Original Article

Study Of Cerebrospinal Fluid Ferritin Level In Children With Meningitis

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Abstract

Background: - Bacterial meningitis is still one of the significant causes of morbidity and mortality in children despite the use of antibiotics. Rapid diagnosis and differentiation between bacterial and aseptic meningitis is important for immediate antibiotic treatment in the former to prevent complications. Therefore, different tests have been developed for rapid diagnosis of bacterial meningitis. One of them is CSF ferritin, which is evaluated in this study. **Aim:** - study aimed to evaluate the cerebrospinal fluid ferritin levels in children with meningitis and differentiation between its bacterial and viral etiologies. **Patients and Methods:** This is a cross sectional comparative study included 50 children with a picture of suspected meningitis, 16 children diagnosed as bacterial meningitis, 17 children as viral meningitis, and 17 children as no meningitis attended the pediatric outpatient's clinic and inpatient department of Kafr Elsheik Fever hospital. We include children with clinical suspicion of meningitis, while Children with CNS neoplasm, Children with irregular respiration, children who had deteriorating level of consciousness, Children with very recent siezures, traumatic CSF puncture or neurodegenerative diseases were excluded from the study. CSF ferritin level measurement was done by Eliza. **Results: -** Our results revealed that CSF ferritin level was statistically significant high in the bacterial group (92.69±36.62 ng/ml) when compared to those with viral (9.27±3.12 ng/ml), or no meningitis (6.31±2.94 ng/ml) groups. CSF ferritin showed a positive correlation with both serum CRP and CSF leucocyte in children with bacterial meningitis. The best cutoff point of CSF Ferritin for early differentiation bacterial from viral meningitis is ≥14.4 ng/ml with sensitivity of 100.00% and specificity of 100% with an area under the curve of 1.000 and (NPV) of 100% and (PPV) of 100%. **Conclusion**: - CSF ferritin levels were significantly elevated in patients with bacterial meningitis vs. aseptic meningitis. The differentiation of bacterial meningitis vs. aseptic meningitis by using CSF ferritin levels shown high specificity and sensitivity. **Recommendation**: We recommend to use CSF Ferritin as a useful biomarker in the early diagnosis of bacterial meningitis and to differentiate it from the viral one.

Keywords: - Cerebrospinal Fluid, Bacterial Meningitis, Viral Meningitis, Children, Antibiotics, CSF Ferritin.

INTRODUCTION

Meningitis is an inflammation of the leptomeninges with infection of the cerebrospinal fluid (CSF) within the subarachnoid space of the brain and spinal cord, and the ventricular system**. [1]** Meningitis is an endemic disease in Egypt. It is prevalent in developing countries, due to low socioeconomic conditions. Bacterial meningitis characterized by the onset of meningeal symptoms (headache, neck stiffness, vomiting, and photophobia) and cerebral dysfunction (confusion, coma).**[2]**

Viral meningitis is often less severe than bacterial meningitis, and most people usually get better on their own (without treatment). However, infants younger than 1 month old and people with weakened immune systems are more likely to have severe illness**. [3]** Rapid differentiation of the bacterial and other etiology is important as it is a threatening condition can lead to acute complications and long term serious neurological damage or even death. **[4]**

A number of biochemical markers have been used for the early diagnosis and differentiation of bacterial and viral meningitis like Ferritin, C-reactive protein (CRP) and lactate dehydrogenase . Ferritin is an acute phase reactant

that is incapable of penetrating the blood brain barrier due to its spherical structure and high molecular weight. So, CSF ferritin levels are not influenced by its blood levels. High concentration of ferritin in the CSF is the consequence of its passage through dissipated blood brain barrier and local synthesis in CNS as well, resulting in increased concentration of ferritin in patients with bacterial meningitis. **[5]**

PATIENTS AND METHODS

The present study is a cross -sectional comparative that was carried out at Kafr Elsheikh Fever Hospital. The study population included 50 patients (16 cases diagnosed with bacterial meningitis, 17 patients as viral meningitis and 17 cases as no- meningitis), their ages ranged from 3 months to 12 years. Diagnostic criteria included symptoms and signs of fever, headache, meningeal irritation like neck rigidity. 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. Patients with impression of meningitis but with no CSF pleocytosis were not considered meningitis and were included in the no- meningitis group. Cerebrospinal fluid ferritin was measured by ELIZA method.

Inclusion criteria

1) Age ranges from 3 months to 12 years.
2) Picture of suspected Meningitis.

Exclusion criteria

1) CNS neoplasm.
2) Deteriorating level of consciousness.
3) Irregular respirations.
4) Very recent seizures.
5) Traumatic CSF puncture.
6) Neurodegenerative diseases.

ETHICAL CONSIDERATION

The present study was approved by the Research Ethics Committee of the Faculty of Medicine for Girls, Al Azhar University. Informed consent was obtained from all patient's parents for participation in the study.

STATISTICAL ANALYSIS

Data were collected, coded, revised, and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. Independent t-test was used in the comparison between two groups with quantitative data, and parametric distribution and Mann-Whitney test was used in the comparison between two groups with quantitative data and non-parametric distribution.

The comparison between more than two groups with quantitative data and parametric distribution were done by using One Way Analysis of Variance (ANOVA) test and Kruskall-Wallis test was used in the comparison between more than two groups with quantitative data and non-parametric distribution. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

P > 0.05: Non-significant (NS); **P < 0.05:** Significant (S); **P < 0.01:** Highly significant (HS)

RESULTS

The patients were divided into three groups based on their CSF leukocyte count group-1 no-meningitis (12 females and 5 males); group- 2 bacterial meningitis (6 females and 10 males) and group-3 aseptic meningitis (6 females and

11 males). The male is the predominant sex in patients with meningitis in our study **(Table 1)** and the most affected is from 3 months to 2 years **(Table 2).**

The most common presenting symptom in patients with suspected meningitis was fever (88%) followed by vomiting (64%) while the most common presenting sign was neck rigidity (74%) **(Table 3).** Mean of age was (5.19±4.06) years in No meningitis, was (4.43±4.34) years in viral and was (5.11±3.79) years in Bacterial with no significant difference between the 3 groups regarding age and sex **(Table 4).**

There was increased fever in viral group, increase in neck rigidity in bacterial group (**Table 5,6).**

Gram staining of CSF revealed gram-positive in 11 patients of bacterial meningitis (68.8%) and gram negative in 3 cases (18.8 %). The most common infectious agent in the CSF culture of bacterial cases was Streptococcus pneumoniae **(Table 7).** CSF ferritin levels were found to have positive correlation with serum CRP and CSF leukocytes in the bacterial meningitis group. However, no such relation was observed in the no-meningitis or aseptic meningitis groups **(Figure 1,2,3).** Mean of CSF Ferritin was 6.31 ±2.94 in No meningitis, 9.27±3.12 in Viral, 92.69±36.62 in Bacterial group with significant increase of its level in bacterial group **(Table 8).** ROC curve analysis revealed cut-off point of >14.4 ng/mL for CSF ferritin with a sensitivity of 100 % and specificity of 100 % to discriminate bacterial from aseptic meningitis **(Table 9 & Figure 4).**

Table 1: Sex distribution among the studied groups with suspected meningitis

Sex	No	Percent %
Male	26	56%
Female	24	48%
Total	50	100%

Table 2: Age distribution among the studied groups with suspected meningitis

Age (years)	Male	Female	Total	Total percent %
3m-2y	10	7	17	34%
>2y-4y	5	7	12	24%
>4y-6y	3	1	4	8%
>6y-8y	4	1	5	10%
>8y-10y	3	2	5	10%
>10y-12y	4	3	7	14%
Total	26	24	50	100%

Table 3: Presenting symptoms and signs among the studied groups with suspected meningitis

Symptoms & signs	No	Percent %
Fever	44	88%
Vomiting	32	64%
Irritability	19	38%
Headache	18	36%
Disturbed conscious level (DCL)	10	20%
Neck rigidity	37	74%
Kernig's sign	26	52%
Brudizinski sign	24	48%

Table (4): comparison between the studied groups regarding sex and age

		No meningitis (No=17)		Viral (No=17)		Bacterial (No=16)		Chi square test/ One way ANOVA	
		No	%	No	%	No	%	x^2/f*	p value
Sex	Female	12	70.6%	6	35.3%	6	37.4%	8.075	0.089
	Male	5	29.4%	11	64.7%	10	62.5%		
Age (years)	Mean± SD	5.19	4.06	4.43	4.34	5.11	3.79	0.179*	0.836

Table (5): Comparison between the studied groups regarding symptoms

		No meningitis (No=17)		Viral (No=17)		Bacterial (No=16)		Chi square test	
		No	%	No	%	No	%	x^2	p value
Fever	Yes	11	64.7%	17	100.0%	16	100.0%	13.235	<0.001
	No	6	35.3%	0	0.0%	0	0.0%		
Headache	Yes	5	29.4%	7	41.2%	6	37.5%	0.534	0.766
	No	12	70.6%	10	58.8%	10	62.5%		
Vomiting	Yes	9	52.9%	10	58.8%	13	81.2%	3.166	0.205
	No	8	47.1%	7	41.2%	3	18.8%		
Irritability	Yes	9	52.9%	5	29.4%	5	31.2%	12.118	0.059
	No	8	47.1%	12	70.6%	11	68.7%		
Level of consciousness	Disturbed	0	0.0%	4	23.5%	6	37.4%	8.523	0.074
	conscious	17	100.0%	13	76.5%	10	62.5%		

Table (6): Comparison between the studied groups regarding signs

		No meningitis (No=17)		Viral (No=17)		Bacterial (No=16)		Chi square test	
		No	%	No	%	No	%	x^2	p value
Neck rigidity	Yes	9	52.90%	12	70.6%	16	100.0%	36.732	<0.001
	No	8	47.10%	5	29.4%	0	0.0%		
Kernig's sign	Yes	1	5.90%	11	64.7%	14	87.5%	4.652	0.098
	No	16	94.10%	6	35.3%	2	12.5%		
Brudziniski	Yes	2	11.80%	12	70.6%	10	62.5%	16.904	<0.001
	No	15	88.20%	5	29.4%	6	37.5%		
Rash	Yes	2	11.80%	0	0.0%	1	6.2%	5.834	0.212
	No	15	88.20%	17	100.0%	15	93.7%		

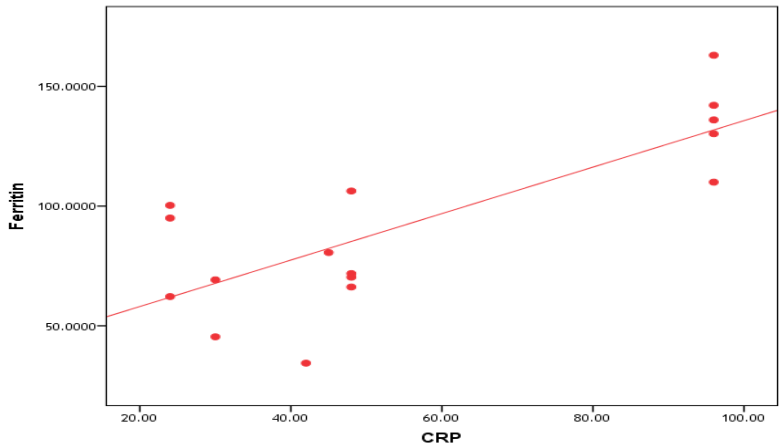

Figure (1): Positive correlation between CSF ferritin and CRP in bacterial group

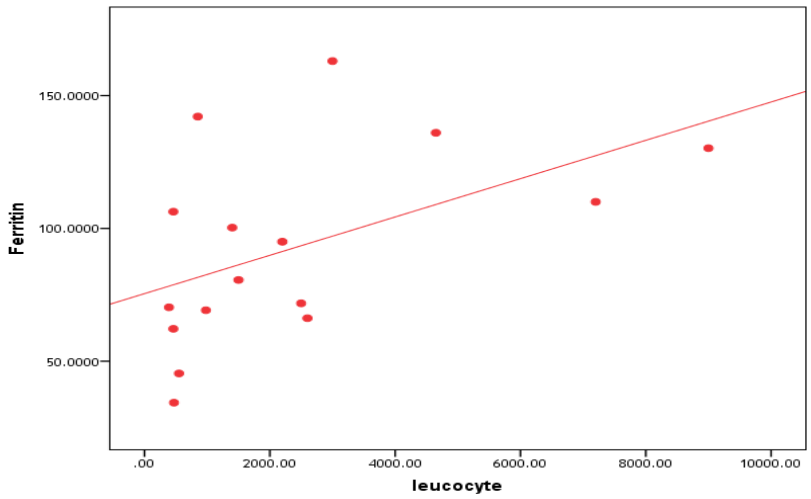

Figure (2): Positive correlation between CSF ferritin and CSF leukocytes in bacterial group.

Table (7): Comparison between the studied groups regarding Gram stain and CSF culture.

		No meningitis (No=17)		Viral (No=17)		Bacterial (No=16)		Chi square test	
		No	%	No	%	No	%	x^2	p value
Gram stain	Negative	0	0.0%	0	0.0%	3	18.8%	NA	NA
	Positive	0	0.0%	0	0.0%	11	68.8%		
CSF culture	E coli	0	0.0%	0	0.0%	1	6.2%	41.319	<0.001
	N.meningitidis	0	0.0%	0	0.0%	2	12.5%		
	No growth	17	100.0%	17	100.0%	2	12.5%		
	Staph aureus	0	0.0%	0	0.0%	3	18.8%		
	Strept. pneumonae	0	0.0%	0	0.0%	8	50.0%		

Table (8): Comparison between the studied groups regarding CSF ferritin

	No meningitis (No=17)		Viral (No=17)		Bacterial (No=16)		One way ANOVA	
	Mean± SD		Mean± SD		Mean± SD		f	p value
Ferritin	6.31	2.94	9.27	3.12	92.69	36.62	90.367	<0.001
Post Hoc Test								
	No meningitis vs Viral		**No meningitis vs Bacterial**			**Viral VS Bacterial**		
Ferritin	0.680		0.000			0.000		

	Cut off point	AUC	Sensitivity	Specificity	-PV	+PV
Ferritin	≥14.4	1.000	100.00	100.00	100.00	100.00

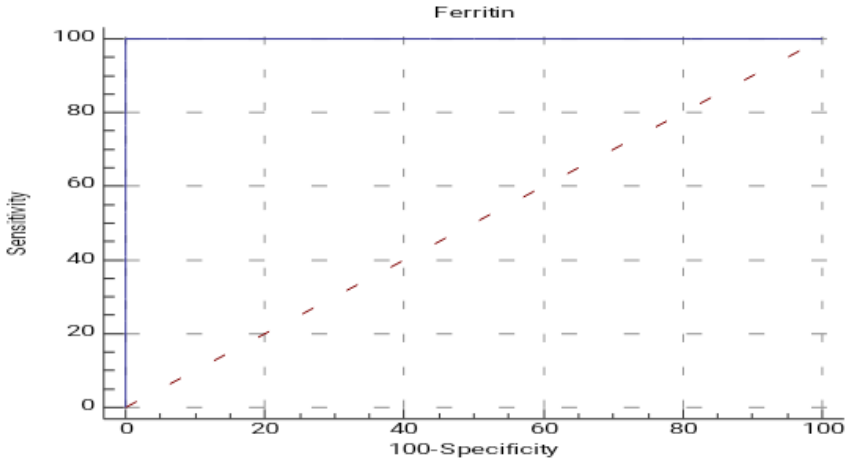

Table (9) & Figure (4) ROC curve showed the cutoff point, AUC, sensitivity and specificity of CSF Ferritin for discrimination between bacterial and viral meningitis groups.

DISCUSSION

Meningitis is an inflammation (swelling) of the protective membranes covering the brain and spinal cord. A bacterial or viral infection of the fluid surrounding the brain and spinal cord usually causes the swelling. However, injuries, cancer, certain drugs, and other types of infections also can cause meningitis. **[6]**

Despite the availability of modern therapies, meningitis remains a potentially life-threatening infection in children with mortality rates reaching up to 25%. It is important to note that routine childhood immunization has significantly decreased the number of serious infections. However, meningitis remain problematic particularly in developing countries where immunization rates are suboptimal. **[7]**

We aimed to assess cerebrospinal fluid (CSF) level of Ferritin in children with Meningitis and differentiation between its bacterial and viral causes. This is a cross sectional comparative study included fifty infant and young children, their ages ranged from 3 months to 12 years and classified into three groups: bacterial meningitis, viral meningitis and no meningitis group based on medical history, clinical presentations and CSF criteria.

In the present study, we found that no significant difference was observed with respect to gender in the 3 groups.

Also, in our study, we found that the most common presenting symptom in patients with bacterial meningitis was fever (100%) followed by vomiting (81.2%) then headache (37.5%) and irritability (31.2%), while the most common presenting sign was rigidity of neck (100%) followed by kernig's sign (87.5%) and brudzinski's sign (62.5%). Regardless of etiology, most patients with meningitis have similar clinical manifestations. **[6]**

According to our results, there is a significant increase in CSF protein, leukocytes and PMN% in bacterial meningitis group compared to the other groups. Increases in CSF protein are commonly seen with bacterial meningitis; also, CSF leukocyte and neutrophils, while there is increase in CSF lymphocytes with a viral meningitis**.[8]** Raised CSF protein levels are result of increased vascular permeability of the blood–brain barrier (BBB) and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space**. [9]**

In the present study, there is significant decrease in CSF glucose level in patients with bacterial meningitis group compared to the other groups. In accordance with our study, **Muller et al.** (2015) **[10]** found that CSF glucose concentration is usually reduced in bacterial meningitis.

In the present study, 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. In our study ferritin cut off point was >14.4ng/mL with a sensitivity of 100% and specificity of 100 % When comparing bacterial from aseptic meningitis. In two separate studies carried out by **Garcia et al. (2021) [11]** and **Rezaei et al. (2013) [12]** cerebrospinal fluid ferritin levels was considered to be significantly higher in bacterial meningitis. It was concluded that CSF ferritin could be used as a rapid test to differentiate bacterial meningitis from aseptic meningitis. We also found that there is significant positive correlation between CSF Ferritin level in bacterial group and CRP serum level and CSF leukocyte level, while there is no correlation between CSF Ferritin level and CSF analysis &laboratory data of both viral and no meningitis groups. Our findings are similar to **Rezaei et al.** (2013) **[12]** who reported that CSF Ferritin was both positively correlated with CSF protein and CSF WBCs count in children with bacterial meningitis.

CONCLUSION

In conclusion in our study CSF ferritin levels were significantly elevated in patients with bacterial meningitis vs. aseptic meningitis. The differentiation of bacterial meningitis vs. aseptic meningitis by using CSF ferritin levels shown high specificity and sensitivity.

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Conflicts of interest: There are no conflicts of interest**.**

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