Original Article

Study of Hyponatremia in Acute CNS Infections in A Tertiary Center

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Keywords: *Meningitis, Encephalitis, CNS infection, Tuberculosis, Hyponatremia, CNS TB, Meningoencephalitis*

Abstract

Introduction: Hyponatremia significantly contributes to morbidity and mortality in CNS infections. Accurate diagnosis and timely intervention of hyponatremia is necessary as it can exacerbate the symptoms and may cause delay in management.

Methods: This cross-sectional study was done in 146 consenting adults diagnosed with acute CNS infections at Tribhuvan University Teaching Hospital (TUTH) over one year. All participants underwent clinical assessments, including cerebrospinal fluid (CSF) analysis, blood tests, and imaging. Prevalence and severity of hyponatremia was studied. Data was entered into MS Excel and subsequently transformed into IBM SPSS Software version 25 for statistical assessment.

Results: Hyponatremia was prevalent in 34.25% of cases; of which 56% were moderate in severity. Altered mental state, fever, and headache were common clinical features. In terms of etiology, viral infections (45.8%), followed by CNS TB (30.8%) were common.

Conclusion: Our study identified that hyponatremia was prevalent in more than one third of patients having CNS infections, encephalitis being the most common clinical syndrome. In terms of etiology, viral infections constituted the majority, followed by tubercular, bacterial, fungal, and parasitic infections.

Introduction

Despite the development of antibiotics, vaccinations, and other medical treatments, CNS infections continue to cause significant morbidity and mortality around the world.[1] Meningitis, encephalitis, and brain abscesses are different forms in which CNS infections manifest. Meningoencephalitis is a term used to describe patients with overlapping clinical characteristics of meningeal irritation and brain parenchymal involvement.[2] The majority of CNS infections are community-acquired, but in case of trauma or intracranial cerebrospinal fluid shunts and external drains, certain patients may develop healthcare-associated meningitis.[3]

The burden of CNS infections is unequally distributed geographically, affecting primarily low and middle-income nations. Because population-wide data are sparse, there is a great deal of variation in the kind and location of CNS infections, and under-diagnosis and under-reporting in resource-limited settings are suspected. Thus, getting a credible worldwide assessment of the volume and burden of CNS infections has been difficult.[4]

The causative agents of acute CNS infections cannot be determined on clinical symptoms but rather require microbiological testing to determine the causing agents and facilitate prompt treatment. Although a variety of species, including bacteria, viruses, fungi, and protozoans, are capable of infecting brain tissue and causing encephalitis; viruses, particularly the herpes simplex virus (HSV), are the most common.[5] *Mycobacterium tuberculosis* is a common consideration in endemic parts of the world like our subcontinent.[6] *Neisseria meningitidis, Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Listeria monocytogenes* are among the species typically isolated in adult cases of community-acquired bacterial meningitis. Enterovirus and Herpes Simplex Virus are the two most common viral etiologies of CNS infections present in Nepal.[7]

Hyponatremia, defined as a serum sodium level of less than 135 mmol/L, is one of the leading causes of morbidity and mortality associated with CNS infection. The overall incidence of hyponatremia associated with CNS illness has been estimated to be 30%–66%.[8] Hyponatremia has been a hypothesized and observed risk in acute CNS illness.

Understanding hyponatremia in acute CNS infection is important because the diagnosis may be delayed if the neurological symptoms are attributed to hyponatremia and hyponatremia itself may exacerbate the manifestations of CNS infection. Also, in most epidemiological studies, hyponatremia is found to predict a greater mortality rate for

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hospitalized patients and improvement in hyponatremia is associated with a decreased risk of mortality.[9]

This research holds significant clinical relevance, providing a comprehensive understanding of the implications of hyponatremia in the specific context of acute CNS infections. The findings may contribute to the development of targeted management strategies and interventions, improving patient outcomes. Additionally, by elucidating factors associated with adverse outcomes, the study may guide clinicians in risk stratification and early identification of individuals at higher risk. The ultimate aim is to enhance the quality of care for patients with hyponatremia in the context of acute CNS infections, offering valuable insights for medical practitioners, researchers, and policymakers alike.

To the best of our knowledge, it is the first study of its type in Nepal and has given a picture of the problem in our context.

Materials and Methods

146 adults patients more than or equal to 18 years admitted and treated for central nervous system infection in Tribhuvan University Teaching Hospital (TUTH) ER, Wards and OPD that include meningitis, encephalitis, meningoencephalitis and brain abscess who fulfilled the inclusion and exclusion criteria and gave consent were enrolled in the study. It was a cross-sectional observational study in which the participants were sampled by convenience sampling method.

Inclusion and Exclusion criteria

Inclusion Criteria

- Age> 18 years
- Diagnosed as Acute CNS Infection by the primary treating physician and team.

Exclusion Criteria

- Patients with primary renal, liver or heart disease which explains the hyponatremia.
- Patients on diuretic therapy, poor intake, and whose urinary sodium is <20 mEq/L.
- Lumbar puncture performed to investigate non-infectious pathology such as neurological disease (e.g., multiple sclerosis), malignancy, subarachnoid hemorrhage or perioperative sampling of intracranial shunts and drains.
- Normocellular cerebrospinal fluid where infection has been excluded.
- Repeated cerebrospinal fluid samples for the same patient (only the index admission results used).

Variables and Definitions

1. **Age Category**

   Age of patients was categorized as young adults (18-35 years), Middle age adults (36-55 years) and older adults (>55 years).[10]

2. **Seizure**

   One or more episodes of new onset of generalized or focal onset, motor, or non-motor seizures.

3. **Weight Loss**

   Unintentional weight loss of at least 5% of usual body weight in the preceding 6-12 months and no the expected outcome of treatment of known illness.[11]

4. **Hypertension**

   Repeated Office BP measurement revealing SBP≥140 mm of Hg and/or DBP≥90 mm of Hg.[12]

5. **Diabetes**

   Fasting Blood Sugar ≥126 mg/dl or 2hour post prandial ≥200 mg/dl or HbA1c ≥6.5% or RBS ≥200 with classic symptoms of hyperglycemia/hyperglycemic crisis.[13]

6. **CSF Parameters**

   CSF parameters were taken at presentation and analyzed within 1 hour of lumbar puncture. Pleocytosis is defined as increased cell count ; >5 leukocytes/μL in CSF.[14]

7. **Meningitis Syndrome**

   Meningitis syndrome is clinically defined by presence of headache, photophobia and neck stiffness.[15]

8. **Encephalitis Syndrome**

   The criteria for encephalitis syndrome by International encephalitis consortium is given below.[16]

   Major Criterion (required)

   Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified.

   Minor Criteria

   (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)

   a) Documented fever ≥38° C (100.4°F) within the 72 h before or after presentation

   b) Generalized or partial seizures not fully attributable to a preexisting seizure disorder

   c) New onset of focal neurologic findings

   d) CSF WBC count ≥5/cu.mm

   e) Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset.

   f) Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause.

   Confirmed encephalitis requires one of the following:

   a) Pathologic confirmation of brain inflammation consistent with encephalitis

   b) Defined pathologic, microbiologic, or serologic evidence of acute infection with a microorganism strongly associated with encephalitis from an appropriate clinical specimen.

   c) Laboratory evidence of an autoimmune condition strongly associated with encephalitis.

9. **CNS TB**

   CNS TB is diagnosed on the basis of following criteria.[17]

   a) Microbiologically confirmed : Positive CSF Cartridge-based nucleic acid amplification test (CBNAAT), Polymerase chain reaction (PCR), or culture

   b) Clinically diagnosed: Presumptive CNS TB plus characteristic brain imaging or evidence of active TB in other organs (e.g. lungs, lymph nodes, etc.) plus negative evaluation of alternative diagnosis.

10. Hyponatremia

Hyponatremia is defined as the serum Sodium level of <135 mmol/L at two samples ≥ 12 hours apart.[18]

Mild: 130 - 134 mmol/L

Moderate: 120 -129 mmol/ L

Severe hyponatremia: <120 mmol/L

For hyperglycemia in diabetic patients, a correction factor for serum sodium of +1.6 mmol/L is to be applied for every 5.6 mmol/L increase in blood glucose above the upper limit of the reference range.[19]

11. Glasgow Coma Scale

Table 1: Glasgow Coma Scale (GCS)[20]

Parameters	Score
Eye opening	
Spontaneous	4
Response to verbal command	3
Response to pain	2
No eye opening	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible words	2
No verbal response	1
Best motor response	
Obeys commands	6
Localizing response to pain	5
Withdrawal response to pain	4
Flexion to pain	3
Extension to pain	2
No motor response	1
Total	15

12. Modified Rankin Scale

Table 2: Modified Rankin Scale (mRS)[21]

0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Statistical Analysis

Data was entered into Microsoft Excel v2309 and subsequently transformed into STATA 14 for statistical assessment. Descriptive statistics, which included percentage, mean, and standard deviation, were computed, and the results were presented in both tabular and graphical formats. The interpretation was based on 95% confidence level with statistical significance defined as P value <0.05.

Results and Analysis

From Asar 2079 BS to Shrawan 2080 BS, a total of 177 patients were admitted at TUTH as acute CNS infection. Among them, 31 individuals did not satisfy the inclusion and exclusion criteria and were thus excluded from the study. The study proceeded by enrolling 146 eligible patients, as determined by the primary treating physician and team as acute CNS infection.

Baseline characteristics of patients with acute CNS infections

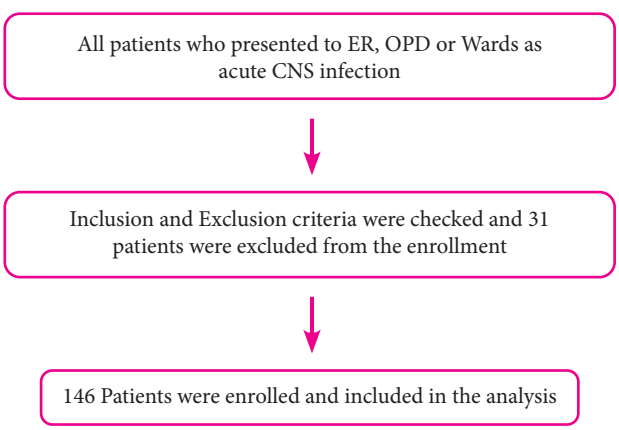

Figure 1: *Study Flow Chart*

Table 3 summarizes the baseline characteristics of patients with CNS infections. The mean age of patients with CNS infection was 46.50 ± 18.7 years with minimum age of 18years and maximum age of 87 years. On average, patients in the hyponatremia group were older, with a mean age of 51.94(18.3) years in comparison to in the normal sodium group with a lower mean age of 43.67(18.6) years. The infections were more prevalent in males, with a female-to-male ratio of 0.51:1. Hypertension (17.1%) was the most prevalent co-morbidity in CNS infection cases, followed by diabetes mellitus (11.6%). A history of tuberculosis was present in 12.3% of patients.

The mean pulse rate was higher in patients with hyponatremia, that was 100.62[17] beats per minute than the normal sodium patients 91.1(19.3) beats per minute. The mean duration of illness was found to be 19.11±19.95 days. Upon admission, the baseline mRS indicated that 12.33% of patients had an mRS ≤ 2, while 87.67% had an mRS>2 and most of them had normal sodium level.

Table 3: Baseline characteristics of patients with CNS infections

Baseline Characteristics at Admisssion		Normal Sodium (n=96) n (%)	Hyponatremia (n=50 n (%)	Total (n=146) N (%)
Age (Years)		43.67±18.33	51.94±18.67	46.50±18.7
Young Adults (18-35 years)		38 (74.5)	13 (25.5)	51 (34.9)
Middle-aged adults (36-55 years)		28 (70.0)	12 (30.0)	40 (27.4)
Older adults (>55 years)		30 (54.5)	25 (45.5)	55 (37.7)
Sex	Male	63 (64.9)	34 (35.1)	97 (66.4)
	Female	33 (67.3)	16 (32.7)	49 (33.6)
Co-morbidities	Hypertension	15 (60.0)	10 (40)	25 (17.1)
	Diabetes Mellitus	12 (70.6)	5 (29.4)	17 (11.6)
	CAD	2 (66.7)	1 (33.3)	3 (2.1)
Vitals	SBP (mm of Hg)	120.1±19.01	118.3±26.3	119.52±21.7
	DBP (mm of Hg)	75.2±11.80	74.1±14.7	74.8±12.8
	Pulse Rate (Beats per min)	91.1±19.3	100.6±17.7	94.42±19.30
Duration of illness (days)		17.14±17.87	22.90±13.153	19.11±19.95
GCS	<=8	8 (80)	2 (20)	10 (6.8)
	9-12	31 (66)	16 (34)	47 (32.2)
	13-15	57 (64)	32 (36)	89 (61)
mRS	<=2	14 (77.7)	4 (22.2)	18 (12.3)
	>2	82 (64.06)	46 (35.9)	128 (87.6)

Clinical features at presentation

Altered mental state was present in 76.0% of patients and was the commonest clinical presentation of CNS infection in our study. It was followed by fever (69.2%) and headache (67.1%). These were followed by neck stiffness (44.5%), vomiting (38.4%), seizure (21.2%), FND (18.5%), photophobia (17.1%), weight loss (9.6%), fatigue (4.8%) and dizziness (2.7%) as shown by the following bar chart in Figure 2.

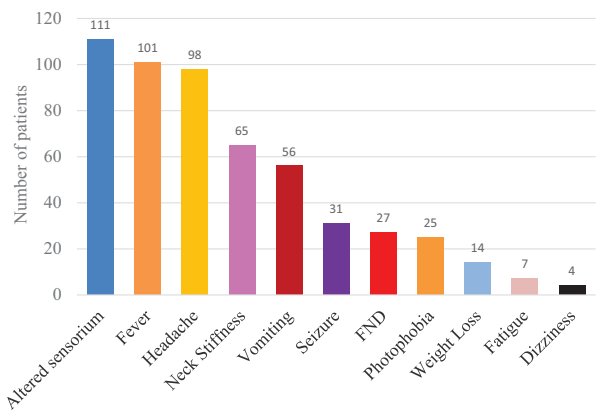

Figure 2: *Clinical features of patients with acute CNS infections*

Altered mental state, fever, and headache were the most common symptoms reported by patients with hyponatremia and normal sodium. Additionally, specific symptoms such as neck stiffness, vomiting, and seizures were more common in patients with normal sodium, while fatigue was observed more in cases of hyponatremia as depicted in table 4.

Most of the patients with CNS infections were presented as encephalitis (48%) followed by meningitis (31.5%) and meningoencephalitis (20.5%) syndromes. Almost about two-thirds of cases (65.2-66.7%) had normal sodium in each syndromic group. Hyponatremia was prevalent in almost one-third (33.3-34.8%) of each clinical syndrome with the highest prevalence in the meningitis group (35%).

Table 4: Clinical characteristics at presentation

Clinical characteristics	Normal Sodium (n=96) n (%)	Hyponatremia (n=50) n (%)	Total (n=146) n(%)
Clinical symptoms			
Altered Mental State	72(65)	39(35)	111(76)
Fever	63(62)	38(38)	101(69)
Headache	62(63)	36(37)	98(67)
Neck stiffness	46(71)	19(29)	65(44)
Vomiting	38(67)	18(32)	56(38)
Seizure	23(74)	8(26)	31(21)
FND	20(74)	7(26)	27(18)
Photophobia	15(60)	10(40)	25(17)
Significant weight loss	7(50)	7(50)	14(9)
Fatigue	3(43)	4(57)	7(4.8)
Dizziness	2(50)	2(50)	4(2.7)
Clinical syndrome			
Encephalitis	46 (65.7)	24 (34.3)	70 (48.0)
Meningitis	30 (65.2)	16 (34.8)	46 (31.5)
Meningoencephalitis	20 (66.7)	10 (33.3)	30 (20.5)

Etiology of CNS Infection

Based on etiology, acute CNS infection was classified into bacterial, tubercular, viral, fungal, and parasitic. Prevalence of viral etiology was the highest accounting for 45.8% of total cases out of which 28.3% had hyponatremia. It was followed by Tubercular etiology accounting for 30.8% of total cases among which 48.9% had hyponatremia. Bacteria were the cause of CNS infection in 13% of cases and 84.2% of those cases had normal sodium levels. Cryptococcus neoformans was the only fungus isolated in our study by Antigen test, India Ink preparation and one by culture method. It accounted for 9.6% of total cases and 35.7% of them had hyponatremia. Only one case of CNS toxoplasmosis was reported as shown in table 5.

Table 5: Etiology of CNS infection and hyponatremia

Etiology	Normal Sodium (n=96) n (%)	Hyponatremia (n=50) n (%)	Total (n=146) n (%)
Viral	49(71.6)	19 (28.3)	68 (45.8)
CNS TB	23 (51.1)	22 (48.9)	45 (30.8)
Bacterial	16(84.2)	3 (15.7)	19(13)
Fungal	8(64.2)	5(35.7)	13(9.6)
Parasitic	0	1(100)	1(0.6)

Prevalence of hyponatremia in acute CNS infection

Out of 146 patients, 50 patients had hyponatremia at presentation accounting to 34.25% of total cases. Most of the patients had moderate hyponatremia (56%) followed by mild hyponatremia (38%) and severe hyponatremia (6%) as depicted by the graph below in figure 3.

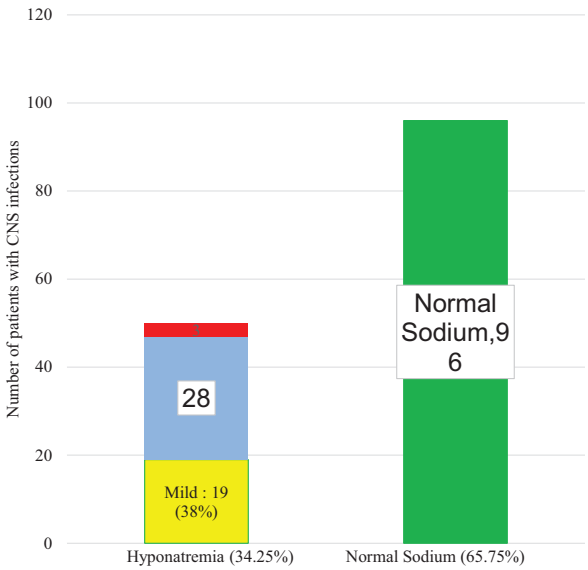

Figure 3: *Prevalence of Hyponatremia and its severity*

Discussion

The present study, "Study of hyponatremia in acute CNS infections in a tertiary care center of Nepal" with a cohort of 146 patients is the first study to the best of our knowledge in Nepal to contribute valuable insights into the association between hyponatremia and various clinical parameters in the context of acute CNS infections.

Baseline characteristics of the study population

The mean age of the patients in our study was 46.50 ± 18.70 years, which is similar to a previous multinational study that enrolled patients with >15 years and showed a mean age of 47.63 (SD ± 19.8) years.[22] However, a meta-analysis that enrolled patients from newborn to elderly showed a mean age of 35.8 years.[4] The difference in the latter might be due to the inclusion of all age group population from neonates to elderly unlike our study in which only adults were included.

The prevalence of CNS infection was higher in males (66.4%) with a female to male ratio of 0.51:1. A study done in TUTH from 2019 to 2021 also showed that the infection was more common in males with a male to female ratio of 1.43:1.[23] A study conducted in Far North Queensland, Australia with 725 cases of CNS infection and another study conducted in North India with 401 cases of CNS infection also showed a higher prevalence in males (55.3% and 54.86%, respectively), but it was lower than that in our study.[24,25]

Clinical characteristics of patients at presentation

An altered mental state was present in 76.0% of patients and was the commonest clinical presentation of CNS infection in our study which was followed by fever (69.2%) and headache (67.1%). A study done by Gajurel et al at TUTH in which fever (67.40%, n = 64, N = 95) was followed by altered sensorium (58.90%, n = 56, N = 95), and headache (53.60%, n = 51, N = 95) were the most common presenting symptoms.(23) A similar study done in India that studied the clinical spectrum of CNS infections also highlighted fever (94.5%) as the most common presenting symptom followed by altered mental status (76.6%) and headache (70.6%).[25] The higher prevalence of altered sensorium can be explained by the fact that most of the cases were referred after being treated as undifferentiated fever by antibiotics at outer center. Other reasons might be the delay in seeking health care, associated dyselectrolytemia, age factors and polypharmacy. Generalizing the results, altered sensorium, fever and headache were the commonest symptoms of acute CNS infections that align with other national and international studies.

Etiology of CNS infection

Our study revealed viruses to be the most common cause (45.8%) of acute CNS infection followed by Tubercular etiology accounting for 30.8% of total cases. As per the study done by Gajurel et al at TUTH, Tubercular (32.60%) was the most common etiology, followed by viral (27.40%).(23) Similar study done in Patan Hospital showed that etiology could be identified in only 38% of 87 cases studied. Most of them had viral etiology; JEV and Enteroviruses.[7] Another observational study conducted in Malaysia found out that tuberculous meningitis was not only the most diagnosed CNS infection, but also a cause of significant mortality and morbidity among the patients.[26] Variation in the results across different studies might be attributed to the changing epidemiology of CNS infection in our context, modalities of diagnosis, clinical suspicion and geographical differences.

Prevalence of hyponatremia and its severity

This study revealed that 34.25% of our patients with acute CNS infections had hyponatremia which was comparable to an Australian study by Lim et.al from 2015 to 2018 in which the prevalence was 39% of 184 patients enrolled.[27] Similarly, another study from Pakistan done in 2014 had found hyponatremia to be present in 42.71% of patients.[28] Another study done by UK Mishra in India showed that hyponatremia was present in 27.8% of Acute encephalitis syndrome.[8] An Irish study done in 192 patients had hyponatremia in 42.71% of cases.[29] Similar was the findings from a study from 2001 in which 32.3% patients had hyponatremia.[30] These studies point out that a third of patients with acute CNS infections have hyponatremia which may be a part of the disease process itself.

Clinical syndrome and hyponatremia

Out of 146 patients, 48% of cases in our study presented with encephalitis, followed by meningitis (31.5%) and meningoencephalitis (20.5%) syndrome. The Australian network study done by Lim et al revealed that an encephalitis syndrome was present in 25% (46/184) of patients, while the others manifested a meningitis syndrome.[27] The differences might be due to differences in syndrome defining criteria and inclusion criteria.

Same study by Lim et al showed that hyponatremia was more severe and frequent in patients with encephalitis compared to meningitis (odds ratio = 3.03, 95% CI: 1.43–6.39, after adjusting for age).[27] HSV was associated with highest odds of having hyponatremia in the same study.

Conclusion

Our study identified that hyponatremia was prevalent in more than one third of patients having CNS infections, encephalitis being the most common clinical syndrome. In terms of etiology, viral infections constituted the majority, followed by tubercular, bacterial, fungal, and parasitic infections.

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