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Treatment Response Utilizing CSF IL-1β Level In Bacterial Meningitis Patients

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ABSTRACT

Background: Bacterial meningitis is a serious infectious disease that is mainly caused by the inflammatory reaction. This inflammation leads to the release of biomarkers into the cerebrospinal fluid (CSF). **Aim:** The study aimed to evaluate the levels of IL-1β in the cerebrospinal fluid (CSF) during the acute phase and on day 14 after treatment, as well as to investigate their correlation with clinical outcomes. **Methods:** This prospective observational study included 40 patients with bacterial meningitis treated at Alexandria Fever Hospital between January and December 2021. Patients were classified according to outcome (death, complete recovery, or complicated course). Clinical, laboratory and radiological parameters were recorded, and CSF IL-1β was measured by ELISA at baseline and day 14. **Result:** Baseline CSF IL-1β was significantly higher among patients with poor outcomes (p = 0.01). Day-14 levels showed no statistically significant association with outcome. **Conclusion:** Higher acute-phase CSF IL-1β is associated with adverse outcomes in bacterial meningitis, whereas post-treatment levels are non-discriminatory. Larger, methodologically robust studies are required for validation.

Keywords: Bacterial meningitis, Cerebrospinal fluid, IL-1β, Treatment response.

INTRODUCTION

Bacterial meningitis is an inflammatory infection of the meningeal layers covering the brain and spinal cord. It continues to be a major cause of morbidity and mortality worldwide (1). The most common pathogens are Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae, which cross the blood–brain barrier and trigger an innate immune cascade dominated by cytokine release (2). Bacteraemia facilitates haematogenous spread and translocation across the blood–brain barrier, a process achieved by a limited number of organisms, most notably N. meningitidis and S. pneumoniae. Direct extension from otitis media or sinusitis, entry via congenital or acquired dural defects, and nosocomial infection following neurosurgical procedures are additional routes to central nervous system (CNS) invasion.

Bacterial access to the subarachnoid space elicits meningeal inflammation leading to headache and fever. Subsequent disruption of the blood–brain barrier and the associated inflammatory response cause cerebral oedema, raised intracranial pressure, and reduced cerebral perfusion, with clinical progression to altered mental status, seizures, and focal neurological deficits (3). The classic triad of fever, neck stiffness, and altered mental status occurs in only about 41% of patients with bacterial meningitis, and is most frequently observed in older adults. Early features typically

include fever, headache, and confusion, which may evolve to obtundation, focal deficits, and seizures. History-taking should document recent neurosurgical procedures, immunisation status, and living circumstances. Clinical signs may show nuchal rigidity or positive Kernig's or Brudzinski's signs. However, the absence of these does not reliably rule out the disease. Brudzinski's sign occurs when passive flexion of the neck causes involuntary flexion of the knee. Kernig's sign is resistance or pain with knee extension when the patient is supine, and their hip is flexed to 90 degrees. These signs are thought to be secondary to meningeal irritation. The fundoscopic exam may reveal papilledema due to increased intracranial pressure. A rapidly spreading petechial rash, known as purpura fulminans, would suggest a Meningococcal infection(3).

Pathogenesis of bacterial meningitis can be related to cytokine release that may contribute to the sequence of events that lead to meningeal inflammation in bacterial meningitis. Lately, studies on bacterial meningitis, suggest that the release of certain cytokines, such as interleukin 1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), may be responsible for the severe inflammatory responses in meningitis and may correlate with morbidity and mortality. Interleukin-1β (IL-1β) is the main cytokine in innate immunity, notably activated macrophages, and cell tissue. It has been shown that high levels of IL-1β can occur in the cerebrospinal fluid (CSF) of patients with acute infection of the central nervous system (CNS)(4,5). The purpose of this study was to determine the level of interleukin- 1ß (IL-1β) in the CSF as a predictor of outcome in patients with bacterial meningitis.

METHODS

Study design and setting

This prospective observational study was conducted in the Emergency Unit of Alexandria Fever Hospital from January to December 2021. Forty consecutive patients with bacterial meningitis, diagnosed according to standard clinical and laboratory criteria, were enrolled.

Participants and outcomes

Participants were classified into three outcome groups based on their clinical course and disposition: deaths, complete resolution, and complicated cases.

Eligibility criteria

Adolescents and adults with a clinical diagnosis of bacterial meningitis who underwent diagnostic lumbar puncture were eligible. We excluded patients with alternative causes of raised intracranial pressure (e.g., brain tumour, brain abscess), pregnant patients, and those with systemic inflammatory conditions such as diabetes mellitus

Procedures and specimen handling

Cerebrospinal fluid (CSF) samples were centrifuged and stored at −80 °C until analysis. Interleukin-1β (IL-1β) concentrations were measured using a commercial ELISA kit (R&D Systems, Minneapolis, USA) according to the manufacturer's instructions. All samples were assayed in duplicate, with calibration curves generated from supplied standards. Laboratory technicians were blinded to clinical data and outcomes.

Ethics

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University (approval number 5-2/5-7/21/2021; session held on 5 July 2021). Written informed consent was obtained from all participants or their guardians prior to enrolment.

Statistical analysis

Analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables are summarised as mean ± standard deviation or median (interquartile range), as appropriate; categorical variables as frequencies and percentages. Given the small sample size and few adverse events, non-parametric tests were used where possible. Confidence intervals and multivariable modelling were not reported to avoid over-interpretation of unstable estimates. A two-sided p-value ≤ 0.05 was considered statistically significant.

RESULTS

Participant characteristics

Forty patients were enrolled (24 males, 16 females; mean ± SD age, 39 ± 13 years).

Microbiological findings

On Gram stain, 7.5% of cases showed Gram-negative coccobacilli, 7.5%

Gram-negative diplococci, and 85.0% Gram-positive diplococci. Culture identified *Streptococcus pneumoniae* in 85.0% of cases, *Neisseria meningitidis* in 7.5%, and *Haemophilus influenzae* in 7.5%.

CSF IL-1β: acute phase versus post-treatment

Mean baseline CSF IL-1β was significantly higher than the post-treatment level (775.7 ± 143.5 pg/mL vs 616.6 ± 168.3 pg/mL; $p < 0.001$), as shown in **Table 1**.

Clinical outcomes

Overall, 7.5% of patients died, 87.5% improved, and 5.0% had complications (see **Table 2**). There was a statistically significant association between outcome and both Gram stain and culture results.

CSF IL-1β by outcome category

CSF IL-1β values by outcome category are presented in **Table 3**. There was a statistically significant difference across outcome groups in the acute phase, but not after treatment.

Table 1: *CSF IL-1β concentrations in the acute phase and after treatment*

	Acute phase	After treatment	T	P
CSF IL1β (pg/ml)				
Min. – Max.	447.9 – 1075.9	329.0 – 898.8		
Mean ± SD.	775.7 ± 143.5	616.6 ± 168.3	9.119*	<0.001*
Median (IQR)	814.0 (660.4 – 869.6)	606.2 (485.8 – 775.0)		

*IQR: Inter quartile range, SD: Standard deviation, T: Paired t-test. p: p value for comparing between In acute phase and After treatment. *: Statistically significant at p ≤ 0.05. There was a highly statistically significant difference between in acute phase and after treatment as regard CSF IL1β.*

Table 2: *Distribution of outcomes*

	No.	%
Outcome		
Died	3	7.5
Improved	35	87.5
Complicated	2	5.0

Table 3: *CSF IL-1β (pg/mL) according to outcome*

CSF IL1β (pg/ml)	Outcome			F	P
	Died (n = 3)	Improved (n = 35)	Complicated (n = 2)		
In acute phase					
Mean ± SD.	982.7 ± 80.71	766.5 ± 134.2	625.9 ± 36.27	5.206*	0.010*
Median (Min. – Max.)	937.2(935.0-1075.9)	810.4(447.9-1059.8)	625.9(600.3- 651.5)		
After treatment					
Mean ± SD.	762.2 ± 26.81	610.6 ± 171.5	504.5 ± 111.0	1.641	0.208
Median (Min. – Max.)	776.7(731.3 – 778.7)	599.0(329.0 – 898.8)	504.5(426.1- 583.0)		

*SD, standard deviation; F, one-way ANOVA; p, p value for comparison across outcome categories. *Statistically significant at p ≤ 0.05.*

DISCUSSION

Bacterial meningitis (BM) is a serious disease that may extend to the brain parenchyma, resulting in substantial morbidity and mortality (1). The most common causative bacteria include *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, Group B *Streptococcus*, *Staphylococcus aureus*, and *Listeria monocytogenes*. In this prospective observational study, elevated acute-phase CSF IL-1β concentrations were associated with mortality and adverse outcomes, whereas day-14 levels were not discriminatory. There was a statistically significant difference between the acute phase and after treatment with respect to CSF indices.

The association between higher IL-1β and poor prognosis is biologically plausible. IL-1β reflects innate immune activation, promotes leucocyte infiltration, and increases blood–brain barrier permeability, leading to cerebral oedema and metabolic derangement. Following therapy, IL-1β levels decline, likely reflecting regression to the

mean and corticosteroid-mediated suppression of inflammatory cytokines, which may explain the absence of day-14 discrimination.

Our findings align with prior literature. ElKapany (6) reported a statistically significant difference in CSF indices between patients with bacterial meningitis and control groups. Shozan et al. (7) similarly observed a statistically significant difference in CSF appearance between bacterial meningitis and controls, noting a hazy CSF in 90% of bacterial cases. Abdelkader et al. (8) found higher CSF protein levels in the bacterial group than in controls ($P < 0.001$), consistent with Makoo et al. (9). The elevated CSF protein in bacterial meningitis may result from disruption and markedly increased permeability of the blood–brain barrier.

We also observed a highly statistically significant difference between the acute phase and after treatment, particularly in CSF glucose, protein, lactate, total WBCs, lymphocyte count and percentage, and neutrophil count and percentage. Sarhat et al. (10) reported higher mean serum total protein, interleukin-6, IL-1, IL-8, CRP, TNF-α, and IL-10 in patients than in controls, alongside a significant decrease in serum glucose. Abdelkader et al. (8) similarly reported highly significant differences in CSF WBCs, polymorph percentage, lymphocyte percentage, CSF protein, CSF glucose, and the CSF/serum glucose ratio between groups ($P < 0.001$).

In this study, Gram stain showed 7.5% Gram-negative coccobacilli, 7.5% Gram-negative diplococci, and 85.0% Gram-positive diplococci. Culture yielded *Streptococcus pneumoniae* in 85.0%, *Neisseria meningitidis* in 7.5%, and *Haemophilus influenzae* in 7.5%. Abdelkader et al. (8) reported *S. pneumoniae* in 75%, *N. meningitidis* in 18.75%, and *H. influenzae* in 6.25% of cases. Ceyhan et al. (11) found that the three primary organisms causing community-acquired bacterial meningitis in children from Kosovo were *N. meningitidis*, *H. influenzae*, and *S. pneumoniae*. In Abdelkader et al. (5), 67.6% of isolates were Gram-positive and 32.4% Gram-negative, with *S. pneumoniae* predominating among Gram-positive isolates. Troendle (12) reported that blood cultures detect the causative organism in 71% of cases, identifying the pathogen in 50–80% of paediatric and adult cases; the yield decreases by 20% with prior antibiotic treatment.

Our team found a highly statistically significant difference between the acute phase and after treatment with respect to CSF IL-1β. Mosaad et al. (13) reported CSF IL-1 levels of 75.8 ± 89.1 in cases versus 26.2 ± 18.0 in controls, a highly statistically significant difference, with 45.24% sensitivity and 85.7% specificity. In this study, there was a statistically significant difference between outcomes with respect to symptoms (photophobia and DLC) and signs (squint and DLC). Peng et al. (14) showed that poor prognosis was associated with unequal pupil size in both eyes. Sheded et al. (15) found that blindness was common among patients infected with *N. meningitidis* (14.3%) and was associated with poor outcome, consistent with Scarborough et al. (16), who reported 3% blindness in *N. meningitidis* patients, and Hammad et al. (17), who detected optic atrophy in 9% and reported visual impairment in 4% of studied patients. Our study emphasised a statistically significant difference between outcomes with respect to ESR 2nd hour, whereas Abdelkader et al. (8) found a significant difference in ESR between patient groups at admission and three days after treatment ($P < 0.05$). Peng et al. (14) also associated abnormal ESR with poor prognosis.

Consistent with our finding of a statistically significant difference between outcomes with respect to acute-phase CSF IL-1β, Tang et al. (18) observed that IL-1β and TNF-α concentrations decreased as patients improved clinically during treatment. Mustafa et al. (19) found IL-1β in 95% of samples, with a mean (± SD) of 944 ± 1293 pg/mL; patients with CSF IL-1β > 500 pg/mL were more likely to have neurological sequelae ($p = 0.001$).

Strengths and limitations: Strengths include prospective sampling at two time points, clinically adjudicated outcomes, and a real-world organism spectrum. Limitations comprise the small, single-centre sample (n = 40) with only five adverse events; limited statistical power precluding confidence-interval or multivariable analyses; potential selection bias; incomplete assay standardisation; and the absence of simultaneous blood cytokine measurements, which limits peripheral inflammatory profiling. These constraints were acknowledged to avoid over-interpretation.

Clinical implications: CSF IL-1β may serve as an early risk-stratification biomarker that complements routine CSF indices. Implementation would depend on assay availability, cost, and turnaround time—key feasibility considerations in East-African and similar settings.

CONCLUSION

Excessive activation of the immune response, characterised by elevated IL-1β, has been observed in CNS infection. We suggest a possible role for IL-1β and tumour necrosis factor

as mediators of meningeal inflammation in patients with bacterial meningitis. In this small, single-centre cohort, higher baseline CSF IL-1β was associated with mortality and adverse outcomes, whereas day-14 levels were not discriminatory. Larger, methodologically robust studies with predefined thresholds and external validation are needed before IL-1β can be recommended for prognostic use.

Declarations

Availability of data and materials: The datasets generated or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests. No financial or non-financial benefits have been or will be received from any party related directly or indirectly to the subject of this article.

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