [24,25]

Unusual presentations of brain tuberculosis

Tuberculosis is well known to be a great mimicker. We have documented several patients with tuberculomas presenting in unusual locations (isolated brain stem tuberculomas, sphenoid sinus tuberculoma, sellar tuberculoma etc.), tuberculoma with unusual presentation (cortical tuberculoma with a subdural hematoma and a large cerebellar

tuberculoma mimicking a malignant brain tumour) and tuberculosis of a craniotomy bone flap. [32-38]

Trends in brain and spine tuberculosis

We studied the trends in the relative prevalence and presentation of brain and spine tuberculosis over two 7 year periods (2000 to 2013) involving 243 patients and found that in the second era, there was a 14.5% increase in the number of patients with spine TB as compared to those with brain TB. [39] The other significant finding was an alarming increase in the percentage of patients with MDR TB (0% in the first era to 27% in the second era). [39] The resistance was almost always of the secondary type.

In recent years, the author surveyed several Indian neurosurgeons informally and found that almost all report a notable decrease in the overall number of patients with brain TB presenting to them. This change is more marked in south than in the north of the country.

Duration of ATT

There is a lack of consensus on the duration of ATT that is needed in patients being treated empirically (without a biopsy diagnosis) or with residual tuberculoma after a biopsy or partial excision. In the last century, most Indian neurosurgeons and neurologists would not consider an ATT regime of less than 18 months for brain tuberculosis (TBM or tuberculoma). However, following the success with short-course chemotherapy for pulmonary and non-CNS tuberculosis, there is a trend for instituting similar short-course regimes of 9 to 12 months of ATT for CNS tuberculosis as well.

One size fits all?

Several guidelines drafted by national and international bodies recommend a uniform policy of 9 to 12 months of ATT for all patients with brain tuberculosis specifically TBM. [40-44] The INDEX-TB guidelines of the Indian Council of Medical Research (ICMR) mention a duration of 9 months for all extra-pulmonary TB including TBM. [44,45] There is a dissent note in the INDEX-TBguidelines by the neurologist members who insisted that for CNS TB 18 months of ATT was mandatory. There are no specific guidelines for the duration of ATT for patients with tuberculomas. But some experts insist that a uniform duration of 12 months of ATT is adequate and there is no need for imaging at the end of therapy. [43] The rationale for not using imaging to decide on continuation or cessation of ATT is that even if the imaging shows an enhancing lesion, the enhancement represents "scar tissue" and is not active. The "scar tissue" is believed to resolve spontaneously over a period of time without any intervention. However, long term studies on the outcome of large enhancing residues especially those with associated edema have not been done. Therefore, the validity of such a "one size fits all" approach to the duration of ATT is suspect.

Using imaging to tailor duration of ATT

We have managed several patients in whom histologically verified tuberculomas are persistent on neuro-imaging even after 18 months of ATT. In a prospective study in 28 patients with histologically proven tuberculomas, we found that 69.2% had residual disease on imaging done after 18 months of ATT. [11] While some of these residues might represent "scar tissue" it is likely that some had active disease and require prolongation of ATT beyond 18 months. In another study from our centre on 86 patients with brain tuberculomas, we had to prolong ATT beyond 24 months in 19 (22%) of 86 patients. [46] The prolonged therapy was guided by the presence of enhancing residue of the tuberculoma on brain imaging. The sole predictor of the need for prolonged therapy on multivariate analysis was multiple lesions and size >2.5 cm trended towards significance.

Case for reducing the duration of ATT

It is possible to reduce the duration of ATT in patients with brain tuberculomas to 12 months provided an image at that point does not reveal any residue or shows a "tiny" (<1 cm) enhancing residue with no surrounding edema in an asymptomatic patient. The small residue might represent scar tissue and may resolve spontaneously. Another scenario to consider for a reduction in the duration of ATT would be when a solitary tuberculoma has been excised totally and there is no residue on MR imaging done after 6 or 9 months of ATT.

Our protocol

For over 25 years the author's unit followed a standardized protocol of drugs for ATT. For the first three months the ATT regime consists of isoniazid, rifampicin and ethambutol (substituted by pyrazinamide in children as they may not report visual dysfunction which can occur with ethambutol). [46] After three months the regime is changed to a two drug regime of isoniazid and rifampicin for 15 months. [46] Further continuation of ATT is based on neuro-imaging findings. We have treated some patients with ATT for up to 4 years as neuro-imaging continued to show large enhancing masses with edema. [46] However, if the tuberculoma is totally excised and there is no recurrence at 12 months or if the residue is <1 cm in size with no edema, ATT may be stopped at that point in time. The regime was, of course, modified if the culture studies showed resistance to any of these drugs. Generally, isoniazid was continued even if there in vitro resistance in the belief that in vivo activity may be different from in vitro findings and isoniazid penetrates the blood brain barrier the best amongst all the anti-tuberculous drugs.

MDR/XDR tuberculosis

For brain tuberculosis caused by MDR/XDR bacilli, the duration of ATT might have to be prolonged beyond 18 months and the drugs used will have to be modified based on culture studies if available or empirical second and third line drugs.

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