

EVALUATION OF CSF FERRITIN AS AN EARLY MARKER FOR DIFFERENTIATING MENINGITIS IN PEDIATRIC PATIENTS

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Background and Objectives: - Bacterial meningitis is a medical emergency with a potential for serious neurological damage or even death. Rapid diagnosis is important and henceforth critical for the early intervention by antibiotic therapy to prevent complications. Therefore the aim of the present study was to evaluate CSF ferritin levels in children with different etiologies of meningitis. **Materials and Methods:** - 65 children (1-124 months) with suspected meningitis admitted at Chacha Nehru Bal Chikitsalya hospital were included in the study. CSF sample was analyzed for glucose, protein, cell count, ferritin, gram stain and culture. **Results:** - Based on the laboratory findings the 65 children were classified into 3 groups: 21 cases had bacterial meningitis, 18 had aseptic (viral) meningitis and 26 cases as the no-meningitis group. A significant relationship was observed between age and ferritin level in the non-meningitis group ($p < 0.05$). CSF ferritin in bacterial meningitis group was 34.80 ± 11.20 ng/mL and was significantly higher than the aseptic meningitis group. Cut off value of ferritin to differentiate meningitis vs. no-meningitis group was estimated at 18.2ng/ml with a sensitivity of 94.9% and specificity of 96.2 %. However on differentiating bacterial from aseptic meningitis cutoff value was 20.3 ng/mL with a sensitivity of 98% and specificity of 33.3%. **Conclusion:** - CSF ferritin levels were found to be significantly different between the meningitis and the no-meningitis groups. However due to low specificity it may not prove useful for the early differentiation of different types of meningitis. Further studies are required on a larger sample size before we can substantiate our findings.

Keywords: - CSF ferritin, bacterial meningitis, viral meningitis, pleocytosis, antibiotic therapy.

INTRODUCTION

Meningitis is a potentially life-threatening condition. The potential for serious neurological damage or even death necessitates its prompt medical attention and evaluation. Examination of the cerebrospinal fluid (CSF) may provide critically important diagnostic information about the disease. Rapid differentiation of the bacterial and other etiology is important due to its acute complications and long term morbidity especially in children. A number of biochemical markers have been used for the early diagnosis and differentiation of bacterial and viral meningitis like lactate, C-reactive protein (CRP) and lactate dehydrogenase (LDH) which however are found to have a low specificity and

cytokines which are available only at well equipped sophisticated centres.^{1,2} Ferritin is an acute phase reactant protein with a molecular weight of 45000 Daltons. Due to its spherical structure and high molecular weight it is unable to penetrate the blood brain barrier and therefore CSF levels are independent from its blood levels.³ In a study by Sinde et al, CSF ferritin level more than 18 ng/ml was consistent with bacterial meningitis.⁴ In our country the prevalence of bacterial meningitis is high. To the best of our knowledge limited studies are available in our country which have evaluated CSF ferritin levels for the early diagnosis of meningitis. Therefore in this study we sought to evaluate the diagnostic value of cerebrospinal ferritin levels to differentiate bacterial from aseptic (viral) meningitis in children with neurological findings.

MATERIALS AND METHODS

The present pilot study was carried out at Chacha Nehru Bal Chikitsalya, New Delhi for a period of 6 months. The study population comprised of 65 patients (39 cases diagnosed with

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viral or bacterial meningitis and 26 patients as no-meningitis). Diagnostic criteria included symptoms and signs of fever, headache, meningeal irritation like neck rigidity, sensitivity to bright light and decreased level of consciousness. In infants with nonspecific signs and symptoms fever, irritability, poor feeding and lethargy were considered. Patients were divided into three groups based on their specifications of cerebrospinal fluid samples-bacterial meningitis, aseptic (viral) meningitis and no-meningitis. The diagnostic criteria of bacterial meningitis included presence of more than five leukocytes in cubic millimeter of cerebrospinal fluid with dominance of polymorphonuclear cells, low sugar and high protein in cerebrospinal fluid, positive gram staining and positive culture of cerebrospinal fluid. Diagnostic criteria for aseptic meningitis were presence of more than five leukocytes in cubic millimeter of cerebrospinal fluid with the dominance of mononuclear cells, almost normal sugar and protein in cerebrospinal fluid, negative gram staining and culture of cerebrospinal fluid. Patients with impression of meningitis but with no CSF pleocytosis, negative gram stain and negative CSF culture were not considered meningitis and were included in the no-meningitis group. Cerebrospinal fluid ferritin was measured by *chemiluminescence* assay on Access-2 Beckman Coulter analyser.

STATISTICAL ANALYSIS

Data was expressed as mean $\pm$ standard deviation values. The data between the groups was analyzed by using 1 way analysis of variance (ANOVA). A p-value of less than 0.05 was accepted as significant. Receiver Operator Characteristic (ROC) curve was generated to assess the appropriate cut off point for ferritin and desired sensitivity and specificity. All statistics were performed by using SPSS for windows 12.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 68.91 ± 21.67 months (range 1-124 months) and included 38 (59 %) males and 27 (42%) females. The patients were divided into three groups based on their CSF leukocyte count into group-1 no-meningitis; group-2 bacterial meningitis and group-3 aseptic meningitis (Table 1). No significant difference was observed between the 3 groups for consciousness state ($p = 0.43$), fever ($p = 0.59$), Kernig's sign ($p = 0.33$), Brudzinski's sign ($p = 0.20$) and convulsions ($p = 0.53$).

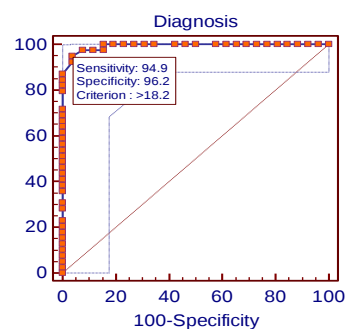
Blood cultures were positive in only 2 patients (9.52%) of bacterial meningitis. Gram staining of CSF revealed gram-positive cocci in one case (4.76%) and gram positive diplococci in 2 cases (9.52%). CSF culture was positive in only 1 patient of bacterial meningitis (4.76%). CSF ferritin levels

were found to increase with age in the no-meningitis group up to the age of 1 year ($p < 0.05$). However no such relation was observed in the bacterial or aseptic meningitis group. A significant increase in CSF ferritin levels were found in the meningitis patients as compared to the no-meningitis group (Table 1). Bacterial meningitis patients showed higher levels of CSF ferritin in comparison to aseptic (viral) meningitis. ROC curve analysis revealed cut-off point of 18.2 ng/mL for CSF ferritin with a sensitivity of 94.9 % and specificity of 96.2 % for diagnosis of meningitis. The same analysis showed cut-off value of 20.3 ng/mL with a sensitivity of 98 % and specificity of 33.3 % to discriminate bacterial from aseptic meningitis (Figure 1).

Table 1
CSF Analysis in three groups of meningitis patients

Parameter	Groups		
	No-meningitis	Bacterial meningitis	Aseptic meningitis
N	26	21	18
Leucocyte (cells/mm ³)	3.88 $\pm$ 1.56	160.81 $\pm$ 11.23*	33.56 $\pm$ 27.98
Protein (mg/dL)	38.44 $\pm$ 23.79	123.09 $\pm$ 0.46*	63.56 $\pm$ 31.22
Glucose (mg/dL)	68.02 $\pm$ 21.72	22.94 $\pm$ 17.86*	39.32 $\pm$ 19.82
Ferritin (mg/dL)	9.57 $\pm$ 5.51	34.80 $\pm$ 11.02*	29.89 $\pm$ 11.18

* $p < 0.001$ in comparison to other groups



Area under the ROC curve (AUC)	0.993
Standard Error ^a	0.00605
95% Confidence interval ^b	0.931 to 1.000
z statistic	81.460
Significance level p (Area=0.5)	<0.0001

Figure 1
ROC curve for CSF ferritin in children with meningitis

DISCUSSION

Bacterial meningitis is a potentially serious infection occurring in children with a high rate of mortality and risk of long term morbidity. Early

and rapid diagnostic and therapeutic approach for patients suspected with bacterial meningitis is therefore essential. At present no clinical or laboratory diagnostic method can solely prove or disprove bacterial meningitis instantly and accurately in patients with CSF pleocytosis and most of the methods used for its diagnosis are with major limitations.⁵

The present study was aimed to evaluate the diagnostic capability of CSF ferritin as a marker for the early differentiation of acute bacterial from aseptic (viral) meningitis in order to start antibiotic therapy as soon as possible. Patients were evaluated by their clinical and laboratory signs based on their specifications of CSF and divided into 3 groups mainly no meningitis, bacterial meningitis and aseptic (viral) meningitis. CSF ferritin levels were found to increase with age in the control group. No significant difference was observed with respect to gender in the 3 groups. No significant difference was observed regarding clinical signs like fever, altered consciousness, convulsions, Kernig's sign and Brudzinski's sign. Blood cultures were mostly negative and no significant difference was observed. Gram staining and CSF culture was reported in only a few cases of bacterial meningitis. This was in contrast to a study done by Roos et al in which 60-90 % cases were reported positive.⁶ This 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 CSF analysis of 3 groups regarding their W.B.C count, protein, sugar and ferritin levels. Our findings were similar to the results of Kim et al,⁷ Monteiro de Almeida et al⁸, Sinde et al⁴ and Campbell et al.⁹ CSF ferritin was also found to increase with age up to one year of age which was in accordance to a report by Takahashi et al⁵. CSF ferritin levels were significantly elevated in the meningitis patients in comparison to the control group. A significantly higher level of CSF ferritin was observed in the bacterial meningitis patients compared to the aseptic meningitis group. The substantial increase in the CSF ferritin level could be explained as a result of increased permeability during inflammation and regional synthesis and release from inflammatory cells.^{6,7,10} In our study ferritin cut off point was 18.2 ng/mL with a sensitivity of 94.9 % and specificity of 96.2 %. When comparing bacterial from aseptic meningitis ferritin cutoff point was 20.3 ng/ mL and had sensitivity of 98% and specificity of 33.3%. In two separate studies carried out in Iran by Lak¹¹ and Rahimimiy¹² in children more than 13 years of age cerebrospinal fluid ferritin levels with a cutoff point 10 ng/mL was considered for the diagnosis of bacterial meningitis and when compared to protein and sugar was found to be more valuable in diagnosing

bacterial meningitis. It was concluded that CSF ferritin could be used as a rapid test to differentiate bacterial meningitis from aseptic meningitis and febrile convulsive disorder. In a study by Kim et al⁷ the diagnostic power of CSF ferritin was evaluated in 203 children with meningitis. Cerebrospinal fluid ferritin was significantly higher in the group with bacterial meningitis compared to the viral meningitis and no meningitis groups and had a positive relation white blood cell count and cerebrospinal fluid protein but a negative relation with cerebrospinal fluid glucose. The cutoff degree for early diagnosis of bacterial meningitis was 15.6 ng/mL. Takahashi and his co-workers also evaluated cerebrospinal fluid ferritin along with $\beta 2$ microglobuline in patients with meningitis caused by different etiologies. Cutoff point degree of ferritin was 7.5 μ g/L in five children with bacterial meningitis which was further confirmed by positive culture with a sensitivity of 100% and specificity of 78%.⁵ They concluded that the serial measurements of CSF ferritin were valuable in evaluating response to antibiotic therapy in bacterial meningitis. However their results were applicable on patients older than six months. Katnik et al¹³ carried out a study on 47 adults and children with bacterial meningitis confirmed by culture. They reported cerebrospinal fluid ferritin cutoff point 18ng/mL with a positive predictive value of 94.1% and negative predictive value of 100%. In the study by Milman et al¹⁴ ferritin was not helpful in differentiating meningitis from cerebro-vascular diseases. Ferritin cutoff point obtained in our study was similar to studies by Kim et al⁷, Almeida and his co-workers,⁸ Katnik et al¹³ and Ricardo et al.¹⁵ High sensitivity and specificity of ferritin cutoff point to differentiate meningitis and non-meningitis patients was in accordance to the study by Takahashi and his co-workers⁵. Low specificity of ferritin cutoff point in differentiating bacterial and aseptic meningitis was observed by Sato et al¹⁶ and Hallgren et al¹⁷ and was similar to our findings.

CONCLUSION

In conclusion in our study CSF ferritin levels were significantly elevated in patients with meningitis vs. no-meningitis and bacterial meningitis vs. aseptic meningitis. However differentiation of the bacterial meningitis vs. aseptic meningitis by using CSF ferritin levels shown low specificity. Further studies are required on a larger sample size before we can substantiate our findings.

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