Original Article

Utility of cerebrospinal fluid cortisol level in acute bacterial meningitis

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Abstract

Background: Meningitis remains a serious clinical problem in developing as well as developed countries. Delay in diagnosis and treatment results in significant morbidity and mortality. The role and levels of intrathecal endogenous cortisol is not known. **Objective:** To study the cerebrospinal fluid (CSF) cortisol levels and to evaluate its role as a diagnostic and therapeutic marker in acute bacterial meningitis. **Materials and Methods:** Thirty patients with acute bacterial meningitis with no prior treatment were evaluated. Cortisol levels were compared with 20 patients with aseptic (viral) meningitis and 25 control subjects. **Results:** Mean CSF cortisol level was 13.85, 3.47, and 1.05 in bacterial meningitis, aseptic meningitis, and controls, respectively. Mean CSF cortisol level in bacterial meningitis was significantly higher as compared to controls ($P < 0.001$). There was significant difference in CSFcortisol levels in bacterial and aseptic meningitis ($P < 0.001$). **Conclusions:** Cortisol levels in CSF are highly elevated in patients with acute bacterial meningitis. This suggests that intrathecalcortisol may serve as a valuable, rapid, relatively inexpensive diagnostic marker in discriminatingbetween bacterial and aseptic meningitis. This helps in earlier institution of appropriate treatment and thereby decreasing morbidity and mortality.

Key Words

Aseptic meningitis, bacterial meningitis, cortisol, CSF, diagnostic, therapeutic

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Introduction

Meningitis is an inflammation of the leptomeninges and underlying subarachnoid cerebrospinal fluid (CSF). Various infective etiologies are implicated in its causation like bacterial, tubercular, viral, and fungal. Bacterial meningitis is a commonest infectious disease of central nervous system (CNS) in developing countries and also a major global health problem even in developed world. It represents a serious disease with a case fatality as high as 25% and are associated with significant morbidity and mortality.[1] Furthermore, long-term sequelae such as hearing loss, palsies, and personality changes affect approximately 40% of survivors.[2] Early and prompt initiation of antibiotic therapy are crucial in improving the outcome of acute bacterial meningitis. It is necessary to distinguish bacterial meningitis from aseptic meningitis in acute phase of the disease. The signs and symptoms, results of routine CSF analysis, and radiological findings are often inadequate in making a definitive diagnosis. Clearly, prompt laboratory test is required to differentiate these various types of meningitis. Gram's stain of CSF is rapid methods of detection of organism, but lack sensitivity. Similarly, culture of CSF is another method of diagnosis, but it is time consuming. Polymerase chain reaction (PCR) test is a highly sensitive and specific test, but is very costly and not widely available. Therefore, for differentiation of bacterial meningitis from aseptic meningitis, a reliable and cost effective test is needed.[3] Determination of CSF cortisol levels may be a valuable, rapid, relatively inexpensive diagnostic marker in discriminatingbetween bacterial and aseptic meningitis.[4] Detection of high level of CSF cortisol has shown promising results in the diagnosis of bacterial meningitis. It is known that exogenous corticosteroids improves the outcome of bacterial meningitis, less is known about the role played by important endogenous anti-inflammatory mediators, such as cortisol in CSF during the course of bacterial meningitis. Whether cortisol levels are increased in CSF during bacterial meningitis and their prognostic value are still not known. The objective of this study was to determine the CSF cortisol levels and to evaluate its role as a diagnostic and therapeutic marker in acute bacterial meningitis.

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Materials and Methods

Patients and setting

A total of 60 patients clinically suspected of meningitis who were admitted in MS Ramaiah Hospitals, Bangalore, India were recruited for the study. The study period was from July 2009 to July 2011 and was approved by the institute ethics committee. All subjects or their caregivers gave written informed consent after full explanationand detailed description of study method. The inclusion criteria included age 18 years or greater, patients presenting with fever, headache, and signs of meningeal irritation and lumbar punctureperformed upon admission to the hospital. Partially treated cases (which included antibiotics and steroids) were excluded from the study. A bacterial etiology was diagnosed by positive bacterial blood or CSF cultures. A viral etiologywas diagnosed by detection of viral deoxyribonucleic acid (DNA) in CSF using PCR. The CSF cortisol was repeated after 72 h after the initiation of treatment. All patients and controls were examined by one of the authors (AM). The study was prospective, cross-sectional, observational, and hospital-based.

Investigations

All the patients underwent thorough clinical examination. The following information was documented in the predesigned proforma: Characteristics of fever, headache, level of consciousness, details about convulsions, focal neurological deficits, history of head injury, surgeries, and comorbidities such as diabetes, pulmonary or extrapulmonary tuberculosis. Following investigations were carried out in all the patients that include complete blood count, renal, hepatic function tests, serum electrolytes, random blood sugar: At the time of lumbar puncture, serum cortisol, serum procalcitonin, chest X-ray, ultrasonography abdomen, blood culture, CSF study: Cytochemical analysis — cell count, cell type, protein, sugar, cortisol estimation by chemiluminescent method, gram stain and Ziehl–Neelsen (ZN) stain, culture for mycobacteria and bacteria, and herpes simplex virus (HSV) and varicella-zoster virus (VZV) PCR. Neuroimaging in the form of computed tomography (CT) head or magnetic resonance imaging (MRI) brain was done in all patients to rule out structural brain lesion before lumbar puncture. CSF examination was done as soon as patient got admitted before first dose of antibiotics or steroids were given.

Analysis of CSF-cortisol level

A fresh sample of CSF obtained by the lumbar puncture was collected in heparinized vial, and analyzed for cortisol estimation by direct chemiluminescence assay using ADVIA Centaur CP system. The ADVIA Centaur CP cortisol assay is a competitive immunoassay using direct chemiluminescent technology. Cortisol in the patient sample competes with acridinium ester-labeled cortisol in the Lite Reagent for binding to polyclonal rabbit anticortisol antibody in the solid phase. The polyclonal rabbit anticortisol antibody is bound to monoclonal mouse anti-rabbit antibody, which is covalently coupled to paramagnetic particles in the solid phase.

The different types of meningitis were categorized according to cytochemical parameters:[5] a) Bacterial meningitis: Cloudy or turbid appearance; protein: >45 mg/dl; white blood cells: 10-10,000/μl; neutrophil predominance; glucose: <40 mg/dl; CSF/serum glucose: <0.4. b) Viral meningitis: Protein: 20-80 mg/dl; cell counts: 25-500 cells/μl; lymphocytic predominance; glucose: Normal to decreased.

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 17. The continuous variables were expressed as mean ± standard deviation and categorical variables as frequency and percentage. The normality of the distribution was assessed by the skewness of the values. The association between CSF cortisol and serum cortisol, and CSF cortisol and serum procalcitonin was assessed using Pearson's correlation coefficient, positive or negative r value indicating positive or negative correlation. For the analysis of continuous variables, nonparametric testing (Mann–Whitney test and Wilcoxon's test) was employed. $P < 0.05$ was taken as statistically significant.

Results

Ten patients were excluded who met the exclusion criteria. Fifty patients were included in the study. Thirty patients were suspected to be suffering from bacterial (subsequently confirmed in majority) and 20 patients from aseptic (viral) meningitis. Twenty-five patients (15 males and ten females) without any preexisting neurological disorders who underwent spinal anesthesia were included as controls.

Demographic and clinical data of bacterial meningitis

Thirty patients clinically suspected of acute bacterial meningitis were recruited during the study period. Mean age of the patients was 42.6 ± 18.3 years (range: 17–80). There was almost equal proportion of males (n = 16) and females (n = 14) with M:F ratio of 1.14:1. The most common clinical symptom was fever (30/30), headache (30/30), altered level of consciousness (24/30), and convulsions (10/30). The most common clinical signs were neck stiffness (30/30), drowsiness (16/24), irritability (6/24), stupor (2/24), cranial nerve deficits (2/30), and transient hemiparesis (2/30). The duration of symptoms was less than 24 h in six (20%), 24-48 h in 14 (46.7%), and more than 48 h in 10 (33.3%) patients.

Clinical course and etiology of bacterial meningitis

Eleven out of 30 patients (36.7%) with bacterial meningitis presented with sepsis on admission. Favorable outcomes of bacterial meningitis were observed in 19 patients (63.4%) and three patients (10%) succumbed to bacterial meningitis. The bacterial etiology of bacterial meningitis was confirmed in 17 patients (56.7%). Out of these 17 cases of bacterial meningitis, seven (41.7%) were caused by *Streptococcus pneumoniae*, five (29.4%) by *Neisseria meningitidis*, three (17.6%) by *Staphylococcus aureus*, and one (5.9%) each by *Escherichia coli* and *Streptococcus haemolyticus*.

Demographic and clinical data of aseptic (viral) meningitis

Twenty patients clinically suspected of acute aseptic meningitis were recruited during the study period. Mean age of the patients was 38.2 ± 16.2 years (range: 18-60). There was male preponderance (n = 12) and females (n = 8) with

M:F ratio of 1.5:1. The most common clinical symptom was fever (20/20), headache (20/20), altered level of consciousness (14/20), and convulsions (12/20). The most common clinical signs were neck stiffness (20/20), drowsiness (9/14), and irritability (5/14). The duration of symptoms was less than 24 h in four (20%), 24-48 hours in six (30%), and more than 48 hours in 10 (50%) patients.

Clinical course of viral meningitis

Twenty patients had CSF features suggestive of viral meningitis. CSF HSV PCR was positive in eight patients, VZV PCR was positive in five patients, and unknown etiology in seven patients. Favorable outcomes of viral meningitis were observed in all 16 patients (80%).

Cytology and chemistry of CSF

Serum and CSF cytological and clinical chemistry parameters in the bacterial and aseptic meningitis groups are summarized in Table 1. The mean blood WBC count in bacterial meningitis group was higher as compared to aseptic meningitis group.

Cortisol level in CSF and serum

The comparison of CSF cortisol levels between groups is shown in Figure 1. The mean CSF cortisol level in bacterial meningitis group was significantly higher as compared to aseptic meningitis and control groups ($P < 0.0001$). The mean serum cortisol in the bacterial meningitis group was 59.87 ± 12.3. There is positive correlation between serum cortisol levels and CSF cortisol levels in bacterial meningitis, as depicted in Figure 2 ($P < 0.001$). However, there was no correlation between serum cortisol levels and CSF cortisol levels in aseptic meningitis and control groups.

CSF cortisol and serum procalcitonin in bacterial meningitis

The mean serum procalcitonin levels in bacterial meningitis group were 8.71 ± 4.9 (range: 1.6-17.2). The CSF cortisol levels significantly correlated with serum procalcitonin level in bacterial meningitis group, as depicted in Figure 3 ($P < 0.001$).

Table 1: Cytological and clinical chemistry parameters in blood and CSF in patients with bacterial and aseptic meningitis

Parameters	Bacterial meningitis (n = 30)	Aseptic (viral) meningitis (n = 20)
Blood		
WBC count (cells/mm^3)	14,900 (10,925-19,525)	6,950 (3,700-8,920)
CSF		
WBC count (cells/mm^3)	366 (105-1120)	146 (110-200)
Cell type (predominant)	Neutrophils	Lymphocytes
Protein (mg/dl)	264.3 (97-1,263)	47.6 (37-74)
Glucose (mg/dl)	37.4 (28-56)	48.9 (43-55)
CSF/serum glucose ratio	0.3 (0.19-0.42)	0.49 (0.38-0.54)

Data are presented as mean (range). WBC = White blood cell, CSF = Cerebrospinal fluid

CSF cortisol level in bacterial meningitis in response to treatment

Patients with bacterial meningitis received intravenous antibiotics based on the culture and sensitivity results or otherwise empirical if culture were negative. There was significant reduction in the mean CSF cortisol level in response to the treatment (13.85 vs 1.55 μg/dL; $P < 0.0001$).

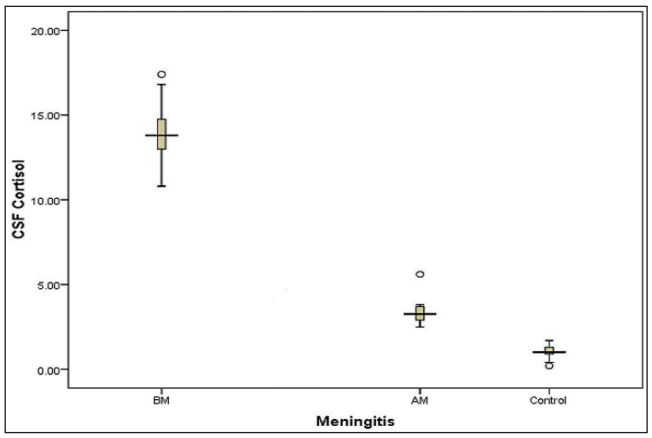

Figure 1: Comparison of CSF cortisol levels between bacterial, aseptic (viral) meningitis, and control. Solid lines denote mean values. AM = Aseptic (viral) meningitis, BM = bacterial meningitis, CSF = Cerebrospinal fluid

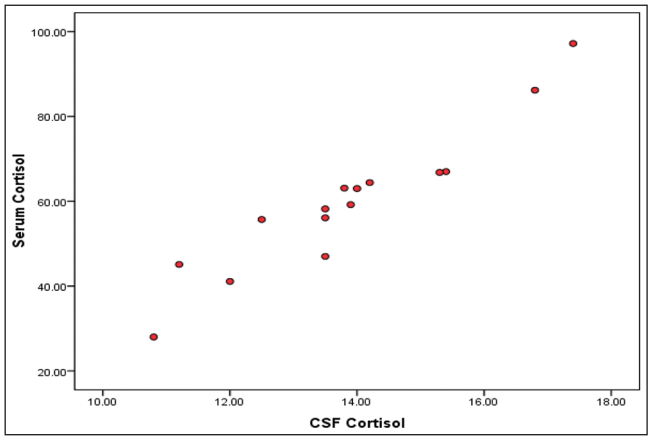

Figure 2: Correlation of CSF and serum cortisol levels in bacterial meningitis. Pearson's correlation test was used

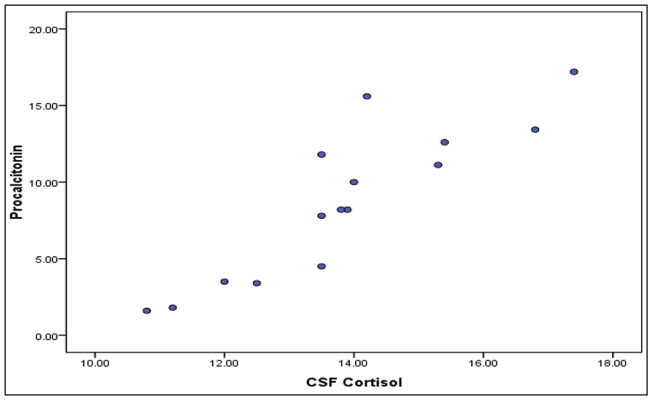

Figure 3: Correlation of CSF cortisol and serum procalcitonin levels in bacterial meningitis. Pearson's correlation test was used

Discussion

The present study was aimed at determining the CSF cortisol levels in acute bacterial meningitis as compared to aseptic meningitis and control and to evaluate its role as a diagnostic and therapeutic marker in acute bacterial meningitis.

Cortisol is the major glucocorticoid in humans, maintaining the stress reaction of the body to all kinds of physical and psychological discomfort. Increase in cortisol secretion takes place very quickly, within minutes in acute stress conditions, and can stay at high levels for long periods, sometimes days, months, and even years.[6]

Following are the mechanisms postulated in increased CSF cortisol in bacterial meningitis:

a. Bacterial meningitis is associated with systemic inflammation, intense stress response, and compromised blood brain barrier.[7] In normal circumstances, the balance between CSF cortisol and blood cortisol levels is controlled by active efflux of the hormone from the brain;[8] however, disturbance of this mechanism by inflammationalong with reduced ability of brain cells to metabolize sterol molecules, may lead to persistent increase in CSF cortisol.[4]
b. There is *de novo* synthesis ofcortisol in the brain which is catalyzed by the enzyme 11β-hydroxysteroiddehydrogenase type 1.[9]
c. During critical illness, cortisol-binding globulin and albumin blood levels decrease by about 50%, leading to an increase in biological active free cortisol. Elevated free cortisol in circulation aided by bacterial meningitis induced damage to the blood-brain barrier results in increased CSF cortisol level.[10]

Apart from bacterial meningitis, increased CSF cortisol levels have also been reported in multiple sclerosis, Alzheimer's disease, depression, and posttraumatic stress disorder.[13-15]

We have found that CSF cortisol concentrations were significantly elevated in patients with bacterial meningitis as compared with concentrations in patients with viral meningitis as well as in healthy control individuals. Study by Holub *et al*., (2007) also reported that the mean CSF cortisol was significantly elevated in bacterial meningitis (133 nmol/l) as compared to aseptic (17 nmmo/l) and controls (10 nmol/l).[4] Study by Holub *et al*., (2006) showed that the mean CSF cortisol was significantly elevated in aseptic meningitis compared to controls.[16] In the present study, similar observations were made; mean CSF cortisol level in viral meningitis (3.47) was higher as compared to controls (1.05).

There was significant reduction in the cortisol levels (13.85 vs 1.55) in CSF following antibiotic treatment in bacterial meningitis in our studyreflecting its utility in monitoring treatment response. Similar observations were also reported by Holub *et al*., (2007) and Beran *et al*., (2011).[4,17]

This is the first study in India on CSF cortisol during the acute stage of bacterial meningitis. Till date, there are only few studies on CSF cortisol in bacterial and aseptic meningitis.[4,17] However, there are studies on serum cortisol levels in bacterial meningitis. Study by van Woensel *et al*., (2001) with regard to serum cortisol levels during the course of meningococcal meningitis, reported higher concentrations in patients with meningococcal meningitis than in those with fulminant meningococcal sepsis, which is the most severe form of invasive meningococcal disease.[18] Study by Singhi and Bansal (2006) reported that the mean serum cortisol levels were significantly higher in bacterial meningitis compared to aseptic meningitis.[20] Our study also showed elevated serum cortisol levels along with a significant correlation between high CSF and serum cortisol levels in patients with bacterial meningitis. Similar observations were also made by Holub *et al*., (2007) whereina direct correlation between mean CSF cortisol levels (133 nmol/l) and mean serum cortisol levels (939 nmol/l), that is, as the CSF cortisollevel raises, there is rise in the serum cortisollevels.[4] The difference between our and Holub *et al*., findings and those reported by van Woensel *et al*., may be due to the fact that fulminant meningococcal sepsis is associated with a blunted cortisol response; whereas, this response is preserved during the course of meningitis.[4,18,19] We found, a direct correlation between mean CSF cortisol levels (13.85) and mean serum procalcitonin levels (8.71). Similar observations were made by Viallon *et al*., (1999) and Schwarz *et al*., (2000).[21,22]

This study is not devoid of limitations. Smaller cohort of patients in each group in this study is one of the limitations. Correlation of CSF cortisol with disease severity and long-term outcome scores were not carried out. No single CSF test has yet been proved to be fully reliable in distinguishing bacterial meningitis from aseptic meningitis. For rapid etiological diagnosis in meningitis, various CSF parameters along with a new parameter in the form of CSF cortisol assay must be combined. The results of the present study should be a basis for larger, prospective clinical study regarding utility of CSF cortisol as a diagnostic as well as therapeutic biomarker.

Conclusion

CSF cortisol levels were significantly higher in bacterial meningitis group as compared to viral meningitis group. It can be useful guide to monitor the response to therapy in bacterial meningitis. CSF cortisol levels directly correlated with serum cortisol and serum procalcitonin levels. CSF cortisol may help in differentiating bacterial meningitis from viral meningitis.

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