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Central Nervous System Infections in the Intensive Care Units and Risk Factors for Mortality; Retrospective Study

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Abstract

Aim: This study was designed to analyze demographic, clinical and laboratory characteristics beside risk factors that affect the mortality rate of patients hospitalized in ICUs with diagnosis of CNS infection.

Methods: Patients that have been hospitalized at ICU on pre-CNS infection were retrospectively studied. Beside the clinical laboratory characteristics of the patients, mortality rate and risk factors that affect the mortality were recorded to be analyzed later.

Results: Following the evaluation of 118 ICU patients who were suspected to have CNS infection, 62 of them, with full diagnosis of CNS infection, were included in the study. Bacterial meningitis was the diagnosis for 40 (66%) of these patients while 18 of the total (30%) was diagnosed with viral encephalitis and 3 of them (4%) was diagnosed with tuberculous meningitis. When these factors were investigated in a multivariable study, age and time from the onset of symptoms to hospital admission were independent risk factors (CI: 1,098(1,031-1,169), 1,614(1,037-1,278).

Conclusion: The mortality rate of the patients that were subjects of the study was 52,5%. Age and time from the onset of symptoms to hospital admission were independent risk factors that affect the mortality.

Key words: Intensive Care, Meningitis, Encephalitis,

Introduction

Central nervous system infections like meningitis, encephalitis and brain abscess are rare in ICUs; they are not easy to diagnose and they have high mortality rates. These pathologies require fast diagnosis and, more importantly, on-time administration of proper antimicrobial treatments in order to decrease morbidity and mortality rates.

Many patients with CNS infection encounter increased intracranial pressure, status epilepticus, deep coma and respiratory paralysis, and they must be treated in ICU due to high mortality rate. It was reported that the mortality rate of bacterial meningitis is between 20 and 45% while it is 70% in the untreated herpes simplex encephalitis and 30% in treated ones.[1-7]

In a study conducted in Africa, it was stated that the mortality rate of ICU requiring CNS infection patients was 39%, and many of the patients were infected with HIV and cryptococcus.[8]

Another report from Portugal revealed that secondary infection (pneumonia, endocarditis and sinusitis) rates of patients with bacterial meningitis who need intensive care were high. The mortality rate of these patients were 40%, and the most important factor that affected this rate was old age and APACHE II scores.[6]

In a retrospective study conducted in the USA, the mortality rate was 18 while the most important factors affecting the mortality were cerebral edema, status epilepticus and thrombocytopenia.[9]

Causes, characteristics and mortality rates of CNS infections are various in different geographical areas. Therefore, the spectrum and results of CNS infections in ICUs need to be documented.

This study was designed to analyze demographic, clinical and laboratory characteristics beside risk factors that affect the mortality rate of patients hospitalized in ICUs on diagnosis of central nervous system infection; it is rare, difficult to diagnose, highly mortal and fast in progress with possible sequels.

Patients and Methods

This study was conducted on patients who were hospitalized in Erciyes University Faculty of Medicine Department of Internal Medicine, Anesthesiology and Reanimation ICU between 6 January 2010 and 1 April 2020 on diagnosis of CNS infection. The ethical approval of this study was given by the Ethics Committee of Erciyes University (283/2020).

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The diagnoses of CNS infections were based on clinical and radiological examinations, cerebrospinal fluid analyses and CNS imaging findings.

The CSF WBC count of negative culture was accepted as >100/mm3 based on the clinical symptoms and findings of bacterial meningitis and acute bacterial meningitis. The conclusive diagnosis of bacterial meningitis depends of either gram or culture positivity, or both, for bacteria known to cause meningitis.

The criteria for viral meningitis/encephalitis were high fever and altered sensorium or behavioral abnormality along with CSF pleocytosis. The specific cause of encephalitis was verified by CSF PCR (herpes simplex virus) test.

Diagnosis of TBM (tuberculous meningitis) was based on MR and CSF findings. Basic criteria for TBM were high fever, neck stiffness and altered mental status. Supporting findings for TBM were; 1. CSF cells .2×109 /L with lymphocytic predominance, protein 1 g/L, sterile bacterial and fungal culture and absence of cryptococcal antigen; 2. CT or MRI showing exudates, hydrocephalus, tuberculoma or infarction; 3. extra-CNS tuberculosis. Presence of any two of the basic or supporting criteria was accepted as a TBM diagnosis. Presence of acid fast bacilli (AFB) in BOS staining or culture, PCR and/or IgM ELISA was the conclusive indicator of TBM.

Demographical characteristics of patients, duration of disease, fever, headache, vomiting, seizure, focal neurological deficit, difficult breathing, intracranial pressure level, neuroradiological findings and laboratory results of the patients were obtained from electronic medical records. Age, gender, comormidity features and Charlson Comorbidity indices of the patients were recorded. Consciousness was analyzed through Glasgow Coma Scale (GCS). The SOFA score at hospitalization, GCS, symptoms, neck stiffness, Kerning's sign, total blood count, liver and kidney functions, electrolyte levels, prothrombin times, INR, procalcitonin, C-reactive Protein (CRP) levels and APACHE II scores on the first day were also recorded. Invasive mechanical ventilation requirement, length of mechanical ventilator days, length of in-bed period, and length of ICU period, mortality rate and risk factors affecting the mortality were evaluated as well.

Statistical

Continuous variables were summarized as medians and interquartile ranges. Statistical analyses of obtained data were performed using SPSS software, version 22.0 (SPSS, Chicago, IL). Data were analyzed using chi-square test, Fisher exact test, and independent *t* test. P□value < 0.05 was considered statistically significant.

The predictors of death were analyzed using univariate regression analysis; the variables included were age, time from the onset of symptoms to hospital admission GCS score, APACHE II score, SOFA, IMV, length of mechanical ventilation, ICU length of stay, hospital length of stay. Variables with a p value of 0.1 in univariate analysis were included in the multivariate regression analysis using Hosser–Lemeshow goodness-of-fit. A variable was considered significant if the two-tailed p value was 0.05.

Results

This retrospective study was conducted on 118 patients who were hospitalized at ICU of Erciyes University School of Medicine Department of Internal Medicina and Anesthesiology in the last 10 years with pre-diagnosis of CNS infection. CNS was excluded from 57 of these patients. Average age of our patients was 55 (range 38-71) and 43 of them (71%) were male. Median Charlson morbidity index of our patients was 2 (range 0-4) and 38 of them (61%) had risk factors in terms of CNS infection. The time from the onset of symptoms to hospital admission median was 2 (range 1-7); the most common symptoms were mental impairment (93%) and body temperature (84%).

The most common finding in physical examination was low GCS (98%) and 62% of them had neck stiffness.

The SOFA score of our patients at hospital admission was 4 (range 2-5) while the APACHE II value was 17 (range 10-21).

Considering the laboratory results, the median of blood glucose was 120 (range; 94-154) and WBC level was 11490 (range 7660-17420). Procalcitonin level was low (0,2 range 0,08-1,75) while CRP was high (median 59, range 26-155). LDH levels of these patients were high as well (median 356, range 283-465). CSF and blood cultures were obtained from these patients. There was no growth in blood samples of 77% of the patients and no growth in CSF of 82% of the patients. CSF results of six patients (10%) revealed viral PCR (HSV1) and results of two patients (3%) revealed positive mycobacterial PCR.

There were positive findings in the MR images of 54 patients (89%) accordant with their diagnoses. Forty patients (66%) were diagnosed with bacterial meningitis while eighteen patients (30%) were diagnosed with viral encephalitis and three of them (4%) with tuberculous meningitis. Thirty patients received Acyclovir, twenty-six patients received Meronem, twenty-one patients received Seftriakson, and three patients received anti-TBC treatment. Nineteen patients received Vancomycin and two patients received Linezolid medications part in addition the abovementioned medications.

Thirty-four patients (56%) needed mechanical ventilation and the median of length of mechanical ventilation was 14 (range 5-18).

The median length of ICU stay was 10 (range 4-17) and the length of hospitalization was 15 (range 10-22). The mortality rate determined during the study was 52, 5%.

The comparison of laboratory and clinical findings of bacterial meningitis and viral meningitis/encephalitis patients were given in Table 2. The WBC median of CSF for bacterial meningitis patients was 303 (range 55-1465) while it was 60 (range 9-119) for viral meningitis/encephalitis incidents (p: 0,004). The glucose levels of bacterial meningitis patients were lower in CSF were lower than that of viral meningitis/encephalitis patients (p: 0,011). As the number of tuberculous meningitis patients was very few, their characteristics were not compared with that of bacterial meningitis patients and viral meningitis/encephalitis patients. The findings of TBM patients were given in Table 3. All of TBM patients needed invasive mechanical ventilation and they all died.

The univariable and multivariable analyses of factors effective on mortality were given in Table 4. Considering these factors, the univariable analysis revealed that age, GCS, SOFA and APACHE II scores, Charlson Morbidity Index, time from the onset of symptoms to hospital admission, and IMV need were effective on mortality (p<0,05).

When the multivariable analyses was done, age and time from the onset of symptoms to hospital admission were independent risk factors (respectively CI: 1,098(1,031-1,169), 1,614(1,037-1,278)).

Table 1. Demographical characteristics, clinical characteristics and treatment codes of patients with CNS infection

Characteristics	Patients n:61
Age, y median (IQR)	55(38-71)
Male sex no.(%)	43(71)
Charlson Comorbidity Index no.(%)	2(0-4)
Risk factors no.(%)	38(61)
Immune-compromised state	9(15)
Old age	9(15)
Sinusitis	5(8)
Otitis	6(9)
CNS surgery	7(10)
Head trauma	1(2)
Spinal anesthesia	1(2)
Time of onset of Symptom day, median (IQR)	2(1-7)
Presenting symptoms no.(%)	
Fever	51(84)
Headache	30(49)
Altered mental status	57(93)
Seizure	16(26)
Nausea and Vomiting	32(52)
Examination	
Stiff neck,	38(62)
Kerning's sign	20(32)
Focal neurologic deficits	19(31)
GCS<15	59(98)
SOFA	4(2-5)
APACHE II	17(10-21)
Blood glucose	120(94-154)
White Cell count per mm3 median (IQR)	11490(7660-17420)
C reactive protein mg/l median (IQR)	59(26-155)
Procalcitonin ng/ml median (IQR)	0,2(0,08-1,75)
LDH U/L median (IQR)	356(283-465)
Blood cultures no.(%)	
No bacteria	47(77)
Staphylococcus sp.	9(15)
Acinetobacter sp.	3(6)
S. Pneumonia	1(2)
CSF cultures no.(%)	
No bacteria	50(82)
S. Pneumonia	7(10)
N. Meningitis	1(2)
E. Coli	1(2)
Acinetobacter sp.	1(2)
Staphylococcus sp.	1(2)
CSF Viral PCR (HSV 1) no.(%)	6(10)
CSF mycobacteria PCR no.(%)	2(3)
Positive MR findings	54(89)
Bacterial meningitis	40(66)
Viral meningitis/encephalitis	18(30)
Tuberculous meningitis	3(4)
Medication no.(%)	
Seftriakson	21(34)
Meronem	26(43)
Vancomycin	19(31)
Linezolid	2(3)
Asiklovir	30(49)
Anti TBC	3(6)
Invasive mechanical ventilator n. (%)	35(56)
Mechanical ventilation length of stay d, median (IQR)	14(5-18)
ICU length of stay d, median (IQR)	10(4-17)
Hospital length of stay d median (IQR)	15(10-22)
Death n (%)	32(%53)

Abbreviations; APACHE II: Acute Physiology and Chronic Health Evaluation score II, CSF: Cerebrospinal fluid ICU: intensive care unit. IQR, interquartile range. GCS, Glaskow coma score. n: number SOFA: Sequential Organ Failure Assessment score, y: year.

Table 2. Comparison of bacterial meningitis patients and viral meningitis/encephalitis patients in terms of laboratory and clinical findings

Characteristics	Bacterial meningitis N:40)	Viral meningitis/encephalitis (N:18)	p
CSF WBC /ul median (IQR)	303(55-1465)	60(9-119)	0,004
Blood WBC 103/ul median (IQR)	11.490(7.580-16.100)	11.680(7.955-18.215)	0,522
CSF Glucose mg/dl median (IQR)	45(16-80)	68(51-77,75)	0,011
Blood Glucose mg/dl median (IQR)	126 (99-154)	116 (90-140)	0,393
CSF chlorine mmol/L median (IQR)	116(108-123)	119(110-123)	0,470
Blood chlorine mmol/L median (IQR)	106(99-110)	99(94,5-106)	0,032
CRP mg/L median (IQR)	59(30-164)	49(17-145)	0,196
Procalcitonin ng/ml median (IQR)	0,25(0,007-3,05)	0,19(0,008-0,31)	0,480
APACHE II median (IQR)	16(10-20)	20(6-25)	0,207
GCS median (IQR)	9(3-12)	9(3-12)	0,938
SOFA median (IQR)	3(2-4)	4(2-5)	0,632
Invasive Mechanical ventilation n.(%)	26(%65)	7(%39)	0,12
Mechanical ventilation length of stay d, median (IQR)	13(5-19)	15(8-21)	0,703
ICU length of stay median(IQR)	10(4-17)	10(4-20)	0,811
Hospital length of stay d, median(IQR)	14(11-22)	16(10-23)	0,554
Mortality n (%)	24(%60)	8(%45)	0,417

Abbreviations; APACHE II: Acute Physiology and Chronic Health Evaluation score II, CSF: Cerebrospinal fluid ICU: intensive care unit. IQR, interquartile range. GCS, Glaskow coma score. n: number SOFA: Sequential Organ Failure Assessment score,

Table 3. Laboratory and clinical characteristics of tuberculous meningitis patients

Characteristics	Patients n:3
CSF WBC /ul median(IQR	83(50- *)
Blood WBC 103/ul median(IQR)	8260(1140- *)
CSF Glucose mg/dl median(IQR)	19(10-*)
Blood Glucose mg/dl median(IQR)	128(102- *)
CSF chlorine mmol/L median(IQR)	113(112- *)
Blood chlorine mmol/L median(IQR)	105(97-*)
CRP mg/L median(IQR)	50(8,6- *)
Procalcitonin ng/ml median(IQR)	0,1(0,09-*)
APACHE II median(IQR)	19(18-*)
GCS median(IQR)	7(3-*)
Invasive Mechanical Ventilation n.(%)	3(100)
Mechanical ventilation length of stay d, median(IQR)	9(5-*)
ICU length of stay d, median(IQR)	9(7-*)
Hospital length of stay d, median(IQR)	22(21-*)
Mortality n(%)	3(100)

Abbreviations; APACHE II: Acute Physiology and Chronic Health Evaluation score II, CSF: Cerebrospinal fluid ICU: intensive care unit. IQR, interquartile range. GCS, Glaskow coma score. n: number SOFA: Sequential Organ Failure Assessment score, (* Not calculated due to lack of number of patients)

Table 4. The univariable and multivariable evaluation of factors affecting mortality of CNS-diagnosed patients

	Univariable HR	p	Multivariable HR	p
Age	1,058(1,025-1,093)	0,001	1,098(1,031-1,169)	0,003
GCS	0,785(0,682-0,907)	0,001		
Sofa	1,763(1,237-2,511)	0,002		
APACHE II	1,185(1,078-1,302)	<0,001		
Time from the onset of symptoms to hospital admission	1,244(1,034-1,496)	0,02	1,614(1,037-1,278)	0,008
Charlson Comorbidity Index	1,901(1,326-2,726)	<0,001		
Invasive Mechanical ventilation	0,107(0,033-0,343)	<0,001		
Mechanical ventilator length of stay d, median(IOR)	0,993(0,948-1,040)	0,771		
ICU length of stay	1,014(0,980-1,049)	0,419		
Hospital length of stay	0,999(0,978-1,022)	0,957		

Discussion

This study was designed to evaluate ICU patients hospitalized due to CNS infection in the last ten years. Sixty-six percent of 61 patients were diagnosed with bacterial meningitis while 30% was diagnosed with viral encephalitis and 4% was diagnosed with tuberculous meningitis. The mortality rate was 53% and the independent risk factors for mortality were age and time from the onset of symptoms to hospital admission. As the time from the onset of symptoms to hospital admission lengthens, mortality rate was higher as well.

Proulx et al.[10] reported an independently increasing relationship between the delay in using antibiotics and mortality due to acute bacterial meningitis. Similarly, there are studies reporting that the delay in using antimicrobials for viral encephalitis, especially >48 hours after hospitalization, have increased morbidity and mortality dramatically.[11,12]

Appearance typical symptoms of patients with meningitis and encephalitis like nausea, vomiting, headache, photophobia, confusion, high fever and loss of consciousness, take hours, maybe days.[13] The most common symptoms of the patients in the current study were high fever and loss of consciousness. The median time from the onset of symptoms to hospital admission was approximately 2 (1-7) days. This was an independent risk factor for mortality of the patients in the study.

CRP values, which are one of the infection parameters at hospital admission, were high while procalcitonin levels were low. There was no statistically significant difference between procalcitonin levels and CRP values considering bacterial meningitis and viral meningitis/encephalitis patients. Dashti et al.[14] stated in the study conducted to determine predictors of viral and bacterial meningitis on infants that procalcitonin values were similar in viral and bacterial meningitis, and that it is not a diagnostic predictor. There were more leucocytes, and lower glucose values in the CSF of patients with bacterial meningitis than that of those with viral meningitis/encephalitis.

Similar to many studies in the literature, the current study determined active microorganisms in the CSF of very few patients.[14-16] This is because BOS sampling was performed after antibiotic treatment not to delay the treatment or because patients have received antibiotic treatment for another reason. The antibiotic medications for gram-negative bacteria were Meronem and Seftriakson while Vancomycin and Linezolid were the medications for gram-positive bacteria. Anti-tuberculosis treatment was done for tuberculous meningitis while Asiklovir was the medication for viral encephalitis.

The mortality rate of the study was 53% and, considering the factors for mortality, age, GCS, SOFA and APACHE scores, Charlson morbidity index, time from the onset of symptoms to hospital admission and the need for IMV were effective in the univariable analysis (p<0,05).

Flores-Cordero et al.[17] reported in a study on patients with community-based bacterial meningitis that age, APACHE II score and GCS were associated with vital clinical outcomes (death and serious neurological deficits). The independent risk factor for mortality was APACHE II score in same study.

In a retrospective study done in India, it was stated that GCS, APACHE II score and SIRS findings on admission were not effective on mortality; however, the length of stay at hospital and the presence of pneumonia during admission to ICU were effective on mortality.[15]

A study conducted on tuberculous meningitis patients showed that APACHE II and GCS were reliable indicators for predicting the course of disease and in-hospital mortality.[18]

Another study on severe purulent bacterial meningitis reported that univariable logistic regression analysis revealed that age, APACHE II, SAPS, SOFA and GCS scores, length of stay in ICU and length of stay in hospital were risk factors for mortality. The multivariable of the same study analysis showed that SAPS II score, length of stay in ICU and length of stay in hospital were independent risk factors for mortality.[19] The current study showed that age and time from the onset of symptoms to hospital admission were independent risk factors for mortality.

Advanced age is considered as a risk factor for vital outcomes in CNS infections. However, very few studies have

evaluated the effect of advanced age on prognosis of critical patients with CNS infections. Advanced age was an independent risk factor on mortality in the current study. Lai et al.[20] have specifically studied on bacterial meningitis data of patients over 65 admitted to a tertiary center. They have found higher rate of meningitis incidence along with higher mortality rate (% 34,8 and % 39 respectively). Fernandes et al. have studied for seven years on 65 acute bacterial meningitis patients over 18 admitted in ICU, and found that APACHE score was 23 and in-hospital mortality rate was 40%. Advanced age was also stated as an independent risk factor in this study.[6]

Another study conducted on bacterial meningitis patients found out that mortality rate was 44%, and the authors stated that this might be associated with severity of the disease and/or with the delayed admission to ICU.[21]

We believe that the current study contributed to the data on critical CNS infection patients. In fact, we collected data about risk factors, microbiological documentation, antibiotics and results of treatments of all adult CNS infection patients admitted to ICU over a 10-year period.

It is acceptable that the current study had some limitations; relatively low number of patients, lack of standardized treatment protocols and lack of info about procedure time from the hospitalization to antibiotic use.

Consequently, the mortality rate of patients hospitalized in ICU with diagnosis of CNS infection was high. Age and time from the onset of symptoms to hospital admission were the independent risk factors on mortality.

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