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Usefulness of Cerebrospinal fluid Procalcitonin in Diagnosis of Neonatal Meningitis

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ABSTRACT

Background: To evaluate the diagnostic utility of Cerebrospinal fluid (CSF) Procalcitonin in the diagnosis of neonatal meningitis.
Study Design: Prospective Observational Study.
Methods: We included 43 neonates with sepsis and suspected meningitis as study subjects. These neonates were categorized into meningitis and non-meningitis groups based on CSF cytology and biochemical parameters.
Results: Among the subjects, 22 neonates were categorized into the meningitis group and 21 neonates were in the non-meningitis group, based on Cerebrospinal fluid cytology and biochemical parameters. The mean CSF Procalcitonin values were 0.48 ± 0.37 ng/ml and 0.20 ± 0.08 ng/ml in the meningitis and non-meningitis groups, respectively. A CSF Procalcitonin cut-off value of 0.13 ng/ml demonstrated a sensitivity of 86.36% and a specificity of 23.81% in diagnosing neonatal meningitis. This cut-off value also yielded a positive predictive value of 54.29% and a negative predictive value of 62.50%, with an area under the curve of 0.789 (0.645-0.933).
Conclusion: CSF Procalcitonin serves as a reliable biomarker. CSF procalcitonin levels can be utilized as an additional diagnostic marker alongside traditional markers such as CSF protein, sugar, cell count, and culture, particularly when CSF culture results are negative, lumbar puncture is traumatic, or the biochemical and cytological analysis of CSF is inconclusive.

Keywords: Diagnosis, Meningitis, Neonates, Procalcitonin

Introduction

Neonatal meningitis is a potentially fatal disease, affecting 0.8–6.1 neonates per 1,000 live births, with a higher incidence observed in preterm and chronically hospitalized neonates (1). Approximately 10% of affected neonates die, and 20–50% of survivors develop complications such as seizures, cognitive deficiencies, motor abnormalities, and vision and hearing impairments (2). The confirmatory diagnosis of neonatal meningitis is established through positive results from cerebrospinal fluid (CSF) cultures in a clinically compatible case. However, studies have indicated that around 15% to 30% of meningitis cases, proven by CSF examination, exhibit negative cultures (3). Furthermore, research suggests that, with the exception of CSF culture, no other CSF parameters, either alone or in combination, can reliably exclude the diagnosis of meningitis in neonates (4). Compared to older children and adults, interpreting CSF findings in neonates presents challenges, particularly in preterm neonates who have a more permeable blood–brain barrier, leading to higher levels of sugar and protein (4).

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The classic findings of low CSF glucose, CSF pleocytosis, and elevated CSF protein levels are more commonly observed in Gram-negative meningitis and late-onset Gram-positive meningitis (4). Moreover, reliance on classical parameters for meningitis diagnosis has other significant limitations, such as blood contamination of CSF following a traumatic lumbar puncture (LP). To overcome the challenges associated with established CSF parameters, a search for alternative markers for early, rapid, and reliable diagnosis of meningitis in neonates has commenced. Procalcitonin (PCT) is one such marker that has recently been studied.

In healthy individuals, Procalcitonin is synthesized in the thyroid C cells (parafollicular cells) from a CALC-1 gene located on chromosome 11. The initial mRNA product is known as pre-procalcitonin. This is then modified into 116 amino acid Procalcitonin, which is subsequently converted to calcitonin. The calcitonin hormone plays a role in calcium and phosphorus homeostasis. Normally, the CALC-1 gene in thyroid C cells is induced by elevated calcium levels, calcitonin gene-related peptide (CGRP), glucocorticoids, gastrin, glucagon, or β-adrenergic stimulation. Generally, all Procalcitonin formed in thyroid C cells is converted to calcitonin, preventing its release into the circulation. Consequently, the Procalcitonin level in healthy subjects is very low (0.05 ng/mL). However, during inflammatory conditions, the release of Procalcitonin is independent of the aforementioned regulations. In inflammatory conditions, Procalcitonin is primarily produced through two alternative mechanisms: a direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolites from microbes, and an indirect pathway induced by various inflammatory mediators such as TNF-α and IL-6. Increased production of Procalcitonin during bacterial infection and its association with sepsis was first demonstrated by Asscot et al. (5).

The objectives of our study are to assess the utility of CSF Procalcitonin as a diagnostic marker for neonatal meningitis and to establish a cut-off value for CSF Procalcitonin that can be considered significant in diagnosing neonatal meningitis.

Methods

The study was conducted in a tertiary-level neonatal care unit at SDM College of Medical Sciences and Hospital, Dharwad, Karnataka State, India, from November 2019 to December 2020.

This was a prospective observational study involving 43 neonates with sepsis who were suspected of having bacterial meningitis. Given the similarity in clinical features between sepsis and meningitis, the suspicion of meningitis was based on positive bacterial blood cultures and clinical manifestations of meningitis, such as apnea, seizures, shock, poor feeding, poor weight gain, lethargy, irritability, or temperature instability. Neonates with another focus of infection (e.g., septic arthritis, postoperative cases, injection site abscess) and neonates with extremely low birth weight (due to their more permeable blood–brain barrier, leading to higher levels of CSF sugar and protein, which affect the interpretation of CSF parameters) were excluded from our study.

Detailed maternal history and perinatal risk factors were recorded. A comprehensive clinical evaluation of the neonates, including general and systemic examinations, was performed for all participants. The data collected for the study included gestational age, perinatal risk factors for sepsis or meningitis, birth weight, sex, mode of delivery, history of any invasive procedures, duration of NICU stay, sepsis screen values, and blood cultures with isolated organisms. Lumbar puncture was performed with all aseptic precautions, and CSF samples were collected and analyzed for CSF cytology, CSF protein and glucose levels, and CSF culture and Gram staining. Additionally, CSF Procalcitonin was estimated. In our study, meningitis was defined based on the National Neonatology Forum, India October 2010 guidelines for CSF parameter cut-off values. The CSF Procalcitonin values were measured quantitatively by the Chemiluminescence method using the ADVIA Centaur CP machine. All subjects were closely monitored throughout their NICU stay.

Statistical analysis

The study data were collected in a predesigned proforma. Statistical analysis was performed using SPSS version 20 software. Correlations between variables and statistical differences were analyzed using Pearson's chi-squared test and the Mann-Whitney U test. The reliability of CSF Procalcitonin for the diagnosis of neonatal meningitis was assessed by constructing a Receiver Operating Characteristic (ROC) curve. Sensitivity, specificity, and likelihood ratios of positive and negative results with 95% confidence intervals were calculated, with statistical significance set at $p<0.05$.

Ethical approval

The study received approval from the institutional ethical committee (Ref: SDMIEC: 195:2019), and informed consent was obtained from the parents of all neonates included in this study prior to their enrollment.

Results

A total of 43 subjects were included in our study, all of whom met the inclusion and exclusion criteria. Subjects were categorized as neonates with meningitis or without meningitis based on the CSF analysis report, with meningitis defined according to the National Neonatology Forum, India October 2010 guidelines cut-off values.

Out of the 43 subjects, 22 had meningitis and 21 had no meningitis. Among the neonates with meningitis, the majority were female, comprising 17 (77.27%) infants. Of the 22 neonates with meningitis, 12 were delivered via Cesarean section (LSCS), and the remaining 10 were delivered via normal vaginal delivery (Table 1).

Table 1. Comparison of various baseline characteristics of neonates with meningitis and without meningitis group

Baseline charecterstics		Meningitis group	% distribution	Non meningitis group	% Distribution
Gender distribution	Male	5	22.73	10	47.62
	Female	17	77.27	11	52.38
Gestational age distribution	Early preterm	5	22.73	6	28.57
	Late preterm	4	18.18	4	19.05
	Term	13	59.09	11	52.38
Mode of delivery distribution	LSCS	12	54.55	16	76.19
	Vaginal delivery	10	45.45	5	23.81
Inborn/ Outborn distribution	Inborn	13	59.09	15	71.43
	Outborn	9	40.91	6	28.57
Invasive procedure underwent distribution	Yes	8	36.36	8	38.10
	No	14	63.64	13	61.90

In meningitis group lethargy was the most common clinical finding, with11 (50%) neonates presenting this symptom. Other symptoms were respiratory distress in 9(40.91%), apnoea in 7 (31.82%), irritability in 7 (31.82%), shock in 7 (31.82%), seizure in 6 (27.27%) and fever in 6(27.27%) neonates. In meningitis group 16 (72.73%) neonates had blood culture proven sepsis, while the remaining 6(27.27%) neonates blood cultures were reported as no growth.The mean CSF Procalcitonin value in meningitis group was 0.48 ng/ml, whereas in non-meningitis group the mean value was 0.20 ng/ml with standard deviation of 0.37 ng/ml and 0.08 ng/ml in meningitis and non-meningitis groups, respectively. On statistical analysis we found that there is a significant difference in CSF Procalcitonin value in meningitis group compared to non-meningitis group with p-value of 0.0015 (Table 2).

Table 2. Comparison of Levels of CSF parameters between meningitis and non-meningitis babies

CSF parameters	Meningitis		Non-Meningitis		p-value
	Mean	Std.Dev.	Mean	Std.Dev.	
CSF protein	131.00	65.89	93.07	39.71	0.0284*
CSF sugar	48.85	33.32	50.62	14.48	0.8235
CSF procalcitonin (PCT)	0.48	0.37	0.20	0.08	0.0015*
CSF Total leukocyte counts (TLC)	20.59	33.36	3.71	2.33	0.0259*

*p<0.05, # applied Mann-Whitney U test

Table 3. Area under the curve's values of various CSF analysis parameters

Test Result Variable(s)	Area	Std. Error	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CSF protein	0.6950	0.0820	0.0290*	0.5340	0.8560
CSF sugar	0.3690	0.0870	0.1420	0.1980	0.5400
CSF Procalcitonin (PCT)	0.7890	0.0740	0.0010*	0.6450	0.9330
CSF Total leukocyte counts (TLC)	0.8660	0.0590	0.0001*	0.7510	0.9810

*p<0.05

Table 4. Diagnostic value of the various parameters studied

Test Result Variable(s)	AUC	95%CI		Optimal cut off	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy
CSF protein	0.6950	0.5340	0.8560	60.25	90.91%	23.81%	55.56%	71.43%	1.19	0.38	58.14%
CSF sugar	0.3690	0.1980	0.5400	39.50	54.55%	19.05%	41.38%	28.57%	0.67	2.39	37.21%
CSF Procalcitonin (PCT)	0.7890	0.6450	0.9330	0.13	86.36%	23.81%	54.29%	62.50%	1.13	0.57	55.81%
CSF Total leukocyte counts (TLC)	0.8660	0.7510	0.9810	1.50	95.45%	19.05%	55.26%	80.00%	1.18	0.24	58.14%

The cutoff CSF Procalcitonin value of 0.13 ng/ml had sensitivity of 86.36% and specificity of 23.81% in diagnosing neonatal meningitis. This cutoff value also had a positive predictive value of 54.29% and negative predictive value of 62.50% with the area under the curve for neonatal meningitis being 0.789.(0.645-0.933.) (Table 3-4, Figure 1).

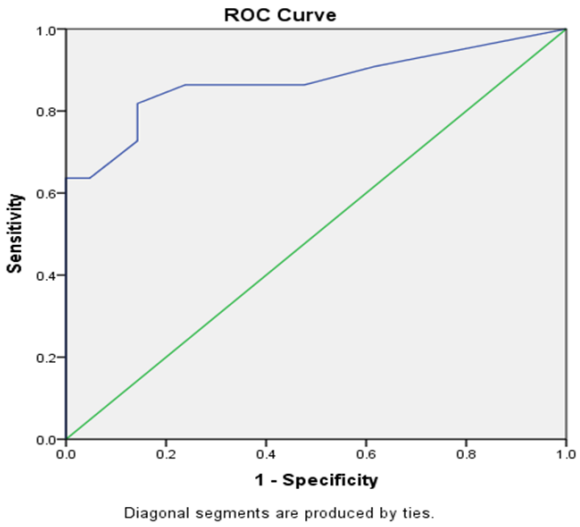

Figure 1. Receiver operating characteristic curve analysis to diagnose neonatal meningitis by CSF Procalcitonin level estimation

Discussion

Numerous studies on neonatal populations have evaluated the utility of serum Procalcitonin as a marker for neonatal sepsis, either alone or in conjunction with other biomarkers such as Interleukin-6 and C-reactive protein. However, there is a limited number of studies concerning the usefulness of CSF Procalcitonin in diagnosing neonatal meningitis. Our study aims to delineate the role of CSF Procalcitonin in diagnosing neonatal meningitis and to establish a cut-off CSF Procalcitonin value that can be considered significant for this diagnosis.

A study conducted by Reshi et al. found significantly higher mean CSF Procalcitonin levels in the meningitis group compared to those without meningitis. The mean CSF Procalcitonin values observed in the meningitis and non-meningitis groups were 0.47 (0.38–0.88) and 0.26 (0.21–0.28), respectively. They determined that at a value of 0.33 ng/ml, CSF Procalcitonin exhibits a sensitivity of 92%, specificity of 87%, a positive predictive value of 85.2%, and a negative predictive value of 93%. The area under the curve of 0.926 indicates that CSF Procalcitonin possesses high accuracy in detecting neonatal meningitis (6).

Another study by Benakappa N et al. found CSF Procalcitonin to be a reliable biomarker in the diagnosis of neonatal meningitis, with an Area Under the Curve of 0.867 (0.77 -0.95). They concluded that at a level of 0.12 ng/ml, CSF Procalcitonin demonstrates good sensitivity of 83% and specificity of 84%, suggesting it is a valuable diagnostic marker for neonatal meningitis (7).

A study by Rajial T et al. reported a significant difference in the mean CSF Procalcitonin values among neonates with confirmed cases, probable cases, and non-meningitis cases, with mean CSF Procalcitonin values of 0.31 ng/ml, 0.22 ng/ml, and 0.11 ng/ml, respectively. At a cut-off value of 0.20 ng/ml, CSF Procalcitonin showed a sensitivity and specificity of 95.25% and 96%, respectively, in diagnosing neonatal meningitis (8).

Shokrollahi et al. investigated the role of CSF procalcitonin in post-neonatal children with meningitis and found significantly higher mean CSF Procalcitonin levels in the bacterial meningitis group compared to the aseptic meningitis group (1.55 ± 1.19 versus 0.39 ± 0.33 ng/ml, $p < 0.001$) (9).

The present study demonstrated that CSF Procalcitonin is a reliable biomarker in the diagnosis of neonatal meningitis. In our study, the mean CSF Procalcitonin values were 0.48 ± 0.37 ng/ml in the meningitis group and 0.20 ± 0.08 ng/ml in the non-meningitis group. A cut-off CSF Procalcitonin value of 0.13 ng/ml yielded a sensitivity of 86.36% and a specificity of 23.81% in diagnosing neonatal meningitis. Additionally, this cut-off value had a positive predictive value of 54.29% and a negative predictive value of 62.50%, with an area under the curve of 0.789 (0.645-0.933).

Our study had a few limitations. Primarily, CSF Procalcitonin was measured only once at the time

of CSF analysis; serial CSF Procalcitonin levels were not assessed to monitor treatment response. The additional measurement of serum Procalcitonin would have been beneficial in identifying the severity of sepsis and its relationship with CSF values, but this was not feasible in our study. Furthermore, our study included a small number of reference standard positive cases.

Conclusion

CSF Procalcitonin is a reliable biomarker that can be utilized for diagnosing neonatal meningitis. It can serve as an additional biomarker in diagnosing neonatal meningitis when lumbar puncture is traumatic and CSF biochemistry and cytology findings are inconclusive.

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Conflicts of interest

No Conflicts of Interest.

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