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Evaluation of children with acute central nervous system infections admitted to the pediatric intensive care unit and pediatric ward: a retrospective study

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Abstract

Objectives Acute central nervous system (CNS) infections in children can lead to neurological complications and mortality. This study aimed to identify the clinical manifestations, laboratory parameters, and cerebrospinal fluid characteristics indicative of CNS infections and define the risk factors that lead to pediatric intensive care unit (PICU) admission in the pediatric population of Şanlıurfa, a city in southeastern Turkey.

Methods This retrospective analysis included patients aged 1 month to 18 years who were treated for acute CNS infections in the Şanlıurfa Training and Research Hospital between January 2020 and May 2023. Clinical data were obtained from the hospital electronic medical records.

Results A total of 68 patients with acute CNS infections were included in this study. The median patient age was 3 (0.94–8.75) years. Fever was the most prevalent symptom in 92.6% of the patients. Of the total, 25% ($n=17$) of the patients had an identified causative agent and 35.3% ($n=24$) were admitted to the PICU. Serum C-reactive protein (CRP) levels were significantly higher in patients with bacterial meningitis than in those with viral meningitis ($p=0.007$). Patients with impaired consciousness and seizure were significantly more likely to require admission to the PICU than patients without these conditions (both $p<0.001$). Patients requiring PICU admission had significantly higher platelet counts ($p=0.01$).

Conclusions Impaired consciousness, seizure, and thrombocytosis on admission were important risk factors for PICU admission. Serum CRP levels can serve as an indicator of bacterial meningitis. A combination of physical findings from clinical evaluations and laboratory data is necessary to accurately diagnose bacterial CNS infections.

Keywords Central nervous system infections, Children, Encephalitis, Meningitis, Pediatric intensive care unit

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Introduction

Acute central nervous system (CNS) infections require timely diagnosis and intervention to achieve positive outcome [1]. Encephalitis or meningitis can be caused by more than hundreds of viral and bacterial species, but in most cases, viruses are the predominant infective agents. Various factors, such as age, geography, and mode of transmission, can influence the prevalence of causative pathogens [2]. Children under 5 years of age have the highest risk [3]. The severity of meningitis depends on the causative agent. Enteroviruses are the causative agents in approximately 85% of viral meningitis cases, typically resolving within 72 h [4]. Acute bacterial meningitis (ABM) can be life threatening if left untreated, and the World Health Organization (WHO) reported that, globally, approximately 170,000 deaths occur each year because of ABM, with a potential case fatality rate of up to 50% if left untreated. The risk of experiencing major or minor consequences of bacterial meningitis is estimated at 12.3%–35.3% [5]. *Streptococcus pneumoniae* (*S. pneumoniae*) continues to be the predominant bacterial pathogen causing ABM worldwide, even as more countries adopt pneumococcal conjugate vaccines [6]. Precise pathogen detection in cerebrospinal fluid (CSF) is crucial for diagnosing CNS infections and bacterial meningitis; however, its sensitivity may be affected by the prior use of antimicrobials [7]. Bacterial identification in the CSF using polymerase chain reaction (PCR) has improved the efficiency of detecting bacterial pathogens and is widely used to identify the pathogens responsible for CNS infections [7]. Cranial computed tomography (CT) is often performed to exclude hemorrhage, shift, herniation, severe hydrocephalus, and other contraindications to a lumbar puncture. Cranial magnetic resonance imaging (MRI) is conducted to detect early changes in encephalitis. Standard MRI sequences include T1, T2, and fluid attenuated inversion recovery (FLAIR) images. Diffusion-weighted imaging (DWI) is also conducted for early diagnosis of cerebral ischemia and infections [8]. Rapid assessment and immediate treatment of CNS infections in children can reduce the risk of fatal outcomes and long-term neurological complications [1].

The goals of this study were (1) to identify the clinical manifestations, laboratory parameters, and characteristics of CSF indicative of CNS infections in pediatric patients in Şanlıurfa, a city in southeastern Turkey; (2) to define the risk factors associated with critical illness in children with acute CNS infections that necessitate admission to the pediatric intensive care unit (PICU); and (3) to evaluate the clinical outcomes of these patients in order to gain insights for improved infectious management and treatment.

Materials and methods

Study setting

The study was conducted at the Şanlıurfa Training and Research Hospital, which is well-known for its 400-bed pediatric department. This hospital, located in Şanlıurfa, a city in southeastern Turkey, serves a significant number of children and provides medical treatment to patients from neighboring areas and districts. The study sample consisted of pediatric patients from low to middle socioeconomic backgrounds.

Study design

Patients with acute encephalitis or meningitis aged 1 month to 18 years who were admitted to the Şanlıurfa Training and Research Hospital between January 2020 and May 2023 were retrospectively identified from the electronic medical record system of the hospital using the International Classification of Diseases, 10th Revision, codes pertaining to the diagnosis of acute central nervous system infection (A81–89 and G00–05). All the medical records of patients with specific diagnoses were thoroughly reviewed to confirm the presence of acute encephalitis or meningitis. The diagnosis of encephalitis is defined as acute encephalopathy lasting 24 h or longer, with symptoms such as seizure, irritability, unusual behavior, focal neurologic signs, changes in mental status, or decreased consciousness, along with evidence of central nervous system inflammation and previous or concurrent symptoms of infectious disease (such as fever, respiratory tract symptoms, or gastrointestinal symptoms). This diagnosis is supported by findings in cerebrospinal fluid (CSF), electroencephalogram (EEG), or neuroimaging that are consistent with encephalitis [9].

All children participating in the study were healthy before their inclusion, except for those closely monitored by the pediatric neurology team due to shunt catheters, premature birth, and encephalomalacia. The study sample included children with orbital fractures following trauma or arachnoid cysts, and a pediatric radiologist reviewed the scans to confirm the presence of encephalitis-related lesions. Patients diagnosed with meningitis based on the WHO criteria were included in the study if they had sudden fever (38.0 °C axillary), nuchal rigidity, headache, altered consciousness, or signs of meningeal irritation, along with consistent CSF findings from a lumbar puncture [10]. Typical changes in the CSF seen in viral meningitis are as follows: (A) white blood cell (WBC) count: 10–500 cells/microL; (B) glucose: normal or a little decreased ($\geq$ 40% of serum value); (C) protein level: normal or a slightly increased (< 150 mg/dL) [4, 10]. Typical changes in the CSF see in in bacterial meningitis are as follows: (A) WBC count: > 1000 cells/microL; (B)

glucose: < 60% of serum value; (C) protein: 100–500 mg/dL [1, 11].

Patients diagnosed with meningitis were divided into two groups based on whether the causative pathogen was detected. In the group with confirmed pathogens causing meningitis, the pathogens were identified in either the CSF or blood using culture or PCR. In the clinical meningitis group, typical clinical features and CSF findings consistent with meningitis were observed; however, no pathogens were detected [11].

Data collection

Sociodemographic characteristics of patients (age, sex), length of stay, admission to the PICU, symptoms at admission (e.g., fever, headache, vomiting, impaired consciousness, meningeal irritation signs, and convulsions), diagnostic data from CSF tests, including CSF leukocyte counts, CSF glucose and protein concentrations, and CSF PCR assay results that detected 12 pathogens, and CSF culture were collected using standardized forms. C-reactive protein (CRP) levels and hemogram findings, including WBC count, hemoglobin level, neutrophil-to-lymphocyte ratio, platelet count, and percentage of neutrophils and lymphocytes, were recorded. Pathogen growth in bacterial cultures extracted from the CSF and/or whole blood was noted. The results of cranial imaging techniques, such as cranial computed tomography (CT), magnetic resonance imaging (MRI), transfontanelle ultrasonography (USG), and EEG, were also recorded. Cranial MR scan was performed with intravenous contrast administration to visualize dural, meningeal, or parenchymal contrast enhancement as an indicator of blood–brain barrier destruction due to infection [8]. MR imaging sequences that were used in our study were classical conventional brain MRI sequences such as T1-weighted images for anatomic imaging and hemorrhage, T2-weighted and FLAIR (fluid attenuation inversion recovery) sequences to reveal "edema" [8]. Complications, such as subdural effusion and hydrocephalus, were also documented. Patients with missing data were excluded.

This study was approved by the Harran University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: HRÜ/24.04.35).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics (version 25.0; IBM SPSS Statistics, Armonk, NY, IBM Corp.). For normally distributed variables, means with standard deviations were used, whereas non-normally distributed variables were represented using medians with interquartile ranges represented by the 25th and 75th percentiles. An independent sample t-test was employed for continuous variables with normal distribution, and the Mann–Whitney U test was used for non-normally distributed variables. Fisher's exact test was used when the expected values were < 5. Statistical significance was set at $p < 0.05$.

Results

Demographic characteristics and clinical manifestations of patients

Between January 2020 and May 2023, 73 pediatric patients were diagnosed with CNS infections. Upon re-examining the hospital records, five patients were not included due to insufficient information; finally, 68 patients were included in the study.

Among the patients included in the study, 13 (19.1%) were females and 55 (80.9%) were males. The median patient age was 3 (0.94–8.75) years. The age distribution was as follows: 17 patients (25%) were aged < 1 year old, 25 patients (36.8%) were aged between 1 and 5 years, and 26 patients (38.2%) were aged between 5 and 18 years. The median length of hospitalization was 13 days. and 24 (35.3%) patients required admission to the PICU. Of the 24 patients admitted to the PICU, 17 (70.8%) received noninvasive ventilation, 5 (20.8%) required both invasive ventilation and inotropes, and 2 (8.4%) received oxygen therapy.

Fever was the most prevalent symptom, observed in 92.6% of the patients ($n = 63$). The clinical findings of the patients are summarized in Table 1. Out of the 68 patients, 75% ($n = 51$) were diagnosed with meningitis (clinically + confirmed) and 25% ($n = 17$) were diagnosed with encephalitis. Among the 51 patients with meningitis, 29.4% ($n = 15$) had an identified causative agent. The remaining 36 patients were diagnosed with clinical meningitis based on their CSF examination and clinical findings; however, the causative agent could not be determined. Patients diagnosed with confirmed meningitis were hospitalized for a significantly longer duration than those with clinical meningitis ($p = 0.047$). Patients with confirmed meningitis had higher CRP levels and CSF leukocyte counts than those with clinical meningitis;

Table 1 Clinical findings of the patients at admission

Clinical findings	n (%)
Fever	63 (92.6)
Headache	13 (19.1)
Impaired consciousness	20 (29.4)
Convulsions	22 (32.4)
Vomiting	14 (20.6)
Meningeal irritation sign	8 (11.8)

however, these differences were not statistically significant ($p=0.129$ and $p=0.782$, respectively). No statistically significant differences were found between the groups in terms of clinical findings, acute-phase reactants, or CSF biochemical findings (Table 2).

Causative agents

None of the patients showed any growth in the blood cultures. A total of 17 pathogens were detected in the CSF of all patients. Enteroviruses were the most frequent viral agents ($n=6$). Two patients developed encephalitis caused by herpes simplex virus type 1 (HSV-1). The most common bacterial agent was *S. pneumoniae* ($n=3$). The CRP levels were significantly higher in patients with bacterial meningitis than in those with viral meningitis ($p=0.007$; Table 3).

Characteristics of patients treated in the PICU

Patients who experienced impaired consciousness and seizure were significantly more likely to require PICU admission (both $p<0.001$). Our study found that patients who required PICU admission had significantly lower CSF leukocyte counts ($p<0.001$) and significantly higher platelet counts ($p=0.01$) than those who were not admitted to the PICU (Table 4).

Neuroimaging findings

Sixty-five patients were subjected to cranial neuroimaging, such as MRI, CT, and transfontanelle USG. Among these patients, three underwent transfontanelle USG exclusively, 29 patients underwent cranial CT exclusively, 17 patients underwent both cranial CT and MRI, and the remaining patients ($n=16$) underwent only cranial MRI. Regarding the neuroimaging results, 48 patients (70.5%) had normal findings, 1 (1.5%) had hydrocephalus, 1 (1.5%) had subacute ischemia, 5 (7.3%) had shunt catheters, 1 (1.5%) had orbital fracture, 1 (1.5%) had cerebral infarction, 1 (1.5%) had pial contrast enhancement, and 4 (5.9%) had diffusion restriction on MRI. One patient with acute HSV-1 encephalitis showed bilateral frontotemporal cerebral parenchymal diffusion restriction (Fig. 1). Another patient with pial contrast showed enhancement on MRI (Fig. 2). Two patients (2.9%) exhibited imaging findings consistent with acute sinusitis, and one presented with imaging findings of arachnoid cyst.

Outcomes

In cases of suspected encephalitis in children, initial empirical antimicrobial treatment included intravenous acyclovir for potential HSV infection and vancomycin and ceftriaxone for potential bacterial meningitis. Within the study group, 25% of the patients ($n=17$) received initial empirical treatment with parenteral acyclovir,

Table 2 The demographic and laboratory characteristics of patients diagnosed with confirmed meningitis and clinical meningitis

Characteristics	Confirmed meningitis ($n=15$)	Clinical meningitis ($n=36$)	P
Age in years, median (IQR)	4 (2–8)	3.5 (0.7–10)	0.686; Z = -0.404
Length of stay (days)	14 (12–15)	12 (9–14)	0.047*; Z = -1.986
Need for PICU admission, n (%)	5 (33.3)	7 (19.4)	0.302 β
Fever, n (%)	15 (100)	35 (97.2)	1 β
Headache, n (%)	3 (20)	9 (25)	1 β
Vomiting, n (%)	5 (33.3)	8 (22.2)	0.487 β
Meningeal irritation sign, n (%)	3 (20)	5 (13.8)	0.679 β
Laboratory findings			
Median WBC count/mm^3 (IQR)	11,570 (8000–19400)	11 220 (8890–16590)	0.465; Z = -0.730
Mean Hb (g/dl) ± SD	11.2 ± 0.55	11.08 ± 0.29	0.768 α
Median Plt count (IQR) (10^3/µl)	311,000 (272,300–414000)	277,000 (219,000–468000)	0.539; Z = -0.614
Median CRP (mg/L) (IQR)	42.1 (18.1–119)	23.5 (1.9–95)	0.129; Z = -1.519
Median neutrophil percentage (IQR)	76.6 (58–81)	69.1 (45.6–84.9)	0.435; Z = -0.781
Median lymphocyte percentage (IQR)	17.9 (6–24.5)	21 (10.1–41.9)	0.340; Z = -0.955
Median CSF protein (mg/dL) (IQR)	63.5 (31.6–150)	44.6 (26.4–118.4)	0.502; Z = -0.672
Median CSF glucose (mg/dL) (IQR)	63.6 (52.1–66.7)	60.3 (29.9–76.3)	0.549; Z = -0.600
Median CSF leukocyte number/microL (IQR)	210 (30–1360)	100 (40–980)	0.782; Z = -0.277

WBC White blood cell, *CRP* C-reactive protein, *Hb* Hemoglobin, *Plt* Platelet, *CSF* Cerebrospinal fluid, *SD* Standard deviation, *PICU* Pediatric intensive care unit, *IQR* Interquartile range (25%–75%)

* $p<0.05$ statistically significant; Z, Mann–Whitney U test; α, Independent samples t-test; β, Fisher's exact test

Table 3 Demographic and laboratory characteristics of patients with confirmed viral CNS infection (encephalitis + meningitis) and bacterial CNS infection

Characteristics	Viral CNS infection (*n* = 8)	Bacterial CNS infection (*n* = 9)	P
Age in years, median (IQR)	6 (1.6–8.75)	3 (0.75–6)	0.289; Z = -1.061
Length of stay (days)	14 (10.5–15.75)	14 (13–27)	0.354; Z = -0.927
Need for PICU admission, n (%)	1 (12.5)	5 (55.5)	0.131 β
Fever, n (%)	8 (100)	9 (100)	-
Headache, n (%)	2 (40)	1 (11.1)	0.576 β
Median WBC count/mm^3 (IQR)	12,790 (8282–18,042)	19,140 (10,447–21475)	0.336; Z = -0.962
Mean Hb (g/dl) ± SD	12.05 ± 1.33	10.62 ± 2.35	0.154 α
Median NLR (IQR)	3.9 (1.1–5.6)	4.9 (2.4–15)	0.386; Z = -0.866
Median Plt count (IQR) (10^3/µl)	302,500 (202,500–415000)	361,400 (293,500–470950)	0.336; Z = -0.962
Median CRP (mg/L) (IQR)	15.2 (1.1–29.5)	78.2 (33.9–249.6)	0.007*; Z = -2.694
Median neutrophil percentage (IQR)	71.8 (41.1–77)	77.9 (56.5–86.4)	0.194; Z = -1.300
Median lymphocyte percentage (IQR)	17.9 (14.05–45.9)	5.5 (2.5–15.8)	0.501; Z = -0.674
Median CSF protein (mg/dL) (IQR)	42.3 (27.9–62.1)	68.9 (32.5–294.6)	0.102; Z = -1.636
Median CSF glucose (mg/dL) (IQR)	64.1 (63.5–66.5)	53.9 (19.5–89.6)	0.178; Z = -1.348
Median CSF leukocyte number (IQR)/microL	85 (30–252)	385 (40–1520)	0.527; Z = -0.632
CSF PCR assay (n)	HSV-1 (2) Enterovirus (6)	*E. coli* (1)	
CSF culture (n)	-	*S. pneumoniae* (3) *S. viridians* (1) L. monocytogenes (1) *S. epidermidis* (1) *S. hominis* (1) *S. marcescens* (1)	

CNS Central nervous system, *WBC* White blood cell, *CRP* C-reactive protein, *Hb* Hemoglobin, *Plt* Platelet, *CSF* Cerebrospinal fluid, *SD* Standard deviation, *PICU* Pediatric intensive care unit, *IQR* Interquartile range (25%–75%), *NLR* Neutrophil-to-lymphocyte ratio, *E. coli Escherichia coli*, *S. Pneumoniae Streptococcus pneumoniae*, *S. viridians Streptococcus viridians*, *L. monocytogenes Listeria monocytogenes*, *S. epidermidis Staphylococcus epidermidis*, *S. hominis Staphylococcus* hominis, *S. marcescens Serratia* marcescens, *HSV* Herpes simplex virus

* $p < 0.05$ statistically significant; Z, Mann–Whitney U test; α, Independent samples t-test; β, Fisher's exact test

vancomycin, and ceftriaxone. Respiratory influenza testing ruled out influenza, while mycoplasma pneumonia was not detected in CSF PCR tests and *M. pneumoniae* serology testing could not be conducted in the hospital. As a result, oral azithromycin was empirically added to the treatment plan for patients with fever and respiratory symptoms ($n = 9$). Antibiotic and antiviral treatment were adjusted according to the CSF test and follow-up neuroimaging results. Patients with positive HSV PCR results ($n = 2$) based on CSF samples continued acyclovir treatment for 21 days, while those with negative HSV PCR results ($n = 8$) discontinued acyclovir if there was no clinical suspicion of HSV encephalitis. A follow-up control lumbar puncture was performed in patients ($n = 2$) with neurological findings, and acyclovir therapy was stopped because the second CSF HSV PCR was still negative. Acyclovir treatment was continued ($n = 5$) in critically ill patients with severe neurological findings who could not undergo a second CSF testing. All patients admitted with probable meningitis ($n = 51$) were initially treated with vancomycin and ceftriaxone. Antibiotic treatments were discontinued during follow-up for patients with no growth in CSF cultures and with CSF biochemistry and CSF cell count test results compatible with viral meningitis. Treatments were adjusted according to the microorganisms identified in the CSF culture. Patients with CSF biochemistry and cell counts indicative of bacterial meningitis completed at least 10 days of treatment, even if the CSF culture showed no growth.

Among the patients who could be followed, six of the previously healthy patients experienced neurological complications, such as hydrocephalus and cognitive impairment. Four of the six patients had high platelet levels when they were first diagnosed, and their CRP levels were above the normal range. One patient was diagnosed with HSV-1 encephalitis, and the other, with *S. pneumoniae* meningitis. In one case, *S. pneumoniae* was detected in a respiratory tract sample using PCR analysis but was not detected in the CSF culture or CSF PCR. The causative agent could not be identified in the remaining patients with neurological complications. Death due to multi-organ failure was observed in one

Table 4 Comparison of children with acute central nervous system infections requiring admission to the pediatric intensive care unit and pediatric ward

Characteristics	CNS infection necessitating admission to the PICU ($n=24$)	CNS infection necessitating admission to the pediatric ward ($n=44$)	P
Meningitis, n (%)	12 (50)	39 (88.6)	0.001 *
Encephalitis, n (%)	12 (50)	5 (11.4)	
Age in years, median (IQR)	2 (0.94–3.75)	4.5 (0.75–9.75)	0.214; Z = -1.241
Fever, n (%)	21 (87.5)	42 (95.4)	0.337 β
Impaired consciousness, n (%)	14 (58.3)	6 (13.6)	< 0.001*
Seizure, n (%)	15 (62.5)	7 (15.9)	< 0.001*
Vomiting, n (%)	2 (8.3)	12 (27.2)	0.114 β
Meningeal irritation sign	1 (4.1)	7 (15.9)	0.244 β
Median WBC count/mm^3 (IQR)	13,740 (10,922–18815)	10,350 (8270–17210)	0.156; Z = -1.419
Median NLR (IQR)	3.7 (1.3–9.7)	3.4(1.04–8.7)	0.627; Z = -0.487
Mean Hb (g/dl) ± SD	10.6 ± 1.5	11.2 ± 2.03	0.191 α
Median Plt count (IQR) (10^3/μl)	361,700 (278,750–543725)	270,000 (219,000–375000)	0.01*; Z = -2.589
Median CRP mg/L (IQR)	8.3 (1.1–24.7)	34.2(1.4–104.1)	0.06; Z = -1.868
Median neutrophil percentage (IQR)	74.5 (37.5–80.5)	66.3(53–78.9)	0.764; Z = -0.300
Median lymphocyte percentage (IQR)	20.6 (9.4–38.8)	20.8 (7.8–42.3)	0.957; Z = -0.053
Median CSF protein (mg/dl) (IQR)	30.4 (17.5–81)	40.6 (26.3–102.1)	0.209; Z = -1.258
Median CSF glucose (mg/dl) (IQR)	68.9 (54.1–80.5)	63.2(53.3–74.1)	0.243; Z = -1.168
Median CSF leukocyte number/microL (IQR)	10 (0–45)	160 (40–980)	< 0.001*; Z = -4.266
Causative agent of the CNS infection (n)	*L. monocytogenes* (1) *S. epidermidis* (1) *S. hominis* (1) *S. marcescens* (1)	HSV-1 (2) Enterovirus (6) *E.coli* (1) *S. pneumoniae* (3) *S. viridians* (1)	

WBC White blood cell, *CRP* C-reactive protein, *Hb* Hemoglobin, *Plt*, Platelet, *CSF* Cerebrospinal fluid, *SD* Standard deviation, *PICU* Pediatric intensive care unit, *IQR* Interquartile range (25%–75%), *NLR* Neutrophil-to-lymphocyte ratio, *E. coli Escherichia coli*, *S. Pneumoniae Streptococcus pneumoniae*, *S. viridians Streptococcus viridians*, *L. monocytogenes Listeria monocytogenes*, *S. epidermidis Staphylococcus* epidermidis, *S. hominis Staphylococcus hominis*, *S. marcescens Serratia marcescens*, *HSV* Herpes simplex virus

* $p < 0.05$ statistically significant; Z, Mann–Whitney U test; β, Fisher's exact test; α, independent samples t-test

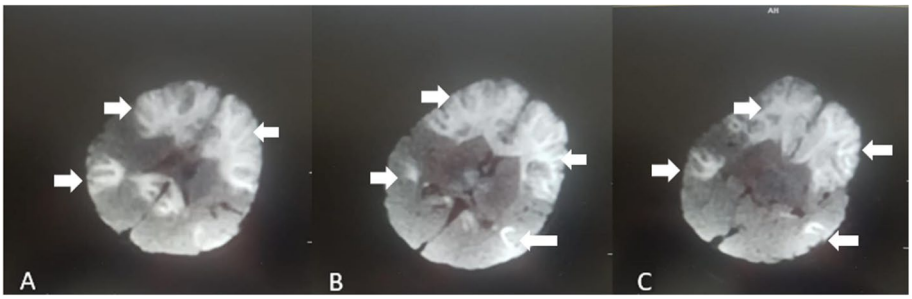

Fig. 1 **A**-**C** Cranial magnetic resonance image of a patient with encephalitis caused by herpes simplex virus type 1 shows bilateral frontotemporal cerebral parenchymal diffusion restriction (arrows)

patient. Upon admission, the patient presented with a high WBC count of 30,600/mm^3, with 87.4% neutrophil dominance. Both CSF and clinical findings indicated meningitis. The patient was hemodynamically unstable and required inotropes and invasive mechanical ventilation. However, the pathogen causing the meningitis could not be identified.

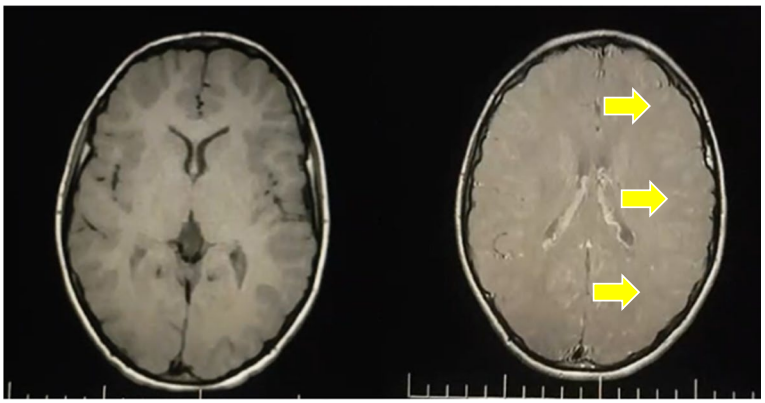

Fig. 2 **A**, **B** Brain magnetic resonance images: pre- and post-contrast axial T1 images show subtle pial contrast enhancement (arrows)

Discussion

We thoroughly analyzed the data of hospitalized children to authenticate the clinical and CSF indicators of CNS infections and to identify the risk factors that predispose patients to PICU admission. Fever was the most frequently reported symptom at presentation. Causative agents were detected in 25% of the CSF samples analyzed microbiologically, using PCR and culture.

CRP levels were significantly elevated in patients with bacterial meningitis. Patients with encephalitis often required admission to the PICU, and patients with thrombocytosis needed to stay in the PICU longer than those without thrombocytosis. Except for the length of hospital stay, the clinical findings and laboratory test results did not differ significantly between patients with a clinical diagnosis of meningitis and those with a confirmed diagnosis.

Bacterial meningitis is an infectious disease that can be life threatening, especially in children, and imposes a significant disease burden [1]. In our study, most patients had meningitis. CSF protein levels were normal in three confirmed ABM cases, and CSF glucose levels were normal in two. Our findings indicated that bacteria may be present in the CSF even when CSF parameters appeared normal. Consistent with our findings, in a previous study of patients with confirmed ABM, 6.2% had normal CSF WBC count, 29.5% had normal CSF glucose level, and 24.5% had normal CSF protein levels. In addition, 8.6% had normal results for all CSF parameters, including WBC count and glucose and protein levels [12]. Higher leukocyte and protein levels, and lower glucose levels are expected in patients with bacterial CNS infections; however, bacterial meningitis may result in a low CSF WBC count during the early stages [11]. As reported in previous studies, single CSF parameters may not be effective in distinguishing between bacterial and viral meningitis [12]. In our study, CRP levels were significantly elevated in patients with bacterial CNS infections; hence CRP levels are essential for empirical treatment approaches until culture results are obtained. A previous study found that children with bacterial meningitis and high CRP levels at disease onset were more likely to develop refractory bacterial meningitis [2].

After administering parenteral antibiotics to patients with bacterial meningitis, performing a lumbar puncture within a few hours may yield negative CSF culture findings [12]. In a recent study of pediatric patients with bacterial meningitis, 46.9% of the patients were probable cases, and the CSF culture positivity rate was only 15% [1]. Consistent with other studies, 15.6% of all the patients with meningitis in our study had a positive CSF culture [1], indicating a low prevalence of CSF culture positivity among children with meningitis. Therefore, non-culture tests should be conducted for timely pathogen detection or in patients who have taken antibiotics.

Identifying common pathogens of ABM in children is crucial, as they vary by age and affect treatment decisions [12]. In our study, the most common bacterial agent was *S. pneumoniae*, whereas the most common viral agents were enteroviruses. In a recent study conducted in Turkey, *S. pneumoniae* was found to be the most common causative agent of meningitis [13]. However, we encountered different pathogens possibly because of the heterogeneous patient population. The detection of *Staphylococcus epidermidis (S. epidermidis)* and *S. hominis* in our study may be linked to the presence of ventriculoperitoneal shunt infections. This infection is due to complications involving *S. epidermidis* colonization and biofilm formation in medical device insertions, such as intraventricular shunts [14]. *Listeria monocytogenes (L. monocytogenes*) causes meningitis and meningoencephalitis in immunocompromised patients, neonates, and older adults [15] and is an infrequent causative pathogen of meningoencephalitis in previously healthy

immunocompetent children [15]. In our study, *L. monocytogenes* was detected in the CSF cultures of a previously healthy 16-year-old patient. This finding is crucial for raising awareness about this pathogen, and physicians should consider this bacterium as a potential cause of CNS infections in previously healthy, immunocompetent children during diagnosis. The patient with *L. monocytogenes*-induced meningitis was effectively managed with a treatment regimen of ampicillin and gentamicin.

The presence of a low leukocyte count in the CSF has been reported as a definitive factor associated with PICU admission [16]. Patients diagnosed with encephalitis often require PICU admission because of the potentially life-threatening nature of the disease. The higher number of patients diagnosed with encephalitis among patients with CNS infections requiring PICU admission may have led to a significantly lower CSF leukocyte count in patients hospitalized in the PICU than in patients in the pediatric ward. A study involving pediatric patients with ABM found that a low WBC count in the CSF, along with elevated protein and/or reduced glucose levels, was associated with adverse outcomes [12]. The rare absence of pleocytosis in the CSF often leads to unfavorable patient outcomes [17]. A decreased WBC count in the CSF may indicate a compromised host immunity and an inadequate response, leading to unfavorable clinical outcomes [12].

The presence of generalized seizure and status epilepticus in pediatric patients with encephalitis has been identified as a factor associated with the need for PICU admission [16]. Impaired consciousness is an independent risk factor associated with a less favorable prognosis in pediatric patients with ABM [2]. Our study demonstrated that a significantly higher number of patients presenting with impaired consciousness and seizure upon admission required PICU admission. Increased activity of the reticular activation system and damage to the cerebral cortex can contribute to impaired consciousness [2].

An elevated platelet counts due to increased megakaryocyte production and thrombopoiesis is a characteristic of secondary thrombocytosis, and underlying infections usually cause this reactive process [18]. The relationship between platelet counts and the outcomes of pediatric infections is still a topic of debate [19]. Patients with lower respiratory tract infections and elevated platelet counts may experience severe clinical progression [20]. Thrombocytosis is linked to the severity of urinary tract infections [21]. Our study found a significant increase in platelet counts among patients with CNS infections requiring PICU care compared with those not needing PICU care. This finding suggests a link between platelet count and the severity of CNS infection requiring PICU admission. None of the patients experienced thromboembolic complications, and reactive thrombocytosis manifested as a CNS infection. Subsequent to infection treatment, the thrombocytosis subsided, rendering additional therapeutic interventions unnecessary.

Despite the administration of effective antimicrobial therapies, neurological morbidity and mortality are challenges in the management of ABM. Certain bacterial substances, such as endotoxins and peptidoglycans activate inflammatory responses in the body, leading to brain inflammation and edema [5]. In a previous study involving 146 children with encephalitis, 49% had persistent neurological issues after a follow-up of 5.8 years [22]. A previous study found that 6.4% of children with post-meningitis-related neurodevelopmental disabilities experienced cognitive impairment during long-term observation [23]. Patients with viral encephalitis admitted with coma, and convulsions, requiring PICU admission may have unfavorable outcomes, particularly those with HSV encephalitis [22]. CNS infections caused by *S. pneumoniae* increase the risk of cognitive disabilities, seizures, hearing loss, and motor function disorders [23]. Consistent with previous studies, our patients with CNS infection resulting in neurological complications had a documented history of PICU admission, diagnosis of HSV encephalitis, and pneumococcal meningitis. Children diagnosed with CNS infections, especially those with a history of PICU admission or infections caused by HSV or *S. pneumoniae*, should receive long-term follow-up care [23].

For imaging of patients with encephalitis, non-contrast head CT can be the first step in clinic practice. Because it is fast and accessible as a cross-sectional imaging, head CT is performed to rule out contraindications of lumbar puncture such as, herniation, shift, hemorrhage, and severe hydrocephalus [24]. Cranial MRI is the best imaging technique for visualizing brain tissue [8]. MRI findings for CNS infections include hyperintensities in the hemispheres, basal ganglions, brain stem, or cerebellum on T2-weighted and FLAIR images and diffusion restriction on diffusion-weighted images; meningeal, pial, and dural contrast enhancement can be observed after contrast administration. Complications such as abscess, ventriculitis, hemorrhage, ischemia, dural sinus thrombosis, parenchymal necrosis, and encephalomalacia can also be visualized on MRI [25]. Regarding brain MRI, certain imaging patterns have been discussed in literature; abnormal image findings in specific anatomic parts have been found to be related with certain etiologies [26]. For instance, infection with HSV type 1 is known to affect the hemispheric cortex and white matter, usually the temporal lobes [8, 25]. In our study, the patients with encephalitis due to HSV type 1 had similar imaging findings, such as bilateral frontotemporal diffusion restriction on DW

images. Another pattern relates to pathogens that cause vasculopathy resulting in ischemia [27]. Diffusion restriction can be visualized precisely on diffusion sequences of MRI [27, 28]. Chicken pox virus, herpes simplex virus, Epstein Barr virus, enterovirus and tuberculosis are the pathogens related to this finding [26]. Therefore, diffusion-weighted MRI must be considered when examining such cases [26, 28]. A focused approach including laboratory investigation, CSF analysis, and neuroimaging can be used to effectively screen patients for specific causative agents [29].

This study explored the factors related to severe clinical course that necessitated admission to the PICU. Specifically, the presence of generalized seizure, status epilepticus, specific causative agents, and low WBC count in the CSF were indicators of PICU admission. We recommend monitoring children with CNS infections in the PICU for generalized seizure upon admission and the diagnosis of encephalitis. This recommendation also extends to pediatric patients with impaired consciousness, those requiring noninvasive or invasive ventilation, and hemodynamically unstable patients in need of inotropic support. Conversely, patients without impaired consciousness and seizure can be monitored in the pediatric ward.

Droplet precautions should be taken if a patient is suspected of having *Neisseria meningitidis* or Hib meningitis. These patients should be accommodated in private rooms to minimize the risk of transmission. Droplet and contact precautions should be promptly initiated when a hospitalized patient is diagnosed with encephalitis [30].

The current study has numerous strengths and its findings are relevant to clinicians managing pediatric patients with CNS infections. However, the major limitation of this study must be acknowledged, namely the small study group given the reliance on retrospectively acquired data from one hospital. Specific analyses such as tests for procalcitonin levels in the CSF could not be performed because of the lack of the necessary equipment and resources at our hospital.

Conclusion

The findings of this study of pediatric patients with CNS infections provide valuable insights on the early recognition of children at risk of requiring PICU admission. The need for PICU admission may be linked to factors such as impaired consciousness and the presence of seizure and thrombocytosis upon admission. Serum CRP level is an important biomarker that can be used to indicate the presence of bacterial meningitis. Our research indicates the importance of not disregarding the possibility of bacterial meningitis, even when the initial CSF examination results appear normal. A combination of CSF parameters, CRP levels, and clinical evaluation is often necessary to accurately diagnose bacterial CNS infections.

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Authors' contributions
M.D. conceptualized the idea for research or article/hypothesis generation. M.D and T.E planned the methods to generate hypothesis. M.D., T.E. and H.F.A. collected and processed the data. M.D. and F.K. were responsible for supervision and follow-up of the organization of project. H.Ş. and M.D analyzed the data. M.D., H.Ş. and H.T. wrote the manuscript and prepared the figures and tables. M.D. and H.T completed the critical review of the manuscript. The authors read and approved the final manuscript.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available to ensure the privacy of the study participants. But are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Harran University Faculty of Medicine (No. HRÜ/24.04.35), and the requirement for informed consent was waived by the Ethics Committee of the Harran University Faculty of Medicine because of the retrospective nature of the study.

Competing interests
The authors declare no competing interests.

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