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Research Article

Identifying Clinical and Biochemical Predictors of Seizures in Children with Acute Bacterial Meningitis: Insights from a Cross-Sectional Study

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Abstract

Background: The occurrence of seizures in bacterial meningitis is important, as it has been reported to increase the risk of complications; however, its frequency and predictors are not well studied yet. ***Objective***: To assess the frequency, clinical, and biochemical predictors of seizures in children with acute bacterial meningitis. ***Method***: A cross-sectional study recruited confirmed acute bacterial meningitis cases based on positive CSF culture and sensitivity among children aged 2 months to 15 years admitted to the Central Child Teaching Hospital emergency department in Iraq. Patients were divided into two groups based on seizure at presentation time. Demographic characteristics [age, gender, residence, duration of fever and disease, presenting complaints and antibiotic intake]; hematological [WBC, neutrophils] Lymphocyte, N/L ratio, packed cell volume, platelets, blood sugar**,** and cerebrospinal fluid (CSF) indices were compared between groups. ***Results***: Seizures had a frequency of 18% among the 122 children and were significantly higher in younger cases with female predominance. By multivariate analysis and odds ratio (OR), predictors for seizure were as follows: CSF lymphocytes (OR=0.25, 95%CI=0.08–0.26), *lethargy* (OR=8.15, 95%CI=1.03-68.65), headache (OR=0.09, 95%CI=0.02-0.45), neck stiffness (OR=0.07, 95% CI=0.01-0.61) and *poor feeding* (OR=4.8, 95%CI=1.21–18.97). ***Conclusions***: CSF lymphocytes reliably predicted seizure with good sensitivity and specificity of 75% and 73%. Lethargy and poor feeding had the highest odds as clinical predictors of seizures. Together, those results can help with risk stratification and allocate resources for high-risk cases to improve patient outcomes.

Keywords: Bacterial meningitis**,** Cerebrospinal fluid, Seizure.

تحديد التنبؤات السريرية والكيميائية الحيوية للنوبات لدى الأطفال المصابين بالتهاب السحايا الجرثومي الحاد: رؤى من دراسة مقطعية

الخلاصة

الخلفية: حدوث نوبات في التهاب السحايا الجرثومي أمر مهم، حيث تم الإبلاغ عن أنه يزيد من خطر حدوث مضاعفات. ومع ذلك، لم يتم دراسة تواترها ومتنبئاتها بشكل جيد حتى الآن. **الهدف**: تقييم تواتر التنبؤات السريرية والكيميائية الحيوية للنوبات لدى الأطفال المصابين بالتهاب السحايا الجرثومي الحاد. **الطريقة**: تابعت الدراسة المقطعية حالات التهاب السحايا الجرثومي الحاد المؤكدة بناء على نتائج CSF الإيجابية والحساسية بين الأطفال الذين تتراوح أعمارهم بين شهرين و 15 عاما الذين تم إدخالهم إلى قسم الطوارئ في مستشفى الأطفال التعليمي المركزي في العراق. تم تقسيم المرضى إلى مجموعتين بناء على النوبة في وقت العرض. الخصائص الديمغرافية [العمر والجنس والإقامة ومدة الحمى والمرض وتقديم الشكاوى وتناول المضادات الحيوية] ؛ تمت مقارنة مؤشرات الدم [WBC ، العدلات] الخلايا الليمفاوية ، نسبة N / L ، حجم الخلايا المعبأة ، الصفائح الدموية ، سكر الدم ، ومؤشرات السائل النخاعي (CSFبين المجموعات. **النتائج**: كان تواتر النوبات 18٪ بين 122 طفلا وكانت أعلى بكثير في الحالات الأصغر سنا مع غلبة الإناث. من خلال التحليل متعدد المتغيرات ونسبة الأرجحية ، كانت التنبؤات بالنوبات على النحو التالي: الخلايا الليمفاوية CSF OR= 0.25، 95٪ ، الخمول OR = 8.15 ، الصداع OR = 0.09 ، تصلب الرقبة OR = 0.07، وسوء التغذية OR = 4.8. **الاستنتاجات**: تنبأت الخلايا الليمفاوية CSF بشكل موثوق بالنوبة بحساسية جيدة وخصوصية 75٪ و 73٪. كان للخمول وسوء التغذية أعلى الاحتمالات كمتنبئات سريرية للنوبات. يمكن أن تساعد هذه النتائج في تقسيم المخاطر وتخصيص الموارد للحالات عالية الخطورة لتحسين نتائج علاج المرضى.

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INTRODUCTION

Bacterial meningitis is the predominant type of central nervous system infection in childhood. It carries a high risk of morbidity and mortality in childhood [1]. The incidence is higher in young infants and low- to medium-income countries [2]. Bacterial meningitis can present with a wide range of clinical manifestations, which mainly depend on the age of the patients. Seizure is one of the neurological manifestations reported to occur at different frequencies in meningitis during childhood [3]. In febrile children, seizures increase the possibility of meningitis; however, this applies only outside the febrile-seizure age range, and the risk depends mainly on the type of seizure, particularly if it is of a complex type [4,5]. The underlying pathogenesis of seizures in acute bacterial meningitis may include increased intracranial pressure, inflammatory neuronal excitation, and necrosis [6]. Previous studies reported that children with bacterial meningitis who presented with seizures had a more severe course than children who did not develop seizures [7,8]. In adult studies, acute bacterial meningitis patients who presented with seizures more often had cerebrospinal fluid (CSF) leucocytes <1000/mL, CSF protein >3.0 g/L, an increased erythrocyte sedimentation rate, a pneumococcal etiology, and focal cerebral abnormalities [6,9]. Studies on elderly patients argued for the prophylactic administration of anticonvulsants to patients with acute bacterial meningitis, regardless of the presence of seizures at presentation [10]. Similar studies in the pediatric age group are sparse, and information about the frequency and risk factors for seizures in children with bacterial meningitis is limited, especially in developing countries. The current study aimed to assess the frequency and risk factors [including clinical, biochemical, and hematological indices] for seizures in children diagnosed with acute bacterial meningitis to improve patient outcomes.

METHODS

Study design and setting

A cross-sectional study recruited children diagnosed with acute bacterial meningitis based on positive CSF culture and sensitivity for a 12-month period. We enrolled cases admitted to the Central Child Teaching Hospital's emergency department in Baghdad, Iraq, from the 1st of November 2023 to the 31st of April 2024. The ethical committee at Mustansiriyah University approved the study on 11/2023. After obtaining informed consent from their parents, patients were divided into two groups based on the presence of seizures during the presentation. See Figure 1, highlighting the process of patient recruitment.

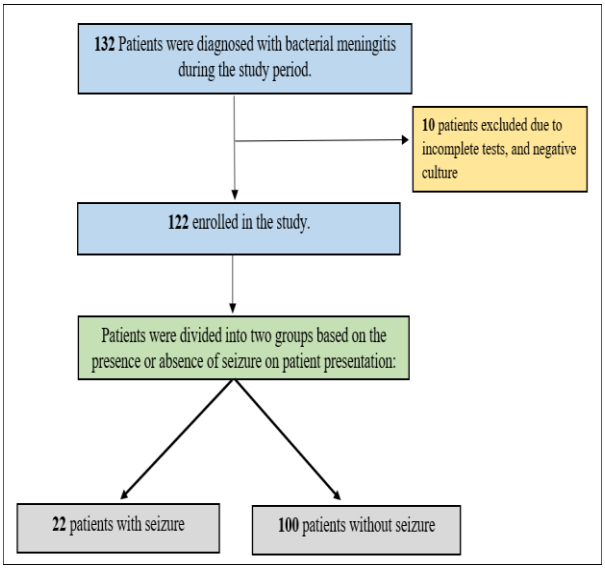

Figure 1: study flowchart.

Inclusion criteria

Children aged 2 months to 15 years who were diagnosed with acute bacterial meningitis and had neither an underlying chronic illness nor were on chronic medication.

Exclusion criteria

Cases with incomplete or missing data and negative culture and sensitivity tests were excluded.

Outcome measurements

Three sets of data were measured in this study and the results were compared between the two groups. First, we collected three types of information: first, demographic information like age, gender, place of residence, length of fever and illness, symptoms, and antibiotic use; second, hematological information like WBC and neutrophils; third, cerebrospinal fluid (CSF) information like CSF cells, CSF neutrophils, CSF lymphocytes, CSF sugar, and CSF protein.

Statistical analysis

The SPSS program, version 25.0, was utilized for conducting statistical analyses (SPSS, Chicago). The Shapiro-Wilk test was used to determine the normality of continuous data, and the student t-test was used to analyze data with a normal distribution that was given as the mean and standard deviation. The Mann-Whitney U test analyzed non-normally distributed data and provided the median and range. The Chi-square/Fischer exact test was used to analyze categorical variables, which were reported as numbers and percentages. Values that were deemed statistically significant had a *p*-value of less than 0.05.

RESULTS

A total of 122 children were included in this study. The frequency of seizures on presentation was 18%. Those with seizures were much younger than those without seizures (median 1.0 *vs*. 8.0 years; $p<0.001$). Furthermore, female gender was predominant in the seizure group compared to the non-seizure cases (20% *vs*. 63.64%; $p= 0.003$). Residence didn't show significant differences. Among the presenting clinical features, lethargy and poor feeding were more significantly seen in children with seizures ($p= 0.005$, 0.018, respectively). In contrast, headache and neck stiffness were reported more in children presented without seizures with statistical significance ($p= 0.001$ and 0.006, respectively). The other clinical characteristics, including duration of fever, illness, and prior antibiotic administration, showed no statistically significant differences between both groups (Table 1).

Table 1: Association of clinical and demographic characteristics with seizure in children with meningitis

Variables	Without seizure (n=100)	With seizure (n=22)	*p*-value
Age (year)	7.34±4.0	2.85±3.89	<0.001
Gender			
Male	80(80)	8(36.36)	0.003
Female	20(20)	14(63.64)	
Residence			
Rural	54(54)	12(54.55)	0.974
Urban	46(46)	10(45.45)	
Disease duration (week)			
One week	80(80)	18(81.82)	0.891
> 1 week	20(20)	4(18.18)	
Duration of fever	4.83±5.57	5.55±5.75	0.892
Complaints(day)			
Vomiting	74(74)	10(45.45)	0.064
Lethargy	54(54)	22(100)	0.005
Headache	72(72)	4(18.18)	0.001
Neck stiffness	58(58)	2(9.09)	0.006
Diarrhea	10(10)	0(0)	0.574
Poor feeding	20(20)	12(54.55)	0.018
Rash	0(0)	2(9.09)	0.180
Prior antibiotics			
Not received	30(30)	6(27.27)	0.857
Received	70(70)	16(72.73)	

Values are expressed as frequencies, percentages, and mean±SD.

Patients with seizures showed higher levels of four hematological indices, including WBC, neutrophil percentage, absolute neutrophil count, and neutrophil/lymphocyte ratio, but these did not reach statistical significance. On the other hand, lymphocyte counts and percentages, packed cell volume, platelet count, and serum sugar were comparable in both groups (Table 2). CSF lymphocytes were the only CSF index in the study to show a significant association with seizures. Cases with lower mean CSF lymphocytes tend to present with seizures more significantly than those with higher CSF lymphocytes (p=0.014) (Table 3). We used the receiver operating characteristic curve to determine the predictive values of CSF lymphocytes in anticipating seizures in children with meningitis. The AUC was 0.739, 95% CI= 0.560–0.918, p= 0.041. The sensitivity and specificity of CSF lymphocytes at a cut-off value of <8.5 $\times 10^9$/L were 75% and 73%, respectively (Figure 2).

Table 2: Association of hematologic indices with seizure in children with meningitis

Variables	Without seizure (n=100)	With seizure (n=22)	*p*-value
WBC $\times 10^9$/L	13.0±5.12	15.76±10.72	0.976
Neutrophils (%)	63.8±19.57	69.3±16.63	0.376
Absolute Neutrophils $\times 10^9$/L	7.55±5.12	11.46±8.98	0.256
Lymphocyte (%)	28.39±17.2	25.29±15.83	0.669
Absolute lymphocyte $\times 10^9$/L	3.04±2.54	3.78±2.76	0.430
N/L ratio	3.94±4.16	5.54±6.35	0.494
PCV (%)	32.38±3.	31.4±2.8	0.912
PLT $\times 10^9$/L	332.6±112.27	333.2±112.6	0.623
Blood sugar (mmol/L)	5.21±1.18	5.6±1.75	0.893

Values are expressed as mean±SD. N/L: Neutrophil to lymphocyte ratio, PLT: platelets, PCV: packed cell volume; WBC: white blood cell.

Table 3: Association of CSF indices with seizure in children with meningitis

Variables	Without seizure (n=100)	With seizure (n=22)	*p*-value
CSF cells $\times 10^9$/L	104.22±193.6	92.45±101.57	1.00
CSF neutrophils $\times 10^9$/L	58.56±167.4	74.0±105.48	0.578
CSF Lymphocytes $\times 10^9$/L	50.75±81.45	18.45±35.66	0.014
CSF sugar (mmol/L)	3.22±0.92	2.82±1.32	0.647
CSF protein (mg/dl)	0.31±0.26	0.46±0.45	0.697

Values are expressed as mean±SD. CSF: cerebrospinal fluid.

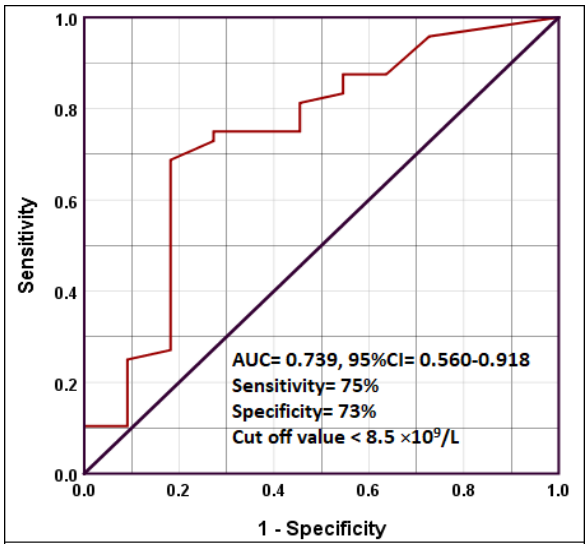

Figure 2: Receiver operating curve for CSF lymphocyte in the context of predicting seizure in children with meningitis

Variables significantly associated with seizure in univariate analysis were subjected to the multivariate analysis model to determine the independent factors associated with seizure. Each of the CSF lymphocytes (OR= 0.25, 95% CI= 0.08-0.26), lethargy (OR= 8.15, 95% CI= 1.03-68.65), headache (OR= 0.09, 95% CI= 0.02-0.45), neck stiffness (OR= 0.07, 95% CI= 0.01-0.61) and poor feeding (OR= 4.8, 95%CI= 1.21- 18.97) are independently associated with seizures in children with meningitis (Table 4).

Table 4: Multivariate analysis of factors associated with seizures

Variables	Odds Ratio (OR)	95% CI	*p*-value
CSF lymphocyte	0.25	(0.08-0.26)	0.014
Lethargy	8.15	(1.03-68.65)	0.044
Poor feeding	4.8	(1.21-18.97)	0.025
Headache	0.09	(0.02-0.45)	0.007
Neck stiffness	0.07	(0.01-0.610)	0.016

DISCUSSION

The frequency of seizures in the current sample of children with meningitis is 18%; female and younger children were more likely to be presented with seizures. Hematological indices fail to show meaningful differences between groups. In contrast, CSF lymphocytes are shown to have value in predicting seizures. As for clinical predictors, lethargy, headache, neck stiffness, and poor feeding were all independently associated with seizures in children with meningitis. The occurrence of seizures in meningitis is important, as it has been reported to increase the risk of complications [7,11], as well as the mortality rates in affected cases [12]. The frequency of seizures in the present study was 18%, which agrees with a meta-analysis by Najaf-Zadeh *et al*., who reported a seizure frequency of 16.7% in children with bacterial meningitis [13]. On the other hand, this frequency is low compared to a study done four years ago in the same hospital. In Iran, Nakhaei *et al*. [7] reported a seizure frequency of 37% in acute bacterial meningitis, while in a Brazilian study by Gomes *et al*., the frequency was 38.1% [14]. The highest frequency was reported in Taiwan (47%), according to Zhang *et al*. [15]. A study by Shatran *et al*. [16] in the same hospital as the current study reported a seizure frequency of 64.7%. The reported seizure discrepancy could be attributed to how bacterial meningitis was diagnosed. Shatran *et al*. used PCR to confirm bacterial meningitis rather than the CSF culture used in the current study. The former, PCR, is known to be superior to CSF culture in diagnosing bacterial meningitis as it is not affected by prior antibiotic administration to the patient, which was seen in more than two-thirds of the patients in the current study [17–19]. The age and gender of patients diagnosed with meningitis are important determinants of whether a seizure will occur. In the current study, younger children and female genders had a significantly higher risk of developing seizures, and the outcomes matched previously published data [7,12]. The young age at the time of diagnosis is proven to be associated with a higher risk of long-term disabilities [20]. In an adult study, Wang et al. demonstrated that gender does not correlate with seizures; this could represent a difference in pediatric studies from adult studies [21]. In the current study, residence does not correlate with seizure occurrence on presentation. As far as the authors know, no previous study studied the relationship between the residence and the presentation of children with bacterial meningitis. However, previous studies showed that children living in areas with impoverished living conditions have a higher mortality rate, which could be attributed to difficulties in accessing high-quality healthcare faced by these populations [22]. The total WBC, neutrophil count, and N/L ratio were higher in patients who presented with a seizure but failed to show a statistically significant difference. This indicates that the hematological indices included in the present study failed to predict seizure occurrence among the cases, which is in line with data from an adult sample [6]. The data in the present study indicate that CSF lymphocytosis is significantly higher in patients without seizures. At the same time, all other CSF indices were unrelated to the seizure, aligning with previous studies [6]. CSF lymphocytosis is well documented in acute bacterial and viral meningitis, and while bacterial meningitis is classically related to CSF neutrophilia, the type of WBC pleocytosis was proved by many studies to be of lesser importance in differentiating bacterial from viral meningitis [23]. The findings of the current study indicate that patients with lethargy and poor feeding had a higher chance of developing seizures. On the other hand, the presence of CSF lymphocytosis, headache, and neck stiffness was independently associated with lesser odds of developing seizures. In a retrospective Brazilian study, Corrêa-Lima *et al*. [12] identified five independent predictors for acute symptomatic seizure in children with bacterial meningitis, which include age less than 2 years, pneumococcal etiology, altered mental status and cerebrospinal fluid leukocyte count below 1000 cells. In an adult sample study, Zoons *et al*. [6] identified three factors significantly related to seizures: pneumococcal etiology, structural lesions on brain imaging, and underlying predisposing medical conditions [6]. So, in both these studies, pneumococcal etiology was the only predictor of seizure occurrence in children and adults with bacterial meningitis.

Limitations of the study

Since PCR testing, which is superior in diagnosing bacterial meningitis cases, was not available, we diagnosed acute bacterial meningitis based on positive results from gram staining, CSF culture, and sensitivity. The study excluded patients with negative culture and sensitivity, despite previous studies reporting a negative CSF culture in up to 30% of patients with acute bacterial meningitis [24–26]. Another limitation is the design of the study. A cross-sectional study enables the assessment of incidence and risk factors within a single time snippet. Due to the limitations of the study design, we were unable to follow those patients after the acute phase of the illness to verify if those predictors could correlate with recurrent seizures. We recommend a longitudinal study design to explore those associations.

Study strengths

This study had strict inclusion criteria where the age range and gender were clearly defined to mirror the risk of younger and female genders developing seizures. We have comprehensively collected demographic, hematological, and biochemical predictors to develop a reliable prediction model for a holistic patient approach. By establishing such models, we can identify high-risk cases for seizures, facilitating closer monitoring, resource allocation, and therapeutic interventions. There are currently no criteria or guidelines for predicting seizures in bacterial meningitis. The current study's results can help guide further large-scale multicentric studies to help establish such criteria.

Conclusion

About 18% of children diagnosed with acute bacterial meningitis have seizures. A constellation of clinical presentation and CSF lymphocyte count were identified as predictors of seizure in children diagnosed with bacterial meningitis. We identified five factors associated with the development of seizures in children diagnosed with bacterial meningitis: CSF lymphocyte count, lethargy, poor feeding, neck stiffness, and headache.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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