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The Relationship between Hyponatremia and Bacterial and Non-Bacterial Meningitis and Its Complications

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ABSTRACT

Background and Objective: Considering the lack of knowledge and the difference in the prevalence of hyponatremia in non-bacterial meningitis and bacterial meningitis, this study was conducted with the aim of determining the relationship between hyponatremia and bacterial and non-bacterial meningitis and its complications.

Methods: This cross-sectional study was conducted on 183 children with meningitis referred to Shafizadeh Amirkola Children's Hospital in three age groups: 1 month to 2 years, 2-5 years, and 5-18 years. Based on cerebrospinal fluid analysis, cases of bacterial meningitis were considered to be WBC>100 with preference for PMN, glucose less than 40% of serum sugar and protein more than 1 g/L or positive culture or smear. Cases of non-bacterial meningitis were considered as WBC<100 with preference for lymphocyte, glucose more than 60% of serum sugar and protein less than 1 g/L or negative culture or smear. Gender of children, duration of hospitalization and occurrence of seizures in two groups of bacterial and non-bacterial meningitis with and without hyponatremia were investigated and compared.

Findings: In this study, the mean age of boys (68.26±47.10) with meningitis was higher than that of girls (42.56±32.50) ($p<0.001$). The mean age of meningitis patients with hyponatremia (51.87±47.56) was lower than that of patients without hyponatremia (72.54±45.03) ($p=0.002$). The frequency of hyponatremia in children with meningitis aged less than 2 years compared to other age groups (52 patients) ($p=0.002$), as well as infants who had seizure (37 patients) ($p=0.001$) has been significantly higher. In children who had hyponatremia, the duration of hospitalization was significantly longer (108 patients) ($p=0.01$).

Conclusion: Based on the results of the present study, it was found that younger children are at greater risk for hyponatremia, and the presence of hyponatremia at the beginning of diagnosis suggests a greater risk for seizures and increased length of hospitalization. However, the risk of hyponatremia in both types of bacterial and non-bacterial meningitis is almost the same.

Keywords: *Hyponatremia, Meningitis, Bacterial.*

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Introduction

Meningitis, as an inflammatory disease and medical emergency, causes a high rate of mortality worldwide (1-3). The highest prevalence of meningitis is in infancy and childhood (4). Symptoms of meningitis include fever, headache and changes in the level of consciousness. The occurrence of symptoms at different ages is varied. Most of the signs and symptoms in children are few and usually appear as moodiness, restlessness, lethargy and loss of appetite (1, 2, 5). Meningitis has various causes, including infectious causes such as bacteria and viruses as well as non-infectious causes such as drug. Bacterial agents are usually more dangerous than non-bacterial agents, and the severity of symptoms and complications in bacterial meningitis is usually much higher (1, 6). Hyponatremia is defined as serum sodium below 135 mmol/L (7). Hyponatremia is a very common complication in neurological diseases, especially in meningitis due to the role of the central nervous system in regulating sodium and water in the body (8). Hyponatremia in meningitis patients can be caused by fever, vomiting, diarrhea, severe sweating, not receiving enough oral fluids, taking mannitol to remove edema, poisoning with anticonvulsant drugs, administering a large volume of hypotonic fluid aggressively, syndrome of inappropriate secretion of antidiuretic hormone, cerebral salt wasting syndrome and early or delayed hypophysis dysfunction (2, 7, 9). The aim of this study is to accelerate and predict hyponatremia disorder in children with bacterial and non-bacterial meningitis and to replace the appropriate fluid before starting treatment and to determine the relationship between hyponatremia and bacterial and non-bacterial meningitis and its complications.

Methods

This cross-sectional study was conducted after being approved by the Ethics Committee of Babol University of Medical Sciences with the code IR.MUBABOL.REC.1399.241 during the years 2011 to 2020. 183 children with meningitis referred to Amirkola Children's Educational-Treatment Center, and based on the analysis of cerebrospinal fluid in chocolate agar, blood or thioglycollate culture medium, the researcher separated them into two categories of bacterial and non-bacterial meningitis. Cases of bacterial meningitis were considered to be WBC>100 preferably PMN (Polymorphonuclear Neutrophils), glucose less than 40% of serum sugar and protein more than 1 g/L or positive culture or smear, and cases of non-bacterial meningitis or aseptic as WBC<100 with preference for lymphocyte, glucose more than 60% of serum sugar and protein less than 1 g/L or negative culture or smear.

Hyponatremia was considered based on serum sodium level less than 135 mEq/L. Exclusion criteria included children aged less than one month and older than 18 years, cell count less than 5 preferably more than 90% lymphocytes in cerebrospinal fluid examination, hyponatremia during hospitalization, history of taking antibiotics or diuretic drugs, underlying diseases of liver, kidney, and heart, high blood pressure, immune system deficiency, vomiting and severe diarrhea. In terms of age, they were placed in three age groups: one month to 2 years, 2-5 years, and 5-18 years, and hyponatremia was compared in these three age groups. Hyponatremia was compared in both boys and girls. The average duration of hospitalization and the occurrence of seizures in two groups of bacterial and non-bacterial meningitis who had hyponatremia and those who did not have hyponatremia were also investigated and compared. To analyze the data, chi-square test and independent T-test were used, and to evaluate the normality of the data, the Shapiro-Wilk test was used, and $p<0.05$ was considered significant.

Results

183 children including 121 boys (66.1%) with an average age of 68.26±47.10 months and 62 girls (33.9%) with an average age of 42.56±32.50 months admitted to Amirkola Children's Hospital with a diagnosis of meningitis were included in the study during 2011-2020 (p<0.001). The average age of the patients was 59.55±47.58 months (minimum age 1 month and maximum 18 years).

The average age of meningitis patients with hyponatremia (51.87±47.56) was lower than that of patients without hyponatremia (72.54±45.03) (p=0.002). The frequency of hyponatremia in children with meningitis with an age of less than 2 years compared to other age groups (52 patients) (p=0.002) as well as infants who had seizures (37 patients) (p=0.001) was significantly higher. In children who had hyponatremia, the duration of hospitalization was significantly longer (108 patients) (p=0.01).

The results about the frequency of bacterial and non-bacterial meningitis according to age showed that non-bacterial meningitis in all three age groups: less than 2 years (42 people) (64.6%), 2 to 5 years (25 people) (65.8%) and more than 5 years (23 people) (28.7%), was higher than bacterial meningitis. However, meningitis has no significant relationship with children's age (Figure 1).

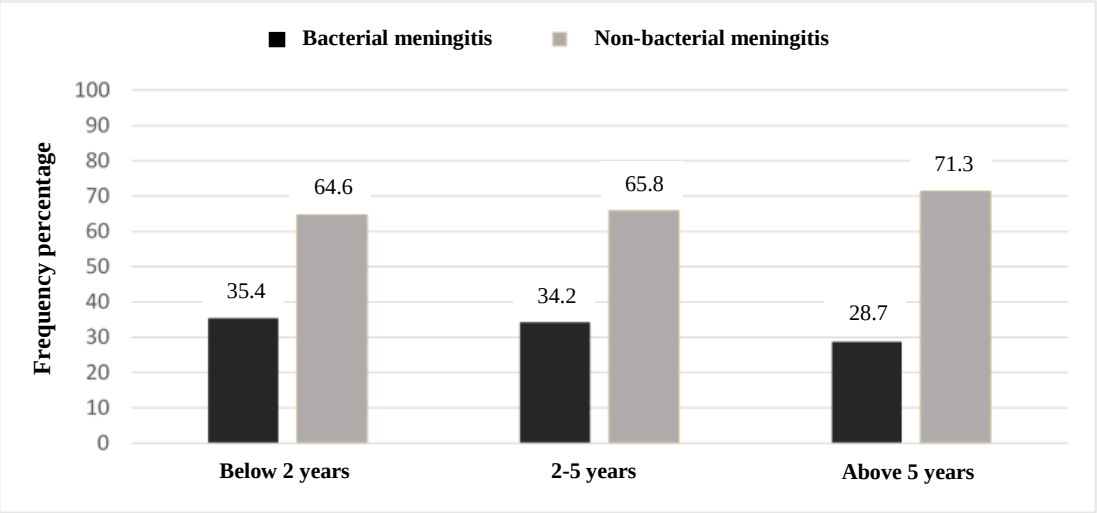

Figure 1. Comparison of the frequency of bacterial and non-bacterial meningitis by age

In the study of the variables of age, gender, type of meningitis, seizure and hospitalization period based on the presence and absence of hyponatremia, the results showed that the frequency of hyponatremia was significantly higher in children with meningitis with an age of less than 2 years compared to other age groups (p<0.002). The frequency of hyponatremia in bacterial and non-bacterial meningitis was not significantly different (p=0.19, 95% CI=0.7-2-97, OR=1.53). Also, the frequency of hyponatremia was significantly higher in children who suffered from seizures compared to children without seizures (p<0.001, 95% CI=1.72-9.91, OR=4.13). In children who had hyponatremia, the hospitalization period of 7 days or less compared to more than 7 days was not significantly different (p<0.30, 95%CI=0.18-1.68, OR=0.55) (Table 1). In examining the variables of age, gender, hyponatremia, seizures and hospitalization period based on the type of meningitis, the results showed that the incidence of hyponatremia in children with non-bacterial meningitis was higher than that of bacterial meningitis, but this difference was not statistically significant (Table 2). The frequency of seizures in children with bacterial meningitis was significantly higher than non-bacterial meningitis (p<0.001). The length of hospitalization in children with bacterial meningitis was significantly longer (p<0.01).

Table 1. Comparison of the frequency of hyponatremia in children with bacterial and non-bacterial meningitis

Variable	Hyponatremia		p-value*
	Yes Frequency(relative frequency)	No Frequency(relative frequency)	
Age (years)			
2>	52(80)	13(20)	
2-5	21(55.3)	17(44.7)	0.002
5<	43(53.7)	37(46.3)	
Gender			
Boy	74(61.2)	47(38.8)	0.51
Girl	41(66.1)	21(33.9)	
Type of meningitis			
Bacterial	41(69.5)	18(30.5)	0.19
Non-bacterial	74(59.7)	50(40.3)	
Seizure			
Yes	37(84.1)	7(15.9)	0.001
No	78(56.1)	61(43.9)	
Hospitalization period (days)			
1-7	7(50)	7(50)	0.01
7-14	95(60.9)	61(39.1)	
14<	13(100)	-	

***Using the Chi-square test**

Table 2. Comparison of the frequency and relative frequency of bacterial and non-bacterial meningitis in the examined children

Variable	Type of meningitis		p-value*
	Bacterial Frequency(relative frequency)	Non-bacterial Frequency (relative frequency)	
Age (years)			
2>	23(35.4)	42(64.6)	
2-5	13(34.2)	25(65.8)	0.66
5<	23(28.7)	57(71.3)	
Gender			
Boy	35(28.9)	86(71.1)	0.18
Girl	24(38.7)	38(61.3)	
Hyponatremia			
No	18(26.5)	50(73.5)	0.19
Yes	41(35.7)	74(64.3)	
Seizure			
Yes	23(52.3)	21(47.7)	0.001
No	36(25.9)	103(74.1)	
Hospitalization period (days)			
1-7	1(7.1)	13(92.2)	
7-14	50(32.1)	106(67.9)	0.01
14<	8(61.5)	5(38.5)	

***Using the Chi-square test**

Discussion

In the present study, hyponatremia was 69.5% in children with bacterial meningitis and 59.7% in non-bacterial meningitis, and hyponatremia was more common in bacterial meningitis. Although the relationship between hyponatremia and bacterial meningitis was not statistically significant, the frequency of hyponatremia was higher in children with bacterial meningitis, which is clinically important.

Based on the results of a study by Inamdar et al., Cerebral Salt Wasting Syndrome has been diagnosed as an important cause of hyponatremia in children with tuberculosis meningitis, and its prevalence is higher than SIADH (Syndrome of Inappropriate Antidiuretic Hormone) (10). It was also seen in the study of Zheng et al. that in the course of meningitis, hyperglycemia occurs with the increase of glucagon, catecholamines, and cortisol, which causes an increase in blood osmolality, resulting in the transfer of intracellular fluid to the outside and hyponatremia (7).

In a study conducted by Na et al., the initial level of serum sodium in patients with tuberculosis meningitis was lower than in patients with bacterial and non-bacterial meningitis. They stated that early assessment of serum sodium level can provide information for differential diagnosis of tuberculous meningitis from bacterial or non-bacterial meningitis (11). In the current study, hyponatremia in children with bacterial meningitis was more than non-bacterial meningitis, which is due to the increase of ADH and the reabsorption of water and salt in any critically ill patient or in need of special care and involvement of the central nervous system. Therefore, in patients with bacterial brain infection and poor general condition, this disorder along with hyponatremia is expected to be seen more.

The frequency of hyponatremia in all children with bacterial and non-bacterial meningitis in the present study was 62.8%. In the study of Zheng et al., out of 175 children with meningitis, hyponatremia was observed in 116 (66.4%) (7), and the frequency of hyponatremia was similar to the present study. Brouwer et al. found in a study that 57% of patients over 16 years who had bacterial meningitis, and hyponatremia was also observed in them (12). Meanwhile, in the study of Inamdar et al., less than half of the children with tuberculous meningitis had hyponatremia during their stay in the hospital (10). The reason for this difference can be the small number of samples in the mentioned studies, and of course there are few studies regarding the association between central nervous system infection and hyponatremia.

The prevalence of hyponatremia in patients with bacterial meningitis in the study of Mujtaba et al. was 25.6% (2). According to the above-mentioned studies, although the incidence of hyponatremia is varied, the risk of developing hyponatremia in these patients is high and they need more serious care. In the study of Ghabouli Shahroodi et al., hyponatremia due to syndrome of inappropriate antidiuretic hormone ADH release was seen in 30% of infants and 57% of children with enteroviral meningitis (4). The results of several studies show that moderate and severe hyponatremia significantly increases the chance of seizures and impaired consciousness, shock, acute respiratory arrest requiring mechanical ventilation, and the possibility of seizures and its recurrence is higher in children with low serum sodium levels. Also, patients with meningitis and hyponatremia were at a higher risk of mortality and complications (7, 13, 14). This is consistent with the results of the present study, as hyponatremia was higher in children with meningitis who had seizures. Also, there is a direct relationship between the incidence of some pediatric medical emergencies, including seizures, cardiorespiratory arrest, and permanent brain damage, with a decrease in sodium serum levels, which was seen in the present study.

In the study of Brouwer et al., signs and symptoms of meningitis, such as headache, seizures, and impaired consciousness, were seen in similar proportions in patients with severe hyponatremia, mild hyponatremia, and patients who did not have hyponatremia (12). However, in the present study, hyponatremia was higher in patients with seizures.

The reason for this difference can be due to the age difference in the target group of the study; in our study, the research population of patients was less than 18 years old, and in the study of Brouwer et al., it was more than 16 years old. Also, in the present study, the cause of seizures was not investigated, and it is not known whether the cause of seizures was hyponatremia or whether seizures and hyponatremia were associated with each other. In any case, this finding highlights the importance of hyponatremia with seizures in children with meningitis.

In the evaluation of hyponatremia in children with bacterial and non-bacterial meningitis, children under 2 years had the highest rate of hyponatremia. The average age of children with bacterial and non-bacterial meningitis in whom hyponatremia was observed was lower than that of children without hyponatremia. The above finding shows that children at younger ages are more at risk of hyponatremia with meningitis, which shows the importance of paying attention to this complication in meningitis.

In their study, Zheng et al. concluded that the length of hospitalization was significantly longer among patients with meningitis and hyponatremia, and hyponatremia prolonged the length of hospitalization (7). The results of the present study showed that children who had hyponatremia had a longer hospitalization period than children without hyponatremia. Also, with the occurrence of hyponatremia, the hospitalization period has increased to more than 14 days. Hyponatremia was observed in all children who were hospitalized for more than 14 days. The limitations of this study can be mentioned due to the high number of negative cultures and the lack of identification of the isolated microorganism and the division of patients into two categories of possible bacterial and non-bacterial meningitis.

Based on the present study, it was found that the presence of hyponatremia at the beginning of the diagnosis suggests a greater risk for seizures and an increase in the duration of hospitalization, and it can be considered as a marker in brain infections, whose presence during the diagnosis of the disease indicates more severe inflammatory symptoms and this problem requires a wider and longer treatment. Younger children are also at greater risk for hyponatremia, although the risk of hyponatremia is about the same in both bacterial and nonbacterial meningitis. Based on the results, it is recommended to evaluate electrolytes in children with meningitis, especially at younger ages.

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