

The Comparisons of Ferritin Level in CSF of Children with Bacterial and Viral Meningitis

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ABSTRACT: Bacterial meningitis is one of the most potentially serious infections occurring in children. This infection is associated with a high rate of acute complications and risk of long-term morbidity. The diagnosis of meningitis is confirmed by analysis of the CSF. Early and rapid therapeutic approach to patients with presumed bacterial meningitis is essential. In this cross sectional study 45 patients with the diagnostic criteria for meningitis, based on increase of WBC in CSF, as case and 118 subjects as control were assigned. Cases were classified into two groups of bacterial and viral meningitis according to CSF pleocytosis. Control group had sign and symptom of meningitis without CSF pleocytosis and the CSF culture was negative. Blood, CSF culture and measurement of ferritin level in CSF were done by radioimmunoassay method. 163 children with impression of meningitis were studied. Glucose level of CSF in control group was higher than cases and ferritin was lower than cases. In bacterial meningitis patients; protein and ferritin levels of CSF were higher than the other groups ($p < 0.01$). In patients with diagnosis of viral meningitis CSF protein level was lower than the others. A significant relationship observed between age and ferritin levels in control ($p < 0.01$) and bacterial meningitis group ($p < 0.05$), there was no correlation in those patients who had viral meningitis. Ferritin level of CSF was significantly different between cases and controls. Results of study indicate that the ferritin level is useful to differentiate bacterial meningitis from viral meningitis.

Key words: Ferritin, CSF, Meningitis, Pleocytosis, Bacterial Meningitis, Viral Meningitis

INTRODUCTIN

Bacterial meningitis is a medical emergency which is curable, but by the same token could be lethal; therefore making a diagnosis of this disease and its causes are truly crucial. CSF analysis plays an important role on diagnosis of this disease especially for unclear cases. It is vital to differentiate aseptic from bacterial cases in emergency situation due to high occurrences of viral meningitis (Kim Y et al., 2003; Monteiro et al. 2008).

Considering that the current available paraclinic methods for early diagnosis of meningitis are associated with low sensitivities, a number of biologic markers have become into account for differentiation of bacterial and viral meningitis. One of them is assessing the ferritin levels in CSF resulting in reducing the duration of hospital admission as well as avoiding useless therapeutic measures and hospital costs. Reports published regarding the measurement of the CSF ferritin level show that CSF ferritin levels more than 18 ng/ml is consistent with bacterial meningitis; meanwhile, previous antibiotic therapies have no effects on CSF ferritin (Sindic et al., 1981). Considering the role of CSF ferritin on

differentiation of bacterial and viral meningitis and the importance of early diagnosis of bacterial meningitis especially for patients who have been treated partially by antibiotics, this study was conducted which aimed for earlier diagnosis and differentiation of bacterial from aseptic (viral) meningitis by evaluation of CSF ferritin levels on patients presenting neurological findings.

METHODS AND MATERIALS

A cross-sectional study was carried out among 163 patients (118 patients as controls and 45 as cases diagnosed with bacterial and viral meningitis) in the Children's hospital in Bandar Abbas. Diagnostic criteria were fever, meningial irritation; like neck rigidity, decreased level of consciousness (drowsy to coma). For patients less than 18 months who had nonspecific signs and symptoms, the following criteria were considered: fever, lethargy, irritability or poor feeding. Patients diagnosed with bacterial or aseptic meningitis were those who had pleocytosis in their CSF to differentiate cases from control group. Between 1 to 3 months pelocytosis

defined as WBC count more than 10 per cubic millimeter and those who were older than 3 months it was considered while CSF had more than 6 WBC per cubic millimeter. The diagnostic clues of bacterial meningitis were one of the following criteria: 1. Positive culture; 2. Positive gram staining of cerebrospinal fluid; 3. Dominance of polymorphonuclear cells in CSF analysis. The diagnostic criteria of viral (aseptic) meningitis: 1. Negative CSF culture; 2. Negative CSF smears; 3. Lymphocyte pleocytosis. The diagnostic criteria for control group: 1. Patients with impression of meningitis; 2. No CSF pleocytosis; 3. Negative CSF culture; 4. Negative CSF Gram stain (Roos et al., 2008; Tunkel and Michael, 2010; Feigin and Pearlman, 2004). Blood and CSF samples were obtained for investigating biochemical, cultural and gram stain findings and CSF ferritin levels measured by radioimmunoassay method. Lumbar puncture (LP) for gathering CSF fluid was conducted and based on CSF analysis the patients were divided into three groups; control (Non Meningitis), bacterial meningitis and viral (aseptic) meningitis. The study protocol was approved by the ethics committee of Hormozgan University of medical science. All parents of participants accepted the conditions of the study and signed their informed written consent.

Data were analyzed using the statistics package for social sciences 16 (SPSS, Chicago, IL, USA).

RESULTS

163 patients suffering from serious neurological complications were assessed in this study including 92 (54.6%) males and 71 (43.6%) females. The mean age of patients was 18 months, (range was 1-121 months).

Control group (Non Meningitis): This group was composed of 118 individuals including 69 males and 49

females. The mean age of patients was 15 months. The mean CSF glucose of this group was higher than the other groups ($p < 0.05$, Table 1) and the mean CSF ferritin level was lower than the others, ranging from zero to 37 ng/ml. An increment in the levels of ferritin in CSF by increasing the age of control group was observed ($p < 0.05$).

Bacterial meningitis group: 33 patients diagnosed by bacterial meningitis were 17 males and 16 females. The mean age of patients was 26 months, with the maximum age of 72 months old. The mean CSF protein and ferritin levels were higher than the others ($p < 0.001$ and $p < 0.01$, respectively). Same as controls, it was shown that CSF ferritin level increase with age ($p < 0.01$). The ferritin concentration in CSF ranged from 0.5 to 7800 ng/ml and was significantly different from control and viral groups ($p < 0.001$).

Aseptic (Viral meningitis): Viral meningitis identified in twelve patients who had equal distribution for gender (6 males and 6 females). The mean age in this group was 21 months and maximum age of patient in this group was 82 months old. The mean concentration of CSF protein was less than the other groups (Table 1). There was no significant correlation between age and CSF ferritin level.

By using 15.6 ng/ml and 7.5 ng/ml as the cut off points for ferritin levels in CSF; three patients in control group had CSF ferritin levels higher than 15.6 ng/ml. While four patients (12%) of bacterial meningitis group had less than 15.6 ng/ml and two patients had CSF ferritin levels lower than 7.5 ng/ml. In viral meningitis group five patients (41%) had CSF ferritin higher than 7.5 ng/ml and the level was higher than 15.6 ng/ml in four patients (33%).

Table 1. Results of CSF analysis in three groups

Leukocyte (per mm ³)	Protein (mg/dl)	Glucose (mg/dl)	Ferritin (ng/ml)	Number	Group
2.7 ± 0.31	19.9 ± 35.6	20.4 ± 65.6	0.40 ± 9.08	118	Non meningitis
3428 ± 1654.5**	29.8 ± 81**	14.4 ± 48.6	1348 ± 429*	33	Bacterial meningitis
710.9 ± 271.2	13.9 ± 23	15.1 ± 54.6	35.58 ± 19.73	12	Aseptic meningitis

* $p < 0.01$ and ** $p < 0.001$ in comparison to the other groups.

DISCUSSION

Prior to the advent of antibiotics, bacterial meningitis was considered as a fatal disease. Although antibiotic therapy has dramatically improved the prognosis of patients with bacterial meningitis; bacterial meningitis is still a considerable cause of mortality and morbidity especially in children (Roos et al., 2008; Tunkel and Michael, 2010; Feigin and Pearlman, 2004). At the time being there is no clinical or laboratory diagnostic method which can solely prove or disprove bacterial meningitis instantly and accurately in patients with pleocytosis in

cerebrospinal fluid and the most methods used for diagnosing bacterial meningitis are associated with serious limitations (Takahashi et al., 1999). This study was carried out to evaluate ferritin level of cerebrospinal fluid as a guide in early differentiation of acute bacterial from aseptic meningitis in order to start antibiotic therapy as soon as possible. There is previous evidence that CSF ferritin and cytokines are important adjunct biomarkers for early diagnosis of meningitis. Cerebrospinal fluid ferritin levels can also be helpful in diagnosing incompletely

treated bacterial meningitis in which culture is negative due to the previous antibiotic therapy (Roos et al., 2008; Tunkel and Michael, 2010). In our study blood cultures were mostly negative and no significant difference was observed. Gram staining and cerebrospinal fluid culture were reported positive only in one cases of bacterial meningitis. Gram staining of cerebrospinal fluid was reported positive in 60% to 90% of the patients with bacterial meningitis (Roos et al., 2008).

This difference may be due to incorrect staining techniques and sample reading, antibiotic administration before sampling and delay in sending the samples to the laboratory.

There were significant differences in the cerebrospinal fluid analyses of three groups regarding to white blood cells count, protein, sugar and ferritin levels. These findings were similar to the results of Kim et al. (2003); Monteiro de Almeida et al. (2008); Sindic et al. (1981), and Campbell et al. (1986) studies. It was shown that CSF ferritin levels increased with age in control and in bacterial meningitis groups which was similar to the results of Kim et al. (2003). Whereas, Takahashi et al. (1999) showed that the increase in levels of CSF ferritin with age was acceptable up to the age of 1 year old.

The CSF ferritin levels of the bacterial meningitis group were significantly higher than the patients with aseptic meningitis, and the mean levels for aseptic meningitis group (19.7 ng/ml) was higher than controls, findings are similar to the results of the other studies. (Kim et al., 2003; Monteiro de Almeida et al. 2008; Sindic et al., 1981; Campbell et al., 1986; Ricardo et al., 2003; Nachman et al., 1991). Considerable increase in cerebrospinal fluid ferritin levels could be explained by two hypotheses: increase in the permeability during inflammation, and regional synthesis and release from inflammatory cells (Kim et al., 2003; Roos et al., 2008; Tunkel and Michael, 2010). In the study carried out by Kim et al. (2003) the ferritin cut off point was 15.6 ng/ml for diagnosis of bacterial meningitis which was similar to the study done by Ricardo et al. (2003) and 20 ng/ml suggested in Almeida et al. (2008). Takahashi et al. (1999) proposed 7.5 ng/ml as cut off point to differentiate bacterial from viral. In two separate studies carried out in Iran on 64 patients older than 13 years old and 135 patients younger than 14 years old, respectively; cerebrospinal fluid ferritin levels cutoff point 10 ng/ml was considered for the diagnosis of bacterial meningitis and in comparison to protein and sugar levels in cerebrospinal fluid, ferritin was more valuable in diagnosing bacterial meningitis. It was concluded that cerebrospinal fluid ferritin can be used as a rapid test in differentiating bacterial meningitis from aseptic meningitis and febrile convulsive disorder (Lac et al., 2003; Rahimy et al., 1998). Yo et al. (2003) evaluated the diagnostic power of ferritin in CSF among 203 children with

meningitis. CSF ferritin was significantly higher in group with bacterial meningitis compared to the groups with viral meningitis and no meningitis and it had a positive relation with white blood cell count and cerebrospinal fluid protein but a negative relation with cerebrospinal fluid glucose. Bayat et al. (2010) did not suggest CSF ferritin for differentiation of bacterial from aseptic meningitis because of low specificity in the test for adult group in spite of significant difference observed between the aseptic and viral meningitis patients. As the CSF ferritin in patients who had suffered from viral meningitis had a wide range from 0.5-103 ng/ml, It was concluded that ferritin cut off point 15.6 ng/ml in CSF could not be used in differentiating bacterial meningitis from aseptic meningitis. CSF ferritin level in patients had no significant correlation with CSF white blood cell counts, which was in opposition to the results of Kim et al. (2003). Sindic et al. (1981) studied cerebrospinal fluid for ferritin levels in the patients with neurologic disorders and reported low specificity of ferritin levels in CSF for cerebral infections which is in contrast to our study. Campbell et al. (1986) reported high levels of ferritin in CSF for bacterial and fungal meningitis patients.

Deisenhammer et al. (1977) also reported increase in cerebrospinal fluid ferritin levels as a nonspecific finding in HIV-positive patients with acute neurologic episodes. The most of studies aimed in older age group than our study and further studies in children would help to confirm these results. According to the results of this study and due to significant differences in cerebrospinal fluid ferritin levels among three groups it was concluded that CSF ferritin might be used for diagnosis of meningitis also for differentiating bacterial meningitis from aseptic meningitis. It is recommended that further research be undertaken in this field.

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