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Clinical study

The value of serum procalcitonin in acute meningitis in children

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ABSTRACT

Early diagnosis and initial therapy are important to reduce the complications of bacterial meningitis. We aimed to evaluate the diagnostic value of serum procalcitonin in children with acute meningitis. We included 40 children (4 months–14 years) suspected to have acute meningitis in our study. Based on the clinical scenario, physical examination and complete analysis of cerebrospinal fluid, patients were assigned into two groups: bacterial meningitis group (24 patients) and aseptic meningitis group (16 patients). Twenty-five apparently healthy children of matched age and sex served as a control group. Procalcitonin, C-reactive protein, and leukocyte count were measured initially at the time of admission and again after 72 h. Initially, patients with bacterial meningitis showed statistically significant higher values of serum procalcitonin than both patients with aseptic meningitis and the control groups ($p < 0.001$). After 72 h of treatment, patients of bacterial meningitis group showed statistically significant lower values of serum procalcitonin than their initial values ($P < 0.05$). The cutoff point of procalcitonin needed for early diagnosis of bacterial meningitis was >10 ng/ml at the time of admission. However, values of procalcitonin >2 ng/ml had 100% sensitivity. Whereas, the specificity, negative predictive value and positive predictive value of procalcitonin were 63%, 100%, and 67% respectively. Serum Procalcitonin can be used as an early diagnostic marker of acute bacterial meningitis and its differentiation from aseptic meningitis. In acute bacterial meningitis, it can be used to follow the response to antibiotic therapy.

1. Introduction

Acute meningitis in children is a serious condition and carries a high rate of complications. Early identification and proper management are the cornerstones to reduce these complications [1]. Acute meningitis in children remains a diagnostic dilemma as routine laboratory investigations are considered poor discriminator between bacterial and aseptic cases. The identification of an accurate biomarker for the discrimination between bacterial and aseptic causes of acute meningitis would be of great diagnostic value [2]. Positive culture of cerebrospinal fluid (CSF) for the bacterial agent, Gram staining, or presence of specific bacterial antigens in the CSF is considered the gold standard test for the diagnosis of bacterial meningitis in children. They have a high specificity but the sensitivity is poor [3]. In addition, blood culture results require few days to become available. There are other markers in the serum such as CRP and leukocyte count that act as diagnostic aids in cases of bacterial meningitis but they have also poor sensitivity and specificity [3]. That is why we are still in need of more sensitive and specific markers for the diagnosis of bacterial meningitis in children. CRP (C-reactive protein) showed a delayed increase during bacterial infection and can also be elevated in viral infections, limiting its ability to differentiate between bacterial and aseptic meningitis [4]. The detection of bacterial growth in cultures of CSF needs a minimum of 2 days. Also, viral cultures need 3–8 days [5]. The detection of viral antigens by Polymerase chain reaction (PCR), although helpful in diagnosis, is not a simple technique and is not available everywhere. The discovery of novel, rapid and precise diagnostic markers for the early diagnosis of bacterial meningitis had been extensively studied in the last few years [6]. One of these novel biomarkers is procalcitonin (PCT) which considered the best diagnostic marker for diagnosis of bacterial meningitis in children. PCT is undetectable in normal states with a marked increase in bacterial infections [7]. Inflammatory mediators like fibronectin, interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-a) have also been proposed as potential biomarkers, but have not widely accepted for clinical practice [8]. The rise of PCT in bacterial infection is marked and dramatic while in viral infections it remained normal or showed a slight increment [9,10]. PCT rises

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earlier than other markers which increase briefly and intermittently in severe bacterial infections such as CRP [7,11]. Waiting for the results of bacterial cultures and Gram staining leads treating physicians to unnecessary use of antibiotics with possible side effects, higher costs, and increased risk of infection [12]. We aimed to evaluate the diagnostic value of serum PCT in children with acute meningitis.

2. Patients and methods

This prospective study was conducted on 40 children with clinical suspicion of acute meningitis. They were 23 males and 17 females. Their ages ranged from 4 months to 14 years. All patients were admitted to the pediatric department, Al Hada and Taif military hospitals, Saudi Arabia. Twenty-five apparently healthy children of matched age and sex were chosen and served as a control group. The study was conducted in the period from June 2015 to December 2016 after informed consent. Ethical clearance was obtained for the research study. The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments. Exclusion criteria were:

- Local or systemic infection.
- Thyroid or parathyroid disorders.

The diagnosis of acute meningitis was based on history taking, thorough clinical examination, Laboratory investigations included; complete cell count, CRP and complete analysis of CSF with gram staining, cultures, and identification of bacterial antigens in the CSF. According to the results of CSF cytochemical analysis, bacterial cultures, and bacterial antigen, patients were divided into two groups:

Bacterial meningitis group: included 24 patients with acute bacterial meningitis. They were 14 males and 10 females. Their ages ranged from 4 months to 14 years with a mean age of 7.6 ± 4.2 years.

The evidence of bacterial meningitis in CSF has increased protein >2 g/l, decreased glucose ratio <0.4, leukocyte count >1500 × 106/l and predominance of polymorph nuclear leukocyte. Also, identification of bacterial agents in Gram stain and/or bacterial culture help in diagnosis.

Aseptic meningitis group: included 16 patients with aseptic meningitis. They were 9 males and 7 females. Their ages ranged from 4 months to 12 years with a mean age of 5.8 ± 1.6 years. Patients included in this group showed no bacteria on gram stain or bacterial culture of CSF, reduced protein level, increased glucose ratio >0.5 and predominance of lymphocyte in CSF analysis. Also, identification of viral agents in viral culture and positive polymerase chain reactions (PCR) help in diagnosis [1].

- Complete blood count using Cell-Dyne 1600 System (Abbott Park Laboratories, Ilinois, USA).
- C-reactive protein using enzymatic heterogeneous sandwich immunoassay method.
- Measurement of serum PCT levels:

A venous blood sample of 2 ml was withdrawn from each patient at the time of diagnosis and at 72 h of treatment as well as from all controls at the time of enrollment. Serum levels of PCT increase within 3 h, peaked within 6–12 h and then decline slowly [11]. Where possible, samples for the analysis of PCT should be separated and analyzed within 4 h of the withdrawal of blood sample.

Samples can be stored at 2–8 °C for up to 24 h; and samples should be frozen at −20 °C within 48 h. A single freeze–thaw cycle may lead to a reduction in recovery of up to 8%. All samples should be centrifuged prior to analysis to ensure they are free of fibrin or other particulate matter [13]. Measurement of serum levels of PCT was done using the immuno-luminometric method in the Analyzer luminometer equipment using the Lumitest kit (Lumitest PCT kits BRAHMS Diagnostica, Berlin, Germany) according to the manufactureŕs instructions. The detection limit of our assay was 0.10 ng/mL. The assay uses two monoclonal antibodies (antigen-specific) that bind to PCT at 2 different sites. Luminescence was measured automatically by an analyzer (Behring Diagnostics, Marburg, Germany). Calculation of the results was done using the provided software. The inter-assay and intra-assay variability were <6% and 7%, respectively. At room temperature, PCT stability can be regularly checked and measured in blood samples. Serum PCT results can be obtained in 2 h and 20 μl of the serum is needed for the assay [1].

Blood samples for CBC, CRP, liver and kidney function tests, and measurement of serum PCT were taken from all controls at the time of enrollment.

All patients were admitted to the pediatric ward and treated according to the standard protocol with follow up until discharge. Blood samples for CBC, CRP, liver and kidney function tests, and PCT were taken from all patients at the time of diagnosis and at 72 h of treatment.

Lumbar puncture was done for each patient under complete aseptic technique using sterile needles and the CSF sample was analyzed for glucose, protein, and cytology.

All clinical data at the time of diagnosis, and at follow-up of cases were monitored and recorded.

Statistical analysis: Data was carried out using the SPSS 10.0 software. Qualitative data are presented as numbers and percentages, whereas quantitative data are presented as means ± standard deviation with ranges. Student *t*-test was used to test differences in means while Mann-Whitney *U* test was used for non-parametric statistics. The P value <0.05 was considered significant. Sensitivity, specificity, positive, and negative predictive values derived from the receiver operating characteristic (ROC) curve, and area under the ROC curve were determined for the estimated variables.

3. Results

The study was conducted on 40 children with clinical suspicion of acute meningitis, 24 children were diagnosed with bacterial meningitis and 16 children were diagnosed with aseptic meningitis with no evidence of bacterial causes of meningitis. The most frequent clinical manifestations at the time of diagnosis were fever, vomiting, and convulsions respectively (Table 1). Bacterial

Table 1
Clinical characteristics of studied groups.

	Bacterial meningitis group (n = 24)	Aseptic meningitis group (n = 16)	Control group (n = 25)
Age (months) (mean ± SD)	70.4 ± 20	80.6 ± 28	72 ± 25
Sex			
Male No. (%)	14(58.3)	11 (68.7)	15 (60)
Female No. (%)	10(41.7)	5 (31.3)	10 (40)
Clinical presentation			–
Fever No. (%)	24 (100)	11 (68.7)	
Vomiting No. (%)	10 (41.7)	10 (62.5)	
Seizures No. (%)	9 (37.5)	6 (37.5)	
Headache No. (%)	8 (33.3)	9 (56.2)	
Signs of meningeal irritation No. (%)	6 (25)	3 (18.7)	
Photophobia No. (%)	3 (12.5)	1 (6.25)	
Skin rash No. (%)	2 (8.33)	0 (0)	–

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