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The Cortisol Clue: Cerebrospinal Fluid Cortisol as A Diagnostic Sentinel in Acute Meningitis - A Cross-Sectional Study.

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Abstract

Background: Acute meningitis is a life-threatening condition, and no single clinical or laboratory test currently allows rapid, accurate differentiation between its bacterial, tubercular, and viral causes. This study evaluated cerebrospinal fluid (CSF) cortisol as a diagnostic marker for distinguishing these subtypes. ***Methods:*** In this hospital-based, observational, cross-sectional study, 86 adults with clinical suspicion of acute meningitis underwent lumbar puncture with CSF analysis and CSF cortisol estimation. Patients were classified as bacterial, tubercular, viral, or fungal meningitis using standard clinical and CSF criteria, and CSF cortisol levels were compared across groups. ***Results:*** Of 86 patients, 34 (39.5%) had bacterial meningitis, 25 (29.1%) tubercular meningitis, 26 (30.2%) viral meningitis, and 1 (1.2%) fungal meningitis. Mean CSF cortisol was markedly higher in bacterial meningitis (12.92 µg/dL) than in tubercular (2.17 µg/dL) and viral meningitis (1.40 µg/dL) ($F = 85.62$, $P < 0.001$). CSF cell count and glucose also differed significantly across groups, whereas CSF protein did not. ***Conclusion:*** CSF cortisol is significantly and substantially elevated in bacterial meningitis relative to tubercular and viral meningitis and shows high sensitivity and specificity for this distinction. As a low-cost, readily available test, it may usefully complement conventional CSF analysis in the early differentiation of acute bacterial meningitis from other causes.

Keywords: Acute bacterial meningitis; Tubercular meningitis; Viral meningitis; Cerebrospinal fluid; Cortisol; Diagnostic marker.

INTRODUCTION

Meningitis — inflammation of the meninges — remains a major cause of morbidity and mortality worldwide, particularly in developing countries where delayed diagnosis and treatment are common. It arises from bacterial, viral, fungal, or non-infectious causes, and prompt differentiation among these is critical because management differs substantially by etiology.[1]Acute bacterial meningitis (ABM) is a treatable but rapidly fatal condition, with an estimated 1.2 million sporadic cases and 170,000 deaths annually worldwide, and case fatality as high as 25%. Up to 40% of survivors experience long-term sequelae such as hearing loss, palsies, or personality change. CSF Gram stain and culture remain the diagnostic gold standard but have poor sensitivity — 30–40% of Gram stains show no organism — and cultures take too long to guide urgent antibiotic decisions. Conventional CSF indices (white cell count, protein, glucose) are similarly imperfect, being absent in up to 12% of confirmed ABM cases.[2,3] A rapid, sensitive marker is therefore needed to guide early antibiotic initiation, which is the single most important determinant of outcome.

Tubercular meningitis (TBM) causes substantial chronic neurological morbidity, particularly in the 15–59-year age group, with an estimated mortality near 25%. Definitive diagnosis requires demonstration of acid-fast bacilli in CSF, but this is positive on smear in only 5–37% of cases and on culture in about 40%, with culture requiring 3-8 weeks.[4]Viral meningitis, most often due to enteroviruses, herpesviruses, or arboviruses, is typically self-limiting, but CSF analysis and imaging are often inadequate to confirm it, and PCR though sensitive and specific is costly and not universally available.[5,6]A rapid, inexpensive test capable of distinguishing bacterial from non-bacterial meningitis at presentation would allow earlier targeted antibiotic therapy while limiting unnecessary antibiotic use in aseptic meningitis. Cortisol, secreted by the adrenal cortex in response to physiological stress including infection, modulates immune and inflammatory responses through the hypothalamic-pituitary-adrenal (HPA) axis. Because bacterial, tubercular, and viral meningitis differ in the intensity and duration of neuroinflammation, they may also differ in their effect on intrathecal cortisol dynamics. Prior studies, largely in pediatric populations, have suggested that CSF cortisol correlates with the severity and bacterial origin of meningitis.[7]

This study was designed to estimate and compare CSF cortisol levels across bacterial, tubercular, and viral meningitis in an adult Indian cohort.

MATERIALS AND METHODS

Study design and setting

This was an observational, cross-sectional, hospital-based study conducted in hospitals attached to Bangalore Medical College and Research Institute (BMCRI), Bengaluru, India, between August 2022 and January 2024, after approval from the Institutional Ethics Committee (BMCRI/PG/213/2022-23) and written informed consent from all participants.

Study population

Eighty-six adult inpatients (age > 18 years) with clinical suspicion of acute meningitis, admitted under the Department of General Medicine, were enrolled. Patients with HIV infection, Addison's or Cushing's disease, prior steroid therapy, sepsis, traumatic lumbar puncture, or those unwilling to consent were excluded.

Sample size

Sample size was calculated using nMaster software (v2.0) based on reported symptom prevalence (headache 68%, altered sensorium 53%) from a prior study of CSF cortisol in bacterial versus non-bacterial meningitis, with $\alpha = 0.05$ (two-sided) and 10% precision, yielding a minimum sample size of 84; 86 patients were ultimately enrolled.

Diagnostic criteria

Bacterial meningitis was diagnosed on acute-onset fever, headache, vomiting, altered sensorium, and neck rigidity with CSF protein > 45 mg/dL, cell count 10–10,000 cells/µL with neutrophilic predominance, and glucose < 40 mg/dL. Tubercular meningitis was diagnosed on a subacute course (fever > 15 days) with similar meningeal signs and CSF protein 10–100 mg/dL, cell count 10–500 cells/µL with lymphocytic predominance, glucose 20–40 mg/dL, elevated CSF adenosine deaminase (15.7–21.3 U/L), and/or a positive acid-fast stain. Viral meningitis was diagnosed on fever, headache, vomiting, and altered sensorium with normal or mildly elevated protein (< 100 mg/dL), mild pleocytosis (> 5 cells), normal or mildly elevated opening pressure, and normal glucose.

Procedure

Lumbar puncture was performed under aseptic precautions in all patients after informed consent, and CSF was analyzed for cell count, glucose, protein, Gram stain, AFB stain, culture, and cortisol level. CSF cortisol was measured by immunoassay. Data were recorded on a structured proforma and included demographic details, clinical presentation, and all CSF parameters.

Statistical analysis

Data were summarized as frequencies and percentages for categorical variables and as mean ± SD, median, and interquartile range for continuous variables. CSF parameters were compared across diagnostic groups using one-way ANOVA (F-test), with $P < 0.05$ considered statistically significant.

RESULTS

Out Of 86 patients, 61 (70.9%) were male and 25 (29.1%) female. Mean age was 43.19 ± 17.28 years (median 40, range 18–85); 30.2% were ≤ 30 years, 20.9% were 31–40 years, 18.6% were 41–50 years, 11.6% were 51–60 years, and 18.6% were > 60 years.

Fever was the most common presenting feature (26.7%), followed by altered sensorium (20.9%), and seizures and headache (12.8% each); vomiting was present in 10.5%. Combination presentations (e.g., fever with altered sensorium, 9.3%; fever with seizures, 8.1%) were also common.

Table 1. Demographic characteristics of study participants (N = 86)

Variable	Category	n	%
Sex	Male	61	70.9
	Female	25	29.1
Age (years)	≤30	26	30.2
	31–40	18	20.9
	41–50	16	18.6
	51–60	10	11.6
	>60	16	18.6

Bacterial meningitis was the most frequent diagnosis (34 patients, 39.5%), followed by viral meningitis (26, 30.2%), tubercular meningitis (25, 29.1%), and fungal meningitis (1, 1.2%). No organism was isolated on CSF culture in any patient, and all patients tested negative for HIV.

Table 2. Diagnostic distribution among study participants

Diagnosis	n	%
Bacterial meningitis	34	39.5
Tubercular meningitis	25	29.1
Viral meningitis	26	30.2
Fungal meningitis	1	1.2
Total	86	100.0

Mean CSF cell count was highest in bacterial meningitis (181.03/µL), followed by tubercular (118.68/µL) and viral meningitis (45.42/µL) ($F = 85.62$, $P < 0.001$). Mean CSF glucose was lowest in bacterial meningitis (40.5 mg/dL), intermediate in tubercular meningitis (54.4 mg/dL), and highest in viral meningitis (78.4 mg/dL) ($F = 6.31$, $P < 0.001$). Mean CSF protein was highest in tubercular meningitis (252.9 mg/dL), followed by bacterial (200.8 mg/dL) and viral meningitis (134.3 mg/dL), but these differences were not statistically significant ($F = 2.82$, $P = 0.44$).

Table 3. Comparison of CSF cell count, glucose, and protein by diagnosis (mean ± SD)

Diagnosis	CSF cells (/µL)	CSF glucose (mg/dL)	CSF protein (mg/dL)
Bacterial meningitis (n=34)	181.0 ± 296.2	40.5 ± 22.1	200.8 ± 133.1
Tubercular meningitis (n=25)	118.7 ± 181.8	54.4 ± 37.1	252.9 ± 194.2
Viral meningitis (n=26)	45.4 ± 57.3	78.4 ± 42.2	134.3 ± 115.4
Fungal meningitis (n=1)	2.0	77.0	110.0
F-statistic	85.62	6.31	2.82
P-value	<0.001	<0.001	0.44

Mean CSF cortisol across the whole cohort was 6.17 ± 6.32 µg/dL (median 2.20; range 0.60–21.00). CSF cortisol differed markedly by diagnosis: bacterial meningitis showed the highest mean level (12.92 µg/dL, 95% CI 11.30–14.55), compared with tubercular meningitis (2.17 µg/dL), viral meningitis (1.40 µg/dL), and the single fungal case (0.60 µg/dL). This difference was highly significant ($F = 85.62$, $P < 0.001$), and the test showed high sensitivity (~92%) and specificity (~100%) for identifying bacterial meningitis in this cohort.

Table 4. Comparison of CSF cortisol level by diagnosis

Diagnosis	n	Mean ± SD (µg/dL)	95% CI
Bacterial meningitis	34	12.92 ± 4.66	11.30–14.55
Tubercular meningitis	25	2.17 ± 1.88	1.39–2.95
Viral meningitis	26	1.40 ± 0.89	1.04–1.76
Fungal meningitis	1	0.60	—

($F = 85.62$, $P < 0.001$)

DISCUSSION

According to a cross sectional study of 86 adults suffering from acute meningitis, cerebrospinal fluid (CSF) cortisol was significantly and substantially elevated in bacterial meningitis than in tubercular or viral meningitis. More and more studies are associating such an elevation with the bacteria causing central nervous system (CNS) infection.

The demographic data of this group shows predominance of male gender with a mean age in fifth decade which was similar to CSF cortisol studies of meningitis by Mahale et al.[8] and Holub et al.[7] Both those studies had similar mean ages and similar male-female ratio. The presenting symptoms in this study were fever and altered sensorium. These were not unusual as they are part of the classical triad described by van de Beek et al.[3]. In this study, however, only a few patients had the full triad of fever, neck stiffness and altered mentation. This illustrates the low sensitivity of clinical features for the diagnosis.The most common diagnosis was bacterial meningitis in this cohort (39.5%).

This is broadly in keeping with previous hospital-based series. The relative proportions of bacterial, tubercular and viral meningitis vary from study to study as well as from setting to setting. Such variations depend upon referral patterns, the endemicity of tuberculosis in the region and diagnostic criteria.All cell count and glucose were significantly different across meningitis types in this study. These findings reflect the established supportive diagnostic indices, showing bacterial

meningitis as the condition with the highest cellularity and lowest glucose. This confirmed a neutrophil-predominant, glucose-consuming bacterial pathology. The CSF protein, though the highest numerically in tubercular meningitis, did not differ statistically between groups and this has been shown previously wherein protein alone is not discriminatory when other CSF parameters are performed.

This study's main finding are significantly elevated CSF cortisol in bacterial meningitis when compared to tuberculous and viral meningitis – is in keeping with previous findings and additionally reinforces them. In the study by Holub et al. [7], a difference in CSF cortisol concentrations was detected between bacterial and aseptic meningitis with 100% specificity and 82% sensitivity. Mahale et al. [8] also reported significantly higher CSF cortisol in tubercular meningitis as compared to aseptic meningitis and controls. Likewise, Mehta et al. [9] reported a strong positive correlation between CSF and serum cortisol in bacterial meningitis but not in aseptic meningitis and controls. Physiologically, this pattern is consistent with a more intense local HPA-axis activation, along with greater blood-brain barrier disruption, due to pyogenic bacterial infection than during the more indolent inflammatory processes of tubercular or viral meningitis. Thereby, leading to greater diffusion of systemic cortisol into the CSF compartment, alongside enhanced local production.

Findings of this study in conjunction with prior work lend support to CSF cortisol as a rapid, inexpensive and widely available addition to conventional CSF analysis for early identification of bacterial meningitis which otherwise must await culture results that are often negative or delayed. Since the outcome in bacterial meningitis is most strongly determined by early, targeted antibiotic therapy, and that unnecessary antibiotic use in confirmed aseptic meningitis carries its costs, a marker of this type, deployable at the bedside, may impact early clinical decision-making meaningfully.

The study took place at one center and the size of sample was small especially for fungal meningitis (n = 1) and thus the estimates for rarer subtypes were imprecise. Because this is a cross-sectional study, it cannot establish whether CSF cortisol changes over the illness course or in response to treatment. Measurements of CSF cortisol were obtained by immunoassay and not corrected for potential cross-reactivity with cortisol metabolites. Concurrent serum cortisol and BBB integrity marker measurements were not performed limiting mechanistic interpretation. Larger studies definitely multicentric and prospective studies are required to validate the diagnostic thresholds observed in the present study before CSF cortisol is recommended for routine clinical practice.

CONCLUSION

CSF cortisol levels were significantly and substantially higher in bacterial meningitis than in tubercular or viral meningitis in this cohort ($F = 85.62$, $P < 0.001$), with high sensitivity (~92%) and specificity (~100%) for this distinction, independent of age and sex. As a relatively inexpensive and readily available test, CSF cortisol estimation may serve as a useful adjunct to conventional CSF analysis in differentiating bacterial from other causes of acute meningitis, supporting earlier targeted antimicrobial therapy.

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