Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2020; 27 (5): 389-393

Is there any Correlation between Cerebrospinal Fluid and Serum C-reactive Protein in Neonates Suspected to Meningitis?

Mandana Kashaki, M.D.[1], Elahe Norouzi, M.D.[2], Saeideh Heidarali, M.D.[3], Parisa Mohagheghi, M.D.[4], Mahmoud Soltani, M.D.[5], Hamid Karbalaei Hasani, M.D.[6]

1- Assistant Professor of Neonatal-Perinatal Medicine, Shahid Akbarabadi Clinical Research Development Unit (ShACRDU), Iran University of Medical Sciences, Tehran, Iran

2- Assistant Professor of Pediatrics, Neonatologist, Department of Pediatrics, Pediatric Growth and Development Research Center, Iran University of Medical Sciences, Tehran, Iran (Corresponding author: Email: elahenorouzimd@gmail.com)

3- Pediatrician, Iran University of Medical Sciences, Tehran, Iran

4- Associate Professor of Pediatrics, Neonatologist, Department of Pediatrics, Pediatric Growth and Development Research Center, Iran University of Medical Sciences, Tehran, Iran

5- Assistant Professor of Neonatal-Perinatal Medicine, Iran University of Medical Sciences, Tehran, Iran

6- Pediatrics Resident, Iran University of Medical Sciences, Tehran, Iran

Received: 12 May, 2020 Accepted: 25 July, 2020

ARTICLE INFO

Article type:
Original Article

Keywords:
Newborn
Meningitis
Cerebrospinal fluid
C-reactive protein
Sepsis

Abstract

Background: Meningitis is a common life threatening infection in neonatal period. Diagnostic value of CSF-CRP level in bacterial meningitis in children and adults has been studied worldwide, but there are limited studies on CSF-CRP in neonatal meningitis. This study conducted to assess any relation between CSF-CRP and plasma CRP levels and abnormal CSF findings in neonates suspected to meningitis.

Methods: Seventy five hospitalized neonates suspected to meningitis were enrolled in this cross sectional study. All infants were gone through a complete sepsis workup including blood and CSF CRP.

Results: CSF-CRP level had statistically significant correlation with serum WBC (p= 0.048) and also poor correlation with CSF protein level (p= 0.054). Serum CRP level had statistically significant correlation with CSF WBC (p= 0.008).

Conclusion: No correlation found between CSF and serum CRP levels of patients in this study. Although, CSF-CRP is a rapid and easy to interpret test, it can be performed alongside CSF cytology and biochemical analysis, smear and culture as a confirmatory test for definite diagnosis of neonatal meningitis.

Citation: Kashaki M, Norouzi E, Heidarali S, Mohagheghi P, Soltani M , Karbalaei Hasani H. Is there any Correlation between Cerebrospinal Fluid and Serum C-reactive Protein in Neonates Suspected to Meningitis? *Journal of Kerman University of Medical Sciences*, 2020; 27 (5): 389-393.

Introduction

Bacterial meningitis is more common in neonatal period than any other age of life, with incidence of 0.3 per 100 live births in developed countries, and 0.8 to 6.1 per 1000 live births in developing countries (1). Neonatal meningitis mortality has decreased over the past several decades to 10-15 percent, with the higher rates in preterm infants (1-3).

Neurologic morbidity including developmental delay, seizure, cerebral palsy, hydrocephalus, hearing loss, and blindness continues to be seen among affected neonates (1, 4). Therefore, rapid diagnosis and effective treatment is critical.

Suspected neonates should undergo a complete sepsis work up including blood culture (B/C), complete blood count with diff, C-reactive protein (CRP), and lumbar puncture for cerebrospinal fluid (CSF) gram staining and culture, cell count and its differentials, protein and glucose. A CSF white blood cell count of more than 20 -30 cells/µL is considered as the threshold of meningeal inflammation. The positive CSF culture and gram staining has remained the gold standard in the diagnosis of meningitis, but in neonatal group in our setting, negative or undetermined results are common.

CRP, an acute phase reactant, could be detected in serum or cerebrospinal fluid in response to any inflammation (5- 7). The sensitivity of plasma CRP is low in early neonatal infection, and increases 24 to 48 hours after the onset of sepsis symptoms (8). Therefore, serial determinations may be useful for the diagnosis of a bacterial infection and monitoring of response to treatment (9).

There have been some attentions directed to the value of cerebrospinal fluid-CRP (CSF-CRP) levels in the diagnosis of bacterial meningitis in adults and children, because of being an easy to interpret test and providing prompt results. However, there are limited evidences on CSF-CRP levels in correlation with plasma CRP in neonatal sepsis / meningitis. Therefore, this study was conducted to assess any relation between CSF-CRP and plasma CRP levels and abnormal CSF findings in neonates suspected to meningitis in order to evaluate CSF-CRP as a confirmatory test alongside CSF analysis and serum CRP in making a better decision for patient treatment, in time culture results are pending.

Materials and Methods

This hospital based cross- sectional correlational study was conducted in neonatal wards of two hospitals affiliated to Iran University of Medical Sciences in Tehran, Iran from Jan. through Dec. 2019. Seventy five infants under one month of age suspected to meningitis were enrolled in this study. The sample size was obtained 48 based on previous similar researches, and ultimately 75 patients were entered for higher study strength. The diagnosis of sepsis / meningitis was suggested according to the history and clinical findings including unstable body temperature, poor feeding, irritability, seizure, hypotonia, hyporeflexia, bulge fontanelle and positive blood culture. Neonates with neurologic malformation or any contraindication for lumbar puncture, and infants older than one month were excluded.

All infants were gone through a complete sepsis work up including evaluation of CBC with differentials, plasma CRP, blood culture, complete CSF analysis containing assessment of CSF cytology, glucose and protein levels, and CRP concentration, measurement of total and differential WBC, Gram staining and culture of CSF. Plasma and CSF samples were sent for quantitative CRP assay by turbidimetry method using a commercial available kit (BIOSYSTEMS, Aria Pharmed, Iran). CRP titer of 6 mg/L was considered as cut-off point of bacterial infection.

In this study, CSF Gram staining and culture were performed as gold standard test of bacterial meningitis. In cases with negative CSF staining and culture, CSF cytology accompanied with glucose and protein levels were considered diagnostic, and patients with CSF leukocyte count greater than 10 /mm^3 with polymorphonuclears > 60% and CSF glucose level less than ½ of blood sugar level were designated as meningitis.

The protocol of the study was approved by the Ethics Committee of Iran University of Medical Sciences with code number of IR.IUMS.FMD.REC.1398.318. Written informed consent was obtained from parents of all participants, and they were clarified that data would be kept confidential.

Results were presented as mean ±SD for quantitative variables and percentage for categorical variables. The correlation of variables was analyzed by Chi- square, independent t-test and Mann-Withney U test for quantitative and qualitative ones, respectively. All collected data were analyzed statically using SPSS24 for windows. P values of 0.05 or less were considered as statistically significant.

Results

From 75 infants suspected to meningitis, 41 ones (54.7%) were male and 34 ones (45.3%) were female. Mean age of infants was 6.4 ± 7.06 days with range of 1 to 28 days. Mean gestational age of patients was 37.6 ± 1.9 weeks, with range of 30 to 40 weeks. Method of delivery was normal vaginal delivery (NVD) in 68% and cesarean section (C/S) in 32% of the studied patients. Mean birth weight was 2960 ± 618 grams with range of 1330 to 4200g.

Mean, SD, minimum and maximum of the assessed quantitative variables have been listed in table 1.

Table 1. Mean, SD, minimum and maximum of quantitative variables of neonates

	CSF CRP (mg/L)	Serum CRP (mg/L)	CSF WBC (/mm^3)	CSF Pr. (mg/dl)	CSF Glucose (mg/dl)	Blood WBC (/mm^3)
Mean	0.7732	6.36	48.85	141.86	43.47	10600
SD	0.6304	13.17	382.16	39.55	12.35	4860
Min.	0.1	0	0	37	21	2900
Max.	5	61	3200	215	81	27100

CSF: cerebrospinal fluid; CRP: C-reactive protein; WBC: white blood cell.

Among patients suspected to meningitis, two cases had positive blood cultures, and one case had positive CSF culture.

CSF- CRP correlation with other cytology and biochemical findings of CSF, serum CRP level, and blood WBC count have been presented in table 2.

Table 2. Correlation of CSF- CRP with serum and CSF biochemical findings in neonates suspected to meningitis

	Relation with CSF-CRP	
Variable	**P value**	**R**
CSF WBC	0.342	0.119
CSF Protein	0.054	0.231
CSF Glucose	0.140	0.178
Serum CRP	0.119	0.186
Blood WBC	0.048	0.241

Correlation of serum CRP level with serum WBC count and CSF cytology and biochemical findings has been demonstrated in table 3.

Table 3. Correlation of serum CRP with serum and CSF biochemical findings in neonates suspected to meningitis

	Relation with serum CSF	
Variable	**P value**	**R**
Blood WBC	0.059	0.226
CSF CRP	0.119	0.186
CSF WBC	0.008	0.318
CSF Pr.	0.429	0.095
CSF Glucose	0.365	-0.108

CSF: cerebrospinal fluid; CRP: C-reactive protein; WBC: white blood cell.

Discussion

Meningitis is an important cause of mortality and morbidity in neonatal period. There has been a great dilemma in accepting CSF culture as a gold standard test in diagnosing meningitis in the first month of life due to the difficulty of sampling through narrow spaces in lumbar puncture resulting in bloody and questionable CSF samples in some cases, as well as time consuming CSF culture and scarce positive cases. For this, an easy to interpret, rapid, cost- effective and reliable test such as CSF-CRP test along with other blood and CSF laboratory tests is required in neonates suspected to meningitis. In the present study, we investigated any correlation between CSF-CRP and CSF parameters consistent with meningitis as well as with blood CRP and cytology in neonates suspected to meningitis.

CSF-CRP level showed statistically significant correlation with only serum WBC (P= 0.048) and also had poor correlation with CSF protein level (P=0.054). As it is apparent in table 3, serum CRP level had statistically significant correlation with just CSF WBC (P= 0.008).

Most of previous studies have been performed on diagnostic value of CSF-CRP in differentiating bacterial meningitis from aseptic meningitis, in patients elder than 2 months, predominantly adults. There are scarce studies conducted on diagnostic value of CSF-CRP in neonates. In a study on 49 infants suspected to meningitis, Javadinia *et al.* found that CSF-CRP had suitable diagnostic value in differentiating septic and aseptic meningitis with 95% sensitivity and 86% specificity (10).

In limited studies performed on pediatric groups older than 2 months of age, CSF-CRP values have been significantly higher in bacterial meningitis compared to control group or aseptic meningitis, with high sensitivity and specificity (11-14).

Malla *et al.* compared the values of CSF-CRP and blood CRP in laboratory diagnosis of meningitis in children with age of 1 month to 15 years, and showed that both CSF and blood CRP could be used to screen for pyogenic meningitis, because of high sensitivity. They found that CSF-CRP yielded results with higher specificity compared to blood CRP. They concluded that CSF-CRP could be a supportive test along with other CSF findings for diagnosing meningitis (15).

There are studies performed on the role of CSF-CRP in differentiating pyogenic from non-pyogenic meningitis in adult patients. According to these studies, CSF-CRP could be used as a rapid confirmatory test, since elevated CSF-CRP values are highly suggestive of pyogenic meningitis with high sensitivity and specificity (16-19).

Conclusion

In conclusion, no correlation was found between CSF and serum CRP of patients in this study, but there was a statistically significant correlation between serum CRP and CSF WBC, and also between CSF-CRP and serum WBC in the studied infants. Although CSF-CRP is a rapid and easy to interpret test, it is a confirmatory test, which can be performed alongside CSF cytology and biochemical analysis, smear and culture for definite diagnosis of bacterial meningitis in neonatal period.

Acknowledgement

The authors would like to express their gratitude to Shahid Akbarabadi Clinical Research Development Unit (ShACRDU) and Rasoul-e-Akram Medical Center, Iran University of Medical Scinces (IUMS), Tehran, Iran for their cooperation in this study.

References

1. Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. Clin Perinatol 2015; 42(1):29-45.
2. Gaschignard J, Levy C, Romain O, Cohen R, Bingen E, Aujard Y, et al. Neonatal bacterial meningitis: 444 cases in 7 years. Pediatr Infect Dis J 2011; 30(3):212-7.
3. Polin RA, Harris MC. Neonatal bacterial meningitis. Semin Neonatol 2001; 6(2):157-72.
4. Franco SM, Cornelius VE, Andrews BF. Long-term outcome of neonatal meningitis. Am J Dis Child 1992; 146(5):567-71.
5. Niknafs P; Norouzi E; Bahman Bijari B; Baneshi MR. Can we Replace Arterial Blood Gas Analysis by Pulse Oximetry in Neonates with Respiratory Distress Syndrome, who are Treated According to INSURE Protocol? IJMS 2015; 40(3): 264-7.
6. Corrall CJ, Pepple JM, Moxon R, Hughes WT. C-Reactive protein in spinal fluid of children with meningitis. Journal of Pediatrics 1981; 99(3):365-9.
7. Pepys MB. C-reactive protein-fifty years on. Lancet 1981; 1(8221):653-7.
8. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340(6):448-54.
9. Hofer N, Zacharias E, Muller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology 2012; 102(1):25-36.
10. Javadinia S, Tabasi M, Naghdalipour M, Atefi N, Asgarian R, Khezerloo JK, et al. C-reactive protein of cerebrospinal fluid, as a sensitive approach for diagnosis of neonatal meningitis. Afri Health Sci 2019; 19(3):2372-7.
11. Natani BS, Goyal P, Agarwal A, Bhatia S, Kumar M. Study of CSF C-reactive protein in meningitis to differentiate bacterial meningitis from aseptic meningitis in children between 1 month and 12 years of age. Int J Contemp Pediatr 2017; 4(3):943-6.
12. Singh N, Arora S, Kahlon PS. Cerebrospinal fluid C- reactive protein in meningitis. Indian Pediatr 1995; 32:687-8.
13. Prasad PL, Nair MN, Kalghatg AT. Childhood bacterial meningitis and usefulness of C-reactive protein. Med J Armed Forces India 2005; 61(1):13-15.
14. Chandel R, Goyal S, Poswal L, Asif M. Diagnostic value of CSF C-reactive protein in meningitis: A prospective study. International Journal of Biomedical Research 2016; 7(6):387-390.
15. Malla KK, Malla T, Rao KS, Basnet S, Shah R. Is cerebrospinal fluid C-reactive protein a better tool than blood C-reactive protein in laboratory diagnosis of meningitis in children? Sultan Qaboos Univ Med J 2013; 13(1):93-9.
16. Jain S, Nayak R, Sharma A. Role of C- reactive proteins in cerebro-spinal fluid in differentiating pyogenic from nonpyogenic meningitis. International Journal of Research in Medical Sciences 2016; 4(7): 2839-42.
17. Belagavi AC, Shalini M. Cerebrospinal fluid C reactive protein and adenosine deaminase in meningitis in adults. J Assoc Physicians India 2011; 59:557-60.
18. Gedam DS. CRP, an acute phase reactant: role in Differentiating Bacterial and Non-Bacterial CNS Infections. Int J Med Res Rev 2013; 1(2):45-46.
19. Komorowski RA, Farmer SG, Knox KK. Comparison of cerebrospinal fluid C-reactive protein and lactate for diagnosis of meningitis. J Clin Microbiol 1986; 24(6):982-5.