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Original Article

Cerebrospinal Fluid TNF- α , IL-6, and IL-8 in Children With Bacterial MeningitisRajniti Prasad MD^{a,*}, Rishi Kapoor MD^a, Ragini Srivastava MD^b, Om Prakash Mishra MD^a,
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ABSTRACT

OBJECTIVE: We evaluated the levels of cerebrospinal fluid concentrations of tumor necrosis factor- α , interleukin-6, and interleukin-8 in bacterial meningitis in children. **METHODS:** The study included children up to 14 years of age admitted to a pediatric ward with fever, headache, vomiting, and seizures. The diagnosis of bacterial meningitis was based on clinical features: physical examination, blood and cerebrospinal fluid cytochemical findings, Gram stain, and bacterial culture. The cerebrospinal fluid levels of tumor necrosis factor- α , interleukin-6, and interleukin-8 were measured in 57 children with bacterial meningitis, 15 with viral meningitis, and 15 controls by enzyme-linked immunosorbent assay methods. **RESULTS:** The mean concentrations of cerebrospinal fluid, tumor necrosis factor- α , interleukin-6, and interleukin-8 were 1108 ± 183 , 652 ± 287 , and 442 ± 120 pg/mL, respectively, in children with bacterial meningitis and were significantly increased in those in the viral meningitis group (tumor necrosis factor- α : 711 ± 105 , IL-6: 272 ± 161 , IL-8: 175 ± 62 pg/mL; $P < 0.001$) or control (390 ± 37 , 59 ± 17 , 19 ± 13 pg/mL, respectively, $P < 0.001$). At optimum cutoff level based on the receiver operating characteristic curve, cerebrospinal fluid cytokines (tumor necrosis factor- α , interleukin-6, and interleukin-8) showed sensitivity and specificity of 100% for the diagnosis of bacterial meningitis. For differentiation of bacterial from viral meningitis, cerebrospinal fluid level of tumor necrosis factor- α , IL-6, and IL-8 showed sensitivity and specificity of 94.7% and 86.7%, 80.7% and 53.3%, and 89.5% and 86.7%, respectively. **CONCLUSION:** The increased concentration of cerebrospinal fluid tumor necrosis factor- α , interleukin-6, and interleukin-8 in children with meningitis suggests a role in the pathogenesis of bacterial meningitis and these levels might prove to be useful in children whose diagnosis is in question.

Keywords: meningitis, cerebrospinal fluid, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-8 (IL-8)
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Introduction

Bacterial meningitis constitutes about 5% of patients with meningitis and its reported mortality ranges from 2% in infants and children to 30% in neonates and adults.^{1,2} Deafness and neurological sequelae have been reported in one third of survivors.³ Although the prevalence of bacterial meningitis has decreased because of immunization against meningococci and *Haemophilus influenzae* in developed

countries, outcomes have been modestly improved by advanced intensive care, availability of new β -lactam antibiotics, and supportive management.^{4,5} In India and other developing countries, bacterial meningitis still remains the major cause of childhood morbidity and mortality because of poor immunization coverage, late diagnosis, and delayed institution of antibiotic therapy.⁶ Unfortunately, no test is available for early diagnosis of bacterial meningitis with 100% sensitivity and specificity. The routine cerebrospinal fluid (CSF) examination, bacterial antigen testing in CSF, viral culture, and polymerase chain reaction for viral DNA used alone or in combination do not offer 100% sensitivity and specificity for differentiation of bacterial from viral meningitis.⁷ The empirical use of antibiotics in each suspected case causes unnecessary hospitalization, needless antibiotic use, and increased cost.^{8,9}

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TABLE 1.
Characteristics of children included in study

Characteristics	Bacterial Meningitis (n = 57) No (%)	Viral Meningitis (n = 15) No (%)	Controls (n = 15) No (%)	P Value
Mean age (yr)	3.8 ± 4.2	4.6 ± 2.9	4.5 ± 3.6	.63
Sex: male	43 (75.4)	11 (73.3)	8 (53.3)	.24
Female	14 (24.6)	4 (26.7)	7 (46.7)	
Fever	55 (96.5)	14 (93.3)	12 (80)	.352
Seizure	38 (66.7)	7 (46.7)	0	.354
Vomiting	23 (40.4)	7 (46.7)	0	.764
Unconsciousness	17 (29.8)	5 (33.3)	2 (13.3)	.750
Headache	9 (15.8)	4 (26.7)	1 (6.7)	.453
Bulging anterior fontanelle	15 (26.3)	1 (6.7)	0	1.0
Neck rigidity	18 (31.6)	4 (26.7)	0	.043
Kernig's sign	12 (21.1)	4 (26.7)	0 (0)	.115

Cytokines are molecules involved in the modulation of immune and inflammatory processes. Tumor necrosis factor-alpha (TNF- α) is a potent activator of neutrophils and mediates adherence, chemotaxis, degranulation, and the respiratory burst. Interleukin-6 (IL-6) stimulates the growth of B lymphocytes that have differentiated into antibody-producing cells. Interleukin-8 (IL-8) acts as a chemo-attractant for neutrophils to the site of inflammation. A higher concentration of TNF- α and IL-8 in patients with bacterial meningitis was reported in various studies.^{10,11} Besides TNF- α , Tsai et al.¹² also found that elevated levels of IL-6 and IL-8 in CSF are good indicators of meningeal inflammation. Tang et al.¹³ observed that CSF TNF- α had 74% sensitivity and 81% specificity for diagnosis of septic meningitis. There is emerging evidence that the levels of TNF- α , IL-6, and IL-8 may play important roles in pathogenesis of meningitis and are successfully used in early diagnosis as well as differential diagnosis of bacterial and viral meningitis.

TABLE 2.
Laboratory findings in blood and CSF of studied children

	Bacterial Meningitis (A) (Mean ± SD) (Range)	Viral Meningitis (B) (Mean ± SD) (Range)	Control (C) (Mean ± SD) (Range)	A vs B	A vs C	B vs C
Blood						
TLC (μ L)	18,705 ± 10,800 (3900-49,800)	14,513 ± 4498 (7300-22,600)	14,445 ± 4805.7 (6000-20,900)	0.300	0.015	0.08
Neutrophil %	66.42 ± 16.87 (15-95)	69.4 ± 8.87 (50-82)	52.23 ± 20.46 (10-95)	0.530	0.006	0.007
Lymphocytes %	28.17 ± 15.34 (3-80)	25.86 ± 8.34 (12-45)	40.92 ± 18.33 (14-83)	0.600	0.007	0.007
CSF						
TLC (μ L)	1532 ± 4311.49 (36-23040)	133.73 ± 134.36 (30-480)	1.67 ± 2.06 (0-6)	<0.001	<0.001	<0.001
Polymorphs (%)	55.14 ± 29.92 (4-98)	23.20 ± 20.07 (0-50)	0	<0.001	<0.001	<0.001
Lymphocytes (%)	44.86 ± 29.92 (4-98)	71.40 ± 26.22 (50-100)	33.33 ± 48.79 (0-100)	0.004	0.048	0.004
Protein (mg/dL)	170.99 ± 117.18 (60-698)	99.73 ± 37.34 (58-220)	40.73 ± 19.67 (6-80)	<0.001	<0.001	<0.001
Glucose (mg/dL)	37.92 ± 28.40 (0-102)	97.81 ± 29.70 (68-184)	68 ± 19.33 (37-102)	<0.001	<0.001	<0.001
CSF glucose: plasma glucose ratio	0.37 ± 0.25 (0.0-0.97)	0.88 ± 0.12 (0.71-1.12)	0.77 ± 0.14 (0.51-0.97)	<0.001	<0.001	0.05
TNF- α (pg/mL)	1108 ± 183 (643.7-1383.2)	711 ± 105 (556.9-934.2)	390 ± 37 (335.3-461.1)	0.004	<0.001	<0.001
IL-6 (pg/mL)	652 ± 287 (120.4-1236.7)	272 ± 161 (90.8-475.3)	59 ± 17 (37.9-88.2)	<0.001	<0.001	<0.001
IL-8 (pg/mL)	442 ± 120 (127.1-611.6)	175 ± 62 (87.9-285.4)	19 ± 13 (10.2-55.4)	<0.001	<0.001	<0.001

Abbreviations:

CSF = Cerebrospinal fluid
IL = Interleukin
SD = Standard deviation
TLC = Total leukocyte count
TN = Tumor necrosis factor

Over the past few years, CSF levels of TNF- α , IL-6, and IL-8 have been found to be the most sensitive and specific inflammatory markers of bacterial meningitis,¹⁰⁻¹³ but this knowledge has not been adapted to clinical practice. This study was done to evaluate the role of CSF concentrations of TNF- α , IL-6, and IL-8, find the optimum cutoff values in the diagnosis of bacterial meningitis, and document their efficacy in differentiation of bacterial from viral meningitis in Indian children.

Materials and Methods

This prospective cross-sectional study was conducted in a tertiary care hospital between January 2010 and April 2012. Informed consent was obtained from parents or legal guardians for their children to participate in the study. The Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, approved the study protocol.

Inclusion criteria

- Bacterial meningitis:** children having CSF white blood cell counts $>50/\mu$ L with predominant neutrophils; CSF: blood glucose ratio <0.5 , CSF protein >50 mg/dL and positive Gram stain and/or CSF culture. Additional children presenting with history of prior antibiotic use up to 72 hours (partially treated septic meningitis) were also included.
- Viral meningitis:** children showing CSF leucocytosis ($>30/\mu$ L) with lymphocytic predominance; normal CSF: blood glucose ratio, CSF protein (>50 mg/dL), and negative Gram stain.
- Control group:** children admitted to the pediatric ward with febrile seizures, and retropharyngeal abscess, or meningismus who underwent lumbar puncture and had normal CSF.

Exclusion criteria

Children with tuberculous meningitis, neurocysticercosis, space-occupying lesions, human immunodeficiency virus infection, and those on immunosuppressive therapy were excluded from study. Neonates were also excluded.

The demographic and clinical characteristics of patients were recorded in standard proforma. Under full aseptic precaution, blood and CSF samples were taken from cases and controls. Complete blood count,

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