The Diagnostic Parameters in Brain Tuberculosis Meningeal and Parenchymal

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ABSTRACT

The aim of this study was to study the diagnostic parameters in brain tuberculosis (meningeal and parenchymal)

Material and Methods: This study was conducted in the department of Neurosurgery and Neurology SKIMS for a period of two years. A total of 61 patients presenting with brain tuberculosis admitted at skims during these two years were included in the study.

Results: The most presenting symptom in our study was headache found in 95.10% followed by vomiting found in 86.90% of subjects, fever in 78.70%, altered sensorium in 49.20%, seizures in 19.70% and diplopia in 18%. Out of 61 patients cranial nerve involvement was found in 34 (55.73%) with 11 having more than two cranial nerves involved. The most common cranial nerve involved were 3rd and 6th. ADA was positive in 36 of 53 patients of TBM with a sensitivity of 67.9% and a specificity of 75%. PCR proved to be highly specific CT scan of head was abnormal in 56 out of 61 patients (91.8%). 12 (19.70%) were in stage I (meningeal involvement only), 29 (47.50%) were in stage II (parenchymal involvement only) and 15 (24.60%) were in stage III (both parenchymal and meningeal involvement). The most common finding in CT head was meningeal enhancement in 43 patients, hydrocephalus in 37 patients and tuberculomas in 14 patients. The most common sites of tuberculomas were frontal lobe (n=6; 42.8%), parietal lobe (n=4; 28.5%), followed by cerebellum in 2 patients and occipital in two. Nine patients had single and five multiple tuberculomas. Of the 14 patients with tuberculomas, hydrocephalus on CT was seen in 6 patients.

Conclusion: CT scan is a useful diagnostic tool even in very early stages of TBM. Abnormalities reported on CT scan done are hydrocephalus, infarcts, basal enhancement, and tuberculomas. Normal study is reported in up to 20% of the cases.
Introduction

Tuberculosis (TB) continues to be a major health problem throughout the world. About 2 billion (one third of the world's population) people are infected with TB of which about 10% develop clinical disease. The most common form of TB is pulmonary, and the most dangerous is CNS tuberculosis accounting for 5.2% of clinical TB and almost 50% morbidity.

Fever, headache, vomiting, and altered sensorium are the most common symptoms at presentation. Neck rigidity, altered sensorium, cranial nerve palsies, and papilloedema are the most common signs observed. Clues to diagnosis of TBM come from history of contact with a known case of TB. Such history is available in 20% to 30% of the cases only. Diagnosis of TBM is difficult and often a dilemma because the dreaded infection can mimic a variety of CNS diseases. The presence of pulmonary TB in a patient with aseptic meningitis may be suggestive tuberculous etiology, but its absence does not rule it out. However, 50% of the adults and 90% of the children have an abnormal chest x-ray.

Cerebrospinal fluid analysis is an important diagnostic aid in TBM. CSF smear positivity for AFB has been seen in 10% to 90% of cases in various studies and less than 10% of the cases by others. Computed axial tomographic scanning with contrast and magnetic resonance imaging have brought most of the intracranial pathology visible to the naked eye. Abnormalities reported on CT scan done in stages II and III disease are hydrocephalus, infarcts, basal enhancement, and cerebral edema. Normal study is reported in up to 20% of the cases. CT scan is a useful diagnostic tool even in very early stages of TBM.

Drug regimens for CNS TB have never been validated. The optimum duration of treatment is still debated and depends on a case to case basis in spite of World Health Organization guidelines of 2003 which recommends a 12-month treatment. Neurosurgical intervention is required to relieve hydrocephalus, to drain the tubercular brain abscess, and to break the optochiasmatic adhesions to prevent blindness. Regarding steroids, some authorities now routinely use in stages II and III disease as well as for spinal cord disease and significant cerebral edema.

Treatment should be started as swiftly as possible on clinical grounds. Delay in starting treatment is dangerous and often leads to worse prognosis. Reliable independent prognosticators in TBM are extremes of age and advanced disease at presentation. Mortality of treated cases is 10% to 30%. The risk of neurological impairment despite treatment is also a direct correlate of stage of illness at presentation. Neurologic disabilities ranging from mild to severe are reported in 10% to 50% of both adults and children who survived the infection. These include mental retardation and behavioral problems in children, organic brain syndromes in adults, ataxia, hemiparesis, persistent seizure disorders, and cranial nerve palsies. Endocrinopathies like delayed or precocious sexual development, diabetes insipidus, gonadotrophin, or growth hormone deficiency are also reported. The greater the depression of mental status at the initiation of treatment, the worse the outcome. Delay in treatment is also associated with increased neurological sequelae.

Approximately 34 cases of intracranial tuberculomas with paradoxical response to anti tuberculous chemotherapy have been documented worldwide till 1997. The majority of these patients were children or young adults, who had
inoperable intracranial tuberculomas located in high risk regions that developed a few weeks or months after the start of an appropriate chemotherapy. It is interesting that these intracranial tuberculomas developed or enlarged at a stage when systemic tuberculosis was being treated successfully. Patients who are suspected to have a CNS-tuberculosis should receive a prolonged (12-30 months) course of effective anti tuberculous therapy. The evidence of new intracranial tuberculomas or the expansion of older existing lesions does not indicate the need to change the anti tuberculous drug program. In such cases systemic dexamethasone as adjuvant therapy for 4 to 8 weeks is worthwhile and effective. Surgical intervention may be necessary in situations with acute complications of CNS tuberculosis, such as shunting procedures for the treatment of hydrocephalus. When the diagnosis is not ensured and there is no response to therapy within 8 weeks, a stereotactic biopsy on a suspected tuberculoma could be performed. If the largest lesion is not located in high risk deep regions of the brain, it could be totally removed surgically. With this combined management, a satisfactory outcome can be obtained in the majority of cases.18

Methods

This study was conducted after approval from local institutional ethical committee. The patients were subjected to thorough clinical examination and extensive investigations to establish a diagnosis of tuberculosis of brain. Complete hemogram, ESR, chest x-ray, Montaux test were done. CSF of these patients was subjected to detailed cytology, biochemistry ADA and PCR analysis. CSF was also taken for ZN staining &culture. History of contact with a known patient of pulmonary tuberculosis, history of recent or past intake of ATT was also taken. The inclusion criteria and the diagnosis of brain tuberculosis was based on the following parameters:-

(1) Clinical symptoms- headache, vomiting, fever, and signs of meningism of more than 4 weeks duration.
(2) Positive ziel-Neelsen of the CSF
(3) Patients with CSF cytology and biochemistry suggestive of TBM.
   (a) CSF Positive for PCR
   (b) CSF with raised ADA
(4) Therapeutic response to ATT
(5)Imaging findings suggestive of tuberculosis like meningeal enhancement, hydrocephalus, basal exudates, and tuberculomas.

The patients selected were classified into three types according to CT findings.

Radiological staging

On the basis of CT scan findings patients were divided in to three grades:
Grade I: Isolated meningeal involvement.
Grade II: Isolated parenchymal involvement.
Grade III: Compound parenchymal and meningeal involves meningeval.

Results and Observations

The total number of study subjects were 61 with age range of 1-65 years with a mean age of 30.85 ± 16.91 years; 27 of 61(44.3%) were males and 34(55.7%) were females. Six of the patients were below 10 years of age and most were 11-40 years. There was a higher incidence of tubercular meningitis in younger (< 40 years) age group (p <0.05). The most presenting symptom of the study subjects was headache found in 95.10% followed by vomiting found in 86.90% of subjects, fever in 78.70%, altered sensorium in 49.20%, seizures in 19.70% and diplopia in18%.

In our study of 61 patients of brain tuberculosis on clinical examination cranial
nerve involvement was found in 34 (55.73%) with 11 having more than two cranial nerves involved. The most common cranial nerve involved were 3rd and 6th. Focal deficit (monoparesis or hemiparesis) was found in 14 (22.95%) and neck stiffness was found in 35 (74.40%) of patients.

CSF cytology and chemistry was abnormal in 53 of the patients. Eight patients had a normal CSF cytology and chemistry and had no evidence of meningial involvement on CT scan of head. All these patients had CT or MRI evidence of tuberculomas only. Most of the patients of tubercular meningitis (n = 37; 69.8%) had a total leucocyte count of CSF between 100-500. Ninety four percent of patients had a CSF total leucocyte count of < 500/mm³ and 24.5% had a CSF TLC of < 100/mm³. All the patients were having a CSF lymphocytosis of > 50%. A CSF lymphocytosis of >90% was seen in 56.6% of the patients (p = 0.001). There was also a statistically significant relation of CSF sugar < 60% of the corresponding blood sugars (n = 37; 69.8%; p = 0.021) and CSF protein of > 50 mg/dl (n = 43; 82%; p = 0.014) with tubercular meningitis (TBM).

Taking a cut off of > 10U/L as highly suggestive of tubercular meningitis ADA was positive in 36 of 53 patients of TBM with a sensitivity of 67.9% and a specificity of 75%. PCR proved to be highly specific for TBM with a specificity of 100% as there were no false positive results. The sensitivity of PCR in CSF for mycobacterium in our study worked out to be 52.8% as PCR was positive in 28 of 53 patients of TBM [Tab 5]. The false positive results were seen only with ADA due to the fact that ADA is a highly sensitive test whereas PCR has high specificity.

In our study of 61 patients of brain tuberculosis on clinical examination 20 patients (32.80%) were in clinical stage I, 36 patients (59.00%) were in clinical stage II and 5 patients (8.2%) were in clinical III at the time of presentation]. Five patients were deeply comatose on admission with a GCS of < 6/15. CT scan of head was abnormal in 56 of 61 patients (91.8%). On admission. The study subjects were divided into three stages on the basis of CT scan finding at the time presentation and out of total 56 subjects 12 (19.70%) were in stage I (meningeal involvement only), 29 (47.50%) were in stage II (parenchymal involvement only) and 15 (24.60%) were in stage III (both parenchymal and meningeal involvement). The most common finding in CT head was meningeal enhancement in 43 patients, hydrocephalus in 37 patients and tuberculomas in 14 patients. The most common sites of tuberculomas were frontal lobe (n=6; 42.8%), parietal lobe (n=4; 28.5%), followed by cerebellum in 2 patients and occipital in two. Nine patients had single and five multiple tuberculomas. Of the 14 patients with tuberculomas, hydrocephalus on CT was seen in 6 patients.

There was no correlation of higher clinical stage at presentation with higher CT stage (p = 0.627). Ninety five percent (95%) of patients (19 of 20) in clinical stage I had abnormal CT scan in comparison to 88% of stage II. All the patients in stage III had abnormal CT. CT scan is a better diagnostic modality even in stage I of the disease.

Discussion

TBM is common in developing countries, with a high morbidity and mortality. The diagnosis of TBM is based mainly on clinical and laboratory findings, particularly in adults.19 Tubercular meningitis in developing countries is more common in infants and children with an increasing incidence in adolescents and young adults. In populations with low prevalence of TB, most cases of TBM occur in adults, and HIV has definitely increased the risk in adults. As the
prognosis depends on starting treatment early, and confirmatory tests take longer time (culture) or are not available (PCR) in regions where tuberculosis is common, the diagnosis is based on clinical, laboratory and imaging features. CT and MRI are used in the evaluation of TBM and to identify complications and to assess response to treatment.

Six of the patients in our study were below 10 years of age and most (n=39; 60%) were between 11-40 years. There was a higher incidence of tubercular meningitis in younger age group less than 40 years of age (p<0.05). The mean age of our patients was 30.85 ± 16.91 years. Our results were corroborative to the results of Abdul Majid et al\textsuperscript{20} where 55.2\% of the patients were between 20-40 years with a mean age of 29.14 ± 16.28 years and is also close to that reported by Juan Barengufer et al\textsuperscript{4} of 38.8 ± 21.7 years.

Fever, headache, vomiting, and altered sensorium are the most common symptoms at presentation. Neck rigidity, altered sensorium, cranial nerve palsies, and papilloedema are the most common signs as observed by Juan Barengufer et al\textsuperscript{4}. Nabil et al\textsuperscript{21} reported fever in 90\%, headache in 63\% and vomiting in 49\% of the patients; neck stiffness in 68\% and cranial nerve palsy in 50\% of their patients. The most presenting symptom of our study subjects was headache found in 95.10\% followed by vomiting found in 86.90\% of subjects, fever in 78.70\%, altered sensorium in 49.20\% .Cranial nerve involvement was found in 55.73\% with 11 having more than two cranial nerves involved. The most common cranial nerve involved were 3\textsuperscript{rd} and 6\textsuperscript{th}. Focal deficit (monoparesis or hemiparesis) was found in 22.95\% and neck stiffness was found in 74.40\% of patients.

Cerebrospinal fluid analysis is an important diagnostic aid in TBM. Moderate degree of pleocytosis usually not exceeding 500 cells/mm\textsuperscript{3} is common. Cerebrospinal fluid white blood cell count greater than 1200 cells/mm\textsuperscript{3} is extremely rare in TBM.\textsuperscript{5} Cerebrospinal fluid may be normal in rare cases in wherein the disease has been definitively diagnosed.\textsuperscript{8} This occurs because miliary cerebral tuberculomas may give rise to neurological symptoms and signs before involvement of leptomeninges (Kocen and Parsons Hypothesis). Most of the cells in CSF are lymphocytes\textsuperscript{5} and CSF lymphocytosis greater than 50\% has been reported in 80\% to 83\% of the patients.\textsuperscript{4,7} Most of the patients of tubercular meningitis in our study (n = 37; 69.8\%) had a total leucocyte count of CSF between 100-500. Ninety four percent of patients had a CSF total leucocyte count of < 500/mm\textsuperscript{3} and 24.5 \% had a CSF TLC of < 100/mm\textsuperscript{3}. All the patients were having a CSF lymphocytosis of > 50\%. A CSF lymphocytosis of >90\% was seen in 56.6\% of the patients (p = 0.001) showing that a CSF lymphocytosis of > 90\% is highly suggestive of tubercular meningitis.

Low CSF glucose and elevated protein are other characteristic abnormalities seen in TBM. Low CSF glucose occurs in 50-89\% of patients.\textsuperscript{4} Elevated CSF protein (> 50 mg %) has been found in 75\% to 85\% of the patients.\textsuperscript{22} CSF lymphocytosis (>90\%), hypoglycorrhachia (60\% of the corresponding blood glucose), and elevated CSF protein (>50 mg/dL) in a suitable clinical setting are strong diagnostic pointers toward TBM. There was also a statistically significant relation of CSF sugar < 60\% of the corresponding blood sugars (n = 37; 69.8\%; p = 0.021) and CSF protein of > 50 mg/dl (n = 43; 82\%; p = 0.014) with tubercular meningitis (TBM) in our study. In our study CSF cytology and chemistry was abnormal in 53 of the patients. Eight patients had a normal CSF cytology and chemistry and had no evidence of meningeal involvement on CT scan of head. All these patients had CT or MRI evidence of tuberculomas only. Farinha
NJ et al in 2000\(^2\)\(^3\) in their study identified 38 children with CNS tuberculosis: 23 with tuberculous meningitis (TBM), 10 with tuberculous meningitis and associated tuberculomas and five with tuberculomas alone. In our study six patients had TBM with tuberculomas, eight had tuberculomas only, 13 had tubercular meningitis with hydroceplalus and 16 had TBM without any complications.

New approaches for the rapid detection of mycobacterial growth have been developed with the aim to reduce the time needed for diagnosis. Radiometric and non radiometric systems have the advantage of detecting the presence of the bacilli in a much shorter time than the traditional Lowenstein-Jensen culture.\(^2\)\(^4\) Measurement of adenosine deaminase (ADA) activity levels, have proven to be sensitive and specific for tubercular meningitis in special circumstances, such as in regions with a high prevalence of tuberculosis.\(^2\)\(^5\) The levels of adenosine deaminase (ADA), an enzyme found in most cells, are increased in CSF in tubercular meningitis, and this determination has acquired popularity as a diagnostic test in high-incidence areas for TBM because it is not invasive, the assay is not expensive, and it is readily accessible. ADA is involved in the proliferation and differentiation of lymphocytes, especially T lymphocytes. They release ADA when stimulated in the presence of live intracellular microorganisms.\(^2\)\(^6\) For this reason, ADA has been looked on as a marker of cell-mediated immunity and, in particular, as a marker of the activation of T lymphocytes. Baro M et al\(^2\)\(^7\) found that adenosine deaminase values ranged from 3.6 to 31.2 IU/ml in patients with tuberculous meningitis and from 0.1 to 312 i. u. /ml in controls. The ADA activity levels in our study ranged from 6.4 to 35 IU/ml. Gautam N et al in 2007\(^2\)\(^8\) did a comparative study of cerebrospinal fluid adenosine deaminase activity in patients with meningitis. The sensitivity and specificity of CSF ADA activity was 85.0% and 88.0% respectively at cut-off value of 6.97 IU/L to diagnose tubercular meningitis. Rana SV et al in 2010\(^2\)\(^9\) showed a sensitivity of 92.5% and specificity of 97% for the diagnosis of TBM using a cut off level of CSF-ADA >10U/L. In our study taking a cut off of > 10U/L as highly suggestive of tubercular meningitis ADA was positive in 36 of 53 patients of TBM with a sensitivity of 67.9% and a specificity of 75%.

The polymerase chain reaction (PCR) is a new strategy used for the tuberculosis diagnosis, and two kits have been approved by the US Food and Drug Administration for use on clinical samples; however, their cost is prohibitive for developing countries where tuberculosis remains an important public health problem. Querol JM et al in 1996\(^3\)\(^0\) described the utility of polymerase chain reaction (PCR) for the diagnosis in three patients suffering from central nervous system infections, tuberculous meningitis, herpetic encephalitis and cerebral toxoplasmosis. In all three patients, PCR allowed the diagnosis in seven hours, and PCR was consider a rapid sensitive and relatively simple method.

Rana SV et al in 2010\(^2\)\(^9\) compared the adenosine deaminase (ADA) levels and polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) as a rapid method to diagnose tuberculosis meningitis (TBM). Using a cut off level of >10U/L, CSF-ADA had a sensitivity of 92.5% and specificity of 97% for the diagnosis of TBM. PCR for M. tuberculosis had a sensitivity of 44.5% and specificity 92% in the most likely TBM cases. Nguyen LN et al in 1996\(^3\)\(^1\) showed that PCR had a sensitivity of 32%. In our study PCR proved to be highly specific for TBM with a specificity of 100% as there were no false positive results. The sensitivity of PCR in CSF for mycobacterium in our study worked out to be 52.8% as PCR was positive in 28 of 53 patients of TBM. The false positive results were seen only with
ADA due to the fact that ADA is a highly sensitive test whereas PCR has high specificity.

Computed axial tomographic scanning with contrast and magnetic resonance imaging have brought most of the intracranial pathology visible to the naked eye. Abnormalities reported on CT scan done in stages II and III disease are hydrocephalus, infarcts, basal enhancement, and cerebral edema. Normal study is reported in up to 20% of the cases. Abdul Majid et al reported abnormal CT findings in 73.52% patients as basal enhancement in 36%, hydrocephalus in 28%, tuberculomas in 52%, infarcts in 12.0%, cerebral edema in 8.0%, and more than 1 finding in 32.0% of the patients. Normal study was in 26.4%. All patients in stage I disease had abnormal CT findings in comparison to 50% of stage II and 83.3% of stage III disease. CT scan of head was normal in 5 of 61 patients (9%) of our subjects on admission. The study subjects were divided into three stages on the basis of CT scan finding at the time presentation and out of total 56 subjects 19.70% were in CT stage I, 47.50% were in stage II and 24.60% were in stage III (depending upon the involvement of meninges, parenchyma or both). The most common finding in CT head was meningeal enhancement in 76% of patients, hydrocephalous in 66% patients and tuberculomas in 25% patients. Ninety five percent (95%) of patients (19 of 20) in clinical stage I had abnormal CT scan in comparison to 88% of stage II. All the patients in stage III had abnormal CT. CT scan is a better diagnostic modality even in stage I of the disease.

Conclusion

The diagnosis of TBM is based mainly on clinical and laboratory findings, particularly in adults. CT is used in the evaluation of TBM and to identify complications and to assess response to treatment. CT scan is a useful diagnostic tool even in very early stages of TBM. Abnormalities reported on CT scan done are hydrocephalus, infarcts, basal enhancement, and tuberculomas. Normal study is reported in up to 20% of the cases.

References


Figure 1. Shows the clinical characteristics in studied subjects

Figure 2. Shows the clinical examination of studied subjects
**Figure 3.** Shows the Radiological findings of the studied subjects on computer tomography

**Figure 4.** Shows the Sensitivity and Specificity of ADA and PCR in Brain Tubercular