Cerebrospinal fluid ferritin in children with viral and bacterial meningitis

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Accepted: 15 May 2013

ABSTRACT

Despite the fact that the prognosis of bacterial meningitis has been improved by the influence of antibiotics, this disease is still one of the significant causes of morbidity and mortality in children. Rapid differentiation between bacterial and aseptic meningitis, and the need for immediate antibiotic treatment in the former, is crucial in the prognosis of these patients. Ferritin is one of the most sensitive biochemical markers investigated in cerebrospinal fluid (CSF) for the early diagnosis of bacterial meningitis. The present study aims to evaluate the diagnostic capability of CSF ferritin in differentiating bacterial and viral meningitis in the paediatric setting. A cross-sectional study was carried out in the referral Children's Medical Center Hospital, Tehran, during 2008 and 2009. According to the inclusion criteria, CSF samples from 42 patients with suspected meningitis were obtained and divided into two meningitis groups, bacterial (n=18) and viral (n=24). Ferritin and other routine determinants (i.e., leucocytes, protein and glucose) were compared between the two groups. Ferritin concentration in the bacterial meningitis group was 106.39±86.96 ng/dL, which was considerably higher than in the viral meningitis group (10.17±14.09, P<0.001). Mean CSF protein concentration and cell count were significantly higher in the bacterial meningitis group and showed a positive correlation with CSF ferritin. In conclusion, this study suggests that CSF ferritin concentration is an accurate test for the early differentiation of bacterial and aseptic meningitis; however, further investigation on a larger cohort of patients is required to confirm this finding.

KEY WORDS: Cerebrospinal fluid.
Child. Ferritins.
Meningitis, bacterial.
Meningitis, viral.

Introduction

Central nervous system (CNS) infection is one of the most common causes of morbidity and mortality particularly in children. Meningitis can be categorised by the cause of the disease, either virus or bacterium. Viral meningitis, usually referred to as aseptic meningitis, is much more common and is characterised by the less-acute onset of signs and symptoms. In contrast, bacterial meningitis is a more serious cause of morbidity and mortality around the world, predominantly in developing countries.[1,2]

Early initiation of appropriate antibiotic therapy is one of the most important prognostic factors in bacterial CNS infections. Accurate and rapid diagnosis of acute bacterial meningitis is essential because the outcome depends on prompt diagnosis. It is sometimes difficult, however, to differentiate between bacterial and viral meningitis, as many laboratory tests do not offer adequate specificity for early diagnosis.[3] Elevated CSF ferritin concentration has been reported in some neurological disorders such as inflammatory and infectious processes,[4] multiple sclerosis[5] and in patients with CNS malignancy.[6]

The present study aims to evaluate the potential diagnostic value of CSF ferritin as a guide in the early discrimination between bacterial and viral meningitis.

Materials and methods

Children with presumptive bacterial meningitis admitted to the Children's Medical Center Hospital, Tehran, during 2008–2009 (n=55) were recruited for this cross-sectional study. All patients underwent lumbar puncture between the third and fourth lumbar vertebra. The puncture site was disinfected using alcohol and iodine and the procedure was undertaken by a specialist in the technique.

Diagnostic criteria of bacterial meningitis used for inclusion of cases in the study were the presence of a clinical picture compatible with a diagnosis of bacterial meningitis, with either a CSF neutrophilic pleocytosis (predominant polymorphonuclear cells), a positive CSF culture for bacterial pathogens, high protein and low sugar.[3] The CSF diagnostic criteria of viral meningitis were the presence of pleocytosis (predominant mononuclear cells), normal protein and sugar, and negative Gram staining and culture. Accordingly, patients were classified into two meningitis groups: bacterial and viral. Meningitis cases caused by *Mycobacterium tuberculosis* were not included in the study.

The CSF specimens were tested for ferritin, leucocytes, protein, glucose, culture and Gram staining. All isolates were

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Table1. Results of laboratory parameters in cerebrospinal fluid (CSF) for the two groups studied.

	Leucocytes (mm³)	PMN (%)	LYM (%)	Protein (mg/dL)	Glucose (mg/dL)	Ferritin (ng/dL)
Bacterial (Mean±SD)	1601.83±2545.92	79.11±22.67	20.89±22.67	72.78±38.41	37.39±21.14	106.39±86.96
Viral (Mean±SD)	336.17±431.67	40.96±20.92	59.04±20.92	38.04±17.79	55.54±12.05	10.17±14.09
P value	0.024	0.001	0.001	0.001	0.001	0.001

PMN: polymorphonuclear cells; LYM: lymphocytes

identified and processed according to standard techniques.[7] Measurement of CSF ferritin was performed using a direct method of enzyme immunoassay designed for human serum (Immuno-Biological Laboratories [IBL]) according to the manufacturer's instructions.

Statistical analyses between two groups were performed using SPSS17 software. Fisher's exact test and independent test were used to analyse the data. $P \leq 0.05$ was considered significant.

Results

Of the initial 55 patients, 13 showed CSF results that were not compatible with either of the two groups and were excluded from this study. Thus, a total of 42 children were studied, divided into the viral meningitis ($n=24$) and bacterial meningitis ($n=18$) groups. Mean age of patients in the viral and bacterial groups was 58/12±42/68 and 45.34±42.21, respectively ($P=0.022$). Protein and glucose level in CSF showed a statistically significant difference between the two groups (Table 1). Mean concentration of CSF ferritin in bacterial meningitis (106.39±86.96) was significantly higher than in the viral group (10.17±14.09, $P=0.001$). It showed a positive correlation with other routine CSF determinants (i.e., leucocytes, protein) and a negative correlation with glucose level.

The CSF Gram staining and culture were positive in 61% of patients with bacterial meningitis, and grew *Klebsiella* sp. ($n=1$), Gram-negative bacilli ($n=5$) and *Haemophilus influenzae* ($n=5$). Moreover, seven patients with negative culture were diagnosed as bacterial meningitis because other CSF criteria were compatible with this diagnosis.

Discussion

Bacterial meningitis is a serious infectious disease especially in children. Early discrimination between bacterial and viral meningitis is essential for adequate treatment, reducing unnecessary hospitalisation and minimising the adverse effects of empirical antibiotic treatment.[8]

The present cross-sectional study was carried out to evaluate the diagnostic capability of CSF ferritin in the early discrimination of bacterial and viral meningitis. Although clinical assessment is essential for detection of patients with suspected acute bacterial meningitis, a lumbar puncture sample of CSF for analysis is needed for accurate identification of these patients.[3]

Several biomarkers have been used in the early detection of bacterial meningitis, including lactate,[9] including lactate dehydrogenase (LDH), and C-reactive protein (CRP),[10] but they do not offer adequate specificity. In addition, cytokines such as interleukin-1β, tumour necrosis factor-α, interferon-γ and β2-microglubolin have been investigated for this purpose, but routine evaluation of these is limited.[11,12] Culture offers only low sensitivity especially in low-income countries due to limitations in bacteriological culture facilities (e.g., automated culture systems). In addition, a negative culture might be obtained because of widespread use of antibiotics prior to admission.[13]

A marker that can be measured rapidly and with appropriate specificity is ferritin.[9] Ferritin is the main intracellular iron storage protein and cannot penetrate the normal blood-brain barrier, and therefore blood concentration does not influence ferritin level in CSF.[14] Studies suggest that ferritin level is a powerful screening test to detect bacterial meningitis, and findings from the present study are in agreement with other reports that have evaluated the diagnostic value of CSF ferritin in patients with meningitis,[14,15] although others have reported that CSF ferritin is significantly higher in viral meningitis.[16]

Determination of CSF ferritin concentration is a widely available, cheap and rapid diagnostic test. In the present study a clear distinction was observed between CSF ferritin concentration in patients with bacterial meningitis and those with aseptic meningitis (i.e., significantly higher in the bacterial group), and it showed a positive correlation with leucocyte count and protein level.

In conclusion, this study suggests that CSF ferritin concentration is an accurate test for the early differentiation of bacterial and aseptic meningitis; however, larger studies are required to confirm CSF ferritin as a reliable marker for this purpose. □

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