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Original Research Article

Cerebrospinal fluid procalcitonin: a promising diagnostic tool in differentiating bacterial from aseptic meningitis

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ABSTRACT

Background: Procalcitonin in cerebrospinal fluid has been evaluated with regard to its usefulness in distinguishing between the possible causative organisms for infections. CSF PCT as a diagnostic marker has also been evaluated for differentiating bacterial from viral meningitis with conflicting results obtained so far. The current study was designed to see the role of procalcitonin as diagnostic marker and in differentiating bacterial from aseptic meningitis in pediatric age group.
Methods: Children from 5 months to 15 years of age who were suspected cases of meningitis and were admitted to Pediatric Department in SKIMS Srinagar, Jammu and Kashmir were included in this case control prospective study conducted from 2014 to 2016. The total number of 200 children participated in the study among which 100 were cases and 100 controls. Serum and CSF PCT was measured by a fluorescence immunoassay using QDX Instacheck with a detection limit of 0.25-100 ng/ml. Data was analyzed by using standard statistical tests using SPSS 20.
Results: The mean CSF PCT in ng/ml in our study for viral meningitis was 0.59±0.43 (range=0.00-1.90), for bacterial meningitis 4.92±1.50 (range=2.89-10.82) and for controls 0.22±0.11 (range=0.00-0.32), respectively. CSF PCT was significantly higher in viral and bacterial meningitis as compared to controls ($p<0.01$) and significantly higher in bacterial meningitis as compared to viral meningitis ($p<0.01$). An AUC of 1.000 was established using serum and CSF PCT for bacterial meningitis. The diagnostic accuracy of serum and CSF PCT was almost 100% at cut-off of 2.2 ng/ml and 2.89 ng/ml, respectively.
Conclusions: Author have concluded that CSF PCT can be used as a diagnostic marker with better results in differentiation of bacterial from aseptic meningitis.

Keywords: Meningitis, Pediatric age, Procalcitonin

INTRODUCTION

Meningitis is a severe acute infectious disease caused by several microorganisms, including viruses, bacteria, parasites, and fungi. Fatality rates associated with this disease can be as low as 2% in infants and children, and as high as 20-30% in neonates and adults.[1] Because the consequences of delayed diagnosis of bacterial meningitis can be severe, any proposed diagnostic tool must achieve near 100% sensitivity.[2] Among new markers, serum procalcitonin (PCT) level seems to be one of the most sensitive and specific predictors for discriminating between bacterial and non-bacterial infections.[3]

PCT in CSF has been also evaluated with regard to its usefulness in distinguishing between the possible causative organisms (bacterial or viral) for infections. Few published studies have focused on the value of PCT in CSF which present conflicting results. Several authors have reported the quantitative evaluation of CSF PCT as a diagnostic marker of bacterial meningitis (BM) while others found that CSF's PCT levels in patients with meningitis were not different from patients with non-inflammatory central nervous system (CNS) diseases. Hence current study was designed to see the role of procalcitonin as diagnostic marker and in differentiating bacterial from aseptic meningitis in pediatric age group.

METHODS

Children from 5 months to 15 years of age who were suspected cases of meningitis and were admitted to Pediatric Department in SKIMS Srinagar, Jammu and Kashmir were included in this case control prospective study conducted from Jan 2016 to Dec. 2016. The total number of 200 children participated in the study among which 100 were cases and 100 controls. All the cases were further divided into two groups: Bacterial meningitis and Aseptic meningitis group according to WHO case definition criteria.[4] The control group was defined by absence of inflammatory cells in CSF (WBC <5/mm^3) and sterile bacteriologic findings in afebrile children with or without positive meningeal signs.

Patients were excluded if they had received antibiotics in the past seven days or had co-existing morbidities. Informed consent was obtained from parents for their children to participate in the study. A self-structured proforma was used for data collection. Permission for the study was sought from the institutional ethical committee (IEC SKIMS).

Protocol

The demographic and clinical characteristics of the patients like age, sex, vital signs as well as clinical symptoms and signs were recorded on admission. Additionally, blood and CSF samples were collected under complete aseptic conditions according to the standardized techniques before starting the initial antibiotic treatment. Blood samples were taken and used for routine laboratory investigations in addition to serum PCT measurement at admission in all participants. CSF samples were examined for PCT besides routine investigations in all participants.

Procalcitonin assay

Serum was separated from blood samples collected on admission from all patients and stored at -20 ^{0}C, and used subsequently for assaying PCT. After 72hrs of treatment, serum PCT levels were re-estimated for patients with meningitis only. Prognosis of cases was followed over a period of 7 days.

Serum and CSF PCT was measured by a fluorescence immunoassay using QD$_X$ Instacheck. It is a quantitative test requiring 150 µl of serum and CSF. Signal intensity of fluorescence on detector antibody reflects the amount of antigen captured and is processed by QD$_X$ Instacheck Reader. The detection limit is 0.25-100 ng/ml. The normal serum procalitonin with this is <0.5 ng/ml.

Data analysis

Data was analyzed by using standard statistical tests using SPSS 20. Categorical variables were compared employing tests (like chi-square) whereas continuous variables were compared by using student's t test. Values were expressed as Mean±SD and p value <0.05 was considered significant.

RESULTS

Figure 1 shows demographic features of study population. Among cases 67% were males and 33% females and in controls 71% were males and 29% females. Among cases and controls 23% and 16% had age <1 year, 38% and 48% were in age group 1-5 years, 18% and 24% in the age group of 6-10 years and 21% and 12% in the age group >10 years, respectively.

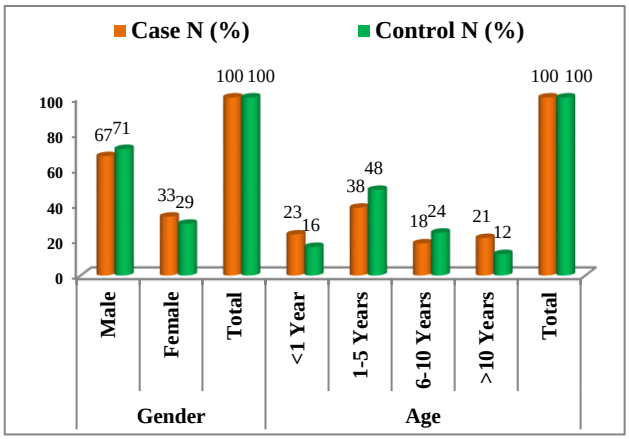

Figure 1: Demographic profile of the study population.

Table 1 shows laboratory investigations of study population. The mean blood procalcitonin (ng/ml) on admission, CSF TLC (mg/dl), CSF protein (mg/dl), CSF sugar (mg/dl) and CSF PCT (ng/ml) were 0.49, 46, 86, 59 and 0.59 respectively for viral meningitis; 14.6, 404, 86, 44 and 4.92 respectively for bacterial meningitis and 0.32, 51, 65 and 0.22 respectively for control group. The statistically significant difference was observed among different groups with serum PCT on admission, CSF TLC, CSF protein, CSF sugar and CSF PCT ($p<0.05$).

On post hoc test for multiple comparisons of different variables the serum procalcitonin on admission was significantly higher in bacterial meningitis (BM) compared to viral meningitis and control group ($p<0.01$).

CSF protein and CSF PCT was also significantly higher in viral and bacterial meningitis compared to control group ($p<0.01$). The CSF sugar was significantly decreased in bacterial meningitis compared to viral and control group ($p<0.01$). The mean differences in CSF PCT and CSF TLC between viral and bacterial meningitis were also highly significant ($p<0.001$).

Table 1: Result of different investigations.

On Admission	Viral meningitis Mean±SD (Min.-Max.)	Bacterial meningitis Mean±SD (Min.-Max.)	Control Mean±SD (Min.-Max.)	Post Hoc Test (sig.)
Serum PCT ng/ml	0.49±0.36 (0.25-2.1)	14.6±4.95 (4.0-26.9)	0.32±0.20 (0.25-1.7)	0.000* 1.000# 0.000$
CSF TLC (mm^3)	46±22 (10-95)	404±403 (100-1800)		0.000*
CSF Protein (mg/dl)	86±25 (50-155)	86±31 (45-210)	51±36 (10-176)	1.000* 0.000# 0.000$
CSF Sugar (mg/dl)	59±18 (21-101)	44±18 (22-94)	65±26 (22-210)	0.006* 0.310# 0.000$
CSF PCT (ng/ml)	0.59±0.43 (0.0-1.9)	4.92±1.50 (2.89-10.82)	0.22±0.11 (0.0-0.32)	0.000* 0.013# 0.000$

*comparison between VM and BM, # comparison between VM and Control, $ comparison between BM and Control

Table 2: Linear regression model for CSF PCT (Dependent Variable).

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	CSF PCT_(Constant)	3.440	0.740		4.650	0.000
	CSF Protein	-0.007	0.006	-0.082	-1.230	0.222
	CSF TLC	0.005	0.001	0.701	10.351	0.000
	CSF Sugar	-0.026	0.009	-0.209	-3.072	0.003
2	CSF PCT_(Constant)	2.771	0.503		5.512	0.000
	CSF TLC	0.005	0.001	0.693	10.253	0.000
	CSF Sugar	-0.025	0.009	-0.198	-2.932	0.004

Table 3: Performance characteristics of CSF procalcitonin in meningitis

	Serum Procalcitonin level				CSF Procalcitonin level			
	Viral Meningitis		Bacterial Meningitis		Viral Meningitis		Bacterial Meningitis	
	0.5-<2.2	≥2.2	0.5-<2.2	≥2.2	0.5-2.88	≥2.88	0.5-2.88	≥2.88
Sensitivity (95% CI)	25.45% (14.67-39.00)	0.00% (0.00-6.49)	0.00% (0.00-7.87)	100.00% (92.13-100.0)	43.64% (30.30-57.68)	0.00% (0.00-6.49)	2.22% (0.06-11.77)	97.78% (88.23-99.94)
Specificity (95% CI)	97.93 % (94.07-99.57)	68.97 % (60.76-76.38)	89.03 % (83.02-93.48)	100.00 % (97.65-100.0)	99.31 % (96.22-99.98)	69.66 % (61.48-77.01)	84.52 % (77.84-89.82)	100.00 % (97.65-100.0)
PPV (95% CI)	82.35% (56.57-96.20)	0.00% (0.00-7.87)	0.00% (0.00-19.51)	100.00% (92.13-100.0)	96.00% (79.65-99.90)	0.00% (0.00-8.04)	4.00% (0.10-20.35)	100.00% (91.96-100.0)
NPV (95% CI)	77.60 % (70.86-83.42)	64.52 % (56.44-72.03)	75.41 % (68.51-81.46)	100.00 % (97.65-100.0)	82.29 % (75.81-87.64)	64.74 % (56.70-72.21)	74.86 % (67.75-81.10)	99.36 % (96.48-99.98)

Table 2 shows relationship of CSF PCT with CSF protein, CSF TLC and CSF sugar. Linear regression model shows significant relationship with CSF TLC and CSF sugar (p=0.000 and p=0.004 respectively). The relationship with CSF protein was statistically not significant (p=0.222). The relationship between CSF PCT and serum PCT is shown in figure 2.

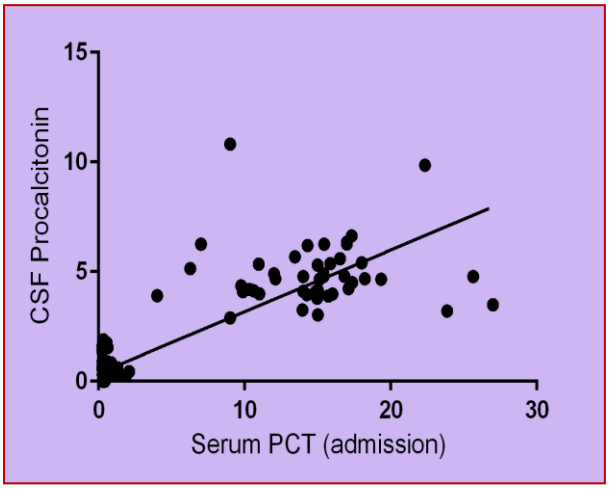

Figure 2: Relationship between CSF PCT and serum PCT.

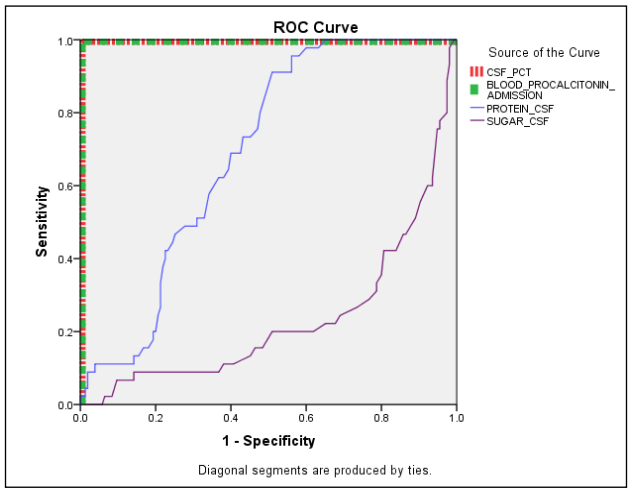

Figure 3: ROC for bacterial meningitis.

Table 3 shows sensitivity, specificity, PPV and NPV of serum and CSF procalcitonin for meningitis at different levels. These performance characteristics of serum PCT for viral meningitis reach their maximum values at 0.50-2.2 ng/ml with sensitivity, specificity, PPV and NPV respectively as 25.45%, 97.93%, 82.35% and 77.60% while for bacterial meningitis these values reached their maximum values at ≥2.2 ng/ml with sensitivity, specificity, PPV and NPV of 100% each. The CSF PCT sensitivity, specificity, PPV and NPV for viral meningitis reached to maximum value at a level of 0.5-2.88 ng/ml with values as 43.64%, 99.31%, 96.0% and 82.29%, respectively while as for bacterial meningitis these values were 97.78%, 100%, 100% and 99.36% at CSF PCT level of ≥2.89 ng/ml.

Figure 3 and 4 shows receiver operating characteristic curve (ROC) for bacterial meningitis. As depicted in the ROC in bacterial meningitis serum PCT and CSF PCT can reach the sensitivity and specificity of 100%. The area under the curve (AUC) is 1.000, 1.000, 0.690 and 0.232 respectively for CSF PCT, serum PCT, CSF protein and CSF sugar. Similarly figure shows ROC for overall meningitis (bacterial and aseptic combined). In this we can see that CSF PCT is superior to serum PCT in overall diagnosis of meningitis. The AUC is 0.912, 0.890, 0.814 and 0.344 respectively for CSF PCT, serum PCT, CSF protein and CSF sugar.

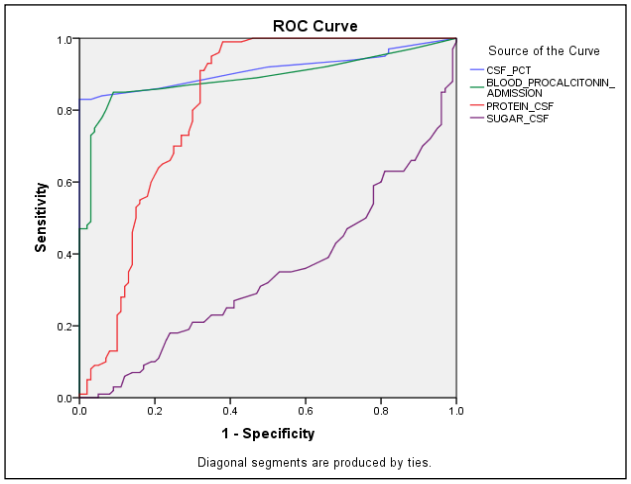

Figure 4: ROC for overall meningitis.

DISCUSSION

This case control study was conducted in Paediatric Department of SKIMS, Srinagar, J and K. It was designed to study the role of CSF PCT in differentiating bacterial from aseptic meningitis. The study was done on patients who were admitted in paediatric department with signs and symptoms suggestive of meningitis. The study included 100 cases of which 55 had bacterial meningitis (BM) and 45 had aseptic meningitis (AM) which were compared with 100 controls. Among cases 67% were males and 33% were females with respect to controls males were 71 % and females 29% with (p value=0.541). These differences in percentage of the males and females was similar to the study conducted by Mayah WW et al, and Sherkatolabbasieh HR et al, in which among cases (58.6 % and 64%) were males and (41.4% and 36%) were females respectively.[5,6] There was no difference in weight, height and BMI among cases and controls.

Mean serum PCT level on admission for bacterial meningitis was 14.60±4.95 (range=4.0-26.99); which was significantly higher (p<0.001) than viral meningitis 0.49±0.36 (range=0.25-2.10) and that of controls 0.32±0.20 (range=0.25-1.70). In a study the mean serum

procalcitonin level on admission in patients with acute bacterial meningitis was 18.3 ng/mL, and the lower level was 4.6 ng/mL, while the higher level in patients with non-bacterial meningitis was 0.62 ng/mL (mean level, 0.38 ng/mL).[6] The results are not only consistent but it is clear from the range of serum procalcitonin level that, there are no overlapping values seen for serum procalcitonin in both groups.

The mean CSF PCT in ng/ml in this study for viral meningitis was 0.59±0.43 (range=0.00-1.90), for bacterial meningitis 4.92±1.50 (range=2.89-10.82) and for controls 0.22±0.11 (range=0.00-0.32), respectively. CSF PCT was significantly higher in viral and bacterial meningitis as compared to controls ($p<0.01$) and significantly higher in bacterial meningitis as compared to viral meningitis ($p<0.01$). These results were consistent with study conducted by Makoo ZB et al, and similar to the study conducted by Konstantinidis T et al, in which mean CSF PCT in bacterial meningitis, viral meningitis and control group were 4.714±1.59, 0.1327±0.03 and <0.1, respectively.[7,8]

Moreover, if we look at the serum and CSF PCT values, it is highly discriminate in all cases. The mean serum PCT level in patients with bacterial meningitis was 14.6 ng/ml, and the lower level was 4.0 ng/ml, while the higher serum PCT level in patients with non-bacterial meningitis was 2.1 ng/ml and the mean was 0.49 ng/ml. The mean CSF PCT level in patients with bacterial meningitis was 4.92 ng/ml, and the lower level was 2.89 ng/ml, while the higher CSF PCT level in patients with non-bacterial meningitis was 1.9 ng/ml and the mean was 0.59 ng/ml. It means that, the highest value of procalcitonin seen in patients in serum or CSF with non-bacterial meningitis is still lower than the lower value of serum or CSF PCT seen in patients with bacterial meningitis. This result is in agreement with that obtained by many researchers. They found that PCT concentration increased in bacterial meningitis with or without shock but remained low in viral meningitis and inflammatory diseases.[9-11]

Mean CSF protein in mg/dl in this study was 86 (50-100); SD=25 for viral meningitis, 86 (45-210); SD=31 for bacterial meningitis and for controls it was 51 (10-176); SD=36. The difference in CSF proteins was statistically significant ($p=0.01$). The mean CSF sugar in mg/dl in viral meningitis, bacterial meningitis and controls were 59 (21-101); SD=18, 44 (22-94); SD=18 and 65 (22-210); SD=26 respectively. The CSF sugar was significantly decreased in bacterial meningitis as compared to viral and controls ($p <0.01$). These results are in consistent with many other studies.[7,12]

As for as linear regression model to compare relationship between CSF PCT and CSF TLC, CSF proteins, CSF sugar is concerned in this study there was significant relation between CSF TLC and CSF sugar ($p=0.000$) and $p=0.004$) respectively. The relationship with CSF protein was not statistically significant ($p=0.222$).

The sensitivity, specificity, PPV and NPV of serum and CSF PCT for viral meningitis in this study were found to be 25.45%, 97.93%, 82.35% and 77.60% and 43.64%, 99.31%, 96.0% and 82.29%, respectively at values 0.50-2.2 ng/ml (serum PCT) and 0.5-2.88 ng/ml (CSF PCT), respectively. These parameters respectively, for bacterial meningitis were found to 100% each and 97.78%, 100%, 100% and 99.36% at values ≥2.2 ng/ml (serum PCT) and ≥2.89 ng/ml (CSF PCT), respectively. Thus, we can say that for picking up bacterial meningitis serum PCT is superior to CSF PCT, while picking viral meningitis CSF PCT shows some superiority over serum PCT and this differentiation between bacterial and viral meningitis is achieved at serum PCT of 2.2 ng/ml and CSF PCT of 2.89 ng/ml. These thresholds although higher than many other studies, were more accurate in differentiating the meningitis. In a study at a threshold of 0.88 ng/mL, the serum PCT showed the highest diagnostic accuracy of 95.0% with sensitivity 87% and specificity 100%, implying that only 6 of the 120 meningitis patients were misdiagnosed. The highest diagnostic accuracy in that study for CSF PCT was 83%, with sensitivity 67% and specificity 100% when a threshold of 0.74ng/mL was selected.[13]

In a study, serum procalcitonin with a cut off of 0.5ng/mL had a sensitivity and negative predictive value of 100%, specificity of 87.09% and positive predictive value of 82.60% which is indicative of the fact that serum procalcitonin is a valuable and powerful biomarker in diagnosing acute bacterial meningitis. Cerebrospinal fluid procalcitonin also with a cut off of 0.5 ng/mL had a sensitivity of 84.21%, specificity of 93.54%, positive predictive value of 88.88% and negative predictive value of 90.62% which indicates that after serum procalcitonin, it could be considered a good biomarker in differentiating acute bacterial meningitis.[7]

The study conducted by Wei TT et al, showed that the overall diagnostic sensitivity of CSF PCT detection was 0.80 (95% CI, 0.61-0.91), specificity was 0.86 (95% CI, 0.70-0.95),. The overall diagnostic sensitivity of blood PCT detection was 0.95 (95% CI, 0.89-0.97), specificity was 0.97 (95% CI, 0.89-0.99).[14]

Of the parameters Gendrel et al, studied (CSF cells, CSF protein, and CRP level), only the PCT was able to differentiate BM and VM in 100% of the cases.[15] This differentiation was achieved at the threshold of 1.8 ng/mL. In 2008, Dubos et al, published a similar study on 180 patients aged from 29 days to 18 years, 96 of which (48%) had BM and AM in 102 patients.[16]

At the threshold of 0.5 ng/mL, the PCT was able to differentiate BM from AM in 100% of the cases with sensitivity of 99% (95% CI 97-100) and specificity of 83% (95% CI 76-90).

Unlike sensitivity and specificity, which can be greatly affected by the threshold chosen, the AUC is a global parameter that estimates the diagnostic accuracy of an index test.[17] We assessed the diagnostic accuracy of both serum and CSF PCT by ROC curve analysis. An equal AUC of 1.000 was established using serum and CSF PCT for bacterial meningitis which was more than that achieved by Wei TT et al, where the AUCs for CSF PCT and blood PCT were 0.90 (95% CI, 0.87-0.92) and 0.98 (95% CI, 0.97-0.99), respectively. The 95% CIs for the AUCs of CSF PCT and blood PCT in their study did not overlap, which indicated that the overall diagnostic accuracy of blood PCT detection was superior to CSF PCT.[14]

Therefore, the overall diagnostic accuracy of serum PCT is similar to CSF PCT in this cohort. Of note, the diagnostic accuracy of serum and CSF PCT was almost 100% and at cut-off of 2.2 ng/ml and 2.89 ng/ml, respectively, implying that 100% of patients with suspected bacterial meningitis can be correctly differentiated with either test. At this cut-off value, the diagnostic specificity was 100%, implying that a patient without BM is very unlikely to have serum PCT level higher than 2.2ng/ml. Our data suggest that the serum PCT could be a reliable marker to distinguish BM from viral meningitis. Our findings were as expected since PCT is a well-recognized marker for bacterial infection.[18-22] Thus, the results from the studies corroborate that PCT in serum and CSF is a potential diagnostic marker for meningitis.

CONCLUSION

In this study it was seen that there is statistically significant difference in CSF PCT among bacterial meningitis, viral meningitis and among controls. CSF PCT was higher in bacterial meningitis than viral meningitis and control group. Among viral meningitis group CSF PCT was higher than controls but less than bacterial group. Hence we conclude that CSF PCT can be used as a diagnostic marker with better results in differentiation of bacterial from aseptic meningitis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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