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Can Clinical Presentations or Hematological Indices Predict Meningitis in Febrile Children?

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ABSTRACT

The aim of this study is to assess the role of clinical presentations and hematological indices in the diagnosis of meningitis in febrile children during a meningitis outbreak. A cross-sectional study, recruiting (236) febrile children underwent lumbar puncture for suspected meningitis. Participants were divided into two groups based on the results of cerebrospinal fluid (CSF) analysis: the case group included all those who carried a diagnosis of meningitis while the rest of the patients whose CSF analysis result was negative for meningitis was taken as a control group. The clinical characteristics, hematological indices were compared between both groups. Children with proved meningitis were significantly of older age and resides more in rural areas than control P value= (0.001), (0.014) respectively. The Neutrophil to lymphocyte ratio and platelet counts were the only significant hematological indices that elevated in children with meningitis P value= (0.001), (0.018) respectively. Headache and neck stiffness were documented more in children with meningitis P value = (<0.001) whilst seizure was significantly less common in children with meningitis P value = (<0.001). During a meningitis outbreak, pediatrician in low resource country can use a constellation of clinical and hematological characteristics to identify febrile children who in need of lumbar puncture to exclude meningitis.

INTRODUCTION

Meningitis is an infectious disease prevalent globally and is of major public health concern [1,2]. In Arabic countries, outbreaks of meningitis frequently occurred in areas of the African meningitis belt. However, the Mediterranean region including Iraq still tackles an outbreak of meningitis every few years among several infectious diseases [3]. In May 2023, Iraq encountered a meningitis outbreak, which started in the north of Iraq mainly in Sulaymaniyah City then rapidly cases were reported in increasing numbers from all over the country [4].

The diagnosis of meningitis in Iraq faces several obstacles with a shortage of diagnostic kits at health care facilities [5]. Physicians including pediatricians started to depend mainly on cerebrospinal fluid (CSF) analysis for the diagnosis of meningitis. Adding to this problem is that obtaining CSF analysis by lumbar puncture in children is dependent on parental approval with high refusal rates documented in Iraq [6]; this together with the lack of confirmation of cases of meningitis has led to underreporting of the cases in Iraq [5]. Meningitis is prevalent in the pediatric age group and undiagnosed cases or delays in the diagnosis can lead to a high mortality rate [7–9]. This all calls for a need to find a constellation of clinical presentations and hematological indices to serve as a diagnostic tool or at least for screening

febrile children during meningitis outbreaks for early case identification and management. Our study aims to assess the role of clinical presentations, hematological indices, and routine CSF analysis in the diagnosis of meningitis in febrile children during a meningitis outbreak in Iraq an example of low low-resource country to reach a cost-effective diagnostic approach based on routine diagnostic labs.

METHODS

Study design and sampling

This is a cross-sectional study, recruiting all children who underwent lumbar puncture for suspected meningitis admitted to the emergency department of Central Child Teaching Hospital, Baghdad -Iraq during the period from the 1st of July to 31st of November 2023. Inclusion criteria: 1. Previously healthy children who underwent lumbar puncture at the emergency department, 2. age above 1 month, 3. family gave informed consent for participation in the study. Exclusion criteria: children with underlying chronic illness or on medications that suppress immunity like steroids or immunosuppressants and those who refused to participate in the study. In addition, neonates were excluded as per hospital policy neonates are exclusively admitted to the neonatal ward and not to the emergency department.

All patients in this study were examined by a pediatric neurologist and requested to have a lumbar puncture done to exclude meningitis. Glucose and protein concentrations and leukocyte count were analyzed for each CSF specimen. Meningitis is diagnosed when CSF shows leukocytes higher than 5 per microliter of CSF irrespective of CSF protein and glucose level [10]. Gram stain and bacterial culture were performed by standard methods for all CSF specimens in Central Child Teaching Hospital. In addition to CSF analysis, all patients in this study had complete blood counts. Demographical and clinical characteristics were taken from patient's files at the emergency department.

Participants in this study were divided into two groups based on the results of CSF analysis: the case group included all those who carried a diagnosis of meningitis while the rest of the patients whose CSF analysis result was negative for meningitis was taken as a control group. The CSF cultures for all patients were negative and PCR was not unavailable, so meningitis was diagnosed based on CSF analysis and clinical judgment [11]. The ethical committee in the College of Medicine approved the study (12/2024).

Statistical analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Normality of the continuous data was tested by Shapiro Wilk test, A Student t-test was used to assess data having a normal distribution, which were given as mean and standard deviation. Non-normally distributed data were examined using the Mann-Whitney U test and provided as median and rang. The Chi-square/Fischer exact test was used to assess categorical variables, which were expressed as numbers and percentages. Any result that was deemed statistically significant had a p-value of less than 0.05.
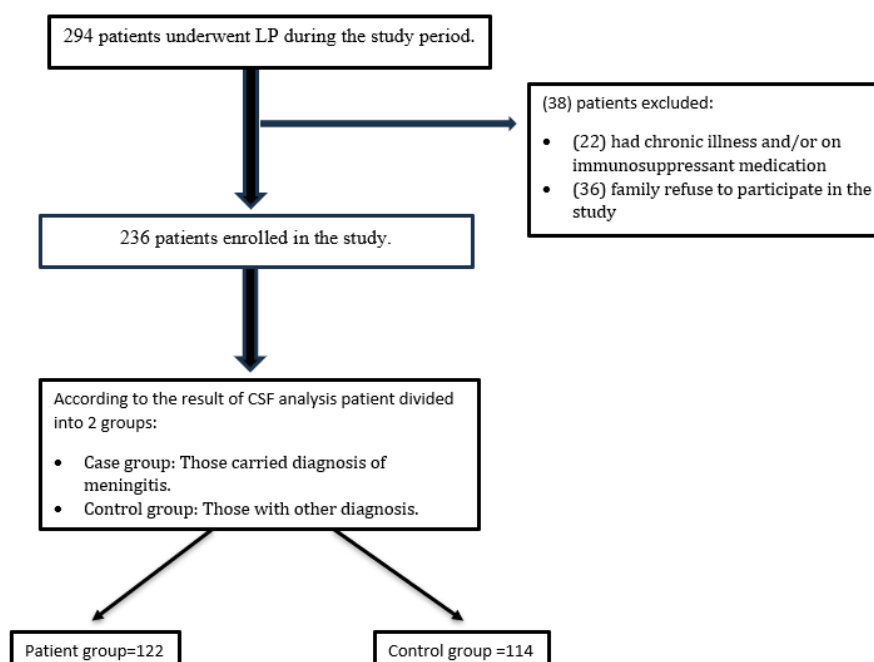

Figure 1. The study flow chart showing how patients enrolled, excluded, and divided into case and control groups.

RESULTS

A total of 236 patients were recruited in this study. The median age of the patients was (7.0 years) which was much higher than that of controls (1.8 years) with a highly significant difference. Similarly, rural residents were more frequent among patients than controls (54.1% vs. 31.58%) with a significant difference (Table 1).

Table 1. Demographic characteristics of the study populations

Variables	Cases (n=122)	Controls (n=114)	p-value
Age, years Mean ±SD Median Range	6.53±4.32 7.0 2.0-13.0	2.4±1.8 1.8 1.0-8.0	<0.001
Gender Male Female	88(72.13%) 34(27.87%)	76(66.67%) 38(33.33%)	0.519
Residence Rural Urban	66(54.1%) 56(45.9%)	36(31.58%) 78(68.42%)	0.014

Two symptoms (headache and neck stiffness) were more common in patients (62.3% and 49.18%, respectively) than in controls (17.54% and 5.25%, respectively) with significant differences. On the other hand, each of vomiting, seizure, and poor feeding were less common among patients (68.85%, 18.03%, and 26.23%, respectively) than controls (78.72%, 59.65% and 56.14%, respectively) with significant differences. Most children in controls group (91.23%) had received prior antibiotics therapy compared with (70.49 %) of patients with a highly significant difference (Table 2).

Table 2. Clinical characteristics of patients and controls

Variables	Cases (n=122)	Controls (n=114)	p-value
Disease duration, week One week More than 1 week	98(80.33%) 24(19.67%)	104(91.23%) 10(8.77%)	0.092
Duration of fever, days Mean ± SD. Median Range	4.95±5.57 3.0 1.0-30	3.86±1.83 3.0 1.0-7.0	0.892
Complains			
Vomiting	84(68.85%)	100(78.72%)	0.019
Lethargy	76(62.3%)	90(78.95%)	0.083
Headache	76(62.3%)	20(17.54%)	<0.001
Seizure	22(18.03%)	68(59.65%)	<0.001
Neck stiffness	60(49.18%)	6(5.25%)	<0.001
Poor feeding	36(26.23%)	64(56.14%)	0.002
Diarrhea	10(8.2%)	14(12.28%)	0.482
Rash	2(1.64%)	0(0%)	1.0
Prior antibiotics Not received Received	36(29.51%) 86(70.49%)	10(8.77%) 104(91.23%)	0.004

The median total WBC, absolute neutrophil and absolute lymphocyte was lower in patients (12.0×10^9/L, 7.0×10^9/L and 2.5×10^9/L, respectively) than controls (17.0×10^9/L, 8.82×10^9/L and 6.72×10^9/L, respectively) with highly significant differences. In contrast, patients demonstrated higher median NLR and PLT (2.5 and 312×10^9/L, respectively) than controls (1.38 and 279×10^9/L, respectively) with significant differences.

Table 3. Hematologic indices in patients and controls

Variables	Cases (n=122)	Controls (n=114)	p-value
WBC, $\times 10^9$/L Mean±SD Median Range	 13.53±6.52 12.0 2.0-38	 17.67±4.19 17.0 5.3-28.0	<0.001
Neutrophil, % Mean±SD Median Range	 64.9±19.0 68.0 1.3-92	 57.6±14.43 55.0 21.0-82.0	0.007
Absolute Neut, $\times 10^9$/L Mean±SD Median Range	 8.25±6.1 7.0 0.0-28.5	 10.35±4.19 8.82 2.39-20.16	0.005
Lymphocyte, % Mean±SD Median Range	 27.75±16.82 26.0 0.6-70	 38.4±13.2 39.0 12.0-64.0	<0.001
Absolute lymph, $\times 10^9$/L Mean±SD Median Range	 3.19±2.58 2.8 0.0-9.95	 6.6±2.33 6.72 1.56-13.44	<0.001
Blood N/L ratio Mean±SD Median Range	 4.28±4.68 2.5 0.34-23	 1.89±1.27 1.38 0.42-6.5	0.001
Packed cell volume, % Mean ±SD Range	 32.2±3.3 25-40	 33.34±2.92 28-38	0.057
PLT, $\times 10^9$/L Mean ±SD Median Range	 332.7±112.6 312 125-805	 287.5±75.65 279 166-488	0.018
Blood sugar, mmol/L Mean ±SD Range	 5.28±1.3 3.5-8.3	 5.53±1.12 3.8-8.8	0.136

PLT: platelets, N/L ratio: neutrophil to lymphocyte ratio.

Patients displayed much higher median CSF cells, neutrophil and lymphocyte (42×10^9/L, 6.0×10^9/L and 15×10^9/L, respectively) than controls (1.0×10^9/L, 0.0×10^9/L and 2.0×10^9/L, respectively) with highly significant differences. In contrast, the median CSF sugar in patients was 3.0 mg/dl which was lower than that of control (3.8 mg/dl) with highly significant difference (Table 4).

Table 4. Cerebrospinal fluid (CSF) indices in patients and controls

Variables	Cases (n=122)	Controls (n=114)	p-value
CSF cells, ×109/L Mean±SD Median Range	 102.1±179.8 42 1.0-1118	 1.02±1.59 1.0 0.0-6.0	**<0.001**
CSF neutrophil, ×109/L Mean±SD Median Range	 61.44±157.1 6.0 0.0-1058	 0.0±0.0 0.0 0.0	**<0.001**
CSF Lymphocyte, ×109/L Mean±SD	 43.91±75.8	 2.32±1.65	**<0.001**

Median	15.0	2.0	
Range	0.0-400	0.0-6.0	
CSF sugar, mg/dl			
Mean±SD	3.14±1.0	4.0±1.07	**<0.001**
Median	3.0	3.8	
Range	0.0-5.3	1.9-6.4	
CSF protein, mg/dl			
Mean±SD	0.33±0.3	0.32±0.33	0.421
Median	0.21	0.3	
Range	0.1-6.4	0.1-1.3	

DISCUSSION

This study showed that during the 2023 meningitis outbreak in Iraq, from febrile children who admitted to the hospital with presumptive diagnosis of meningitis, children with proved meningitis tend to be of older age and resides in rural areas. The Neutrophil to lymphocyte ratio and platelet counts were the only significant hematological indices that elevated in children with meningitis. Headache and neck stiffness were documented more in children with meningitis while seizure was surprisingly significantly less common in children with meningitis. These constellations of clinical and hematological characteristics can help pediatrician to identify febrile children who in need of lumbar puncture to exclude meningitis.

The mean age of patients diagnosed with meningitis in this study was 7 years that was in line with results documented from reports in the regions from north of Iraq during the same outbreak [4] and goes with published data from meningitis outbreaks in other parts of the world, which detected a mean age of 7 years [12–14]. While in outbreaks from other regions like Ghana, children of age range 10-14 was mostly affected in meningitis outbreak [15] .The mean age of febrile patients with proved meningitis was higher than those with negative CSF analysis. This indicates that from febrile patients in whom CSF analysis was requested based on clinical presentation, meningitis tend to affect older age patients this could be attributed to the fact that signs of meningitis in young patients is not specific which results in over requesting lumbar puncture in young age children [16–18]. There is a robust evidence link residence in rural areas with development of meningitis during an outbreak [19–21] and this was evident in this study as children diagnosed with meningitis in this study during meningitis outbreak were significantly resides in rural area (P value=0.014).

On the other hand, gender and the duration of the fever was not significantly related to development of meningitis P-value = (0.519), (0.089) respectively and this match previous published data [14,22,23] .There is an interestingly high percentage of patients in the current study received a prior antibiotic. Although patients with meningitis significantly received a prior antibiotic less than control (P value =0.004), however 70.49% of children who diagnosed as meningitis were already received a prior antibiotic. This percentage is the highest one documented till now as previous studies in children in other parts of the world showed that 11- 27% of children with meningitis had pretreatment with antibiotics [24,25] . This misuse of antibiotics was previously documented in Iraq by Salim et al [26] reporting a high prevalence of antibiotic misuse among Iraqi people ranging from (45%- 92%) with the highest percentage reported in pediatric population.

The signs and symptom of meningitis in children is nonspecific as many cases initially carry other diagnoses [16,17,27] .In this study during 2023 meningitis outbreak in Iraq children with meningitis showed a significantly high presence of headache and neck stiffness than control. The most striking finding is lower reported seizures from children with meningitis than control. This clinical presentation match data from outbreak of meningitis in Germany [14] and Poland [28]. So, the presence of headache and/or neck stiffness in febrile children during outbreak of meningitis can be regarded as an indicator of meningitis that would be useful as a screening tool in practice. Although seizure in febrile children carry fourfold increase the possibility of meningitis, however this applied only in children outside of febrile-seizure age range and mainly depend on the type of seizure as being complex seizure rather than simple seizure [17].

In this study, the hematological indices were significantly different between children with meningitis and control group. Children with meningitis had significantly lower total WBC and absolute neutrophil and lymphocyte counts and this match results of previous studies as leukocytosis are nonspecific sign of inflammation (29,30). On the other hand, a significantly higher neutrophil to lymphocytes ratio and platelet count seen in children with meningitis with P value = (0.001), (0.018) respectively.

The NLR and platelet count are cost- effective and readily available clinical markers of peripheral inflammation so it can be used to aid in selecting children who require lumbar puncture for CSF analysis when suspecting meningitis.

The patients in the current study had diagnosed as meningitis based on CSF analysis in which the CSF showed leukocytosis >5 cells/HPF. All patients had received 7 days of antibiotics because of lack of resources to differentiate

bacterial from viral meningitis. However, the CSF analysis goes with bacterial meningitis with elevated neutrophil and low CSF glucose. Although this study had multiple limitations like being single center study and lack of identification of the causative agent of meningitis however it carries a hope of opening avenues for future research.

CONCLUSION

During a meningitis outbreak, pediatrician in low resource country can use a constellation of clinical and hematological characteristics to identify febrile children who in need of lumbar puncture to exclude meningitis.

Conflicts of Interest

The authors declare no conflicts of interest.

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هل يمكن للأعراض السريرية أو مؤشرات الدم التنبؤ بالتهاب السحايا عند الأطفال المصابين بالحمى؟

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المستخلص

الهدف من هذه الدراسة هو تقييم دور المظاهر السريرية ومؤشرات الدم في تشخيص التهاب السحايا لدى الأطفال المصابين بالحمى أثناء تفشي التهاب السحايا. دراسة مقطعية، أجريت على (236) طفلاً مصاباً بالحمى، خضعوا للبزل القطني للاشتباه في التهاب السحايا. تم تقسيم المشاركين إلى مجموعتين بناءً على نتائج تحليل سائل النخاع الشوكي ضمت مجموعة الحالات جميع الذين حملوا تشخيص التهاب السحايا بينما تم أخذ بقية المرضى الذين كانت نتيجة التحليل لديهم سلبية لالتهاب السحايا كمجموعة مراقبة. تمت مقارنة الخصائص السريرية والمؤشرات الدموية بين المجموعتين. كان الأطفال المصابون بالتهاب السحايا المؤكد في سن أكبر بكثير ويقيمون في المناطق الريفية أكثر من السيطرة، وكانت قيمة (0.001)، (0.014) $P =$ على التوالي. كانت نسبة العدلات إلى الخلايا الليمفاوية وعدد الصفائح الدموية هي المؤشرات الدموية الوحيدة المهمة التي ارتفعت عند الأطفال المصابين بالتهاب السحايا بقيمة (0.001) $P =$ و (0.018) على التوالي. تم توثيق الصداع وتصلب الرقبة بشكل أكبر عند الأطفال المصابين بالتهاب السحايا بقيمة (0.001>) $P =$ بينما كانت النوبة أقل شيوعًا بشكل ملحوظ عند الأطفال المصابين بالتهاب السحايا بقيمة (0.001>) $P =$. أثناء تفشي التهاب السحايا، يمكن لأطباء الأطفال في البلدان ذات الموارد المنخفضة استخدام مجموعة من الخصائص السريرية والدموية لتحديد الأطفال المصابين بالحمى والذين يحتاجون إلى البزل القطني لاستبعاد التهاب السحايا.

الكلمات الدالة: الأطفال، العراق، التهاب السحايا، تفشي المرض.