e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(9); 1179-1183

Original Research Article

Acute Presentation of Central Nervous System Tuberculosis: A Retrospective Study and Review of Literature

Irfan Ahmad Shah[1], Shoaib Yousuf[2], Waseem Mirza[3], Ifra Urooj[3], Khushboo Ahmad[3]

[1]Assistant Professor; Department of Medicine Government Medical College Srinagar
[2]Lecturer, Department of Medicine Government Medical College Srinagar
[3,]Registrar, Department of Medicine Government Medical College Srinagar

Received: 25-06-2023 / Revised: 28-07-2023 / Accepted: 30-08-2023
Corresponding author: Dr. Irfan Ahmad Shah
Conflict of interest: Nil

Abstract:

Tubercular meningitis has been classically described as sub-acute or chronic meningitis that evolves over a course of weeks to months. However in some cases the onset is acute or sometimes abrupt with features of encephalitis. In a review of adult patients of tubercular meningitis, 10 cases were found to have an acute presentation with features of encephalitis. Acute presentation was defined as symptom duration of 07 days or less. The international encephalitis consortium criteria were used for case definition of encephalitis. The patients varied in age between 14 to 35 years. Three patients had definite tubercular etiology while three were probable and four were possible tubercular encephalitis. Encephalopathy manifested in the form of worsening of sensorium in 06 patients, irritability in 02 and behavioral disturbance in 02 patients. The average duration of symptoms before presentation was 5.2 days. Signs of meningeal irritation were present in 09 patients. On CSF analysis, all patients showed pleocytosis with elevated CSF protein, while glucose was low in 08 patients. The average time delay before commencement of anti-tubercular treatment was 11.6 days. Nine patients improved while one died during hospital stay. Acute encephalitic presentation of central nervous system tuberculosis is an under recognized entity that requires a high index of suspicion. Early recognition of this entity can be life-saving and prevent serious complications.

Keywords: Acute Meningitis; Anti-Tubercular Therapy; Encephalitis; Infectious Encephalopathy; Tubercular Meningitis.

Introduction

Central nervous system tuberculosis has a variety of presentations. Tubercular meningitis (TBM) is the most common form. TBM has been classically described as a form of sub-acute or chronic meningitis that evolves or progresses over a course of weeks from prodromal stage to the stage of coma. Owing to this classical teaching, clinicians most often do not consider tuberculosis in the differential diagnosis of acute meningitis or encephalitis. Tubercular encephalitis as a separate entity has mainly been described in retrospective studies on the etiology of encephalitis at various centres in the world.[1-4] In two of these studies 23% and 15.2 % case were found to have tubercular etiology.[3,4] In another such study, the California encephalitis project, 20 cases (about 1%) were found to have tubercular etiology.[5] These studies describing the confirmed causes of encephalitis have been done in developed countries where tuberculosis is non-endemic. Therefore in endemic regions like India, one would expect a greater number of cases of encephalitis having tubercular etiology. Only one prospective study describes a case series of acute presentation of tubercular meningitis. [6]Acute tubercular meningioencephalitis has not been highlighted in the numerous published series on tuberculous meningitis. Even when this acute encephalitic presentation of the disease has been noticed, the patient has been considered as late stage meningitis rather than encephalitis. Very sparingly we find the use of term tubercular meningioencephalitis in literature. Since many of the above retrospective studies on encephalitis show tuberculosis as a major etiology, we expect that a good number of cases among tubercular meningitis patients may actually present acutely with encephalitis.

Materials and methods

In a retrospective analysis of adult patients of tubercular meningitis, 10 cases were selected who had an acute presentation with features of encephalitis. “Acute presentation was defined as symptom duration of up to 07 days. The case definition of encephalitis included any person of any age admitted to hospital with encephalopathy

(altered consciousness that persisted for longer than 24 h, including lethargy, irritability, or a change in personality and behavior) and with two or more of the following: fever or history of fever (≥38·C) during the presenting illness; seizures and/or focal neurological findings (with evidence of brain parenchyma involvement); cerebrospinal fluid (CSF) pleocytosis (more than four white blood cells per μl); electroencephalographic (EEG) findings indicative of encephalitis; and abnormal results of neuroimaging (CT or MRI) suggestive of encephalitis.[7,8]

Patients were classified as having confirmed, probable, or possible cases of tubercular encephalitis according to clinical data, imaging findings, and biological test results. A confirmed case was defined as the identification of mycobacterium in the CSF. A probable case was defined as direct identification of the infectious agent in any biological fluid or sample except CSF. A possible case was defined by the combination of epidemiologic and clinical features, imaging findings, and biochemical analysis results strongly evocative of a disease and response to ATT without identification of MTB in any biological sample. [9] Also the Lancet consensus scoring system was used for detailed grading of definite, probable and possible cases. The score has 20 parameters, which are divided in 4 categories (clinical, CSF, CNS imaging and evidence of TB elsewhere) with a maximum score of 20. A diagnosis of definite tubercular meningitis is made if there is presence of Acid Fast Bacilli (AFB) in CSF analysis, culture or on biopsy of brain or spinal cord. A probable diagnosis is made if the total score is >10 pts if patients have no imaging, or >12 pts if imaging was used. A possible diagnosis is made with scores between 6-9 without imaging or 6-11 with imaging. [10]

Data was analysed for demographic information, clinical findings at presentation and discharge and results of laboratory, EEG, and neuroimaging testing and immediate outcome and sequelae. The relevant literature on tubercular encephalitis was reviewed.

Ethics: Theresearch study confirms to ethical principles as laid down in the Helsinki declaration. Approval of the institute ethical committee was sought via order no. IEC/MD/17/21.

Results

The patients varied in age between 14 and 35 years; males were 04 and 06 were females. In all cases the patients became unwell so rapidly and so obviously that they were admitted to hospital at some time during the first week of their illness. The departure from normal health was usually so abrupt that the interval between the onset of symptoms and admission to hospital could be estimated with fair accuracy. The relevant demographic, clinical and laboratory features in these cases are summarized in Table 1. Apart from encephalopathy which was present in all the patients, the signs of meningeal irritation included fever in 09 cases, headache in 06 cases, vomiting in 03 cases, and 03 cases had seizures. Encephalopathy manifested in the form of worsening of sensorium in 06 patients, irritability in 02 and behavioral disturbance in 02 patients. The average duration of symptoms before presentation was 5.2 days (range 2-7 days). Signs of meningeal irritation were present in 09 patients. The most common focal neurological sign was cranial nerve palsy in 04 patients. Abducens nerve was involved in 02 patients while facial and occulomotor palsy was found in one patient each. One patient with brainstem involvement developed transient left hemiparesis. Two patients were intubated due to very low Glassgow coma scale (GCS) score for one week each and later extubated.

On CSF analysis, all patients showed pleocytosis with average cell count of 231.5 ranging from 20 to 580 cells. Five had neutrophil predominant pleocytosis, while in 05 patients it was mainly lymphocytic. CSF protein was raised in all the patients ranging from 63 mg to 850mg/dl. CSF glucose was low in 08 patients. ADA levels in CSF were raised (≥10 u/l) in 08 patients. None of the cases had a positive CSF smear for AFB. CSF PCR for MTB was done in 09 patients and was positive in 03 of them. Chest x-ray was normal in 09 patients while one had bilateral miliary shadows which were confirmed by chest CT scan. Sputum analysis for AFB was positive in one patient while in one patient with coma AFB was detected in tracheal aspirate.

Cranial MRI was normal in 05 patients, 04 patients showed diffuse meningeal enhancement out of which one had military tuberculomas in left high parietal region, while one had prominent basal enhancement with associated mastoiditis and one had midbrain hyperintensities. No patient had hydrocephalus, tuberculoma or vasculitis/infarcts. (Table 1) EEG was done in 07 patients and showed generalized slowing in 04 patients. Three cases were classified as confirmed tubercular etiology, four were probable and three were possible cases of tubercular meningioencephalitis. Four patients had a Lancet consensus score of >12 while 03 had score of 6-11 and were classified as probable and possible cases respectively.

The average time before commencement of anti-tubercular treatment was 11.6 days (range 06-21 days). 03 patients were initially started on cocktail treatment of meningitis with ceftriaxone, vancomycin and acyclovir in emergency room after CSF analysis, and 02 were started on acyclovir alone. One patient was treated for pyogenic

meningitis for two weeks with no response. One received acyclovir for 2 weeks with persistent symptoms.

All patients were finally treated with daily regimen of antitubercular therapy consisting of 04 drugs isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 02 months followed by maintenance with H and R. All patients received intravenous dexamethasone along with ATT at dose of 16 to 24 mg per day in divided doses followed by oral tapering over 6 -8 weeks.

Nine patients recovered while one died during hospital stay due to progressive encephalopathy. The most common residual symptoms were monocular vision loss in one patient, ophthalmoparesis and hemiparesis in one and unilateral sensoneural hearing loss in one and cognitive dysfunction in one.

Table 1: Demographic, Clinical, Laboratory, Imaging Features and outcome of Cases

Sno.	Age/ Sex	Presenting symptoms	Signs	Duration of Symptoms (days)		CSF analysis: leukocytes (differential), protein, glucose	CSF ADA, AFB smear, PCR MTB	CXR findings,	Cranial MRI findings	Outcome (immediate)
				Before admission	Before treatment					
01	22/f	Fever, altered sensorium, seizures	Neck stiffness, left abducens palsy	02	06	85(N85,L15),90,32	15,N,P	N	Diffuse meningeal enhancement	recovered
02	21/m	Headache, fever, altered sensorium	Neck stiffness, right facial palsy	06	10	150(N28,L72), 192,22	94,N,N	N	Diffuse meningeal enhancement, miliary tuberculomas cerebrum	recovered
03	21/f	Seizures,vomiting Altered sensorium	Neck stiffness, comatose	05	06	20(N65,L35), 180,30	20,P,N	miliary shadows	normal	recovered
04	19/f	Headache, fever, behavioral disturbance	Neck stiffness, right abducens palsy	06	09	260(N11,L89), 120,68	104, N,N	N	normal	recovered
05	14/m	Fever,vomiting, altered sensorium	nil	06	15	300(N90,L10), 250,34	04,N,P	N	normal	recovered
06	30/f	Headache, fever, vomiting, altered sensorium	Neck stiffness, bilateral abducens palsy	07	10	580(N64,L36),150,15	16,N,N	N	Diffuse meningeal enhancement	died
07	25/m	Headache, fever,seizures, altered sensorium	Neck stiffness,	03	09	350(N10,L90),850,52	26,P,N	N	normal	recovered
08	35/f	Fever, irritability, incontenence	Neck stiffness	03	11	80(N30,L70), 95,81	26,N,NA	N	normal	recovered
09	25/m	Headache, fever, behavioral	Neck stiffness, right	07	21	400(N8,L92), 63,48	11.6, N,N	N	Diffuse meningeal enhanceme	recovered

		disturbance	occulo motor palsy palsy						nt	
10	30/f	Headache, fever, vomiting, altered sensorium.	Neck stiffness	07	19	90(N80,L20), 90,30	06,N, P	N	Basal meningeal enhancement, left mastoiditis	recovered

Discussion

It has been estimated that approximately 1% of all patients with tuberculosis have CNS involvement and tubercular meningitis is the most common CNS presentation. [11]A proportion of these cases of TBM actually fulfil the criteria for labelling them as encephalitis and conversely some patients initially admitted as encephalitis turn to have tubercular etiology. Table 2 summarizes the proportion of patients having tubercular etiology in various studies on encephalitis throughout the world. These studies indicate that a definite number of cases of encephalitis do occur due to mycobacterium tuberculosis.

Table 2: Proportion of tuberculosis cases in encephalitis studies

Authors [reference]	Place; Year	Total patients	Tubercular etiology no.
Julia Granerod	England; 2010	203	10 [05%]
Lee	Taiwan; 2003	127	10 [08%]
Sonneville	France; 2015	279	65 [23%]
Mailles	France; 2007	253	20 [15.2]

The California encephalitis project suggested that we should think beyond viruses as causes of encephalitis and should consider tuberculosis in differential diagnosis of encephalitis. It further added that atypical feature like encephalitic symptoms and rapid onset complicate the diagnosis of tubercular meningitis. [5] Stahl pointed out tuberculosis as an important cause of encephalitis and added that time delay between onset and diagnosis is a common feature of tuberculous encephalitis. [12]

In the present study, the majority of patients were admitted with febrile encephalopathy with signs of meningeal irritation. All of the patients belonged to the younger age group of 14- 35 years with a mean age of 24.2 years. The possible cause may be a heightened immunological response to tubercular antigens among the young.

In a study from India in paediatric patients (age <18 years) on etiology of acute febrile encephalopathy, 7.9% patients had tubercular etiology. [13] Utigard et al described a patient of acute tubercular meningitis who presented with encephalopathy and progressed to death rapidly over few days. [14] Maramattom et al described few cases of tubercular encephalitis and suggested than FDG-PET may be helpful instead of MRI scan in detecting cortical changes of tubercular encephalitis. [15]

The encephalitic presentation of tuberculosis is a diagnostic dilemma for the clinician as the first thing that comes in mind with such presentation is either viral encephalitis or bacterial meningitis. The picture at times is further complicated by CSF analysis, which shows neutrophilic pleocytosis in some of these and partially treated bacterial meningitis becomes another possibility. The confirmation of tuberculosis in the present study was done through PCR- MTB and the test though less sensitive is highly specific. The increasing use of rapid tests tuberculosis helps in early diagnosis of tubercular meningioencephalitis cases. Most of these patients are initially treated empirically with antiviral and anti-pyogenic treatment. An early suspicion would prevent unnecessary use of these drugs and prevent their adverse effects. Also early recognition of this entity can be lifesaving and prevent serious complications. We suggest that tubercular work up be done in all cases of CNS infections even when the presentation is acute and encephalopathy is the presenting symptom.

Many of these patients can be classified as stage 2 or 3 of tubercular meningitis according to medical research council (MRC) grading but the classification is mainly a prognostic one and does not hold true for these patients. Most of these patients have good prognosis if treated timely than advanced tubercular meningitis and hence cannot be called as late stage of tubercular meningitis. In the present series, response to treatment even though delayed was good in the majority of cases. Majority of the patients showed signs of clinical recovery during the hospitalization period. This is perhaps because they were early in their disease course and were in younger age group. Taylor et al in their case series of acute tubercular meningitis

has also shown favourable prognosis in majority of the patients and majority of the patients were young adults. [6] Tuberculosis is being increasingly recognized as a cause of encephalitis in neurocritical units. [16]

Limitations

More than half of patients did not have satisfy the definition of definite tubercular etiology and were managed as probable and possible cases however the diagnosis in confirmed cases was based on CSF MTB-PCR test which is a highly specific test used throughout the world. Also long term follow up was not available in all. Therefore more studies are needed in this area to further substantiate the findings of the study.

Conclusion

After analyzing the cases and reviewing the relevant literature , we conclude that a minor subset of patients with CNS tuberculosis do present acutely and fit in the case definition of encephalitis and this fact should be kept in mind while dealing with a case of suspected meningioencephalitis especially in endemic areas like the Indian subcontinent.

References

1. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 2010; 10: 835–44.
2. Lee TC, Tsai CP, Yuan CL, Wei CY, Tsao WL, Lee RJ. Encephalitis in Taiwan: A Prospective Hospital-Based Study. Jpn. J. Infect. Dis. 2003; 56: 193-199.
3. Sonneville R, Gault N, Montmollin E, Klein IF, Mariotte E, Chemam S. Clinical spectrum and outcomes of patients with encephalitis requiring intensive care. European Journal of Neurology 2015; 22:6–16
4. Mailles A, Vaillant V, Stahl JP. Infectious encephalitis in France from 2000 to 2002: the hospital database is a valuable but limited source of information for epidemiological studies [in French]. Med Mal Infect 2007; 37:95–102.
5. Christie LJ, Loeffler AM, Honarmand S, Flood JM, Baxter R, Jacobson S, et al. Diagnostic Challenges of Central Nervous System Tuberculosis. Emerg Infect Dis. 2008;14(9):1473-1475.
6. Taylor KB, Smith HV, Vollum RL. Tubercular meningitis of acute onset. JNNP 1955; 18: 165.
7. Bloch KC, Glaser CA. Encephalitis Surveillance through the Emerging Infections Program, 1997-2010. Emerg Infect Dis. 2015 Sep; 21(9):1562-7.
8. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A et al.Case definitions, diagnostic algorithms, and priorities in encephalitis. Consensus statement of the international encephalitis consortium. CLIN Infect Dis. 2013;57(8):1114-18.
9. Honnorat E, De Broucker T, Mailles A, Stahl JP. Encephalitis due to Mycobacterium tuberculosis in France. Médecine et Maladies Infectieuses 2013; 43(6): 230-238.
10. Marais S, Thwaites G, Schoeman JF, Török ME, Misra UK, Prasad K, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 2010 Nov; 10(11):803-812.
11. Wood M, Anderson M. Chronic meningitis. In: Neurological infections; major problems in Neurology, vol 16. Philadelphia: WB Saunders, 1998; p 169–248.
12. Stahl, J.P. (2019). Tuberculous Encephalitis. In: Sener, A., Erdem, H. (eds) Extrapulmonary Tuberculosis. Springer, Cham. https://doi.org/10.1007/978-3-030-04744-3_9.
13. Karmarkar SA, Aneja S, Khare S, Saini A, Seth A, Chauhan BK. A Study of Acute Febrile Encephalopathy with Special Reference to Viral Etiology. Indian J Pediatr 2008; 75 (8): 801-805.
14. Utigard E, Katyshev V, Isada C, Dani D. Acute onset and rapid progression of tubercular meningitis and ischemic infarcts in an immune competent patient. Neurology 2017; 88 (16): P1.317.
15. Maramattom BV, Santhamma SGN. Tuberculous Encephalitis May Be Undetectable on Magnetic Resonance Imaging but Detectable on 18F-Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography. The American Journal of Tropical Medicine and Hygiene. 2021; 105(4):1031-1037.
16. Diaz-Arias, L.A., Pardo, C.A. &Probasco, J.C. Infectious Encephalitis in the Neurocritical Care Unit. Curr Treat Options Neurol 2020; 22: 18.