Tuberculous Meningitis in Province-2, Southern Nepal

Roshan Kurmi[1]*, Jamil Akhtar[2], Bipin Chaurasiya[2], Ajay Shah[2], Birendra Prasad Gupta[3]

[1]Associate professor of Medicine, National medical college, Birgunj, Nepal,
[2]Terai Hospital and research Centre, Birgunj, Nepal,
[3]Central Diagnostic laboratory and Research centre, Kamalpokhari, Kathmandu, Nepal.

Abstract

Introduction
Tuberculosis (TB) still remains a public health challenge in Nepal. As per the World Health Organisation (WHO), five countries, viz., India, China, Pakistan, Indonesia and South Africa, account for over 70% of the global burden of disease. Tuberculous meningitis (TBM) is the most severe type of extrapulmonary tuberculosis, which remains an undiagnosed disease and sparse data available for this disease in Nepal

Methods:

We included all patients admitted with tubercular meningitis between May 2018 to August 2019.admitted in Terai Hospital and Research centre. Diagnosis of Tubercular meningitis was confirmed by combined clinical sign and symptoms, CSF biochemical values of lymphocytic pleocytosis, high protein, low sugars with high CSF ADA and the therapeutic response to National Tuberculosis programme Category 1 (NTP CAT-1) antituberculous treatment (ATT)

Results:

The mean age was 48.5 ±30 years and male/female ratio was 12/14. Most of them had fever and neck rigidity. CSF studies in all the patients showed lymphocytic exudate with CSF pleocytosis varying from 14to1500cells/cumm. CSF protein was 51-319 mg/dl, CSF sugar was17-165 mg/dl and CSF ADA was10-38 units/l.

Conclusions:

Our study concluded that clinical presentation of fever, nuchal rigidity and CSF lymphocytic pleocytosis with CSF ADA value of ≥ 10 is sufficient to consider the diagnosis of Tubercular meningitis in a resource limited setting where the newer sophisticated and expensive tests are not readily available or affordable

Key words: Tuberculosis, Tuberculous Meningitis, Terai, Province-2, Nepal.

Introduction

Tuberculosis (TB) still remains a public health challenge in Nepal, as it is responsible for ill health among thousands of people each year[1]. As per WHO, it account for over 70% of the global burden of disease[2]. TBM remains an undiagnosed disease in southern Nepal and there are sparse data or study for this disease in Nepal.

The significance of CSF analysis in TBM has been immense. A classic case of TBM usually presents with a CSF of 10–500 cells/μL that are polymorphs initially and lymphocytes later and best performing biochemical parameter for "ruling in" TBM was adenosine deaminase (ADA), with a specificity of 95%[1].

The aim of this study is to determine the age at which tubercular meningitis occur in adult population, clinical presentations and biochemical characteristics of cerebrospinal fluid, and utility combined clinical, CSF analysis data in the diagnosis of TBM in resource limited regions of southern Nepal.

Materials and methods

We studied all the tubercular meningitis patients admitted in Terai Hospital from May 2018 to August 2019..These patients were admitted with clinical history of fever, headache, vomiting with altered sensorium. The fever duration varied from five days to one month and most of them had earlier treatment with some forms of oral and parenteral antibiotics by local health care practitioners at their own villages. The diagnosis of Tubercular meningitis was confirmed by combined clinical sign and symptoms, CSF biochemical values of lymphocytic pleocytosis, with high protein and low sugars and the therapeutic response to antituberculous treatment (ATT).
The ethical approval was received from Institutional Review Committee of National medical college and teaching hospital, Birgunj. Individuals who had undergone surgery previously were excluded from the study. A written informed consent was obtained from the subjects.

Results

The mean age 48.5 ±30 years and male/female ratio 12/14 (Table 1). Most of them (80%) had neck rigidity (Table 2). CSF studies in all the patients showed lymphocytic exudate with CSF pleocytosis varying from 14to1500cells/cumm (average 201.03), CSF Protein was 51-319 mg/dl (average 128.31), CSF sugar was17-165 mg/dl (average 68.03) and CSF ADA was10-38 Units/l (average15.84) (Table 3).TBM was diagnosed on combined clinical presentations, CSF biochemical parameters of lymphocytic pleocytosis with CSF ADA cut off > 10. All the patients showed a good clinical recovery on ATT and all were discharged between 5 to 9thdays of admission.

Table 1 The demographic profile of the patients and their clinical characteristics (n=25)

Variables	Numbers	Percentage
Men	12	41.15%
Women	14	53.83%
Age 18-25	4	15.38%
Age 26-40	5	19.23%
Age 41-75	17	65.38%

Table 2 Clinical presentation of patients

Clinical feature	Number	Percentage
Fever	24	92.3%
Headache	22	84.6%
Vomiting	15	57.69%
Neck rigidity	21	80%
Altered sensorium	13	50%
Seizure	7	26.9%

Cranial nerve deficit	1	3.84%

Table 3 CSF characteristics of the TBM patients

Parameters	Total cell Count/cumm	Lymphocytes /cumm	Sugar mg/dl	Protein mg/dl	ADA unit/l
Range	14-1500	60-100	17-165	51-319	10-38
Mean(average)	201.03	84.46	68.03	121.38	15.84

Discussion

In our study, most of the patients presented with fever, headache and altered sensorium. The fever duration varied from 5 days to a month. One of the patients had 3rd cranial nerve palsy and seven patients had seizures documented during the admission period (Table 2).All the patients were resident of Province 2 in southern Nepal. In National Tuberculosis programme (NTP) report 2017/18 of Nepal, more than three-fifths of all TB cases (21,462, 66%) were reported from Province 2, Province 3 and Province 5. In terms of eco-terrain distribution, Terai belt (southern Nepal) reported more than half of cases (18,590, 57%)[1].

Three studies have investigated the role of GeneXpert in the diagnosis of TBM[4-6], and found the assay to be around 60% sensitive and nearly 100% specific. A 2016 systematic review and meta-analysis found that the overall sensitivities of blood and CSF IFNγ release assays were 78% and 77% respectively, with 61% and 88% specificity[7]. Two systematic reviews and meta-analyses have examined the diagnostic accuracy of CSF levels of adenosine deaminase in TBM[8]. For adenosine deaminase values from 1–4 U/l, the sensitivity and specificity were >93% and <80%, respectively, compared with >96% and <59% for values >8 U/l. A cut-off value of 10 U/L for patients with TBM gave a sensitivity and specificity of 90.62% and 95.65%, respectively; thus proving that CSF ADA activity is a rapid and affordable adjunct in differentiating TBM from non-TBM[9s].

All the patients were started on 4 drug ATT (weight-based rifampicin, isoniazid, pyrazinamide and ethambutol) as per NTP CAT 1 ATT protocol. All the patients showed a good clinical recovery with improvement in sensorium and other parameters. One patient developed jaundice on third day of ATT and was shifted in Modified ATT regimen with streptomycin, ethambutol and ofloxacin. One patient developed progressive visual loss and was diagnosed as ethambutol induced optic neuritis for which ethambutol was withdrawn from treatment regimen. These patients were discharged within 9 days of admission with follow up as scheduled. All the patients were followed up for ATT response and those who did not come for follow up were contacted over phone. Four of the patients lost follow up. All those who were followed up for 6 month had good recovery and they completed ATT treatment.

Although the present study identified TBM in resource limited settings, there were also certain limitations of the study. Firstly, the most significant limitation are the newer tests such as the TB-spot test, CSF IGRA, CSF gene Xpert which were not performed in the patients due to unavailability in the region as well as the tests were unaffordable by the patients included in the study. Furthermore, the current study did not include cases with other meningitis types, such as bacterial and viral meningitis. The present study is only a preliminary analysis of TBM in patients of province 2 of southern Nepal where people have limited healthcare access and people have to pay their own healthcare bills. However, in a resource limited country like Nepal, where the poor people pay their own medical bills and most of them cannot afford even basic medical care, clinical presentations, CSF biochemistry and CSF ADA can be considered as a combined diagnostic tool for establishing the diagnosis of TBM.

Conclusion

All the 26 patients diagnosed as TBM on the combined criteria of clinical presentations and CSF value showed a good recovery on antitubercular therapy and was discharged on treatment. In conclusion, in a resource limited setting and high index of suspicion with high endemicity, the combined clinical history, lymphocytic predominant CSF with CSF ADA value more than 10 unit/L, can be assured as the Diagnostic marker of TBM.

Conflict of Interest: None

Acknowledgement: We acknowledge Department of pathology, Terai Hospital and Research Centre, Birgunj, Nepal for their support.

References

1. Newell JN, Baral SC, Pande SB, Bam DS, Malla P. Family-member DOTS and community DOTS for tuberculosis control in Nepal: cluster-randomised controlled trial. The Lancet. 2006;367(9514):903-909.

2. Organization WH. Global tuberculosis control: surveillance, planning, financing: WHO report 2008. Vol. 393. World Health Organization; 2008. ISBN: 9241563540.

3. Solari L, Soto A, Agapito JC, Acurio V, Vargas D, Battaglioli T, Accinelli RA, Gotuzzo E, Van Der Stuyft P. The validity of cerebrospinal fluid parameters for the diagnosis of tuberculous meningitis. International Journal of Infectious Diseases. 2013;17(12):e1111-e1115.

4. Patel VB, Theron G, Lenders L, Matinyena B, Connolly C, Singh R, Coovadia Y, Ndung'u T, Dheda K. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting: a prospective study. PLoS medicine. 2013;10(10):e1001536.

5. Bahr NC, Tugume L, Rajasingham R, Kiggundu R, Williams DA, Morawski B, Alland D, Meya DB, Rhein J, Boulware DR. Improved diagnostic sensitivity for tuberculous meningitis with Xpert® MTB/RIF of centrifuged CSF. The International Journal of Tuberculosis and Lung Disease. 2015;19(10):1209-1215.

6. Nhu NTQ, Heemskerk D, Chau TTH, Mai NTH, Nghia HDT, Loc PP, Ha DTM, Merson L, Van Thinh TT, Day J. Evaluation of GeneXpert MTB/RIF for diagnosis of tuberculous meningitis. Journal of clinical microbiology. 2014;52(1):226-233.

7. Yu J, Wang Z, Chen L, Li H. Diagnostic accuracy of interferon-gamma release assays for tuberculous meningitis: a meta-analysis. The International Journal of Tuberculosis and Lung Disease. 2016;20(4):494-499.

8. Xu H, Jiang R, Li L, Sha W, Xiao H. Diagnostic value of adenosine deaminase in cerebrospinal fluid for tuberculous meningitis: a meta-analysis. The International Journal of Tuberculosis and Lung Disease. 2010;14(11):1382-1387.

9. Mishra O, Loiwal V, Ali Z, Nath G, Chandra L. Cerebrospinal fluid adenosine deaminase activity for the diagnosis of tuberculous meningitis in children. Journal of tropical pediatrics. 1996;42(3):129-132.