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Assessment of Diagnostic Value of Three Interleukin (1, 6 And 8) In Cerebrospinal Fluid of Children and Adolescent with Meningitis

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Abstract:

Background: *Meningitis is a serious infectious disease of the central nervous system (CNS) with severe complication and numerous mortality. Distinction between aseptic and bacterial meningitis by cerebrospinal fluid (CSF) culture can be difficult and long-term, and other diagnostic methods are under studying for prevention of bacterial meningitis complications. This study aimed to assess the diagnostic value of three CSF biomarkers including interleukin (1, 6 and 8) in the children and adolescent with meningitis.*

Methods: *51 children and adolescent (1month-18 years) with definite meningitis were included in a cross-sectional analytic study. In addition to analysis and culture of CSF, interleukin-1,6,8 levels were determined by ELIZA method in CSF samples obtained from all cases .*

Results*: Frequency of bacterial and aseptic meningitis was equal (49%). Gender had not significant different between two groups (P =0.7). Bacterial group had a higher mean age than aseptic group (P=0.047). The level of IL-1 was not different between two groups(P =0.168). The level of IL-6,8 were significant different (P =0.030 &.047) respectively. Diagnostic values of IL-1 ,6 were 80.77%& 53.85% in bacterial group and 68% & 64% of aseptic group respectively that had not different (P=0.349&0.572). Diagnostic value of IL-8 was noted in the 80.77% of bacterial group and 28.00% of aseptic group that had significant different (P <0.001).*

Conclusion*: Although determining the levels of IL-8 and IL-6 may beuseful in the differential diagnosis of meningitis, only IL-8 has suitable diagnostic value for distinction between bacterial and aseptic meningitis. Further studies have recommended.*

Keywords*: Interleukin, Bacterial meningitis, Aseptic meningitis, Children, Adolescent*

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I. Introduction

Meningitis is an acute andserious infectious disease of the central nervous systemthat associated with severe complication and numerousmortality (1-3).According to causes of disease, meningitisclassified in two group, septic that caused by bacterial agents and aseptic that caused byother pathogens (4). Bacterial meningitis is a serious disease and can be fatal in 2-5% of cases. Early diagnosis and appropriate antibiotic therapy is necessary to prevent morbidity and mortality in patients with bacterial meningitis (5-7). Appropriate diagnosis of meningitis can lead to decreasing complications and preventing unnecessaryantibiotic therapy and hospitalization (4).It is difficult to distinction between the two types of meningitis because of clinical symptoms and laboratory findings aresimilar in two types, particularly when the use of antibiotics are administered prior to analyzing and culture of cerebral spinal fluid (3). Cerebrospinal fluid culture as definitive diagnostic method formeningitisrequires access to facilities and spends a long time (8-6).Thereforeantibiotic therapy performed at beginning of clinical diagnosis of meningitis for prevention of serious complications, whichlead to side effects of antibiotics,patient's discomfort, and increased financial burden of disease (8). Due to these reasons, new diagnostic methodsfor meningitis have been studied.Assessment ofthe cytokinesas immune responses mediators is one of such methods. Detection ofCytokinesatan inflammation site is a better indicator of the severity of clinical disease than the serum levels of the cytokines (10). There are someinflammatory changes of CSF in presence of meningitis;therefore the levels of cytokines have been varied in patients with meningitis (11).

Thepossible role of IL-1, 6 and 8 in the CSF of patients with meningitis has been demonstratedin several studies(10, 11).IL-1 activates the inflammatory cells and stimulatesthe production of other cytokines in the early stages of inflammation(12, 10). In a meta-analysis by Panato (2014), IL-1β has 86.0% sensitivity and 92.3% specificity for distinguishing between bacterial and aseptic meningitis and introduced as a useful prognostic marker for bacterial meningitis (3). Increased CSF concentration of IL-6 is detected inall of meningeal inflammatory diseases (9). There is an important role for IL-6 plus IL-1 ingrowth of lymphocyte-B and induction of fever and acute phase reactions (15-12).In the researches were done inVazquez in 2012 and Pinto Junior in 2005-7,IL-6 levels were higher in the CSF of patients with bacterial meningitis in comparison to aseptic meningitis (9, 15). IL-8 is produced in monocytes and vascular endothelial cells in response to stimulation with bacteria or lipopolysaccharides, and is released from these cells into blood stream or tissue fluids (16) which stimulate the migration of neutrophils to site of inflammation (12-14). IL-8 increases in a variety of the meningeal inflammation particularly acute bacterial meningitis, and has important role to differentiate between types of meningitis (4,9,10,16,17). The functional values of IL-8 for differentiatingseptic from aseptic meningitis has been shownin various studies. In the Abdelmoez survey in 2014, cutoff point for IL-8 level was 3.6 ng / ml, sensitivity was 82.5% and specificity was 85.0% (4), In a research by Ostergaard et al in 1996, cut off point was 3.00 ng / ml, sensitivity was 81% , specificity was 92.0% and positive predictive value was 96%(17). In another study in 2005-2007 Junior Pinto found, cut off point 1.685 ng / ml, sensitivity 100% and specificity 94.0 %(9). In the present study, the CSF concentration of three interleukin (1, 6 and 8) measured in the children and adolescent with meningitis and compared between two bacterial and aseptic meningitisgroups.

II. Methods

In this cross-sectional analytic study, 51 childrenand adolescentwho wereadmitted to Rasul- Akram and Aliasghar hospital (Tehran) in 2014, selected via non-probability sampling and enrolled to the research after obtaining informed consent from their parents or themselves. Inclusion criteria included diagnosis of definite meningitis, age range between one month to 18 years, absence any history of congenital cerebrospinal disease , absence any contraindications for aspiration of CSF(raising the , and absence history of antibioticreceptoin in the last week. Existence of defects of history and impossibility on the access to patient's information, excluded during of the study. A questionnaire that its validity was confirmed by a number of expertswas used for Data collection. Demographic information and data about disease include the types of meningitis were collected from patient history files. Then, all of patients underwent CSFaspiration. There was obtained 2 cm3 of CSF from each patient and samples were sent to laboratory foranalyzing the biochemical tests and microbial cultures. Also the concentration of IL-1, IL-6 and IL-8 were measured by immunoassay and ELISA method.The diagnostic kit for immunoassay and ELIZA were made by Germany. All of information and test results were recorded in the questionnaire and statistically analyzed by SPSS-20 software. The statisticalanalysis was performed viaROC curves tomeasure the diagnostic value of interleukins for differentiating bacterial from aseptic meningitis. Also other values were calculated include sensitivity, specificity, positive/negative predictive value and positive/negative likelihood ratiofor differentiating bacterial from aseptic meningitis, and confidence Interval were determined using the Wilson score method.

III. Results

A total of 51 patients were carried out in this study in two equal groups: 25 with bacterial meningitis and25 withaseptic meningitis (one case has unknown disease type). 33(64.7%)of samples were male ,also the number of males were significantly higher in both bacterial and aseptic groups(17 and 16 patients with bacterial and aseptic meningitis respectively. But gender of patients has not difference between the two groups (P-value = 0.7). Age of the total sample (Mean ± Sd) was 858,40± 358.46days, bacterial group was 814.25 ± 493.6days and aseptic group was131.02 ± 147.3 days. The mean age was higher in the bacterial group than aseptic group (P-value = 0.047). The concentration of IL-1 was 5/ 81±26/73 ngr/L in total, 10/87 ± 37/04 ngr/L in bacterial and 00/55 ± 1/64 ngr/L in aseptic group and the difference between the two groups was not significant(P-value = 0.168).The concentration of IL-6was 56/61 ± 114/97 ngr/L in total, 90/51 ± 139/93ngr/L in bacterial and 21/36 ± 67/84 ngr/Lin aseptic group with significant statistically difference (P-value = 0.030). The concentration of IL-8 was 211/11 ± 565/64 ngr/L in total, 365/40 ± 765/52 ngr/L in bacterial and 50/66 ± 59/34 ngr/L in aseptic group with significant statisticallydifference (P-value = 0. 047). Table-1 shows the frequency of variables in both aseptic and bacterial meningitis group.The color score of CSF samples in bacterial group was2/11 ± 0/60 and in aseptic group was 2/00 ± 0/00, without significant statistically differencebetween two groups (P-value = 0.763). The WBC score of CSF samples in bacterial group was547/58 ± 1940/32number/mm³ and in aseptic group was87/93 ± 183/04number/mm³, without significant statistically difference between two groups (P-value = 0.385). The RBC score of CSF samples in bacterial group was 677/57 ± 2071/06 number/mm³ and in aseptic group was 1358/92 ± 3671/53number/mm³ that difference between the two groups was not significant (P-value

= 0.498). The Glucose concentration of CSF samples in bacterial group was 45/43 ± 24/12 mg/dl and in aseptic group was 53/50 ± 21/69mg/dl that difference between the two groups was not significant (P-value = 0.313). The protein concentration of CSF samples in bacterial group was 94/30 ± 38/12 mg/dl and in aseptic group was 69/43 ± 73/16mg/dl without significant statistically difference between two groups (P-value = 0.421). The cut-off point of each IL for differentiates the type of meningitis specified from ROC curve. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and cut-off pointof IL-1, IL-6 and IL-8 for differentiates between bacterial and aseptic meningitis were showed in Table 2. These variables were significantly higher in IL-8. Table-3 shows the frequencies of diagnostic levels of each IL. Diagnostic levels of IL-1 were found in the 80.77% of bacterialgroup and 68.00% of aseptic group, afnd there was no significant difference between two group (P-value = 0.349). Diagnostic levels of IL-6 were detected in the 53.85% of bacterial group and 64.00% of aseptic group, and there was no significant difference between two group (P-value = 0.572). Diagnostic levels of IL-8 existed in the 80.77% of bacterial group and 28.00% of aseptic group, and the difference between two groups was significant (P-value< 0.001).

Table 1: Frequency ofage,sex and IL levels in bacterial and aseptic meningitis groups

variables		total	bacterial group	Aseptic group	p- value
sex	male	33	17	16	0.7
	female	17	8	9	
Age(days)		358.46± 858.40	493.6±814.25	147.3±131.02	0.047
IL-1 (ngr/L)		5.81±26.73	10.86±37.042	0.54±1.63	0.16
IL-6 (ngr/L)		56.61±114.97	90.5±132.92	21.36±67.84	0.03
IL-8 (ngr/L)		211.11±565.64	365.39±765.52	50.66±59.34	.04

Table 2: Frequency of statistical values for differentiates between bacterial and aseptic meningitis groups

Variable	IL-1	IL-6	IL-8
Cut off level(ngr/L)	0.058	1.179	36.82
Sensitivity (%)	55%	46%	75%
Specificity (%)	61%	42%	78%
Positive predictive value (%)	80%	53%	80%
Negative predictive value (%)	32%	36%	72%
Positive likelihood Ratio	1.42	0.79	3.4
Negative likelihood Ratio	1.36	0.72	3.12
Area under the ROC Curve	0.667	0.50	0.73

Table 3: Frequency of IL diagnostic levels for differentiates between bacterial and aseptic meningitis groups

IL	diagnostic levels(upper& lower of cut off point)	total	bacterial group	Aseptic group	p-value
IL-1	Upper 0.58ngr/L	38	21	17	0.349
	Lower 0.58ngr/L	13	5	8	
IL-6	Upper 1.179ngr/L	30	14	16	0.572
	Lower 1.179ngr/L	21	2	9	
IL-8	Upper 36.82ngr/L	28	21	7	0.000
	Lower 36.82ngr/L	23	5	18	

IV. Discussion

The present study was conducted to determine the diagnostic value of three CSF biomarkers including interleukin (1, 6, 8) for differentiates between bacterial and aseptic groups in children and adolescents with meningitis, and concluded that although the levels of interleukin-6 and interleukin-8 is higher in bacterial meningitis than aseptic, but only IL-8 levels has obvious diagnostic difference between the bacterial and aseptic meningitis. In this study, gender was notdiffering between bacterial and aseptic groups, andmorecases of bothgroups were male.The mean age was higher in bacterial group. TheLevels of IL-6 and IL-8 washigher in thebacterial meningitis, but IL-1 level was not differing between the two groups, that this finding is consistent with similar results. Several studies demonstrated that theincreased CSF levels of IL-6 and IL-8 increases in all of themeningeal inflammatory diseases (9). In twostudiesby Pinto Junior and Abdelmoez, IL-8 level was higher in bacterial than aseptic meningitis (4.9).In Yilmazstudy, IL-8 concentration were significantly higher in two bacterial and tuberculosis meningitis groups than aseptic meningitis and control groups(16). In the research was conducted byOstergaard, IL-8 level in the infectious meningitis (known and unknown cause) was significantly higher than aseptic meningitis, and in aseptic meningitis was higher than patients without meningitis(17). However, the comparison between some results of researches and currentstudy was not possible due to the absence of control (without meningitis) group in the present study. For example, the study by Sulik resulteda

significant increase in the level of IL-8 and IL-1 in patients with aseptic meningitis caused by mumps and Echo virus 30 compared to patients without meningitis (11).Also increased levels of IL-1 beta in the experimental meningitis of rabbit than control animal resulted in the Study by Handa(10).In our study results include color index, WBC, RBC, sugar and protein of CSF had not a significant difference between the two bacterial and aseptic meningitis, butmentioned resultswere shortly lower in the bacterial group inOstergaard study (17). In this study, the cut-off levelof IL-8 is significant higher than other interleukins as well asother values includeSe, Sp, PPV, NPV, PPV, NPV and area under the curve. In other words, IL-8 level is higher than the concentration of IL-6 and IL-1 in bacterial meningitis. Diagnostic value of IL-8 fordifferentiate septic from aseptic meningitis, is different in several studies, that some of the values mentioned in the introduction. The cutoff level for IL-8 in the present study is similar to the results of Abdelmoezand Ostergaard studies (4,17) and somewhat higher than the cut-off pointwas found in Pinto Junior study(9). Butvalues of sensitivity and specificity in present study are less than these results. Sensitivity and specificity ofIL-1 in present study is less than the resultedvalues in recent meta-analysis (3). These resultscould be due to some limitations of present study, such as small sample size, leading to the loss of expected rates. Proper study was not found for diagnostic value of IL-6. In the present study, while more than of bacterial meningitis cases had diagnostic levels of interleukin-1, but this difference was not significant.Also despite high levels of IL-6 in bacterial group, this cytokine has no diagnostic value in distinguishing betweenbacterial from aseptic meningitis. But IL-8 had obvious difference in the diagnostic levels. This result corresponded to other research's findings that confirmed the important role of IL-8 in differentiate of the meningitis types (4, 9, 16, 17).

V. Conclusion

Overall, this study concluded that although the levels of IL-8 and IL-6 is higher in the bacterial than aseptic meningitis, but only IL-8 has suitable diagnostic value for distinction between the two type of disease and suitable for differential diagnosis of meningitis. Because of the important role of cytokines in infectious diseases, conducting similar studies in the future has recommended to find a reliable and accurate diagnostic criterion to differentiate between high-risk types of meningitis from other types. Alsowe suggest a greater number of samples to ensure mneutrophil counts and ore accurate results.Also because in this study the relationship between cytokine levels and neutrophil counts and also neurologic sequela were not considered, these items should be considered in future researches.

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