Original article

Soluble Triggering Receptor Expressed on Myeloid Cells-1 as a marker to differentiate septic from aseptic meningitis in children: comparison with procalcitonin and C-reactive protein

Background: *Differentiating between septic and aseptic meningitis remains a challenge. Procalcitonin (PCT) was suggested by many researchers as a sensitive marker for early diagnosis of septic meningitis but with varying discriminative power. Triggering receptor expressed on myeloid cells-1 (TREM-1), a neutrophil and monocyte receptor, is up-regulated during infection with potential role during sepsis.* ***Objectives:*** *The aim of this study was to evaluate the diagnostic accuracy of soluble TREM-1 in comparison to PCT and C-reactive protein (CRP) in early diagnosis of septic meningitis and its usefulness to distinguish between septic and aseptic meningitis in children.* ***Study design:*** *Fifty-one children aged 2 to 162 months identified as possible cases of meningitis were included in this case control study. Beside Gram staining, cultures of blood and cerebrospinal fluid (CSF) and latex agglutination test of CSF, CRP, serum PCT and soluble TREM-1 (sTREM-1) measurement was done on admission, and after 48-72 hours of treatment.* ***Results:*** *Septic meningitis was diagnosed in 16 (44%) of the studied cases. Although patients with septic meningitis had a significant increase in serum sTREM-1 and PCT levels at the time of admission (median, 25.2 ng/ml and 79.1ng/ml, respectively) in comparison with patients with aseptic meningitis (4.6 ng/ml and 0.7 ng/ml, respectively) and control group (4.1 ng/ml and 0.3 ng/ml, respectively) (p <0.0001), sTREM-1 showed significantly higher sensitivity (93.7%) and specificity (94.3%) in the early prediction of sepsis with an area under the Receiver Operator Characteristic (ROC) curve (95% CI) of 0.94 (0.84 - 0.99) at a cutoff value of 12.4 ng/ml. Moreover, sTREM-1 but not PCT or CRP concentration was significantly lower (P=0.007) at admission in patients with poor outcome than in those with good prognosis.* ***Conclusions:*** *Both serum PCT and sTREM-1 are valuable in early distinguishing septic from aseptic meningitis in children but with markedly higher diagnostic discriminatory power for sTREM-1. Moreover, sTREM-1 has a significant value in predicting the prognosis of cases with septic meningitis.*

Keywords: Soluble Triggering Receptor Expressed on Myeloid Cells-1 – Procalcitonin- C-Reactive Protein - Septic meningitis.

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INTRODUCTION

Acute meningitis in children is mainly aseptic and does not require specific treatment[1]. On the other hand, the mortality and disabling neurological sequelae from septic meningitis among children are significant making early differentiation between aseptic and septic meningitis cases a must[2,3]. As early warning signs and symptoms are often non-specific, and the routine examination of cerebrospinal fluid (CSF) and blood is sometimes misleading[4,5], a rapid and reliable test that accurately predicts sepsis is needed. It would open up an opportunity to initiate antibiotic treatment early and identify children at highest risk of poor outcome especially in developing countries in whom second line antibiotics therapy might be targeted[3,4, 6].

Various diagnostic markers have been suggested to facilitate such aims. These markers include the routine C-reactive protein (CRP)[7], the powerful and massively studied procalcitonin (PCT)[2,8-10] as well as the newly proposed, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)[11,12]. CRP, a molecular mass of 120 kDa with a gene location between 1q21 and 1q23, is an important component of innate defense system

against infections[13]. It recognizes the phosphocholine on the surface of many bacteria, activates the classical complement pathway and facilitates phagocytosis by neutrophils. Due to the lack of its specificity, it is used as an additional marker with more conventional parameters such as number of leukocytes in CSF, blood count and protein level to help the clinician make a differential diagnosis[14-16].

PCT, the calcitonin precursor propeptide, is a 13 kDa protein that is synthesized in C-cells of the thyroid gland and secreted from leukocytes of the peripheral blood[17]. Its gene is located on the short arm of chromosome 11 (11p15.4)[16]. The secretion of PCT was found to increase up to several thousand-fold in the presence of bacterial sepsis but remains normal or slightly increases in viral infections and inflammatory reactions that are not infectious[18,19]. In contrast to CRP levels which rise between 12 and 18 hours after bacterial challenge[20], PCT concentration increases in the serum within two to three hours of the beginning of infection, peaking by 6–12 hours, and returning to normal concentrations within two days[21]. PCT is stable in plasma with plasma half-life of approximately 22 hours. It is also extremely stable in vitro, unlike most cytokines, which makes it not only a promising new marker for early and sensitive identification of infected patients, but also for titration of response to the treatment[10,19,22-25]. Still, PCT is less than a perfect marker as it can be increased in non-infectious conditions, and may remain low in infections[26]. Additionally, interpretation of the studies dealing with PCT is complicated by variation in the choice of the abnormal cut of value, and by the diverse age range and nature of the study populations[22].

On the other hand, TREM-1 is a trans-membrane glycoprotein cell-surface receptor of immunoglobulin superfamily which acts in cooperation with toll-like receptors (TLRs) under the control of nuclear factor-κβ (NF-κβ)[27].The expression of TREM-1 is up-regulated on phagocytic cells in the presence of bacteria and fungi, triggering the secretion of the pro-inflammatory cytokines that amplify the host response to these microbial agents[28,29]. TREM-1 is shed from the membrane of activated phagocytes and is present in a soluble form, sTREM-1, in body fluids. As data demonstrated that expression of membrane-bound TREM-1 on neutrophils and monocytes/ macrophages is strongly altered during sepsis, as is the release of its soluble form with 6 hours peaking, it was highlighted that this protein may be useful in the diagnosis of sepsis[27, 30].

The aim of this study was to evaluate the diagnostic and prognostic utility of these markers in septic meningitis and their usefulness in early distinguishing between septic and aseptic meningitis in Egyptian children presenting with signs and symptoms suggestive of meningitis.

METHODS
Patients:
Fifty-one children (age range: 2-162 months, mean ± SD: 59.1± 31.4, male vs female 29: 22) identified as possible cases of meningitis who were admitted to Pediatric Department in Tanta University Hospital between June 2008 to August 2010, were included in this case control prospective study. Patients were excluded if they had received parenteral antibiotics in the past seven days or had co-existing morbidities. Informed signed consent was obtained from parents for their children to participate in the study.

Meningitis was defined as being septic or aseptic according to WHO case definition criteria[31]: children presenting with clinical symptoms of meningitis; fever, headache, stiff neck, bulging fontanelle or mental status changes, CSF with an elevated protein (>100 mg/dl), decreased glucose (<40 mg/dl) or leukocytosis (white blood cell (WBC) count >100/mm^3) with at least 80% neutrophils and identification of bacteria directly by Gram stain smears or cultures from blood or CSF or indirectly by latex agglutination test of CSF. Aseptic meningitis was defined as the presence of acute onset of meningitis symptoms, WBC of >5/mm^3 of which >50% were mononuclear/lymphocyte cells with the absence of any bacterial meningitis laboratory criteria.

Accordingly, 36 cases had a final diagnosis of meningitis. They were 22 males, and 14 females, aged 2 to 162 months (mean±SD: 59.7±32.3). Septic meningitis was diagnosed in 16 patients (mean age±SD: 56.6±30.6, males vs females 9:7) and aseptic meningitis in 20 cases (mean age ± SD: 58.3±31.4, males vs females 9:11).

Control group:
The control group (15 cases) was defined by absence of inflammatory cells in CSF (WBC <5/mm^3) and sterile bacteriologic findings in afebrile children with positive meningeal signs. They were 7 males and 8 females with a mean age of 55.4±31.8 (range 4-151 months).

Protocol:
Upon admission, the following items were recorded for each enrolled patient: age, sex, vital signs as well as clinical symptoms and signs. Blood samples were withdrawn for routine laboratory

investigations including erythrocyte sedimentation rate (ESR) by Westerngren method, CRP using a nephelometric assay (Dade-Behring, France), WBC counts and blood culture, in addition to PCT and sTREM-1 measurement. CSF samples were examined for protein, glucose, total and differential WBC. After centrifugation the deposits were subjected to Gram stained examination and microbiological culture. Latex agglutination tests using the Wellcogen bacterial antigen kit (Abbott Murex Biotech, UK) were performed on CSF samples suggestive of meningitis, but with negative staining. After 48-72 hours of treatment, CRP, serum PCT and sTREM-1 levels were re-assessed for patients with meningitis only. Prognosis of cases was followed over a period of 7 days.

Methods:

Microbiological Cultures:

Blood and CSF samples were collected under complete aseptic conditions according to the standardized techniques[32]. Microbiological cultivation and identification with detection of antibiogram of isolated organisms were carried out in Microbiology and Immunology Department, Tanta Faculty of Medicine, Egypt. Blood samples (3-5 ml) were cultured in blood culture bottles (Egyptian diagnostic media [EDM], Egypt), incubated at 37°C and examined each 48h for turbidity. Subculture from blood culture flasks and culture of CSF deposits were made on sheep blood agar, incubated both aerobically and anaerobically at 37°C for 48 -72h and any growth was identified according to the standard microbiological protocol. The performance of antibiotic sensitivity test and the results were guided by the Clinical and Laboratory Standards Institute (CLSI) guidelines[33].

Serum analysis:

Procalcitonin assay:

PCT was measured in duplicate by a specific immunoluminometric assay (LUMItest®, Brahms Diagnostica GmbH, Germany). Luminescence was measured automatically on a Berilux Analyzer 250 (Behring Diagnostics, Germany). The detection limit was 0.08 ng/ml, and the intra-assay coefficients of variation at low and high concentrations were 12% and 5%, respectively. The normal serum procalitonin with this is <0.5 ng/ml.

Soluble Triggering Receptor Expressed on Myeloid cells-1 ELISA:

sTREM-1 was measured by commercially available human ELISA kit according to the manufacturer's instructions (Quantikine Human TREM-1 Immunoassay, R&D Systems, USA) using mouse monoclonal antibody specific for human TREM-1. The mean minimum detectable dose was 13.8 pg/ml with intra-assay variability of 3-7% and inter-assay variability of 6-8% when measuring in duplicates.

Statistical analysis

It was performed by using SPSS for Windows, version 9. Data were expressed as range and mean± standard deviation (SD)/median or numbers and percentages. Receiver operator characteristic (ROC) plots were performed using MedCalc software to determine the areas under the curve (AUCs) with 95% confidence intervals for the three markers to predict septic meningitis. Differences between groups in continuous variables were tested for significance with the Mann-Whitney test while univariate analysis was done by Fisher's exact test. For all statistical tests done, *P* value < 0.05 was considered significant.

RESULTS

Out of 51 children enrolled in this study, 36 (70.6%) had a final diagnosis of meningitis. They were 22 (61%) males, and 14 (39%) females, aged 2 to 162 months (mean ± SD: 59.7±32.3). Septic meningitis was diagnosed in 16 (44%, mean age±SD: 56.6±30.6, males vs females 9:7) and aseptic meningitis in 20 (56%, mean age±SD: 58.3±31.4, males vs females 9:11). Fifteen children (7 males and 8 females) with age range of 4-151 months (mean±SD 55.4±31.8) were proven to be non-meningitis cases and served as controls. Eleven of those children were diagnosed with epilepsy and 4 with relapse-free acute lymphoblastic leukemia. There was no difference between the studied groups with respect to age or sex (P>0.05).

The common manifestations at the time of diagnosis in the meningitis groups were fever, headache, nausea or vomiting and convulsions while in the control group were convulsions and nausea or vomiting (figure 1). In the 44% infected cases of bacteriological origin, 7 (43.7%) were found to be *Neisseria meningitidis*, 5 (31.3%) *Haemophilus influenzae*, 3 (18.7%) *Streptococcus pneumoniae* and 1 (6.3%) *Liesteria*. The CSF Gram staining, CSF culture, CSF soluble antigens and blood culture results showed sensitivity of 68.8% (11/16), 81.3% (13/16), 31.3% (5/16) and 25% (4/16), respectively.
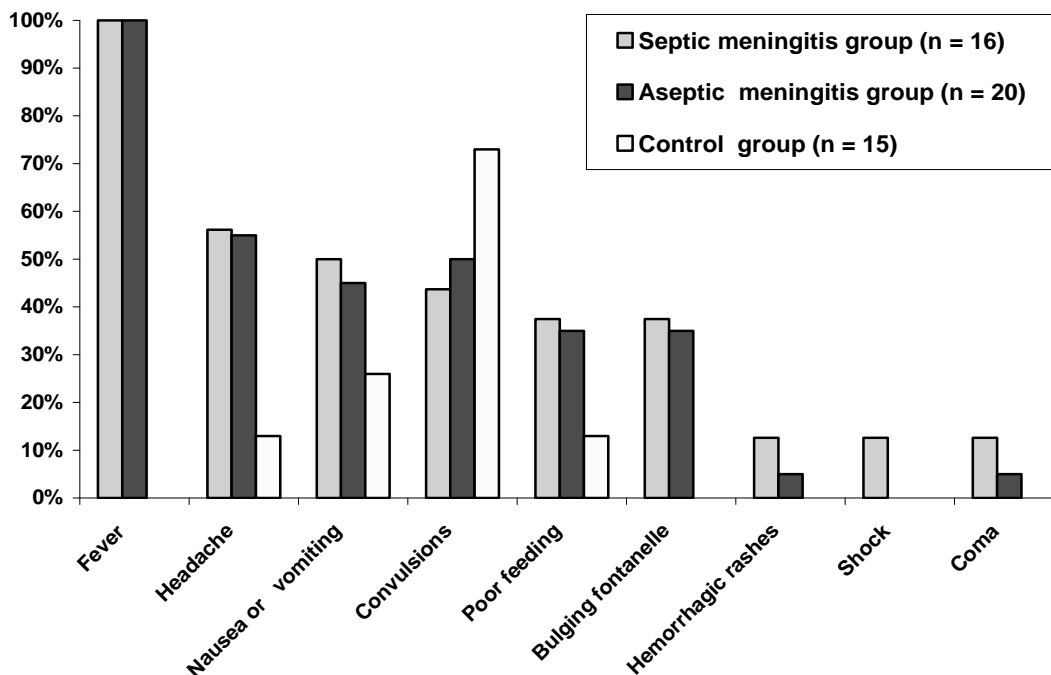
Fig. 1: Clinical manifestations of the studied groups

Routine blood parameters differed significantly between patients with bacterial and aseptic meningitis (table 1). WBC counts and ESR levels were significantly higher in patients with septic meningitis than patients with aseptic meningitis and controls at the time of diagnosis ($P<0.001$). On the other hand, patients with aseptic meningitis had significantly higher WBC ($P <0.05$) than in control group, but with no significant difference regarding ESR ($P >0.05$).

CSF laboratory findings are shown in table 1. Patients with septic meningitis had significantly increased CSF protein, WBC count and neutrophil percentage in comparison with both aseptic meningitis and control groups ($P <0.0001$), while CSF glucose level was significantly lower in patients with septic meningitis than in patients with aseptic meningitis ($P=0.001$) and controls ($P =0.01$).

Baseline CRP, PCT and sTREM-1 levels were significantly higher in patients with septic meningitis than in patients with aseptic meningitis and control groups with P values at or less than 0.0001. On the other hand, patients with aseptic meningitis had significantly higher CRP value ($P=0.014$) than in control group, but with no significant difference regarding serum PCT and sTREM-1 levels ($P >0.05$) (table 2). After 48h, there was no significant difference in CRP ($P=0.09$), PCT ($P=0.28$) and sTREM-1 ($P=0.23$) levels compared to their levels at admission in aseptic meningitis group. On the contrary, CRP ($P=0.02$), PCT ($P=0.04$) and sTREM-1 ($P=0.03$) values were significantly reduced 48‑72h after admission compared to their baseline values in the septic meningitis group. The level of these markers were significantly higher in septic than non septic group after 48-72h ($P=0.003$, PCT: $P=0.0001$ and sTREM-1: $P<0.0001$) (figure 2).

Table 1. Comparison of the routine blood and CSF laboratory findings in the studied groups.

Parameters	Septic meningitis (n = 16)	Aseptic meningitis (n = 20)	Control (n = 15)	T-test	*p* value
Blood					
WBC (x10⁹/mm³)	17.3 ± 7.9 (7.2-22.6)	10.7 ± 4.3 (4.4-12.8)	6.3 ± 1.7 (2.5-8.1)	3.7[a]	0.0007
				5.3[b]	<0.0001
				3.2[c]	0.003
ESR(mm/h)	29.5 ± 16.3 (12.7-45.9)	19.1 ± 10.6 (8.8-28.4)	17.9 ± 5.2 (7.2-20.6)	0.2[a]	0.8
				2.3[b]	0.03
				2.3[c]	0.03
Cerebrospinal fluid (CSF)					
Protein (mg/dl)	155.3 ± 85.2 (113-261)	39.5±20.4 (26-56)	31.5±10.5 (20-43)	1.4[a]	0.2
				5.6[b]	<0.0001
				5.6[c]	<0.0001
Glucose (mg/dl)	23.7±17.5 (12-36)	44.2±16.4 (38-76)	45.8±28.5 (34-69)	0.2[a]	0.8
				2.6[b]	0.01
				3.6[c]	0.001
WBC (/mm³)	348±159 (119-530)	158±89 (36-132)	0.0±0.0	6.8[a]	<0.0001
				8.5[b]	<0.0001
				4.5[c]	<0.0001
Neutrophil (%)	80.1±6.3 (72.3-89.4)	17.8±4.7 (11.2-19.8)	0.0±0.0	14.6[a]	<0.0001
				49.2[b]	<0.0001
				33.9[c]	<0.0001

Values are mean ± SD (range); WBC: white blood cell count; ESR: erythrocyte sedimentation rate.
[a] Control group vs aseptic meningitis group;
[b] Control group vs septic meningitis group;
[c] aseptic meningitis group vs septic meningitis group
*$P<0.05$ is significant using Mann-Whitney test.

Table 2. Comparison of CRP, PCT and sTREM serum levels on admission among the studied groups

	Septic meningitis group (n = 16)	Aseptic meningitis group (n = 20)	Control group (n = 15)	Z	*p* value
CRP (mg/l)	103 (19-362)	21 (6-96)	9 (2-41)	-2.47[a]	0.014*
				-3.95[b]	0.0001*
				-3.65[c]	0.0001*
PCT (ng/ml)	79.1 (0.3-425.5)	0.7 (0.1-5.3)	0.3 (0.1-1.02)	-1.85[a]	0.064
				-4.21[b]	<0.0001*
				-4.06[c]	<0.0001*
sTREM-1 (ng/ml)	25.2 (3.2-64.9)	4.6 (0.1-17.8)	4.1 (0.1-15.3)	-0.07[a]	0.94
				-4.25[b]	<0.0001*
				-4.46[c]	<0.0001*

Values are median (range); CRP: C-reactive protein, PCT: Procalcitonin, sTREM-1: soluble triggering receptor expressed on myeloid cells-1.
[a] Control group vs aseptic meningitis group;
[b] Control group vs septic meningitis group;
[c] aseptic meningitis group vs septic meningitis group
*P<0.05 is significant using Mann-Whitney test.

Table 3. Sensitivity, specificity and positive and negative predictive values (%) of baseline CRP, PCT and sTREM values for septic meningitis.

Marker	Cutoff value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
CRP	>29 mg/l	81.2 (54.4- 96)	80 (63.1-91.6)	68.4 (62-71)	90.6 (88-95)
PCT	>3.3 ng/ml	87.5 (61.7-98.4)	88.6 (73.3-96.8)	82.4 (77-85)	94.1 (89-95)
sTREM-1	>12.4 ng/ml	93.7 (69.8 - 99.8)	94.3 (80.8 - 99.3)	88.2 (84-93)	97.1 (91-99)

Optimum diagnostic cut off values derived from the ROC curve. CRP, C-reactive protein; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; CI, confidence interval; AUC of ROC, area under curve of the receiver operating characteristics curves; PPV, positive predictive value; NPV, negative predictive value.
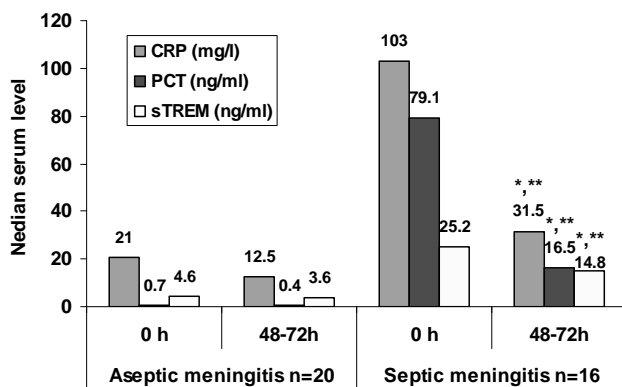

* P is significant (<0.05) on comparing baseline and 48-72h level of each marker
** P is significant (<0.05) on comparing 48-72h level of the markers in septic and aseptic groups

Figure 2. Comparison of CRP, PCT and sTREM-1 serum levels at admission and after 48-72h. *CRP: C-reactive protein, PCT: Procalcitonin, sTREM-1: soluble triggering receptor expressed on myeloid cells-1.*

Median plasma sTREM-1 levels at admission were 4.6 ng/ml in aseptic meningitis cases and 25.2 ng/ml in septic meningitis cases. As shown in figure 3, plasma sTREM-1 levels yielded the highest discriminative value with area under the ROC curve being 0.94 (95% CI, 0.84 - 0.99). Although, this value did not show statistical significance when compared with that of PCT (0.92, 95% CI, 0.81 - 0.98; P>0.05), the difference became significantly evident for CRP (0.87, 95% CI, 0.75 - 0.95; P=0.03).

The sensitivity, specificity, and positive and negative predictive values of CRP, PCT and sTREM-1 are shown in table 3. At a cutoff of 12.4 ng/ml, sTREM-1 yielded a sensitivity of 93.7% and a specificity of 94.3% in differentiating patients with septic from those with aseptic meningitis. Of notice, the use of combination of sTREM-1 and PCT did not affect the sensitivity but increased the specificity to 97.1% with no improvement when CRP values were added.
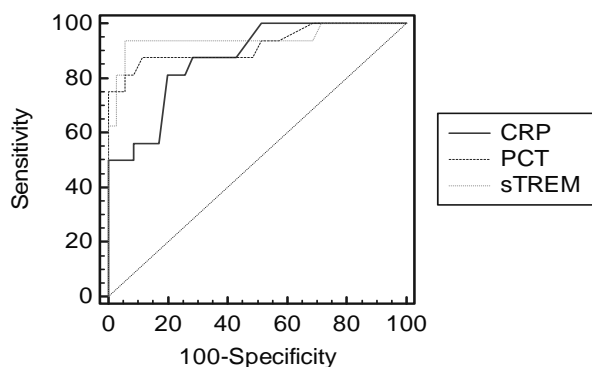
Figure 3. Receiver operating characteristic (ROC) curves comparing baseline C-reactive protein (CRP), procalcitonin (PCT) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) for prediction of septic meningitis. The area under the curve (95% CI) was 0.87 (0.75 - 0.95) for CRP, 0.92 (0.81 - 0.98) for PCT and 0.94 (0.84 - 0.99) for sTREM-1.

The use of these parameters as prognostic markers was also evaluated. Five (31.3%) of 16 patients with septic meningitis showed poor outcome and died. Serum sTREM-1 level [median 14.8 ng/ml (3.2-21.3) vs 43.3 ng/ml (11.8-64.9), Z=2.7; P=0.007) but not PCT [median 52.7 ng/ml (0.3-351.3) vs 81.2 ng/ml (3.2-425.5), Z=1.13, P=0.26) or CRP levels [median 64 ng/ml (28-241) vs 142 ng/ml (19-362), Z=0.17, P=0.87) concentrations were significantly lower at admission in patients with poor than in those with adequate outcome with plateau level (median 16.1 ng/ml) after 48-72hs. Noticeably, the AUCs of ROC for CRP, PCT and sTREM-1 in predicting septic meningitis poor outcome were 0.53 (95% CI 0.42–0.61), 0.62 (95% CI 0.58–0.71) and 0.87 (95% CI 0.78–0.92), respectively.

DISCUSSION

Establishing the diagnosis of septic meningitis is a cornerstone in preventing not only unnecessary antibiotic and hospital admission but also serious neurological damage or even death. Hence, management strategies have been oriented towards the use of combination of clinical and laboratory information such as CBC, neutrophil count, and CRP concentration with up to 40% possibility of overlap between septic and aseptic meningitis cases[34]. Intensive researches have been carried out to find new and rapid diagnostic methods for differential diagnosis of bacterial and viral meningitis with varying degrees of success and only few of them reported in children[35]. Therefore, this work aimed to evaluate the use of sTREM in comparison to PCT and CRP for early diagnosis and differentiation between septic and aseptic meningitis cases in Egyptian children with evaluation of their role as prognostic markers.

Septic meningitis patients had significantly higher baseline PCT levels compared to aseptic meningitis cases and controls. This increase in PCT levels in bacterial meningitis may be due to extracellular multiplication of the causative encapsulated bacteria resulting in a strong systemic inflammatory response[36,37].

A variety of studies and reviews have shown the superior diagnostic accuracy of PCT as compared to other parameters for the diagnosis of sepsis, independent of the origin of infection[12,24-26]. However, on reviewing the results of different studies carried out to evaluate PCT discriminative ability in detecting septic meningitis, controversy was clear with sensitivity and specificity ranging from 57% to 100%, and from 50% to 100%, respectively[8,12,22,36,38-41]. While Hatherill et al.[22] suggested that PCT measurement has the potential to shorten the duration of both antibiotic treatment and hospital stay for their febrile children, Hoffmann et al.,[41] found that PCT serum concentrations did not differ between those suffering from bacterial meningitis and those with viral meningitis. Possible explanation for these divergent results could be the different laboratory methods used or the selected group of patients studied.

Admission PCT level showed non significant higher discriminative power than CRP in distinguishing septic from aseptic meningitis in our study. However, there was significant elevation in CRP but not in PCT baseline values in aseptic meningitis cases compared to controls which points to better specificity of PCT as suggested by Hatherill et al.[22] and clarified by Carrol et al.[42] as

differential kinetics of PCT and CRP. Our data are consistent with results of previous single-center studies among pediatric[10,12,19,43,44] and adult[8,40] patients. On the other hand, Dubos et al.[2] concluded that although PCT level is probably the best biological predictor currently available to distinguish between bacterial and aseptic meningitis, it cannot be used alone with 100% sensitivity and good specificity regardless of the threshold chosen.

PCT cutoff value that gave the best sensitivity and specificity in differentiating septic from aseptic meningitis in this work was 3.3 ng/ml. Interpretation of the literature dealing with PCT is complicated by variation in the choice of the abnormal cutoff value[22]. Consistent with our finding, Carrol et al.[42] pointed out that PCT value of 2 ng/ml might help distinguish severe life threatening bacterial infection from localized and viral disease in febrile children. Similar conclusion was obtained by Marc et al.[45] but with a low threshold value of <0.5 ng/ml. On the other hand Hatherill et al.[22] estimated that an admission PCT value of 20 ng/ml might be used to distinguish children with septic meningitis with high sensitivity and specificity. Christ-Crain and Muller[26] notified that clinically apparent infections are a sequel of complex and variable interactions between host immune response, microbes and their toxins thus, it is far too complex to be reduced to a single cutoff of any specific surrogate marker.

In this study, serum sTREM was evaluated as a new maker in meningitis cases. It was also higher in septic meningitis cases but not in aseptic meningitis cases compared with controls. This may be due to bacterial loads which trigger systemic inflammation and increase sTREM-1 levels[46]. Moreover, serum sTREM cut off value of 12.4 ng/ml showed significantly higher sensitivity and specificity that reached more than 90% with best discriminative power when compared to PCT and CRP. This specificity may be based on the fact that LPS is the main inducer of TREM-1 expression and supported by the finding that stimulation of human monocytes with proinflammatory cytokines induced very small sTREM-1 release unless LPS was added as a costimulus[29, 44, 45].

Previous clinical studies have shown that sTREM-1 levels could differentiate critically ill patients with severe sepsis from those without[11,27, 7]. However, little is known about the role of sTREM in meningitis. In striking contrast to our result, Carrol et al.,[12] in their comparative study of the accuracy of five serum markers in diagnosis of serious bacterial infections (SBI) including

meningitis concluded that PCT but not sTREM-1 was the best diagnostic and prognostic marker in SBI while PCT and CD163 were superior to other markers in predicting fatal outcome. However, measuring sTREM-1 in CSF, unlike PCT, was concluded to be upregulated in patients with bacterial meningitis with high specificity; its presence could potentially assist clinicians in the diagnosis of bacterial meningitis[48,49]. It is to be noted that our results are more practical because measurement of serum sTREM is much less invasive, can be observed regularly in blood samples and can be measured together with routine variables.

The present work also attempted to evaluate the role of the studied parameters in monitoring the response to treatment. Three days after treatment of our septic meningitis cases, the decline of PCT and sTREM values was significant compared to baseline levels although it did not return to normal values as in the control group. This finding suggests that despite treatment, both parameters continue to be high for 48/72 hours and can be used for diagnosis for at least 48 h.[19]. It also clarifies the inflammatory role of these markers as mediators responsible for persistence of inflammatory manifestations[2]. Since these mediators decrease with successful treatment, they may be helpful for follow-up[19].

The prognostic importance of the studied markers was determined in this work. Unlike PCT and CRP, sTREM-1 concentration was significantly low at admission in patients with poor outcome with nearly stationary value after 48-72hs. Additionally, the low baseline sTREM-1 level was found to be the best prognostic factor of the poor outcome with the highest AUC value, denoting that elevated baseline sTREM-1 level could be a valuable predictive marker. Our results support the experimental findings which indicated that the more the release of sTREM-1, the more favorable is the outcome[50]. Human findings showed that significant levels of sTREM-1 were released in the serum of critically ill patients with sepsis, the highest levels being observed in patients who survived[47].

The mechanism by which sTREM modulate the immune response is still unclear. However, the role of TREM-1 as an amplifier of a wide range of proinflammatory response was confirmed[28,44]. Moreover, blockade of TREM-1 signaling using synthetic peptide that mimic part of the extracellular domain of TREM-1 in a mouse model was found to reduce NF-κB activation and cytokine production, thus protecting septic animals from hyper-responsiveness and death[51]. Along similar

lines, elevated sTREM-1 concentrations observed in septic patients may block TREM-1 signaling[11,40]. Bouchon et al.[28] suggested that the increase of sTREM could prevent the engagement of membrane TREM-1 and act as a decoy receptor, as in the TNF- system. Gibot et al.[47] added that sTREM-1 may act as a negative feedback regulator of the inflammatory response making it a promising, therapeutic target.

In conclusion, both serum PCT and sTREM are valuable in the early distinguishing of septic from aseptic meningitis in children but with markedly higher diagnostic discriminatory power for sTREM-1. Moreover, this study pointed to the significant value of sTREM-1in determining septic meningitis prognosis. However, it remains to be confirmed in larger populations.

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