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## Diagnostic value of serum creatine kinase-BB for acute meningitis in adults

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### ABSTRACT

**Objective:** To find out an easy and feasible test instead of cerebrospinal fluid analysis for the diagnosis of acute meningitis.

**Methods:** This cross-sectional study was conducted in 2013 in Ahvaz, a city located in the Southwest Iran including 75 patients with clinical diagnosis of fever, headache, vomiting and neck stiffness suspected to have acute meningitis based on cerebrospinal fluid analysis. In the beginning, the patients were divided into two categories as acute meningitis, and non-acute meningitis. Then, 5 L of blood was taken from each patient to determine serum creatine kinase isoenzyme-BB by using ELISA method. After that, the related data including demographics, clinical and laboratory results were analyzed by SPSS software version 16 using *Chi-square* test for qualitative variables and student's *t*-test for quantitative variables.

**Results:** Among the total 75 patients, 37 (49.3%) were males and 38 (50.7%) were females including 45 patients (60%) with acute meningitis and 30 patients (40%) without acute meningitis. On the other hand, CK-BB serum levels in acute meningitis and non-acute meningitis patients were  $18.23 \pm 7.56$  and  $2.67 \pm 1.62$ , respectively, so significant difference was found between acute meningitis group and non-acute meningitis group ( $P < 0.0001$ ).

**Conclusions:** Serum creatine kinase isoenzyme-BB test is a useful test to differentiate acute meningitis from non-acute meningitis among suspected cases of meningitis disease, so measuring the CK-BB serum level in Iran's health system with an expanded health setting especially in remote areas will be useful and helpful in prompt diagnosis and treatment of the acute meningitis.

## 1. Introduction

Meningitis is an infectious disease affecting the brain membrane and spinal cord[1]. Globally, bacterial meningitis is the most severe type of meningitis, mainly caused by a triad of species *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*[2]. While viral meningitis is usually a self-limiting disease with good prognosis, and bacterial meningitis is potentially fatal, requiring urgent medical assistance and management with antibiotics treatment[3]. Various estimates of the burden of bacterial meningitis have been proposed to date, but they have mainly focused on mortality[4], long-term sequels[5], or etiology-specific morbidity and mortality[6-8].

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The study protocol was performed according to the the ethical standards of the responsible committee on human experimentation and Helsinki declaration and approved by Ethics Committee of Ahvaz Medical College (No.: 1392.334). Informed written consent was obtained from all patients for being included in the study.

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The annual number of invasive disease cases worldwide is estimated to be at least 1.2 million, with 135 000 deaths related to invasive meningococcal disease[9,10]. In countries with high endemicity, the disease burden places an immense strain on the public health system. The risks of long-term disabling sequelae, including cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus and loss of limbs due to tissue necrosis, are the highest in low-income countries, where the burden of bacterial meningitis is the greatest[11]. Despite all the efforts and progress of health, meningitis remains one of the major causes of morbidity and mortality worldwide, especially in developing countries[12,13]. Therefore, acute meningitis due to high mortality and post-meningitis nervous system sequels is a major public health problem worldwide[9]. Although fever, headache, vomiting and neck stiffness are the important clinical pictures of acute meningitis, diagnosis of acute meningitis should be confirmed by cerebrospinal fluid (CSF) analysis[11,12]. Performing lumbar puncture for CSF is mandatory in all patients who are suspected to have meningitis. Lumbar puncture is an invasive and annoying procedure[12], so many children and adults' patients turned it away due to the fear of its consequences. Therefore, non-invasive diagnostic procedures such as blood-based laboratory tests are desired for involved clinicians. Creatine kinases (CK) are expressed in the brain and spinal cord of adult human, which illustrates that CK/

phosphocreatine system plays an important role in the central nervous system. Most human tissues express two CK isoenzymes, namely, muscle-type CK-MM and brain-type CK-BB. Impairment of this system results in a deterioration in energy metabolism, which is represented by many neurologic and age-related diseases[14]. Several studies have been reported that brain damages such as stroke, peripheral neuropathy, spinal cord injury and even meningitis are associated with the increased levels of CK-BB in serum and CSF[14-21]. In contrast, measurements of the CSF CK-BB and serum CK-BB levels are both easy and noninvasive tests[12]. Therefore, measurement of serum CK-BB level can be replaced by CSF analysis. Acute meningitis is relatively a common disease in Khuzestan Province and many adults as well as children are admitted in emergency rooms in hospitals. Fear of lumbar puncture performance in a lot of patients with acute meningitis in the region of study resulted in delayed diagnosis or misdiagnosis, so complications and mortality of the disease are increased. This study was conducted on patients with signs and symptoms of meningeal irritation (e.g. fever, headache, vomiting and neck stiffness) who were referred to Razi Hospital in Ahvaz. The aim of the present study was to find an easy and feasible test in meningitis diagnosis instead of CSF analysis.

## 2. Materials and methods

This cross-sectional study was conducted in 2013 in Razi hospital in Ahvaz, the capital city of Khuzestan Province including patients with meningeal irritation symptoms (e.g. fever, headache, vomiting and neck stiffness) who were admitted to the infectious diseases wards of the hospital.

The sample size based on previous studies was 75 patients, but due to the possibility of withdrawal of patients from lumbar puncture, the primary sample size was 100 patients. The sampling was ended when the number of samples reached 75 patients who were enrolled in the study.

For the diagnoses of acute meningitis, all the patients were undergone lumbar puncture and CSF analyses. According to the normal CSF analysis *i.e.* proteins less than 50 mg/dL, CSF less than 0.6 glucose/serum glucose, WBC less than 5 cell/ $\mu$ L and lactate less than 3.5 mEq/L[22], patients were divided into two categories: patients with abnormal CSF suspected to meningitis were acute meningitis group, and patients with normal CSF analysis were non-acute meningitis group. Then, 5 mL of blood was taken from each patient to determine serum CK-BB and human CK-BB. ELISA kit (Glory science co., Ltd., USA) was applied to determine CK-BB.

First, CK-BB serum levels of patients with acute meningitis were compared to serum CK-BB levels of non-acute meningitis patients. Then the related data containing demographics, clinical and laboratory results including changes in the components of CSF, cell blood count, differential count, erythrocyte sedimentation rate, C-reactive protein, serum CK-BB, date of admission, date of discharge, duration of hospitalization and changes in symptoms were recorded in a pre-designed questionnaire for each patient. Afterwards, the data were analyzed in SPSS software version 16 using *Chi*-square test for qualitative variables and student's *t*-test for quantitative variables with the first type of error 0.05 ( $\alpha = 0.05$ ), and accuracy of 0.1 ( $d = 0.1$ ) was calculated.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. Approval for the study was granted by the Ethics Committee of Ahwaz Medical College (No.: 1392.334). Informed consent was obtained from all patients for being included in the study.

## 3. Results

Of the total 75 studied patients, 37 (49.3%) were males and 38

(50.7%) were females out of which 45 patients (60%) had acute meningitis and 30 patients (40%) had non-acute meningitis. The acute meningitis group included 20 (44.4%) males and 25 (55.6%) females whereas in the non-acute meningitis group, 17 patients (56.6%) were men and 13 (43.4%) were women. CK-BB serum levels in acute meningitis and non-acute meningitis patients were  $18.23 \pm 7.56$  and  $2.67 \pm 1.62$ , respectively, so significant difference was found between acute meningitis and non-acute meningitis groups ( $P < 0.0001$ ). Mean CK-BB serum levels in male and female of acute meningitis and non-acute meningitis groups were  $(19.46 \pm 6.34, 17.25 \pm 8.41)$  and  $(2.3 \pm 1.83), 2.8 \pm 1.04$ , respectively, so that significant differences were not found between men and women in acute meningitis group ( $P = 0.33$ ) and non-acute meningitis group ( $P = 0.38$ ). According to the manufacturer's brochure of CK-BB kit, normal values of CK-BB serum level for men was 0.67–2.50 ng/dL and for women was 1.00–7.67 ng/dL. Given the above normal values, of 45 acute meningitis patients, 44 (97.7%) had levels higher than noted CK-BB (true positive) and one patient (2.3%) had normal level (false negative), respectively. Of 30 non-acute meningitis patients, 18 (60%) had normal levels of CK-BB (true negative) and 12 patients (40%) had higher levels than the specified values (false positive), respectively. As shown in Table 1, this test has a high sensitivity of 97.78%.

**Table 1**

Sensitivity, specificity, positive predictive value and negative predictive value of serum CK-BB test to differentiate the two studied groups.

	Percent	95% Confidence interval
Sensitivity	97.78	99.19–99.63
Specificity	60.00	40.61–77.32
Positive predictive value	78.57	65.56–88.40
Negative predictive value	94.78	73.90–99.12

## 4. Discussion

Differentiating acute meningitis from meningeal irritation in patients with meningitis has always been an important challenge in the management of acute meningitis.

This study revealed that serum CK-BB test is a useful and helpful test for differentiating acute meningitis from non-acute meningitis among suspected cases of meningitis. Increased CK-BB serum levels in our patients with acute meningitis comply with other studies reported an increased amount of CK and CK-isoenzymes in patients with brain damage disorders. CK-BB level above normal limit in serum or CSF in the absence of other diseases is associated with an increase in these enzymes and can be considered as an evidence of central nervous system involvement[14-21]. Of all patients suspected to have meningitis, only 60% had true acute meningitis among which 97.7% had high levels of serum CK-BB.

In the study of Kaste *et al.*, of 23 patients with meningitis, 13 (56.52%) patients had positive results of serum CK-BB[9]. Dubo *et al.*[17] in a study reported that of seven patients with meningitis, only 2 (28.57%) CK-BB tests of patients were positive. The reason for a more proportion of patients having high CK-BB serum levels in our study compared to the above mentioned studies is not clear, but the accuracy of the clinical diagnosis, type of CK-BB kit used, the accuracy of testing, the test sensitivity and perhaps racial differences may be some reasons for such differences.

In the present study, quantitative CK-BB ELISA kit was used whereas previous ones had measured CK-BB by qualitative methods. The current study indicated that the serum high level of CK-BB in acute meningitis cases is not associated with age and sex factors. Unfortunately, the same articles were not found enabling us to compare our results with regard to age and sex, but it can be discussed that increased levels of these enzymes in serum or CSF occurring after brain injury are not influenced by age- and sex-related factors such as female/male hormone, life style and old age.

This study indicated that the measurement of serum CK-BB with a high sensitivity of about 98% is a really valuable test in the diagnosis of acute meningitis. It was also found that this test with a negative predictive value of about 95% is a useful test for differentiating patients without meningitis from meningitis cases. In previous studies, the sensitivity and specificity of CK-BB test had not been determined. Among all previous studies [20,21,23,24], only in Tamimi's study the sensitivity and specificity of CK-CSF level was determined [15]. Only in Tamimi's study, they were determined [15]. It was also reported that CSF-CK with a high specificity rate was a useful and helpful test to rule out bacterial meningitis. Also, the present CK-BB study is more specific than the total CK tested, while in Tamimi's study, the total CK was measured. However, Tamimi and colleagues reported that the sensitivity and specificity of the total CK CSF test alone for diagnosing the bacterial meningitis were 33% and 91%, respectively [15]. They also reported that the negative predictive values for bacterial and aseptic meningitis were 98% and 94%, respectively [15]. Although our findings are not comparable with Tamimi's study because of different design (differentiating bacterial from aseptic versus vs. differentiating acute meningitis from meningeal irritation), methodology (total CK vs. BB -isoenzyme) and samples of the test (CSF vs. serum). Due to the lack of similar studies (in Pub Med and Scopus search), we were forced for this comparison.

It is noteworthy that the serum studies in limited recourse areas are greatly useful and helpful in the early diagnosis and rapid treatment of patients with meningitis. In fact, rapid initiation of treatment for bacterial meningitis results in lower mortality and serious permanent complications. Moreover, distinguishing the cases other than acute meningitis not requiring antibiotic therapy is an important factor in reducing the indiscriminate use of antibiotics which is a major public health issue in the country due to the impact on bacterial resistance.

Limitations of the study: due to irrational use of antibiotics in the region of the study, the diagnosis of acute meningitis by microbial culture is difficult. Therefore, the same as the other developing countries, the diagnosis was based on CSF analysis without bacteriological evidence. This study with its content is unique in its kind in the country and even in the East Mediterranean region, but the section of discussion lacks comparison to such similar studies.

In conclusion, measuring CK-BB serum level in health system of Iran with an expanded health setting especially in remote area may be useful and helpful in prompt diagnosis and treatment of acute meningitis.

### Conflict of interest statement

We declare that we have no conflict of interest.

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