Original Article

PREDICTORS OF BACTERIAL MENINGITIS IN ADULT PATIENTS OF SOUTH WEST IRAN

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ABSTRACT

Objectives: To study the clinical and lab parameters in adult patients with suspected or confirmed bacterial meningitis (BM) to find out the usefull predictors.

Methodology: This was a retrospective study conducted in Razi hospital, a training center affiliated to Ahvaz Joundishapoor University of Medical Sciences in Iran. All patients with meningitis aged 18 years ore more between 2003 and 2007, with CSF pleocytosis and who had not received antibiotic treatment before lumbar puncture were reviewed.

Results: Among 312 patients with CSF pleocytosis, two hundred fifteen (68.9%) had BM and ninety seven (31.1%) had aseptic meningitis (ASM). The mean age for patients with BM was 34.7 ± 17.7 years and for ASM was 32.2 ± 15.5 years (P=0.22, NS). Sixty percent of the cases of BM and 61.2% of the cases of ASM occurred in men (P=0.70, NS). We identified the following predictors of BM: CSF-WBC count>100 per micro liter, CSF-glucose level <40 mg/dl, CSF-protein level>80 mg/dl. Sensitivity, specificity, PPV, NPV of these predictors, and LR for BM are 86.5%,52.6%,80.2%, 63.7% and 104.1 for CSF-WBC count and 72.1%, 83.5%, 90.6%,57.4% and 164.2% for CSF glucose, and 49.7%, 91.8%, 93.4%,45.2% and 104.5% for CSF protein.

Conclusion: The CSF WBC count should not be used alone to rule out bacterial meningitis. When it is combined with other factors such as CSF glucose and protein it helps in decision making in patients suffering from bacterial meningitis.

KEY WORDS: Bacterial meningitis, Aseptic meningitis, Predictors, Cerebrospinal fluid.

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INTRODUCTION

Although, in developed countries immunization by conjugate vaccine against *H.influenza* has decreased the incidence of bacterial meningitis (BM),[1-3] but, in developing countries BM continues as a major public health problems.[4] Unfortunately, meningitis still occurs and, if not treated promptly, brings with it severe morbidity and mortality.[4-6] A great majority of meningeal infections are caused by nonbacterial organisms such as viruses and unnecessary use of broad spectrum antibacterial drugs lead to emergence of multidrug resistant bacteria.[5,6]

The declining incidence rate of culture positive cerebrospinal fluid (CSF) samples and

more incidences of culture-negative CSF pleocytosis; aseptic meningitis (ASM) are a major confounding factor in approach to patients with suspected central nervous system (CNS) infection.[7] Receiving antibacterial drugs before lumbar puncture (LP), result in an increase in the proportion of patients with negative culture results in CSF examination.[4,8] Physicians often are concerned by any degree of CSF pleocytosis in patients who are being assessed for bacterial meningitis. When no other abnormal clinical or biochemical factors consistent with bacterial meningitis are identified, then these patients are often hospitalized and treated empirically with antibiotics.[9-10] Previous studies have suggested formulas to estimate a patient's risk for BM.[4,8,11] It has been shown that the mean CSF white blood cell (WBC) count and CSF glucose are significantly different between patients with BM and those with ASM. Those studies have also shown that mean CSF-WBC count, glucose and protein concentration varies in different countries and different pathogenic bacteria.

Spanos et al reported that a CSF-glucose concentration less than 34 mg/dl, a CSF-protein concentration more than 220 mg/dl, CSF-WBC>2000 cell per micro liter and CSF-PMN>1180 cell per micro liter were predictors of BM rather than ASM with 99% certainly.[12] The foremost textbook of infectious disease[4,6] indicate that CSF-WBC count greater than 5 per micro liter and CSF glucose lower than 60 mg/dl are abnormal.Little information is available in Iran, on positive or negative predictive value (PPV or NPV), likelihood ratio (LR), or specific treatment guideline for given CSF-WBC and glucose level.

The aim of this study was to evaluate the PV and LR of CSF-WBC,CSF-glucose and CSF protein for BM in hospitalized patients in a teaching hospital in Ahvaz a city located in south west Iran.

METHODOLOGY

This study was a retrospective review of the CSF examination for the evaluation of BM. The study population included all patients aged 18 years and more who underwent a LP in the infectious disease ward of Razi hospital to diagnose BM between 2003 and 2007.

Exclusion criteria were: (1) clotted samples, (2) systemic infection such as tuberculosis, brucellosis and HIV/AIDS, (3) any underlying medical condition that altered CSF findings such as neoplasms, metabolic diseases and collagen vascular disease, (4) receiving antibiotic before LP.

Data were extracted from the medical files of patients with meningitis, which contained information on all blood and CSF samples, submitted for culture, biochemical and cytological examination. Additional information was extracted to ensure that inclusion and exclusion criteria were met. Selection criteria for prediction BM were: (1) positive CSF culture , (2) diagnosis of BM including presumptive meningitis, (3) CSF WBC count, (4) CSF glucose and protein data, (5) serum glucose data, (6) completed blood cell count(CBC), (7) clinical variables such as fever, headache, neck stiffness, level of consciousness(LOC),seizures and focal deficits, and (8) receiving antibiotics before LP. Patients were placed in two groups; (1) BM consisted of patients whose CSF culture was positive for common CNS pathogen, CSF pleocytosis in association with decreased CSF glucose and increased CSF protein, and (2) ASM which included all other patients with abnormal CSF examination. Data were analyzed in SPSS (version 16, USA) by using descriptive analysis, t-test, chi square, Fisher exact test and likelihood ratio (LR). Sensitivity, specificity, PPV, NPV and LR were determined. The NPV describes the probability that the patient does not have BM and is a valuable indicator to rule out BM. The LR is the likelihood that a given test result is expected in a patient with BM compared with the likelihood that the same result would be expected in a patient without BM. Because LR is less likely to change with the prevalence of the disorder, is preferred to PPV, NPV and specificity. Cutoff values for predictors were: (1) CSF WBC; less than 10,10 to 100, and greater than 100 cell per micro liter, (2) CSF glucose <40 mg/dl, (3) CSF protein >45, 45-80 and greater

than 80 mg/dl,(4) CBC-PMN>10×10^{3}per micro liter.[13,14]

RESULTS

We identified 457 patients who met the inclusion criteria. We excluded 77 patients because of underlying diseases, 65 patients who had received antibiotic treatment before LP, and 15 patients who were suspected to have tuberculosis, brucellosis, or HIV/AIDS. Patients could be excluded for more than one reason.

Among 312 remaining patients with CSF pleocytosis, 215(68.9%) had BM (definite and presumptive) and 97(31.1%) had ASM. The mean age for patients with BM was 34.7 ± 17.7 years and for ASM was 32.2 ± 15.5 years (P=0.22, NS). Sixty percent of the cases of BM and 61.2% of the cases of ASM occurred in men (P=0.70, NS). Demographic and clinical characteristics are summarized in Table-I.

As shown in Table-I, there is no significant difference between 2 groups with the respect to clinical findings. We identified the following predictors of BM: CSF-WBC count>100 per micro liter, CSF-glucose level<40 mg/dl, CSF-protein level>80 mg/dl, CSF-PMN> 80%, and peripheral blood PMN of 10,000 or more. CSF characteristics are shown in Tables-II & III. As shown in these tables there are significant differences in CSF results between two groups. Sensitivity, specificity, PPV, NPV of these predictors, and LR for BM are shown in Table-IV. Of 80 patients without these predictors, four cases were culture positive for common bacterial pathogen (3 N.meningitidis, 1 S. pneumonia); this means that NPV for these predictors is at least 95%.

DISCUSSION

Bacterial meningitis is an important and life threatening infection.[4] Reducing morbidity and mortality is critically dependent on rapid diagnosis[13] and, perhaps more importantly, on the timely initiation of appropriate antimicrobial

Table-I: Demographic and clinical variables in patients with meningitis admitted in Razi Hospital Iran

Variable		*ASM (n=97) N (percent)*	*BM (n=215) N (percent)*	*P. value*	*LR*
Age(years)	18-24	43(44.4)	85(39.5)	0.37	0.05
	25-44	32(32.9)	83(38.6)		
	45-64	16(16.5)	24(11.2)		
	e”65	6(6.2)	23(10.7)		
Sex	Male	60(61.9)	129(60)	0.70	0.63
	Female	37(38.1)	86(40)		
Clinical finding	Fever	96(98.9)	208(96.7)	0.23	1.55
	Head ache	96(98.9)	210(97.5)	0.67	0.66
	V &N	89(91.7)	195(90.7)	0.83	0.87
	Neck stiffness	93(95.8)	197(91.6)	0.23	2.01
	Decreased LOC	14(14.4)	26(12.1)	0.34	0.32
	Seizure	5(5.1)	3(1.4)	0.11	3.4
	Kernic	9(9.3)	24(11.2)	0.69	0.25
	Brudzenski	9(9.3)	24(11.2)	0.69	0.25
	Lethargy	9(9.3)	17(7.9)	0.66	0.16
	Confusion	6(6.2)	5(2.3)	0.10	2.6
	Coma	1(1.0)	3(1.4)	1.00	0.07

Abbreviations: ASM; aseptic meningitis, BM; bacterial meningitis, LR; likelihood ratio, N; number, V&N; vomiting and nausea, LOC; level of consciousness

Table-II: Cerebrospinal fluid analysis in aseptic and bacterial meningitis in patients with meningitis admitted in Razi hospital, Ahvaz, Iran, 2003-2007

CSF results		*ASM(n=97) N (percent)*	*BM(n=215) N (percent)*	*Pvalue*	*LR*
WBC count	< 10	14(14.4)	2(0.9)		
	10-100	37(38.2)	27(12.6)		
	>100	46(47.4)	186(86.5)	0.0001	104.1
Glucose	>60	73(75.3)	48(22.3)		
	40-60	8(8.2)	12(5.6)		
	<40	16(16.5)	155(72.1)	0.0001	164.2
Protein	<45	83(85.6)	87(40.5)		
	45-80	6(6.2)	21(9.8)		
	>80	8(8.2)	107(49.7)	0.0001	104.5

Abbreviations: ASM; aseptic meningitis, BM; bacterial meningitis, CSF; cerebrospinal fluid , WBC count; white blood cell per micro liter, Glucose in milligram per deciliter, protein in milligram per deciliter, LR; likelihood ratio

therapy.[8] Differentiating BM from ASM is the first step in making decision for treatment. Bonsu et al reported that among children with cerebrospinal fluid (CSF) pleocytosis, the task of separating aseptic from bacterial meningitis is hampered when the CSF Gram stain result is unavailable, delayed, or negative.[14] The present study showed that CSF-WBC count more than 100 per micro liter is a useful tool for prediction of BM. There is a significant relation between increased CSF WBC count and increased risk of BM. When the CSF WBC is100/µl or more, the PPV is high and more likelihood for BM. When the CSF-WBC is less than 100/ µl NPV is high and likelihood for BM is low and is similar to CSF-WBC count less than 10/µl. Previous studies suggested laboratory predictors with controversial results in some reports[4,8,10] whereas our finding is consistent with other such studies.[15,16] The reason for this differences is not clear, but we believe that difference in study design, lab facilities and receiving antibiotic before LP may interfere and biased our results. In suspected case of meningitis with low CSF WBC count, other laboratory tests should be employed to differentiate BM from ASM. In this study four cases of confirmed BM(CSF culture positive for common pathogenic agent) had low WBC count in their CSF samples, but had at least one of the following criteria: CSF glucose<40 mg/dl,CSF protein> 80mg/dl,or CSF –PMN count>10 000 cell/µl. The presence of these criteria independently indicate that the patient is at an increased risk for BM. This finding is in agreement with previous studies.[16,17]

Presence of 4 case of BM in the absence of these variables (3 predictors) means that NPV for these predictors is not 100%, hence, low CSF-WBC, normal CSF glucose and protein concentration does not rule out BM. Previous

Table-III: Mean of WBCcount, glucose and protein concentration in cerebrospinal fluid in patients with meningitis admitted in Razi hospital, Ahvaz, Iran, 2003-2007

CSF results	*ASM(n=97) Mean ± SD*	*BM(n=215) Mean ± SD*	*Pvalue*
WBC count	356.4 ± 1631.8	4021 ± 10352.1	0.001
CSFglucose	68.7 ± 16.1	48.5 ± 17.3	0.0001
CSF protein	32.6 ± 17.7	89.8 ± 76.8	0.0001

Abbreviations: ASM; aseptic meningitis, BM; bacterial meningitis, CSF; cerebrospinal fluid , WBC count; white blood cell per micro liter, Glucose in milligram per deciliter, protein in milligram per deciliter, LR; likelihood ratio,SD; standard deviation.

Table-IV: Sensitivity, specificity, predictive value of cerebrospinal fluid variables and likelihood ratio for bacterial meningitis in patients with meningitis admitted in Razi hospital, Ahvaz, Iran, 2003-2007.

Predictor	*Sensitivity %*	*Specificity %*	*PPV%*	*NPV%*	*LR*
CSF- WBC count>100/µl	86.5	52.6	80.2	63.7	104.1
	72.1	83.5	90.6	57.4	164.2
	49.7	91.8	93.4	45.2	104.5

Abbreviations: CSF; cerebrospinal fluid , WBC count; white blood cell per micro liter, Glucose in milligram per deciliter, protein in milligram per deciliter, PPV;positive predictive value, NPV; negative predictive value.

researchers; Freedman et al,[16] Polk et al[17] and Wong et al[18] reported a number of definite BM in patients without CSF pleocytosis. The present study also explained that other laboratory tests such as CSF glucose concentration and CSF protein concentration in combination with CSF pleocytosis may be useful to differentiate BM from ASM. When the glucose level of CSF is lower than 40 mg/dl, PPV is high (90.6%) and likelihood for BM is high, but when CSF glucose is normal or is higher than 40 mg/dl, NPV is less than 60% and does not rule out BM.

When CSFprotein is higher than 80mg/dl, PPV is 93.4% and more likelihood for BM, but when CSF protein is normal or lower than 80mg/dl, NPV is decreased and BM can not be ruled out. Our study showed that, although these predictors as well as previous studies are useful in separating BM from ASM, but, CSF WBC cutoffs and protein level are similar or different of those studies.[8,10-12,13,14,19] This finding suggests that cutoffs of these predictors may vary in different countries. As described in literature,[4,14,16] this study showed that clinical variables such as fever, headache, neck stiffness, nausea, vomiting, Kernig's and Brudzinski's sign and LOC are not predictors of BM.

Limitations of the study: There were some limitations in our study. Design of this study was retrospective and its validity is lower than prospective, study population were aged 18 years or more whereas bacterial meningitis occurs mostly in childhood, and our patients consisted of definite and presumptive cases and not only definite ones. Further prospective studies based on culture positive or proven cases by antigen detection are recommended.

CONCLUSION

When CSF culturing is not available, delayed or is negative, CSF-WBC count, CSF glucose level, and CSF protein level may help us to differentiate BM from ASM and making decision on immediate initiation of antibiotic treatment. The CSF WBC count should not be used alone to rule out bacterial meningitis, when it is combined with other factors such as CSF glucose and protein, it yields better results than when used alone.

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