

The usefulness of serum delta neutrophil index for differentiating bacterial and viral meningitis in the emergency department

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Objective When managing patients with acute meningitis in an emergency department (ED), early diagnosis of the type of infection (bacterial or viral) considerably affects the clinical course and treatment because of the high mortality and morbidity associated with bacterial meningitis (BM). The serum delta neutrophil index (DNI), a new inflammatory marker, reflects the fraction of circulating immature granulocytes and is elevated in cases of bacterial infection. The objective of this study was to evaluate whether serum DNI can be used to differentiate between BM and viral meningitis (VM) in the ED.

Methods This retrospective, observational study included 104 consecutive patients (aged >18 years) diagnosed with acute meningitis from January 2012 to November 2014 in a regional emergency center. White blood cell and neutrophil counts, C-reactive protein level, and DNI were evaluated regarding their usefulness for differentiating BM and VM.

Results Serum DNI was not significantly higher in the BM group (n=12) than in the VM group (n=92) (0 [interquartile range, 0% to 2.73%] vs. 0 [interquartile range, 0 to 0%], P=0.057). However, the white blood cell count and C-reactive protein level were statistically higher in the BM group (P=0.034 and P=0.026, respectively). Serum DNI was not found to be a statistically useful differential diagnostic parameter (area under the curve, 0.628; 95% confidence interval, 0.438 to 0.818).

Conclusion Currently, there is no evidence that the serum DNI aids in differentiating acute BM from acute VM in the ED.

Keywords Biochemical markers; Meningitis; Delta neutrophil index

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Capsule Summary

What is already known

Serum delta neutrophil index (DNI) values are elevated in the presence of bacterial infection because they reflect circulating immature granulocyte fractions. However, no information is available on the clinical usefulness of serum DNI with respect to the differentiation between bacterial and viral meningitis in patients with acute meningitis.

What is new in the current study

The median serum DNI in bacterial meningitis was similar to that in viral meningitis. This study provides no evidence to support the notion that serum DNI aids the differentiation between acute bacterial and acute viral meningitis in the emergency department.

INTRODUCTION

Bacterial meningitis (BM) is an infectious disease of the central nervous system with significant mortality (3% to 21%) and morbidity rates despite antibiotic developments.^{1,2} Therefore, one of the most important decisions made in an emergency department (ED) is whether a patient with acute meningitis has BM or viral meningitis (VM).³ However, this differentiation can be challenging for clinicians because symptoms and laboratory assays are often similar and overlap. In practice, before definitive cerebrospinal fluid (CSF) bacterial culture results are available, the majority of patients with acute meningitis are treated with broad-spectrum antibiotics targeting BM, because several days are required to culture BM samples,⁴ and although gram staining and bacterial antigen testing of CSF is highly specific, it is not 100% sensitive.⁵⁻⁸

A number of studies have examined the abilities of different tests to differentiate BM and VM. In particular, serum biomarkers may help determine whether a systemic reaction in acute meningitis is due to a bacterial infection. One new inflammatory marker, serum delta neutrophil index (DNI), provides a measure of the proportion of circulating immature granulocytes,⁹⁻¹¹ and because infectious conditions are known to increase levels of immature granulocytes,^{12,13} several investigators have examined its ability to predict the development of sepsis.^{14,15} However, no information is available on the clinical usefulness of serum DNI with respect to the differentiation of BM and VM in patients with acute meningitis.

We considered that serum DNI values might be higher in BM than in VM, and thus, this study was undertaken to determine whether serum DNI can be used to differentiate BM and VM in the ED setting.

METHODS

Study design and data

This retrospective, observational study included 104 consecutive

patients (aged > 18 years) who received a diagnosis of acute meningitis from January 2012 to November 2014 in a regional emergency center. We enrolled patients at a single urban, tertiary-care hospital with an ED that has an annual visit volume in excess of 43,000 and is staffed 24 hours per day with board-certified emergency physicians. Data were collected by retrospectively reviewing electronic medical records. Data collection was conducted by two emergency physicians blinded to the study objectives and hypothesis, and if there was inter-observer disagreement in the interpretation of clinical data, the two emergency physicians reviewed the case together to come to a conclusion. Training of abstractors was conducted before data collection to reduce bias. This study was approved by the institutional review board of the Wonju College of Medicine, Yonsei University.

Age, sex, mortality, white blood cell (WBC) and neutrophil counts, C-reactive protein (CRP) level, and serum DNI values (obtained in the ED) were investigated. Differential diagnoses of BM were confirmed by microbiological tests of blood and CSF. The diagnostic criteria of BM included the following: positive blood or CSF culture or laboratory findings consistent with BM (CSF WBC > 2,000/ μ L [relatively specific], CSF protein > 220 mg/dL [highly predictive], CSF glucose < 34 mg/dL, or CSF to blood glucose ratio < 0.25 [more strongly predictive]).^{7,16} The CSF results from all 104 patients were reviewed, and BM was confirmed by a neurologist.

A specific type of automatic cell analyzer (ADVIA 120/2,120; Siemens, Tarrytown, NY, USA) was used for determining DNI. This is a flow cytometry-based hematologic analyzer that uses two independent WBC analysis methods using a myeloperoxidase channel and a lobularity/nuclear density channel. The DNI in leukocyte differentials was calculated using the following formula: $DNI = (\text{the leukocyte subfraction assayed in the myeloperoxidase channel by cytochemical reaction}) - (\text{the leukocyte subfraction counted in the nuclear lobularity channel by the reflected light beam})$.^{11,17}

Patients with hematologic abnormalities, tuberculosis, or fungal meningitis and those that had received granulocyte colony-

Table 1. General characteristics of the study subjects

Characteristics	Total (n = 104)
Age (yr)	32.0 (24.3–44.0)
Male sex	52 (50.0)
Differential diagnosis	
Viral meningitis	92 (88.5)
Bacterial meningitis	12 (11.5)
Mortality	0 (0)

Values are expressed as medians (interquartile ranges) or number (%).

Table 2. Inflammatory marker values in the two study groups

Markers	Viral meningitis	Bacterial meningitis	P-value
Delta neutrophil index (%)	0.00 (0.00–0.00)	0.00 (0.00–2.73)	0.057
White blood cells (cells/mL)	7,385 (6,133–10,485)	10,485 (7,665–16,035)	0.034
Neutrophils (%)	73.7 (61.6–80.1)	83.1 (60.8–88.4)	0.079
C-reactive protein (mg/dL)	0.29 (0.29–0.79)	1.51 (0.31–9.11)	0.026

Values are medians (interquartile ranges).

Table 3. Multiple logistic regression findings regarding the use of variables for the differential diagnosis of viral meningitis and bacterial meningitis

Markers	Odds ratio	95% confidence interval	P-value
Delta neutrophil index (%)	1.319	0.817–2.131	0.257
White blood cells (cells/mL)	1.000	1.000–1.000	0.090
Neutrophils (%)	0.977	0.916–1.042	0.478
C-reactive protein (mg/dL)	1.084	0.975–1.204	0.135

stimulating factors, glucocorticoid, or another immunosuppressant before study enrollment were excluded.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 20 (IBM Corp., Armonk, NY, USA). Nominal data are presented as frequencies and percentages and continuous data as medians and interquartile ranges. The Mann-Whitney U-test was used to compare continuous variables, and then biomarkers with a P-value of <0.1 were entered into multiple logistic regression to investigate the abilities of serum DNI and other biomarkers (WBC and neutrophil counts and CRP level) to differentiate BM and VM. In addition, the area under the receiver operating characteristic (ROC) curve was used to determine to what extent serum DNI differentiated these two groups. P-values of <0.05 were considered statistically significant.

RESULTS

Of 117 consecutive patients considered for this study, 13 patients with tuberculosis and two patients with fungal meningitis were excluded. Of the 104 patients enrolled, 52 were male (50.0%), and the overall median age was 32.0 years. Ninety-two patients

Table 4. AUC values of variables for the differentiation of viral meningitis and bacterial meningitis

Markers	AUC (95% confidence interval)
Delta neutrophil index (%)	0.628 (0.438–0.818)
White blood cell (cells/mL)	0.687 (0.512–0.862)
Neutrophil (%)	0.657 (0.453–0.861)
C-reactive protein (mg/dL)	0.690 (0.503–0.878)

AUC, area under curve.

were in the VM group and 12 patients were in the BM group (Table 1). In the BM group, the causative pathogens were *Streptococcus pneumoniae*, *Escherichia coli*, and *Listeria monocytogenes*.

The median serum DNI was not statistically significantly higher in the BM group than in the VM group (0 [interquartile range, 0% to 2.73%] vs. 0 [interquartile range, 0% to 0%], $P=0.057$), but the WBC counts and CRP levels were statistically significantly different between the VM and BM groups (Table 2).

To evaluate the usefulness of serum DNI in differentiating VM from BM, we performed multiple logistic regression analysis and evaluated the area under the ROC curve. The odds ratio and 95% confidence interval of serum DNI were 1.319 and 0.817–2.131, respectively, by multiple logistic regression ($P=0.257$) (Table 3), and the area under the ROC curve for serum DNI was 0.628 (Table 4).

DISCUSSION

When managing patients with acute meningitis in the ED, early diagnosis of the type of infection (bacterial or viral) has the greatest impact on the clinical course and treatment, and thus, a number of studies have been undertaken to determine the effectiveness of different tests for differentiating BM and VM. In these previous studies, various common laboratory variables, including

standard CSF variables and inflammatory markers in peripheral blood, such as WBC count and/or CRP level were examined.¹⁸ The use of serum markers has merits, because only a small blood sample is required, which can be processed in 20 minutes,^{19,20} and because knowledge of serum inflammatory markers might improve the sensitivity of etiologic diagnoses.^{6,7} However, no previous study has evaluated the diagnostic accuracy of serum DNI with respect to differentiating BM and VM.

Crossing the blood-brain barrier is a key step in the pathophysiology of meningitis and is more likely in the setting of high-grade bacteremia.²¹ Serum DNI values are elevated in the presence of bacterial infection because they reflect circulating immature granulocyte fractions.⁹⁻¹¹ In addition, serum DNI has been shown to predict mortality in cases of spontaneous bacterial peritonitis²² and to be a marker of disease severity in critically ill patients with sepsis.²³ Therefore, we hypothesized that serum DNI might be increased in acute BM. However, although serum DNI was higher in the BM group than in the VM group, no statistically significant difference was found (Table 2). Furthermore, no evidence was obtained by ROC analysis that serum DNI aids in the differentiation of BM and VM (Table 4). However, we think that further study of this issue is required.

CRP is a plasma protein, and its concentration rises dramatically as a result of cytokine-mediated responses to most forms of tissue injury, infection, and inflammation, and thus, the serum CRP level is widely used in clinical practice as an objective index of disease activity.²⁴ It has been reported that CRP levels and WBC counts can be used to differentiate bacterial and viral infections, especially meningitis infections;²⁵ in the present study, however, like DNI, the predictive values of the CRP levels and WBC counts were not sufficiently high to differentiate BM from VM (Tables 3, 4). Indeed, CRP levels can occasionally be low in bacterial diseases, especially during the early stages, and high CRP levels have been reported in some cases of VM.²⁶

Several limitations of the present study warrant consideration. First, the study had a retrospective design and a relatively small sample size and was conducted at the emergency center of one hospital. Second, it should also be borne in mind that many patients who present at EDs in Korea have used antibiotics, because antibiotics are generally prescribed by primary care physicians to patients with a fever and headache. Inflammatory markers can be affected by co-ingestion of antibiotics. In our study, four patients (33.3%) may have co-ingested antibiotics in the BM group. However, we could not investigate the type and dose of antibiotics because this was a chart review study. There was no difference between patients who had not used antibiotics and those who did with respect to DNI (0.4 [interquartile range, 0% to 2.73%] vs. 0

[interquartile range, 0% to 3.15%], $P = 0.570$). Accordingly, to overcome the limitations, further prospective study will be needed.

In summary, this study provided no evidence to support the notion that serum DNI aids in the differentiation of acute BM from acute VM in the ED.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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