IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 4 Ser.14 (April. 2022), PP 18-24
www.iosrjournals.org

The Etiological Spectrum of Acute Febrile Encephalopathy in Adult Patients

Dr. Zaki Siddiqui [1], Dr. Arvind Kankane [2]
Dr. Uday Pratap Yadav[3]
[1]*Associate Professor, Department of General Medicine, M.L.B., Jhansi, Uttar Pradesh, India*
[2]*Associate Professor and Head, Department of Neurology, M.L.B., Jhansi, Uttar Pradesh, India*
[3]*Junior Resident, Department of General Medicine, M.L.B., Jhansi, Uttar Pradesh, India*

Abstract:
Background: *Acute onset fever with altered mentation is a common problem encountered by the physician practicing in tropical countries. Central nervous system (CNS) infections are the most common cause resulting in fever with altered mentation in children.*
Aim: *In this study, we have tried to analyse the clinic-etiological spectrum of acute febrile encephalopathy in adult patients in Bundelkhand region and the outcome of the patients of different etiological profile.*
Setting and design: *This study is a hospital based cross-sectional observational study conducted in M.L.B Medical College, Jhansi (U.P.). The study includes all acute febrile encephalopathy patients coming to Emergency Department, M.L.B. Medical College.*
Material and methods: *A total of 102 patients with fever of less than 2 weeks duration along with alteration in mentation were studied over a period of 12 months. The demographic variables were recorded in detail. In addition to routine investigations, cerebrospinal fluid analysis and non-contrast computerised tomography were performed in all the subjects. MRI and CSF PCR were done is patients where needed.*
Statistical analysis: *The results were analysed using SPSS statistical software. The values were expressed as mean with standard deviation for contiguous variable as percentage for the others.*
Results: *Out of 102 patients TBM (n=45,44%) was the most common etiology followed by the pyogenic meningitis (N=23,22%). In our study acute viral meningo-encephalitis was found in 18(18%), Septic associated encephalopathy in 12(12%) and cerebral malaria in 4(4%) of patients. Most of the patients (n=80,76%) were discharged, n=22,(24%) were expired during hospital stay.*
Conclusion: *Tubercular meningitis remains the leading cause of AFE in our area. Early detection and management of tuberculosis can prevent this complication which can significantly benefit the patients of Bundelkhand region. Improving access to health care, both therapeutic and diagnostic, early case detection and communication at community level can, can significantly reduce the morbidity and mortality due to AFE.*
Key words: *acute febrile encephalopathy; tubercular meningitis; septic associated encephalopathy; cerebrospinal fluid polymerase chain reaction*

Date of Submission: 18-04-2022 Date of Acceptance: 04-05-2022

I. Introduction

Acute febrile encephalopathy (AFE) is a clinical term used to describe patients presenting with short febrile illnesses with altered mental state. It is a very common clinical entity encountered by every physician in emergency departments. Although AFE is one of the major causes of hospital admissions of children and adults in India, only a few studies have been done so far[1].

Central nervous system (CNS) infections are the most common causes of altered mental status in patients with nontraumatic coma. The various etiologies are viruses, bacteria, or parasites. The classical symptoms of acute bacterial meningitis are fever, headache, meningismus, and progressive decrease in level of consciousness. Usually CNS infection by a viral agent cause meningoencephalitis. Encephalitis is defined as an inflammation of the brain. Acute febrile illness of viral cause have evidence of meningeal involvement characteristic of meningitis, as well as encephalitis characterised by altered level of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma, and evidence of either focal or diffuse neurologic signs and symptoms. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state, focal or generalized seizures[2].

Etiological agents vary across different geographical areas and even between seasons in the same area. In developing countries, high population, inadequate accessibility to health infrastructure, bacterial meningitis, JE, HSV are the common causes of AFE, tuberculous meningitis (TBM) can present with acute, subacute and chronic meningitis, while cerebral malaria is not very uncommon. Sepsis associated encephalopathy (SAE) is quite common in elderly patients and with co-morbidities. Even with best diagnostic efforts, up to 70% cases of suspected viral encephalitis remain of unknown etiology. (Glaser et al 2003[3], 2006[4], Kupila et al 2006[5]). However, cases of antibody mediated autoimmune encephalitis are increasingly recognized as important causes of encephalitis and may present a portion of the unknown and unidentified encephalitis cases but the incidence of autoimmune encephalitis at population level is 0.8/100000. (Dubey et al[6])

Mostly patients with acute febrile encephalopathy can make complete neurological recovery once the underlying cause is identified and treated promptly and appropriately, but considerable skill and knowledge is required to distinguish the various groups. This study is carried out to evaluate the patients presenting with AFE in a tertiary care center in Bundelkhand region of India to understand the etiology, prevalence, and their outcomes, over a period of 1 year

II. Aims And Objectives

- To identify the etiological profile of acute febrile encephalopathy in adult patients (AEF).
- To know outcome in terms of completely recovered, partially recovered (improvement in GCS, Residual deficit) and death occurred in adult patients with acute febrile encephalopathy at the time of discharge

III. Materials And Methods

This study is a hospital based cross-sectional observational study conducted in M.L.B Medical College, Jhansi (U.P.). The study includes all acute febrile encephalopathy patients coming to Emergency Department, M.L.B. Medical College, Jhansi during the period March 2020 to October 2021 who qualify the inclusion criteria. The study is conducted after obtaining permission from the Institutional ethics committee

Inclusion criteria:

 All patients above 18 years of age admitted with fever of less than 2 weeks duration with altered sensorium, either at onset or following fever.

Exclusion criteria:

- Patients with traumatic coma.
- Patients with cerebral palsy and seizure disorder.
- Patients having structural brain disease.
- Patients with metabolic encephalopathy (hepatic encephalopathy, uremic encephalopathy etc.)

Methodology

- The detailed history of the patients is recorded. Any comorbid condition like diabetes mellites, systemic hypertension, tuberculosis, cerebrovascular accident is recorded with ongoing or past history of any form of tuberculosis and they underwent a detailed clinical examination. Hemogram, arterial blood gas analysis, metabolic profile, and electrocardiogram are done in all patients.
- Peripheral smear for malaria parasite is examined in all the patients. And Histidine-rich protein-based immunochromatographic card test for f*alciparum* malaria is performed in patients with negative peripheral smears where clinical suspicion for complicated malaria is high.
- All patients are screened for HIV, HBsAg and HCV.
- All patients undergo X-ray chest P/A view, non-contrast computed tomography (CT) of head (16 slice Philips) installed in department of Radiology of our institution.
- Lumbar puncture is carried out in all the patients at admission and cerebro-spinal fluid (CSF) was analyzed for cytology, protein levels, CSF glucose to blood glucose ratio, gram stain, India ink stain for fungal aetiology. CSF culture sensitivity, CSF adenosine deaminase levels, CBNAAT and COMBO PCR DNA is done in patients where needed. NIV JE MAC Elisa kit is used for JE and TAQMAN (Real Time PCR) kit is used for HSV-1 and HSV-2 from Department of Microbiology KGMU Lucknow.
- Some patients undergo MRI brain (0.3 Tesla Hitachi) when available and where needed.

Patients were classified into broad groups of pyogenic meningitis (PYOGENIC MENINGITIS), viral encephalitis (meningoencephalitis), tubercular meningitis (TBM) and other clinical syndromes on the basis of predesigned diagnostic criteria as following.

Diagnostic criteria used for different etiologies of acute febrile encephalopathy[7]

	DIAGNOSTIC CRITERIA
Pyogenic Meningitis	Fever with altered sensorium + CSF cytology +_ Meningeal enhancement on CT and MRI
Tubercular Meningitis	Fever with altered sensorium + CSF cytology +_ Parenchymal enhancement on CT and MRI +_ CSF ADA>10 +_ CSF PCR
Viral Meningitis	Fever with altered sensorium + CSF cytology +_ Parenchymal enhancement on CT and MRI +_ CSF PCR +_ clinical co-relation
Cerebral Malaria	Fever with altered sensorium + Normal CSF cytology +_ Normal CT and MRI brain +_ HRP antigen test for malaria +_ clinical co-relation
Septic Associated Encephalopathy	Fever with altered sensorium + Normal CSF cytology +_ Normal CT and MRI brain +_ sepsis

Normal composition of CSF[8]

	Normal range
Color	Clear
Specific gravity/pH	1.006–1.007/7.4
Opening pressure	50–200 mm H_2O
RBCs count	Nil
WBC count	0–5 (upto 30 in neonates)
WBC types	Lymphocytes
CSF Proteins	15–40 mg/dL
CSF lactate	1–3 mmol/ L
CSF glucose	50–80 mg/dL (two thirds of blood glucose
Microbial examination	No microorganism

CSF analysis in various types of meningitis

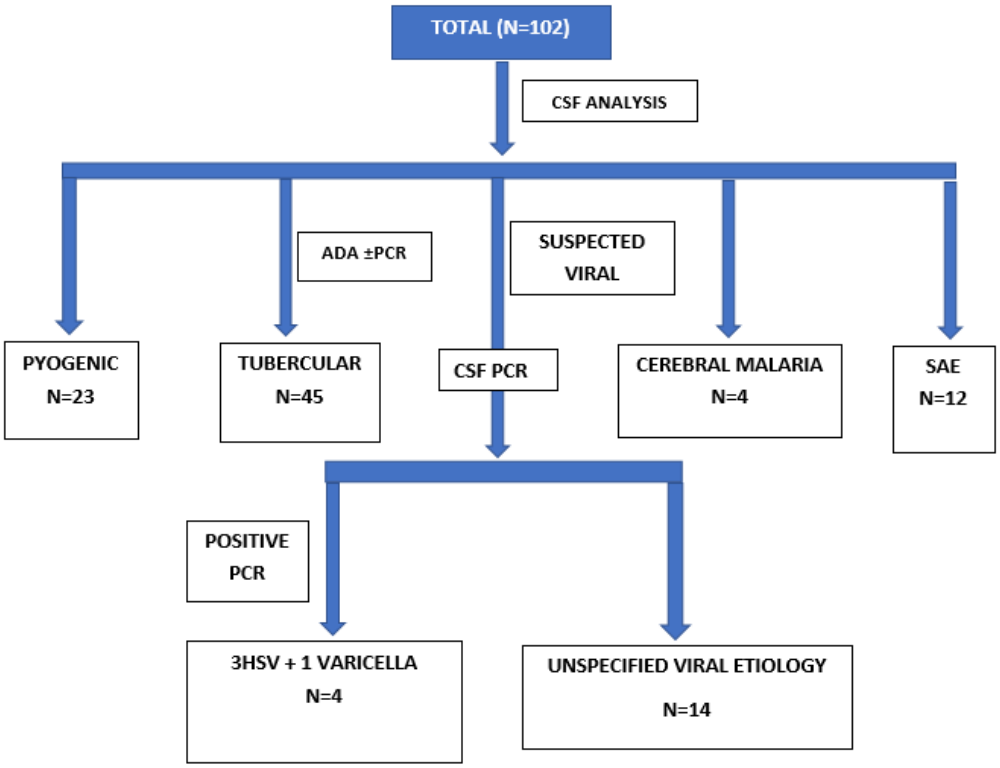
CSF analysis	*Bacterial*	*Tuberculosis*	*Viral*	*Aseptic*
Pressure	Increased	Increased	Normal to elevated	Increased
Color	Turbid	Turbid	Clear	Clear to turbid
Glucose	< 40 mg%	Low	Normal to mild less	Low
Proteins	Elevated	Greatly elevated	Normal to mild elevation	Elevated
Lactate	Elevated (> 6 mmol/L)	Elevated	0–6 mmol/L	Normal
RBCs	Elevated	Elevated	Normal	Elevated
WBCs	10-2000/ cu mm	Elevated, but < 500	>100/ cu mm	Mildly elevated
WBC types	Neutrophils	Lymphocytes	Lymphocytes	Neutrophils
Gram stain	Positive	Acid fast bacilli	Negative	Negative
Microbial Culture	Positive	Positive (yield is high in early stages)	Negative	Negative

[9]

GLASGOW COMA SCALE[10}

Behavior	Response	Score
Eye opening response	Spontaneous--open with blinking at baseline	4
	To verbal stimuli, command, speech	3
	To pain only (not applied to face)	2
	No response	1
Verbal Response	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate words	3
	Incomprehensible speech	2
	No response	1
Motor Response	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Flexion in response to pain (decorticate posturing)	3
	Extension response in response to pain (decerebrate posturing)	2
	No response	1

All the patients underwent lumber puncture. CSF analysis was performed patient were classified and diagnosed according to following scheme.



IV. Result

Variables		PYOGENIC [N=23]	TUBERCULAR [N=45]	SAE [n=12]	VIRAL ENCEPHALITIS [N=18]	CEREBRAL MALARIA [N=4]
Age (mean-37.26)	18-34	12	23	0	6	2
	35-49	5	7	1	7	2
	50-60	2	8	4	4	0
	>65	4	7	7	0	0
Sex	Male	16	23	6	3	3
	Female	7	22	6	15	1
Mean GCS at presentation		10.34	10.6	10.41	11.33	12.1
Fever		23 (100%)	45 (100%)	12 (100%)	18 (100%)	4(100%)
Headache		17 (73%)	33 (73%)	4 (33%)	15 (83.3%)	3(75%)
Neck rigidity		21 (91%)	42 (93%	2 (16%)	15 (83%)	2(50%)
Seizure		2 (8.7%)	4 (8.8%)	2 (16%)	5 (27%)	0
Hydrocephalus		0	27 (60%)	1 (8%)	0	0
Mean duration of hospital stay (in days)		8.95	17.13	8.25	14.44	7.22
Co-morbidity		4	4	5	0	0
Outcome	Fully recovered	15	30	13	4	4
	Partial recovery	2	10	1	0	0
	Death	6	5	4	0	0

1. There is equal distribution of AFE in both the sexes, having no sex predominance**.** The AFE involves all the age groups with mean age of 41.21. In our study the age group which is most affected is 18-34 and least affected is >65.
2. Clinical features across various aetiologies of AFE were fever (100%), altered mental status (100%), headache (71.5%), neck rigidity (80.9%), seizure (12.74%), and ear discharge (2%).

3. Out of 102 patients TBM (n=45,44%) was the most common etiology followed by the pyogenic meningitis (N=23,22%). In our study acute viral meningo-encephalitis was found in 18(18%), Septic associated encephalopathy in 12(12%) and cerebral malaria in 4(4%) of patients.
4. Outcome in terms of discharge or death is documented at the time of discharge. Most of the patients (n=80,76%) were discharged (fully recovered 67+ partially recovered 13), 22(24%) were expired during hospital stay.

V. Discussion

This study was done primarily to look at the wide spectrum of aetiology is that can present as acute febrile encephalopathy to emergency department. Most of the studies has been done previously in different parts of India but this is the first study from Bundelkhand region of India.

The study population included patients from all age groups though younger age group 18 to 34 years is found to be affected most. Though the infectious aetiology can occur in all age groups but the median age of Indian population is 28 years. There-fore all infectious disease shall have higher incidence among younger population.

In study done by Manoj job et al in 2017[11] of 265 adult patient primary aetiology was infectious, out of which bacterial 25% (47), tubercular 24% (45), viral with specific aetiology 9% (19) and unknown aetiology 34% (64) were found. In another retrospective cross-sectional study done by Elham Peidaee et al in Iran in 2017**[12]**, total of 293 patients with the mean age of 49.7 ± 23 were evaluated of whom 77.1% presented with encephalopathy syndrome. The most common diagnosis in patients with clinical syndromes suggestive of central nervous system (CNS) infection was sepsis associated encephalopathy (SAE) (22.9%), followed by bacterial meningitis (14%) and neuro-tuberculosis (9.9%). How-ever in our study of 102 patient tubercular meningitis was most common 44% (45) aetiology followed by pyogenic meningitis 23 (22%). Viral meningitis was found in 18% (18), septic associated encephalopathy in 12% (12) and cerebral malaria in 4% (4).

Tuberculosis has highest prevalence in Uttar Pradesh as published in India TB Report 2019 contributing to 20% of national TB burden (Jhansi -9462). Bundelkhand region is socioeconomically poor with a sparse healthcare infrastructure. Because of less awareness to disease, poor reach to healthcare facility and less adherence to treatment patients present with complication of TB like neuro-tuberculosis which can be the cause of higher prevalence of tubercular meningitis in our study.

A study conducted in South India by E U Maheshwari et al 2019**[13]** on 60 patients of neuro-tuberculosis demonstrated that the age group of the enrolled patients was in the range of 14–59. The mean age was 28 years, with 27 patients (45%) in 20–29 age group and overall CNS-TB has male preponderance with a ratio of male/female 1.86. Nearly 75% of those treated with RNTCP regimen were rendered asymptomatic after completion of treatment. Treatment failure was 8.33%, and death rate was 3.33%. In 16.66% lost to follow-up. In others studies done by Bhargava S et al**[14]** and Offenbacher et al**[15]** reveal that hydrocephalus was found in 78% on brain imaging. In our study total of 45 patients of tubercular meningitis were found with similar results. Patients had mean age of 39.88 years. All enrolled patients were of 18 to 72 years of age. Majority of affected were of the age group of 18 to 34 years. The distribution of illness was almost equal in both male and female. Almost 89% of patients are treated successfully and 11% of patient died. Our study also revealed that most common finding on imaging in the patient with tubercular meningitis to be hydrocephalus (N=27, 60%). The higher mortality rate found in our study can be attributed to the fact that the patients who presented to our hospital were having advance stage of illness due to late presentation.

A study done by P Madhumitha et al 2008**[16]** done in MAMC Delhi of 120 consecutive patients with clinical acute meningitis, had a mean age of 32.58 ± 13.32 years (range 15-70 years). Of these 67 (56%) were male and 53 (44%) were female. Fever (98.3%), headache (95.85%), neck stiffness (90.7%), nausea (94.9%) and vomiting (94%) were the common clinical findings. Ten patients (8.5%) had loss of consciousness while 4 had seizures (3.4%). We also found the similar results. In our study 23 patient had pyogenic meningitis with mean age of 37.26 years (range 20 to 65 year). Out of these 16(69%) were male and 6 (31%) were female. 100% patients presented with fever, 91% had neck rigidity, 73.9% had headache, 8.69% had seizure. Our study is consistent with where 98.3% patient showed fever, 95.85% patients showed headache, 90.7% patients showed neck stiffness and 3.4% had seizures. A national wide multicentered study of Korea by S.Y. Moon et al 2010**[17]** on etiology of community acquired bacterial meningitis demonstrated the mortality rate of 20.5%. We also found 26% of case fatality rate of pyogenic meningitis.

Study conducted in SGPGI Lucknow by J Kalita et al 2017**[18]** on acute infectious encephalitis on 164 patients demonstrated the mean age of 35 years with slight female predominance (61%). Common viruses identified were JE and HSV. The mortality rate was 26%. In our study results were quite similar. 18 patients were found to have viral aetiology, out of which four were having a specific aetiology proven by polymerase chain reaction (4 HSV and 1 varicella) and rest of the patient of suspected viral etiology were categorised on

clinic o-radiological basis. Their mean age was 34 and 15 (83%) were female. The mortality rate of viral aetilogy was 23%.

12 patients were found to have septic associated encephalopathy in our study. It affected older patients with mean age of 66 years (range 40 to 80 years). Both male and female were equally affected. The most common source of sepsis was found to be pneumonia (7 patients) followed by urinary tract infections (4 patients). The study by Angus DC et al[19] also suggests that pneumonia is the most common cause of sepsis. 7 (58%) Seven patients died due to complications of septic associated encephalopathy. The higher rates of mortality can be attributed to the fact that the patient where of elder age group with multiple comorbidities and also there were multiple organ dysfunction found in these patients.

On analysing the outcome, it was seen that 67 patients had recovered completely. 13 patients had partial recovery with neurological sequelae. 22 patients had died.

Comparing the mortality with other studies, like Bhalla et al (2010)[1], Modi et al (2015)[7] and Yatendra Singh et al (2017)[20] where the overall mortality were 16.5% ,13.4% and 21% respectively. The mortality rate recorded in our study was 22% which is similar to that of Yatendra Singh et al (2017)[20] study but higher than that of other studies. As this hospital caters to vast region of Bundelkhand and many of the patients present late at an advance stage of illness due to poor connectivity and poor healthcare infrastructure, mortality rate can be high.

On further analysis it was found that maximum mortality was due to septic associated encephalopathy 31.8% followed by pyogenic meningitis (27.2%) and viral encephalitis. This mortality rate of aetiology was similar with previous studies done by Bhalla at al[1] and Modi et al[7]. The fact that maximum mortality was seen in patients with septic associated encephalopathy symptoms signifies that multi-organ dysfunction may have contributed to a large extent in these patients. (Indraneel Sen et al 2019)[21]

Modi et al[20] study found higher incidence of viral meningoencephalitis in post-monsoon season. We also found the similar result in our study.

There are few limitations to this study. Firstly all the patients who were included in the study where the ones with access to healthcare at tertiary medical Centre or were referred to the Centre which may lead to referral bias. The finding of the study therefore, are not representing the prevalence of aetiology of acute febrile encephalopathy of community. Secondly polymerase chain reaction could not be done for all patient with suspected viral encephalitis and this is limited by availability of the test. We also do not have the test for all viruses by polymerase chain reaction. Thirdly the autoimmune encephalitis aetiology of acute febrile encephalopathy could not be found due to unavailability of the test in Bundelkhand region and due to the high cost.

VI. Conclusion

AFE has high proportion of morbidity and mortality across the various aetiologies. The knowledge about the etiological spectrum of febrile encephalopathy across different geographic regions as well as for different age groups is a necessity for protocol development at the regional level. Our study demonstrated that tubercular meningitis has the highest proportion of acute febrile encephalopathy among adult patients with CNS infection along with pyogenic meningitis and viral meningo-encephalitis in Bundelkhand region. It is considerable to state that in patients presenting with AFE in emergency should be evaluated with high index of suspicion for tubercular meningitis along with other factors. Across the spectrum of AFE, septic associated encephalopathy has the highest mortality burden as the patients were terminally ill with multiple comorbidities. This is the pilot study of Bundelkhand region to determine the clinico-etiological profile of AFE. As the number of study subjects was limited, our findings need to be corroborated in future large scale studies done at community level.

The significant inference derived from our study is that, tubercular meningitis remains the leading cause of AFE in our area. Early detection and management of tuberculosis can prevent this complication which can significantly benefit the patients of Bundelkhand region.

Improving access to health care, both therapeutic and diagnostic, early case detection and communication at community level can, can significantly reduce the morbidity and mortality due to AFE

References

[1]. Bhalla A, Suri V, Varma S, Sharma N, Mahi S, Singh P, et al. Acute febrile encephalopathy in adults from Northwest India. J Emerg Trauma Shock 2010;3:220-4.

[2]. Roos KL, Wilson MR, Tyler KL. Encephalitis. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. Harrison's Principles of Internal Medicine 21e. McGraw Hill; 2021.

[3]. Glaser, C.A., Gilliam, S., Schnurr, D., et al., 2003. California Encephalitis Project, 1998-2000. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. Clin Infect Dis 36, 731-742

[4]. Glaser, C.A., Honamand, S., Anderson, C.J., et al., 2006. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis 43, 1565-1577.

[5]. Kupila, L., Vuorinen, T., Vainionpää, R., et al., 2006. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology 66, 75-80.

[6]. Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol (2018) 83(1):166–77.

[7]. Modi, Aniyang & Atam, Virendra & Jain, Nirdesh & Gutch, Manish & Verma, Rajesh. (2012). The etiological diagnosis and outcome in patients of acute febrile encephalopathy: A prospective observational study at tertiary care center. Neurology India. 60. 168-73. 10.4103/0028-3886.96394

[8]. Seehusen DA, Reeves MM, Fomin DA Am Fam Physician. 2003 Sep 15; 68(6):1103-8.

[9]. Hrishi AP, Sethuraman M. Cerebrospinal Fluid (CSF) Analysis and Interpretation in Neurocritical Care for Acute Neurological Conditions. Indian J Crit Care Med. 2019;23(Suppl 2):S115-S119. doi:10.5005/jp-journals-10071-23187

[10]. https://www.ncbi.nlm.nih.gov/books/NBK513298/

[11]. Manoj Job, S B (2017) Clinical Spectrum, Diagnostic and Outcome Predictors of patients with Acute Febrile Encephalopathy in a Tertiary Hospital in South India. Masters thesis, Christian Medical College, Vellore

[12]. Elham Peidaee, Fereshte Sheybani, HamidReza Naderi, Nasrin Khosravi, Mehdi Jabbari Nooghabi, "The Etiological Spectrum of Febrile Encephalopathy in Adult Patients: A Cross-Sectional Study from a Developing Country", Emergency Medicine International, vol. 2018, Article ID 3587014, 8 pages, 2018

[13]. Maheswari EU, Bhoopathy RM, Bhanu K, Anandan H. Clinical Spectrum of Central Nervous System Tuberculosis and the Efficacy of Revised National Tuberculosis Control Program in its Management. J Neurosci Rural Pract. 2019;10(1):71-77. doi:10.4103/jnrp.jnrp_163_18

[14]. Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis – A CT study. Br J Radiol. 1982;55:189–96.

[15]. Offenbacher H, Fazekas F, Schmidt R, Kleinert R, Payer F, Kleinert G, et al. MRI in tuberculous meningoencephalitis: Report of four cases and review of the neuroimaging literature. J Neurol. 1991;238:340–4.

[16]. Madhumita P, Gupta N. Clinical and bacteriological spectrum of community-acquired acute bacterial meningitis in adults at a tertiary care hospital in northern India. Int J Nutr Pharmacol Neurol Dis [serial online] 2011 [cited 2022 Mar 2];1:194-200

[17]. Moon SY, Chung DR, Kim SW, Chang HH, Lee H, Jung DS, Kim YS, Jung SI, Ryu SY, Heo ST, Moon C, Ki HK, Son JS, Kwon KT, Shin SY, Lee JS, Lee SS, Rhee JY, Lee JA, Joung MK, Cheong HS, Peck KR, Song JH. Changing etiology of community-acquired bacterial meningitis in adults: a nationwide multicenter study in Korea. Eur J Clin Microbiol Infect Dis. 2010 Jul;29(7):793-800. doi: 10.1007/s10096-010-0929-8. Epub 2010 May 1. PMID: 20432052

[18]. J. Kalita, V.E. Mani, S.K. Bhoi, U.K. Misra, Spectrum and outcome of acute infectious encephalitis/encephalopathy in an intensive care unit from India, QJM: An International Journal of Medicine, Volume 110, Issue 3, March 2017, Pages 141–148,

[19]. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001 Jul;29(7):1303-10. doi: 10.1097/00003246-200107000-00002. PMID: 11445675

[20]. Yatendra Singh1, Vivekanand Satyawali2, Jainendra Kumar3, Sandeep Raj Saxena.Acute Febrile Encephalopathy: An Experience from Tertiary Care Centre.Annals of International Medical and Dental Research, Vol (3), Issue (5)Received: July 2017 Accepted: July 2017.

[21]. Sen, Indranil & Bhattacharya, Sougata & Bhakta, Sourav & Ranjan, Sumit. (2019). A STUDY ON ETIOLOGICAL PROFILE IN ADULTS WITH ACUTE FEBRILE ENCEPHALOPATHY IN A TERTIARY CARE CENTRE IN EASTERN INDIA. International Journal of Medical and Biomedical Studies.

Dr. Zaki Siddiqui, et. al. "The Etiological Spectrum of Acute Febrile Encephalopathy in Adult Patients." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(04), 2022, pp. 18-24.