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The Predictive Diagnostic and Prognostic Cut-off Values for Interleukin 8 in Patients with Meningitis in Egypt

M. Mosaad[1,2*], M. Shedid[1], N. Soliman[1], M. Abdou[3], F. Amal[4] and M. Gaber[1]

[1]Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
[2]Department of Internal Medicine, Taibah University, Al-madinah Al –munawwarah, Saudi Arabia.
[3]Department of Internal Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
[4]Department of Clinical Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author FA did the laboratory work, otherwise, all the authors participated in the study design, wrote the protocol, collected the clinical data, did the statistical analysis and literature searches and did analyses of study. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: This work was done to detect the best cut-off values for IL-8 to diagnose CNS infections (meningitis and meningio-encephalitis), to differentiate septic from aseptic types, and to predict mortality.
Methods: A case- control series design was chosen, where 42 patients who were diagnosed clinically as having meningitis and 42 control subjects were subjected for lumbar puncture and their cerebrospinal fluids were examined physically, chemically, cytologically, and bacteriologically; besides the level of interleukin 8 (IL-8) was determined and compared for both groups.
Results: The mean value of IL-8 was 75.8±89.1 in cases group compared to 26.2±18.0 in the

**Corresponding author: Email: mohmosad4@yahoo.com;*

control group which was highly statistically significant; its best significant cut off value for detection of CNS infection (meningitis or meningio-encephalitis) is 44ng/ml, while the best significant cut off value to diagnose septic meningitis was 50 with sensitivity of 52% and specificity of 82.35%. The mortality in our cases was 16.6%, and IL-8 best significant cut off value to detect this mortality was140 with sensitivity of 100% and specificity of 89.47% with +ve likelihood ratio 9.5.
Conclusions: IL-8 in CSF is a valid good significant marker to diagnose the infection, differentiate septic from aseptic types besides the known parameters, and more over it significantly predicts mortality in cases with meningitis and meningio-encephalitis.

Keywords: CSF; Egypt; interleukin-8; meningitis.

1. INTRODUCTION

Meningitis which is a potentially fatal disease, constitute a prevalent common health problem in Egypt and other developing countries [1-4]; it can cause high fatality rate, especially those caused by bacterial types, and frequently leave about one third of the victims with permanent neurological deficit [5,6]. However, though the recent advances in diagnosis and medical care, we still depend on clinical suspicion, and routine cerebrospinal fluid (CSF) in diagnosing meningitis and encephalitis [7,8] especially with the low culture yield in septic meningitis and lack of supplies for viral isolation or detection in aseptic types [3]. The inflammation in the central nervous system (CNS) is initiated and maintained by several cytokines; The inflammatory cascades started with the release of Interleukin 1 and tumor necrosis factors (TNF) from the astroglias, endothelial cells and monocytes in the CNS [9], this will lead to transient and rapid expression of adhesion molecule on the surfaces of the endothelium as intercellular adhesion molecules (ICAM) and CD62 followed by migration of the neutrophils to the affected sites, where they release platelet activating factor, leukotrienes, prostaglandins and toxic oxygen species. The persistent activation of the neutrophils at the inflamed sites depends on some mediators as TNF, IL-8, IL-6, and IL-1. IL-8 is produced mainly by the vascular endothelium and monocytes in response to stimulation with bacterial lipopolysaccharides and released in the CSF and blood [10]; it increases the expression of the integrin on neutrophils to switch the early selectin adhesion to the integrin-mediated adherence of neutrophils to vascular endothelium [11]. So IL-8 has linked by septic meningitis in some researches [12-14], but its use in the diagnosis is not settled in the guidelines, especially when clinical and CSF exam can't differentiate septic from aseptic types; more over the role of IL-8 in predicting the mortality in cases of meningitis, if any, need to be clarified.

1.1 Aim of the work

This work was done to detect the best cut-off values for IL-8 to diagnose CNS infections (meningitis and meningio-encephalitis), to differentiate septic from aseptic types, and to predict mortality.

2. METHODS

2.1 Study Design and Place

A case- control series design was chosen, in 2 hospitals (Fever Hospital and Ismailia General Hospital) in Ismailia, Egypt, during the period from April 2013 to October 2014.

2.2 Study Population

The study population were categorized into 2 groups; Group (1): Consecutive 42 patients with meningitis and meningo-encephalitis admitted to the fever hospital, and Group (2): 42 matched individuals for of the same age and sex with no meningitis or any evidence of infections, and underlying spinal anesthesia for different elective surgical maneuvers in Ismailia General Hospital as control group (as it was not ethical to obtain lumbar puncture from normal subjects).

2.3 Inclusion Criteria

All patients admitted to the hospital with clinical evidence of meningitis.

2.4 Exclusion Criteria

We excluded all the cases that may have abnormal immune response as it may alter the levels of IL-8as 1- Immuno-compromizedpatients.2- history of diabetes.3-

HIV infection.4- patients under treatment by immuno-suppressing drugs or corticosteroids.5- Patients with history of auto-immune diseases.6- Patients with history of chronic inflammations.7- Doubtful or not proven cases for meningitis.

2.5 Diagnosis of Patients

All the patients who fulfilled our criteria and clinically diagnosed as having meningitis or meningio-encephalitis were subjected to lumbar puncture under complete aseptic conditions before starting antibiotics therapy, and examined as follows:

2.5.1 Physical examination

CSF was turbid with high tension in septic meningitis while in aseptic meningitis it was clear or slightly turbid [15].

2.5.2 Chemical examination

The levels of proteins and glucose were assessed; Proteins were markedly increased in septic meningitis (normal level 15-40 mg /dl) while in aseptic meningitis, were slightly increased, while glucose level was reduced in septic meningitis (normal level 40-79 mg/dl) [16].

2.5.3 Cytological examination

In septic meningitis the number of cells were increased and mainly polymorphs but in aseptic meningitis the number of cells didn't not exceed 1000 /ml, and mainly lymphocytes [17].

2.5.4 Bacteriological examination

Cultures made on blood and chocolate agar and incubated aerobically and at 5-10% CO2 Atmosphere [18,19].

2.5.5 Interleukin-8

IL – 8 level was measured in the cerebrospinal fluid (CSF) using enzyme – linked immune assay. The kits obtained from Cloud-Clone Corp Company in United States, using 1 ml of CSF for group (1) and 0.5 ml for group (2) [20].

2.6 Statistical Analysis

Data were statistically analysed by using Statistical Package for Social Sciences (SPSS) version 17. Unpaired t test and Mann-Whitney U test were used. Correlations between different parameters were done using Spearman rank correlation coefficient. P-value <0.01 was considered significant. All data are expressed as mean±SD. Tabulation and graphical representation of data were done as required.

2.7 Ethical Considerations

This study was approved by the ethical committee in the Faculty of Medicine, Suez Canal University, Egypt.

3. RESULTS

The total number studied was 84 subjects, distributed into two groups; group 1 represents 42 patients with meningitis and meningio-encephalitis, and group 2 represents 42 matched control subjects. Table (1) shows that the mean age of the study group (Mean±SD) was 23.02±14.1, and in control group was 22.6±13.6 years, most of cases in both groups were under 30 years (78.5%); The males were the majority of cases in the two groups as 71.4% of cases in the study group and 73.8% in control; while most of the cases with meningitis live in urban areas (66.7%),most of the controls live in rural areas (52.4%); however both groups were matched and there are no significance differences as regard age, gender, or residency. As regards the clinical presentation for the patients with meningitis and meningio-encephalitis, it was shown in (Fig. 1) that the most common presentations among them were fever (95.2%) and neck stiffness (92.9%), while the lowest presentations were irritability and photophobia (14.3%). As regards the final diagnosis and outcomes, Table (2) shows that about (54.8%) of cases diagnosed as aseptic meningitis / meningio-encephalitis, compared to 45.2% with septic type; it also shows that 66.6% of the patients showed complete recovery, 7 patients (16.6%)referred to other hospitals for management of complications, while another 7 patients (16.6%) died in the hospital. As regards the levels of IL-8 in the CSF, Table (3) shows that its Mean±SD was 75.8±89.1 in cases group compared to 26.2±18.0 in the control group which was highly statistically significant; with sensitivity of 45.24% and specificity of 85.7% which is shown in (Fig. 2); it also shows that the best significant cut off value of IL-8 for detection of septic CNS infection (meningitis or meningio-encephalitis) is 50 with sensitivity of 52% and specificity of 82.35%. In Table (4), it shows the correlation between IL-8 and chemical characteristics of CSF; there was a positive

statistical significant correlation of the studied Il-8 levels with protein, WBC and PMN parameters, and statistically significant negative correlation with both glucose level and lymphocytes, while the correlation between age and IL-8 level, however, showed no significant correlation. Finally, using the same ROC curve analysis for best cut off value of IL-8 for detection of mortality among patients with CNS infection (meningitis / meningio-encephalitis), it was 140 with sensitivity of 100% and specificity of 89.47% with +ve likelihood ratio 9.5and p value 0.001 which is highly significant. (Fig. 3).

Table 1. Demographic characteristics among the studied subjects

		Control group (n=42)		Study group (n=42)		p-value
Age	Mean±SD	22.6±13.6		23.02±14.1		0.5 (NS)
gender	Male	31	73.8%	30	71.4%	0.8 (NS)
	Female	11	26.1%	12	28.5%	
Residence	Urban	20	47.6%	28	66.6%	0.07 (NS)
	Rural	22	52.3%	14	33.3%	

Table 2. Distribution of study group patients according to final diagnosis and outcome

		No.	%
Final diagnosis	Aseptic type	23	54.8%
	Septic type	19	45.2%
Outcome	Recovery	28	66.6%
	Referral	7	16.6%
	Death	7	16.6%
Mortality	Yes	7	16.6%
	No	35	83.3%

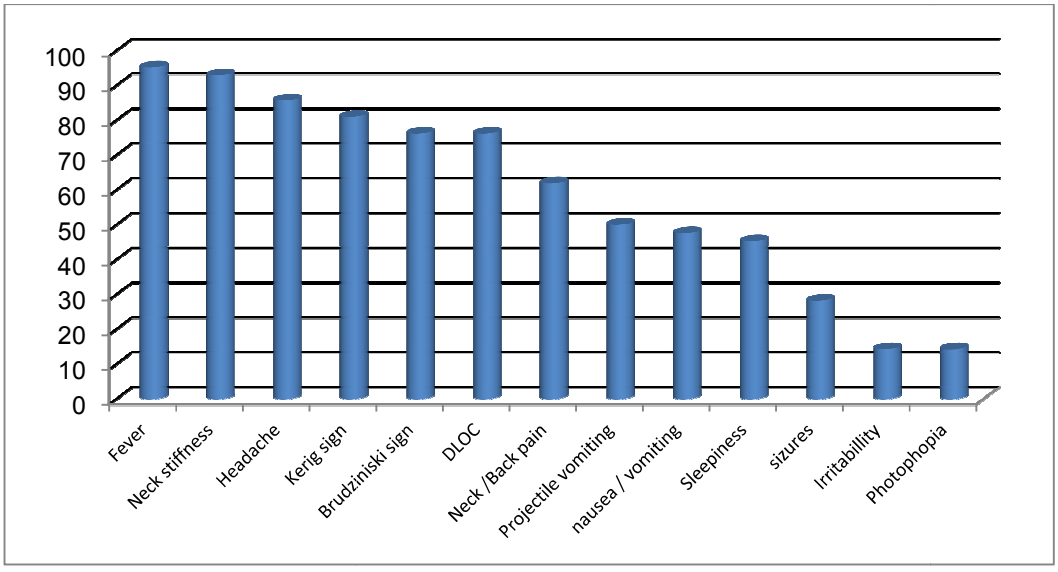

Fig. 1. Clinical characteristics among the study group

Table 3. Comparison between study and control groups regarding IL-8 level

		Control group (n=42)	Study group (n=42)	p-value
Il-8pg/mL	Mean±SD	26.2±18.0	75.8±89.1	0.001*
	Range	3.5–76	4.4–320	

** Statistically significant difference*

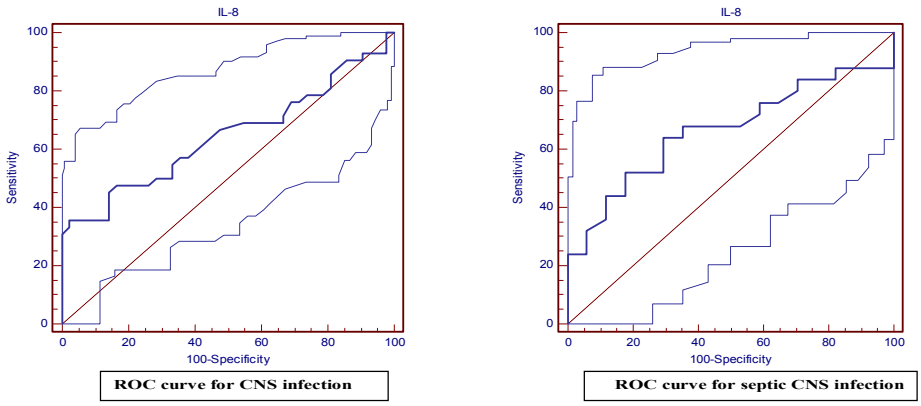

Fig. 2. ROC curve analysis for best cutoff values of IL-8, to detect CNS infection (meningitis / meningio-encephalitis) in the studied patients and septic type among patients with CNS infection

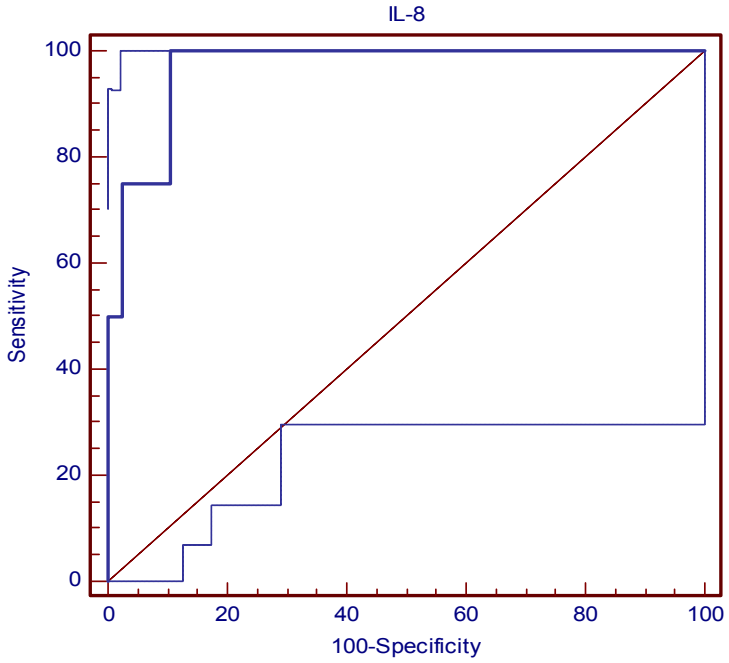

Fig. 3. ROC curve analysis for best cutoff values of IL-8 to detect mortality among patients with CNS infection (meningitis / meningio-encephalitis)

Table 4. Correlation between IL-8 and chemical characteristics of CSF in the study group

Chemical characteristics	IL-8	
	r	p-value
Protein content (mg/dl)	0.4	0.01*
Glucose (mg/dl)	- 0.4	0.007*
WBC (/HPF)	0.6	<0.001*
PMN (%)	0.7	<0.001*
Lymphocytes (%)	- 0.7	<0.001*
Age	0.09	NS 0.4

** Statistically significant difference; NS: none statistically significant difference*

4. DISCUSSION

Meningitis and meningio-encephalitis are common health problems, not only in our country but in most developing countries, causing significant morbidity and mortality in their usual pattern [21-23] and became maximum during epidemics and outbreaks which still emerging in many countries [24,25]. However, decreasing both the morbidity and mortality in those patients depend mainly on early diagnosis and determination of the causative agent [26]; unfortunately this is faced by facts as lack of resources and supplies in our developing countries, besides there is no gold standard test for diagnosis, apart from CSF cultures which have low yields and mostly negative due to various reasons [24-27]. The participation of certain cytokines in initiating and maintaining the inflammatory process in cases of meningitis and meningio-encephalitis, as interleukin-1 (IL-1), interleukin-1 soluble receptor type 2 (IL-1R2), interleukin-8 (IL-8), human interferon gamma (IFN-γ) and human tumour necrosis factor alpha (TNF-α), have been investigated in some researches [12,28,29]. In our study we tried to discover the role of Interleukin-8, as an important inflammatory cytokine, and its predictive values, if any, in the cerebrospinal fluids for the patients with meningitis and meningio-encephalitis. We included 42 patients diagnosed with meningitis and meningio-encephalitis (study group) and 42 normal matched individuals undergoing spinal anesthesia for elective surgical procedures (control group); the mean age of the study group was 23.02 years compared to 22.6 in the control group, the cases younger than 10 years old about (19.1%) while the cases older than 50 years about (7.1%), so it represents a wide range of age including childhood and adulthood; most of our patients were males (71.4%) which goes with many other studies which concluded that CNS infection are more common in males [24,30-32]. Our patients were presented clinically by Fever which was the most common presenting symptom (95.2%) and it is one of the commonest non-specific findings associating systemic infections; also headache was manifested in 85.7% of cases; other manifestations due to meningeal irritation and increased intracranial tension such as (nuchal rigidity (92%), Kernig (81%), Brudzinski signs (76%) and projectile vomiting (50%) were recorded .These are comparable to others who reported the same clinical presentation with the fever and signs of meningeal irritations and increased intracranial pressure being the majority [33,34]. As regards IL-8 we found that it was significantly higher in our patients with meningitis and meningio-encephalitis compared to the control subjects, which was similar to what reported before in vitro [35], and vivo [28,36-39]; the significant cut off point for detection of the CNS infection in our study was 44 pg/ml, raising to be 50 for diagnosing septic meningitis with sensitivity of 52% and specificity of 82.35%, which agree with Ostergaard et al. [39] who studied the CSF IL-8 levels in septic and aseptic meningitis cases and in normal individuals. They found that The CSF IL-8 concentration was significantly higher in septic meningitis of known and unknown etiology than in aseptic meningitis and significantly higher in aseptic meningitis than in patients without meningitis [40]. Another studies reported by Bociaga et al. [41] and Pinto et al. [14], have confirmed the effectiveness of CSF IL-8 level in differentiating between bacterial and viral meningitis cases due to the significantly high levels of IL-8 in the CSF of the bacterial cases. More recently Abdelmoez et al. [12] reported that the best cut off value for IL-8- in early diagnosis of bacterial meningitis is 36 pg/L. Nevertheless, The relation between IL-8 and septic meningitis in our work was powered by finding positive statistical significant correlation of the studied Il-8 levels with CSF protein content, total WBC and PMN counts, and the significant negative correlation between Il-8 level and CSF glucose level and lymphocytes, which all are from the criteria for septic infection. The correlation between age and Il-8 level, however, showed no significant correlation which probably indicate that it's not age dependable. As regards the mortality in our case series, it was high (16.6%), compared to others [42]; while the best cut off value of IL-8 for detection of mortality among patients with CNS infection (meningitis / meningio-encephalitis) was 140 pg/mL with sensitivity of 100% and specificity of 89.47% which make this cytokine not only good predictor for meningitis especially the septic types, but also an excellent predictor for mortality, which need to be searched on large scale and open a new gate for better management in patients with such potentially fatal diseases.

5. CONCLUSION

Introducing the measurement of IL-8 in the routine CSF exam for the patients with meningitis and meningio-encephalitis is considered an adding value for the diagnosis and predicting the mortality.

CONSENT

It is not applicable

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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