American Journal of Infectious Diseases 6 (4): 93-97, 2010
ISSN 1553-6203

Diagnostic Value of Serum and Cerebrospinal Fluid Procalcitonin in Differentiation Bacterial from Aseptic Meningitis

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Abstract: Problem statement: Acute bacterial meningitis is one of the most important causes of medical emergency diseases, which can cause high mortality and morbidity rates. Early antibiotic therapy is life saving in bacterial meningitis. One of the most common etiologies of acute meningitis is viral. Differentiation between bacterial and Aseptic meningitis is mandatory, which leads to avoid useless administration of antibiotics. Various diagnostic tests are available for diagnosis of acute bacterial meningitis; one of these tests is serum procalcitonin. **Approach:** This survey is a descriptive cross-sectional study. During a 2 year period 50 patients over 13 years old who were admitted to Sina and Emam Reza hospitals of Tabriz University of Medical Sciences with presumptive diagnosis of acute meningitis were selected. Serum and Cerebrospinal Fluid (CSF) procalcitonin of the patients were measured by semiquantative chromatographic PCT-Q Assay. Statistical data's of the patients were analyzed by SPSS 15. **Results:** 38% of the patients had acute bacterial and 62% aseptic meningitis, on the basis of positive clinical and lab tests. 0.5ng mL^{-1} of serum pricalcitonin was cut off point, which correlated to sensitivity of 100%, positive predictive value of 82.6%, specificity of 87.09% and negative predictive value of 100%. CSF procalcitonin cut off of 0.5ng mL^{-1} had sensitivity of 100% specificity of 84.21%, positive predictive value of 88.88% and negative predictive value of 90.62%. **Conclusion:** Serum procalcitonin cut off of 0.5 ng mL^{-1} has sensitivity and negative predictive value of 100%. This test can be a valuable measure in screening and differentiation of bacterial from aseptic meningitis.

Key words: Bacterial meningitis, aseptic meningitis, serum procalcitonin, Serum and Cerebrospinal Fluid (CSF), morbidity rates, Lactate Dehydrogenase (LDH), Statistical data's, etiological factors, C- Reactive Protein (CRP), diagnosing acute, lymphocyte meningitis

INTRODUCTION

Acute neurologic system infection is considered an important disease in medicine and early diagnosis, correct decision making and early treatment are vital. Clinical syndromes of neurologic system infection include the following: acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscesses, subdural empyema and infectious thrombophlebitis. All these syndromes start with nonspecific signs such as fever and headache and mostly the signs are similar. The important keys in the primary approach toward these syndromes are the urgent differential diagnosis of these syndromes and their etiological factors and appropriate treatment (Roos and Tyler, 2008).

Acute meningitis has different causes including viruses which are the most common cause.

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Differentiating acute bacterial meningitis from viral meningitis is sometimes baffling for physicians due to the similarities in clinical signs and sometimes even in the results of cerebrospinal fluid analysis, i.e., clinical and laboratory signs cannot always identify the etiological factor. On the other hand early diagnosis of bacterial meningitis and early antibiotic therapy are essentials (Roos and Tyler, 2008; Tunkle *et al*., 2010).

To reach this goal different biochemical markers such as lactate, C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH) and cerebrospinal fluid ferritin are used some of which have low specificity. Procalcitonin is one of the markers having a higher specificity compared to the others (Roos and Tyler, 2008; Tunkle *et al*., 2010; Kifoed *et al*., 2007; Chris *et al*., 2005; Viallon *et al*., 1999; Juan *et al*., 2009). Procalcitonin is a protein composed of 116 amino acids with molecular weight of 12793 Daltons and it is precursor of the hormone calcitonin. Most calcitonin precursors including procalcitonin are found in the serum of normal people with plasma levels less than 0.1 ng mL^{-1} (Chris *et al*., 2005). In bacterial infections including bacterial meningitis, depending on the severity of infection, serum procalcitonin increases (Roos and Tyler, 2008; Tunkle *et al*., 2010).

Considering the importance of distinguishing acute bacterial meningitis from aseptic meningitis, starting antibiotic therapy in bacterial cases and avoiding unnecessary antibiotic therapy in aseptic cases this study was designed to evaluate the diagnostic value of serum and cerebrospinal fluid procalcitonin levels in differentiating acute bacterial meningitis from aseptic meningitis.

MATERIALS AND METHODS

In a descriptive-analytic study carried out on the patients older than 13 years old hospitalized in the infections wards of Imam Reza and Sina Hospitals from 2008-2009 with the primary diagnosis of meningitis, diagnostic value of serum and cerebrospinal fluid procalcitonin levels in differentiating acute bacterial meningitis from aseptic meningitis were evaluated.

All patients with suspicious signs of meningitis were performed lumbar puncture through third and fourth lumbar vertebral spaces in decubitus position after specialist having the site disinfected using alcohol and iodine to assess cerebrospinal fluid regarding cellular analysis, sugar, protein, LDH, staining and culture.

Serum and cerebrospinal fluid procalcitonin were measured by infectious disease specialist using semiquantitative immunochromatographic method and bedside kits (B.R.A.H.M.S PCT-R HENNIGSDORE/GERMANY). This test was performed using six drops of blood or cerebrospinal fluid of the patients on the special sites of the kits and after 30 min the results were compared with kit control strap and the results were divided into following four groups: less than 0.59 ng mL^{-1}, more than or equal to 10 ng mL^{-1} and more than 10 ng mL^{-1}.

The criteria of diagnosing bacterial meningitis were: positive culture of cerebrospinal fluid or positive staining of cerebrospinal fluid or white blood cells count more than 100 with a dominance of polymorphonuclear cells and sugar less than 40 mg dL^{-1} and protein more than 50 mg dL^{-1}.

Obtained data were analyzed using descriptive statistical approaches, chi-square test and unilateral variance analysis and also diagnostic value of the tests was analyzed using SPSS 15 statistical software. $p<0.05$ was considered statistically significant.

RESULTS

This study was carried out on 100 patients, 28 males (56%) and 72 females (44%).

The mean age of the studied patients was 46.32±22.008 years. 19 people (38%) were diagnosed with acute bacterial meningitis (group 1) and 31 people (62%) with aseptic meningitis (group 2)

Regarding meningeal irritation signs, neck stiffness was present in 12 people (63.2%) in group 1 and five people (61.1%) in group 2 ($p<0.001$). Regarding other clinical signs (fever, headache and consciousness disturbance) no significant difference was observed between two groups ($p>0.05$).

The results obtained from the evaluation of Cerebrospinal Fluid (CSF) parameters and serum are presented in Table 1 and 2. Gram staining of the cerebrospinal fluid was positive in eight patients (16%) who were all in acute bacterial meningitis group (42.1%) ($p<0.001$). Serum and CSF procalcitonin levels of the patients in both groups are presented in Table 3.

Table 1: Evaluation CSF parameter between two groups

	Group		
	A	B	P_Value
WBC of CSF	6304.73±4835.71	189.37±83.61	<0.001
Protein of CSF (ng mL^{-1})	172.15±119.12	44.32±33.21	<0.001
Glucose	34.10	84.74	<0.001
LDH	595.97±395.84	130.52±59.16	0.040

Table 2: Evaluation Serum parameter between two groups

	Group		
	A	B	P_value
WBC	29184.21 ± 6169.93	12312.90 ± 6674.66	<0.001
ESR	56.52 ± 26.97	32.83 ± 27.76	0.005

Table 3: Evaluation level of procalcitonin at CSF and serum between two groups

	CSF			Serum		
	Group			Group		
	A	B	P_value	A	B	P_value
<0.5 ng mL^{-1}	3(15.8%)	29(93.5%)	<0.001	0	27(87.1%)	<0.001
0.5-2 ng mL^{-1}	6(31.6%)	1(3.25%)		3(15.8%)	2(6.5%)	
2-10 ng mL^{-1}	7(36.8%)	1(3.25%)		9(47.4%)	2(6.5%)	
>10ng mL^{-1}	3(15.8%)	0		7(36.8%)	0	

Table 4: comparing Sensitivity, specificity, positive and negative predictive values of parameters

	Sensitivity	Specificity	PPV	NPV
Protein concentration of serum	100.00	87.09	82.60	100.00
Protein concentration of CSF	84.21	93.45	88.88	90.62
Gram smear of CSF	42.10	100.00	100.00	73.80
CSF culture	42.10	100.00	100.00	73.80
Blood culture	21.05	96.77	80.00	66.66
CRP	68.42	48.38	44.82	71.42
Leukocyte	84.73	64.51	62.06	95.23
ESR	94.73	48.38	52.94	93.75
LDH of CSF	100.00	54.83	57.57	100.00

Blood culture was positive in five patients (10%) from who four people belonged to group 1(21.1%) and one person belonged to group 2 (3.02%) (p = 0.062). There was no significant difference between two groups regarding CRP (p = 1).

Considering the cutoff level of Procalcitonin 0.5 ng mL^{-1} for differentiating acute bacterial meningitis from aseptic meningitis, serum procalcitonin possessed sensitivity of 100%, specificity of 87.9%, positive predictive value of 82.6% and negative predictive value of 100%. Sensitivity and specificity of CSF procalcitonin in diagnosing acute bacterial meningitis were 84.21 and 93.54% respectively. Positive and negative predictive values were 88.88% and 90.62% respectively. Sensitivity, specificity, positive and negative predictive values were evaluated and compared (Table 4).

DISCUSSION

At the time being there is no clinical or laboratory method which can solely prove or disprove the diagnosis of acute bacterial or viral meningitis instantly and accurately. The present study was carried out to evaluate the predictive value of serum and cerebrospinal fluid procalcitonin in the patients with uncertain acute bacterial meningitis diagnosis. Further studies revealed that 38% of the patients had acute bacterial meningitis and 62% had aseptic meningitis and both groups were homogeneous regarding age and gender variables. Several statistically significant differences were observed between two groups regarding meningeal irritation, mean WBC, protein, sugar, LDH and Procalcitonin and CSF smear and culture (Roos and Tyler, 2008; Tunkle *et al*., 2010; Kifoed *et al*., 2007; Chris *et al*., 2005; Viallon *et al*., 1999; Taskin *et al*., 2004).

There was a statistically significant difference between two groups regarding the mean peripheral blood WBC and ESR whereas no significant difference was observed regarding blood culture and CRP. The difference between two groups was statistically significant regarding serum procalcitonin which was in accordance with the similar studies (Gendrel *et al*., 1997; Viallon *et al*., 2005; Kepa *et al*., 2005; Jereb *et al*., 2001; Ray *et al*., 2007).

Ray *et al*. (2007) in a prospective study carried out on 151 adult patients with meningitis signs concluded that laboratory test results of cerebrospinal fluid are of moderate importance in differentiating bacterial meningitis from the nonbacterial meningitis in cases which Gram staining for bacteria is negative in the beginning however serum procalcitonin is an excellent predictive factor for differentiating acute bacterial meningitis which is similar to our study, the only difference is that in Ray's study CSF procalcitonin levels have not been studied.

Kepa *et al*. (2005) in another study carried out on 17 adult patients with suppurative bacterial meningoencephalitis and 16 patients with lymphocyte meningitis measured the levels of serum and CSF procalcitonin and concluded that using serum procalcitonin is a key element in differentiating bacterial meningitis from viral meningitis. CSF procalcitonin however is less helpful in the diagnosis of acute meningitis compared to serum procalcitonin, this finding is similar to the findings of our study.

In the present study, serum procalcitonin with a cut off of 0.5 ng mL^{-1} 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^{-1} 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.

Jereb *et al*. (2001) in a prospective study carried out on 45 adult patients evaluated the predictive value of serum and CSF procalcitonin levels in diagnosing bacterial meningitis. In their study 20 patients had bacterial meningitis and 25 patients suffered Tick born encephalitis. They concluded that serum procalcitonin more than 0.5 ng mL^{-1} had a 100% positive predictive value for bacterial meningitis and hypothesized that serum and CSF procalcitonin in the levels more than 0.5 ng mL^{-1} was a reliable indicator in diagnosing bacterial infection of central nervous system with Maximal positive predictive value and high negative predictive value which were in accordance with the results obtained from our study.

Viallon *et al*. (1999) in another study carried out on 105 adult patients with bacterial meningitis concluded that serum procalcitonin levels more than 0.2 ng mL^{-1} had a sensitivity and specificity of 100% in diagnosing acute bacterial meningitis. A sensitivity and specificity of serum procalcitonin $\geq$0.5 ng mL^{-1} in our study were 100 and 87.0% prospectively.

On the contrary, in another study carried out by Hoffman *et al*., 2001 they reported a low sensitivity of serum procalcitonin in diagnosing bacterial meningitis in adults especially with unknown etiologic and or hospital acquired reasons which is different from the results obtained from our study. This difference may be due to the fact that all the patients in our study had community acquired meningitis, hospital sources were negative, unusual organisms were rarely responsible for acute bacterial meningitis and very few patients were positive for unusual organisms.

CONCLUSION

Considering the 100% sensitivity and negative predictive value of serum procalcitonin, this test can be used as a powerful and desired screening test in differentiating bacterial meningitis from aseptic meningitis. In addition, thanks to its rapid procedure within 30 min, availability and not needing high-tech equipment serum procalcitonin in association with other parameters seems to be of great help in decision-making for starting antibiotic therapy in the uncertain cases of acute bacterial meningitis and it can also prevent uncontrolled and unnecessary use of antibiotics in aseptic meningitis.

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