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The Role of Serum Procalcitonin in The Diagnosis and Detection of The Outcome of Acute Bacterial Meningitis in Children

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ABSTRACT
Background: Bacterial meningitis is a pediatric emergency that requires quick diagnosis and treatment due to its high death and morbidity rates. Clinically, bacterial meningitis and non-bacterial meningitis are frequently difficult to distinguish from each other. **Aim of work:** To study the role of serum procalcitonin in the diagnosis and differentiation of acute bacterial from non-bacterial reasons for meningitis, in addition to its role in the evaluation of the acute bacterial meningitis outcome.
Patients and Methods: This was a case-control hospital-based prospective study carried out at the Pediatric Department, Sohag University Hospital, and fever hospitals all over Sohag Governorate for 8 months, after obtaining ethical approval. Serum procalcitonin level for cases with bacterial meningitis and controls with non-bacterial meningitis was detected by Ethylenediaminetetraacetic acid (EDTA) and immunoassay device. All participants were followed clinically and by neuroimaging 2 months after the infection.
Results: There was a significant increase in CRP level among cases in comparison to controls but as regards the PCT level among cases and controls, there was no significant difference between them and there was a statistically significant positive correlation between CRP and serum procalcitonin. There was a poor outcome among cases with a significant difference in comparison to controls with a significant correlation between cases outcome and serum procalcitonin.
Conclusion: Serum procalcitonin levels had no significant associations with acute bacterial meningitis and had an important role in predicting its outcome but this should be confirmed by larger and more comprehensive studies.
Keywords: Serum procalcitonin, CRP, Acute bacterial meningitis, Outcome.

INTRODUCTION

Meningitis is one of the most typical illnesses of the central nervous system in newborns and young children, which is caused by bacterial, viral, fungal, or parasitic organisms [(1)]. In children, it is frequently challenging to distinguish between bacterial and non-bacterial aetiologies due to comparable clinical presentation. Bacterial meningitis has a high death and morbidity rate, so it needs to be quickly diagnosed and treated [(2, 3)].

Procalcitonin level is a potentially sensitive measure of severe bacterial infections, including meningitis, numerous studies have shown that bacterial illnesses, such as meningitis, are associated with elevated serum PCT values [(5)].

The function of serum procalcitonin in the diagnosis and prognosis of acute bacterial meningitis in children has not been extensively studied, procalcitonin is produced by the thyroid gland's C cells, as a 116-amino-acid peptide that is converted to calcitonin through post-translational proteolysis. Peripheral blood leukocytes secrete procalcitonin. When bacterial lipopolysaccharides and cytokines linked to severe bacterial infections are present, the level of PCT rises, without an increase in the level of calcitonin, in contrast, people who are infected with viruses only experience a little increase in PCT [(4, 5)].

Studies have demonstrated the effectiveness of PCT as a diagnostic tool for the evaluation of suspected meningitis, enabling early diagnosis of bacterial and non-bacterial aetiologies. According to data, serum PCT provides studied cases with suspected meningitis with a more accurate overall diagnosis while offering similar specificity to conventionally utilized CSF indicators of meningitis [(4)].

This work aimed to study the role of serum procalcitonin in the diagnosis and differentiation of acute bacterial from non-bacterial reasons for meningitis, in addition to its role in the detection of the outcome of acute bacterial meningitis in children.

PATIENTS AND METHODS

This case-control hospital-based study was conducted at the Pediatric Department, Sohag University Hospital, and fever hospitals all over Sohag Governorate for one year starting from acceptance of protocol from the Ethical Committee at Faculty of Medicine, Sohag University, from July 2021 to July 2022.

The study included all patients whose ages ranged from 1 month to 14 years and were

diagnosed as acute bacterial meningitis in the case group and non-bacterial meningitis in the control group, any patient with cerebral palsy, neurodegenerative disease, metabolic disease, and other systemic infections were excluded from the study.

The following was applied to all study participants at the time of presentation. Clinical history, focusing on socio-demographic data: age, gender, residence, and developmental history, before and after the infection. Clinical examination including systemic examination, anthropometric measurements, and complete neurological examination

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Investigations including complete blood count, C reactive protein, cerebrospinal fluid examination (CSF) including Gram staining and/or culture and serum procalcitonin (PCT) for cases and control by using a sample of serum or plasma heparin or EDTA and immunoassay device (Cobas e411Roch diagnostic, Switzerland). Serum procalcitonin had been estimated using the reference ranges of less than 0.5 ng/ml, indicate no sepsis, but 0.5-2 ng/ml, follow-up is recommended and more than 2 ng/ml indicate sepsis [(5)].

Follow-up of all patients included in both of the studied groups 2 months after presentation was done by clinical neurological examination and neuroimaging by MRI brain to detect any residual neurological effect of CNS infection and to detect the relation of this outcome with serum procalcitonin level.

Ethical consideration

Ethical approval was obtained from the Institutional Review Board (IRB) of the Faculty of Medicine at Sohag University and caretakers of study-involved children were asked to offer their informed oral and written consent. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 26 was used for data analysis. Depending on the type of data, means, standard deviations, or median and interquartile range of quantitative variables had been used to characterize them. To validate presumptions for use in parametric tests, Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were utilized. Mann Whitney test (for data that are not normally distributed) and independent sample t-test (for data that are normally distributed) were both used to compare quantitative data among the 2 groups. Categorical variables were presented using their absolute and relative frequencies and were compared by chi-square test. P <0.05 was used as the statistical significance level. If p was ≤ 0.001, highly significant variation had been evident. Spearman rank correlation coefficient test was used to detect the correlations between variables. KW Kruskal Wallis test was used for pairwise comparison between variables.

RESULTS

Sixty patients were included in this study, 30 cases and 30 controls, and were well matched in age and sex, with no significant difference as regard age. There was a significant difference between both groups as regard gender and consanguinity (Table 1).

Table (1) Comparison between studied groups regarding demographic data

	Case group N= (30)	**Control group N= (30)**	**Z**	**P**
	Median (IQR)	**Median (IQR)**		
Age (years)	0.67 (0.38 – 4)	0.92 (0.5 – 3.5)	-1.037	0.3
Gender:			χ^2	
Female	11 (36.7%)	20 (66.7%)	5.406	0.02*
Male	19 (63.3%)	10 (33.3%)		
Consanguinity:			χ^2	
Negative	24 (80%)	10 (33.3%)	Fisher	<0.001**
Positive	6 (20%)	20 (66.7%)		

Z Mann Whitney test, χ^2 Chi square test, IQR interquartile range. * Statistically significant **Statistically highly significant

There was a significant difference between cases and controls regarding the median of platelet count and CRP level, and the mean of HCT (Table 2).

Table (2): Comparison between the studied group regarding laboratory data

	Case group **N= (30)**	Control group **N= (30)**	Z	P
	Median (IQR)	Median (IQR)		
WBCs	13.3 (9.88 – 14.1)	6.9 (5.9 – 15.7)	-1.852	0.064
Platelet count	323 (266 – 453.5)	191 (154 – 344)	-2.889	0.004*
CRP	96(48 – 197.75)	36(24 – 48)	-3.543	<0.001**
MCV	72.35 (67.48 – 78.2)	74.95 (72.9 – 77)	-1.853	0.064
	Mean ± SD	Mean ± SD	t	P
Hemoglobin	9.83 ± 1.41	10.53 ± 1.45	-1.898	0.063
HCT	29.64 ± 6	33.67 ± 4.43	-2.221	0.005*

Z Mann Whitney test, t independent sample t-test, IQR interquartile range. * Statistically significant ** Statistically highly significant . SD Standard Deviation

The median of serum procalcitonin level was greater among cases than controls with no significant difference (Table 3) and there was a positive correlation between CRP and serum procalcitonin (R= 0.257), that was statistically significant (P=0.048) as seen in figure (1).

Table (3): Comparison between studied groups regarding serum procalcitonin

	Case group	Control group	Z	P
	N=thirty (percent)	N=thirty (percent)		
Procalcitonin:				
Median	0.21	0.18	-1.185	0.236
IQR	0.06 – 1.26	0.099 – 0.25		
Range	0.01 – 48.52	0.02 – 0.35		

Z Mann Whitney test. IQR interquartile range.

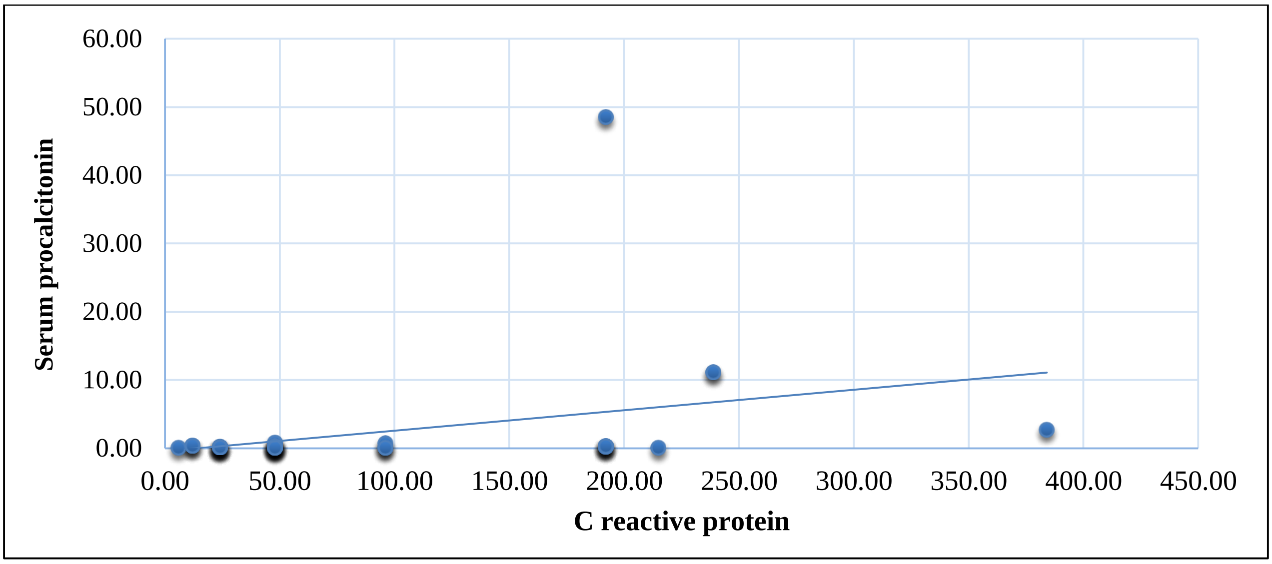

Figure (1): Scatter dot graph showing a significant positive correlation between serum procalcitonin and CRP

As regards the outcome of the studied groups, there was significant difference between both groups (Table 4). Regarding neuroimaging follow-up by MRI of brain, there was a significant difference between both groups (P<0.001) as seen in figure 2.

Table (4): Comparison between the studied groups regarding outcome

	Case group	Control group	χ2	P
	N=30 (%)	N=30 (%)		
Outcome:				
Dead	11 (36.7%)	0 (0%)		
Neurological deficit	9 (30%)	0 (0%)	MC	<0.001**
Complete cure	10 (33.3%)	30 (100%)		

χ^2 Chi square test, ** Statistically highly significant.

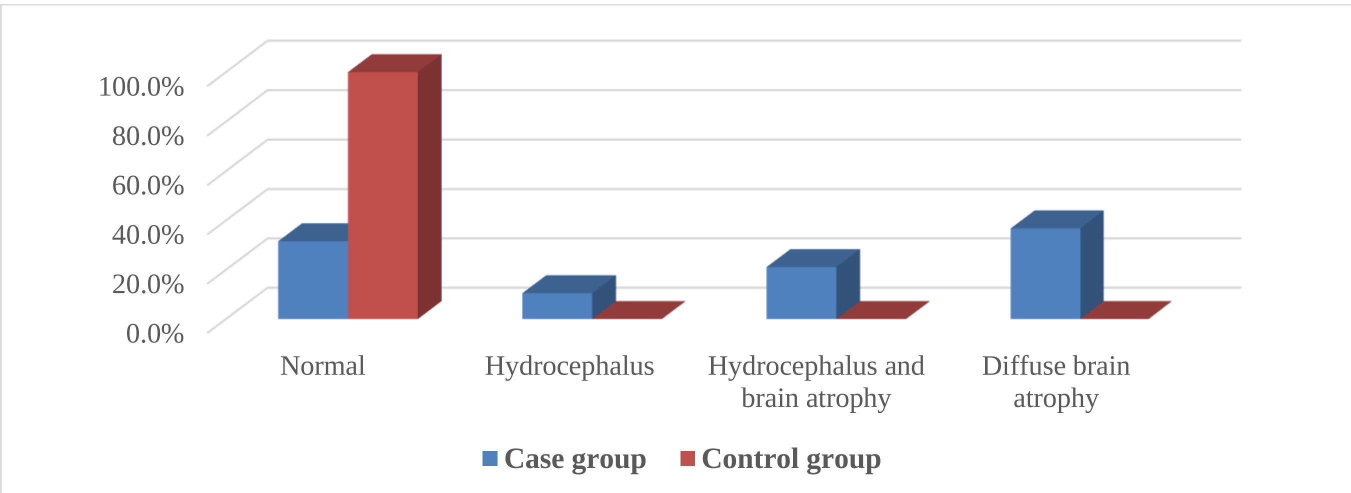

Figure (2): Multiple bar chart showing a comparison between the studied group regarding follow-up neuroimaging.

There was a statistically significant correlation between case outcomes and serum procalcitonin. On pairwise comparison, the median procalcitonin level among patients with neurological deficiency in follow-up was higher than patients with complete cure respectively with a significant difference (Table 5).

Table (5): Relation between serum procalcitonin and cases outcome

Outcome	Median of Procalcitonin (IQR)	KW	P	Pairwise
Complete cure Dead Neurological deficit	0.15(0.099 – 0.3) 0.1 (0.06 – 0.781) 0.46(0.21 – 8.52)	6.402	0.041*	P1 1 P2 0.093 P3 0.046*

KW Kruskal Wallis test, p1 difference between complete cure and dead, p2 difference between dead and neurological deficit, p3 difference between complete cure and neurological deficit, IQR interquartile range. * Statistically significant.

DISCUSSION

Meningitis is one of the most typical illnesses of the central nervous system in newborns and young children, which is caused by bacterial, viral, fungal, or parasitic organisms in children. It is frequently challenging to distinguish between bacterial and non-bacterial aetiologies due to comparable clinical presentation. Procalcitonin level is a potentially sensitive measure of severe bacterial infections, including meningitis, numerous studies have shown that bacterial illnesses, such as meningitis, are associated with elevated serum PCT values [3,6].

In the current study, it was observed that bacterial meningitis was more dominant among males in comparison to controls, respectively (63.3% versus 33.3%) with a significant difference (P=0.02). That was in line with **Choi and Choi** [7] who found that male studied cases tended to be more frequent in the bacterial meningitis group than in the viral meningitis group (54.7 % vs. 28.6 %) with a significant difference (P = 0.08). The male predominance among bacterial meningitis patients can be explained by the fact that throughout infancy and childhood, girls have higher humoral and cellular immunological responses than males [8].

Our study showed a significant difference among studied groups regarding hematocrit, which was lower in the case group (P=0.005), and as regard platelet count and CRP; they were significantly greater in the case group, respectively (P=0.004 and P<0.001), which is inconsistent with **Alkholi *et al.*** [9] who found that studied cases with bacterial meningitis had higher serum levels of CRP and WBC in comparison to controls with viral meningitis with a significant difference (P<0.001).

In this study, we found that procalcitonin level was higher among patients with bacterial meningitis than controls but with no significant difference (P=0.236). This was consistent with **Makoo *et al.*** [10] who revealed no discernible variation in procalcitonin levels among studied patients with bacterial and viral meningitis, which can be explained by that bacterial infections may have low procalcitonin level particularly in early stages of illness.

Muenchhoff and Goulder [8] evaluated the usefulness of serum procalcitonin in distinguishing between aseptic and bacterial meningitis. The research compared serum PCT in fourteen studied cases with bacterial meningitis to serum PCT in sixty-four individuals with aseptic meningitis and found that serum PCT levels of less than 0.15 ng/mL had eighty percent specificity for bacterial meningitis diagnosis.

In contrast to our results, **Chaudhary and Chaudhary** [11] found serum PCT was significantly higher in children with bacterial meningitis than non-bacterial meningitis. The mean PCT level in bacterial meningitis was (2.86 ± 2.45 ng/ml) while that in non-bacterial meningitis was (0.38 ± 0.27 ng/ml) ($p < 0.001$). This result was similar to that of **Umran and Radhi** [12] who found a significant increase in PCT levels among patients with bacterial meningitis in comparison to patients with viral meningitis.

We found in our study a significant positive correlation between CRP and serum procalcitonin (P=0.048), which is supported by **Ibrahim *et al.*** [13] who found a positive correlation between serums PCT and CRP in bacterial positive and negative meningitis (p <0.05). They also found that high PCT levels are strongly correlated with disease severity, and existence of shock or multiple organ dysfunction syndrome makes PCT more useful than serum CRP as diagnostic and prognostic marker. Also, **Tschaikowsky *et al.*** [16] observed a positive relationship between CRP and serum procalcitonin among patients with bacterial meningities(p <0.05).

In this study, we discovered a significant variation among studied groups regarding the outcome, no patients within the control group had died or developed neurological deficit versus deaths in 36.7% within the case group and 30% developed neurological deficits, which was in line with **Gudina *et al.*** [14] who found that 30.8% of patients with bacterial meningitis had an unfavorable neurological outcome and a higher fatality rate was observed among patients with bacterial meningitis in comparison to controls. Also, **Sunwoo *et al.*** [15] found that bacterial meningitis patients were significantly associated with unfavorable neurological outcomes and a higher mortality rate in comparison to viral meningitis patients at 3 months follow-up after the infection (p <0.05).

In this study we demonstrated that there was a statistically significant relation between outcome and serum procalcitonin, in which high serum procalcitonin levels were associated with poor outcome (P=0.041). This agrees with the result of **Park *et al.*** [17] who found that high values of serum PCT (>7.26 ng/mL) were a significant predictor for death in patients with acute bacterial meningitis. Similarly, a previous study by **Schwarz *et al.*** [18] reported that persistent elevation of serum PCT levels, 48 hours after treatment was associated with poor clinical outcomes. Also, **Mohammed *et al.*** [19] found a significant difference in PCT levels when comparing cases with good versus unfavorable outcomes.

CONCLUSION

The PCT level did not present greater accuracy in differentiating bacterial from viral meningitis in comparison to the CRP level, which showed high accuracy in differentiating bacterial meningitis from viral ones, therefore its quantification is recommended in all patients with suspected infectious meningitis. Serum procalcitonin (S-PCT) had an important role in predicting the outcome of bacterial meningitis but this should be confirmed by larger and more comprehensive studies.

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