Bahrain Medical Bulletin, Volume 30, No 1, March 2008

Hyponatremia in Children with Acute Central Nervous System Diseases

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Background: Hyponatremia is a common electrolyte disturbance and its potential neurological sequelae make its differential diagnosis mandatory before any therapeutic intervention.

Objective: The study was conducted to estimate the frequency of hyponatremia among children hospitalized with acute cerebral insult and to look for the possible causes of hyponatremia.

Design: Prospective case-control study.

Setting: Basrah maternity and children hospital.

Method: Case-control study performed on 150 children (87 boys and 63 girls), during 9 months (from the first of October 2003 till the end of June 2004). Their ages ranged from 2-108 months. Seventy five of them presented with acute central nervous system (CNS) manifestations, while the rest were considered as control.

Serum sodium, potassium, glucose and urea nitrogen were estimated and serum osmolality was calculated. In addition, urinary sodium, potassium, glucose, urea and creatinine determination was done, and urine osmolality was calculated.

Result: Eight of 75 pediatric patients (10.7%) with acute CNS diseases had hyponatremia syndrome, 3 of which were diagnosed with inappropriate antidiuretic hormone secretion. Another 2 patients showed signs of dehydration and evidence of cerebral salt wasting. In the remaining 3 patients the clinical and laboratory data were insufficient for further classification. The highest percentage of hyponatremia (3 out of 6 patients; 50%) was found in patients with intracranial diseases. Four out of 38 patients (15.5%) presented with CNS infections.

Mean serum levels of glucose, sodium and osmolality were significantly lower in all patients with acute CNS diseases compared with the control, while urinary urea and osmolality levels were significantly higher in those patients as compared with the control group.

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The study showed that there was a significant decrease in the mean serum level of glucose, sodium and osmolality in hyponatremic patients compared to non-hyponatremic patients. There was also a significant increase in urine sodium/creatinine ratio, urea, and osmolality in hyponatremic patients compared to non-hyponatremic patients.

The study has demonstrated that serum urea was significantly higher in patients with cerebral salt wasting compared to those with syndrome of inappropriate antidiuretic hormone secretion. In addition to that, the 3 groups of hyponatremia have significant differences in the mean urine sodium, urea, osmolality and serum osmolality.

Conclusion: From this study, we may conclude that hyponatremia is not uncommon in patients with acute central nervous system (CNS) insults. Serum sodium should be routinely monitored in these patients to enable early diagnosis and treatment of hyponatremia.

Bahrain Med Bull 2008; 30(1):

Hyponatremia is a common electrolyte disturbance. Its high prevalence and potential neurological sequelae make its differential diagnosis mandatory before any therapeutic intervention[1]. Hyponatremia is a common finding in patients with acute cerebral insult; it is defined as a serum sodium level of less than 130 mEq/L[2]. It can be associated with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, cerebral salt wasting (CSW), treatment of transient/permanent diabetes insipidus (DI), and excessive fluid administration in patients with thirst[2,3].

SIADH secretion is defined by hyponatremia and hypoosmolality resulting from inappropriate continued secretion and/or action of ADH despite normal or increased plasma volume[4]. CSW is defined as renal loss of sodium associated with intracranial disease, leading to hyponatremia and a decrease in extracellular fluid volume. This disorder can be confused clinically with SIADH but is distinguished by the volume status of the patient; patients with CSW are volume contracted, while SIADH is a volume expanded state. The appropriate treatment of patients with CSW is fluid and salt supplementation[5]. The traditional criteria for diagnosis of SIADH secretion are hypotonic hyponatremia (serum sodium less than 130 mEq/L and serum osmolality less than 280 mOsmol/L), high urinary of sodium (more than 20-40 mEq/L), urine osmolality greater than serum osmolality, normal thyroid, adrenal, and renal function, and absence of peripheral edema or dehydration[6].

The main biochemical findings of cerebral salt wasting (CSW) are low plasma osmolality with inappropriate high urine osmolality (urine to plasma osmolality ratio >1), hyponatremia with urine sodium loss more than 20 mmol/1, normal/high haematocrit, and plasma urea. Clinical dehydration, weight loss, orthostatic hypotension, and negative water balance are documented features of CSW[7].

As a careful clinical and biochemical assessment it is important for the diagnosis to be established, for only then can proper treatment be instituted[8]. This study was carried out to estimate the frequency of hyponatremia among children hospitalized with acute CNS insult and to look for the possible causes of hyponatremia; whether due to SIADH or CSW.

METHOD

A prospective case-control study performed on children with acute CNS diseases admitted to pediatric wards of Basrah maternity and children hospital over a period of nine months (from the first of October 2003 till the end of June 2004).

Seventy-five patients with acute neurological diseases were included (44 boys and 31 girls), their ages ranged from 2 months to 108 months. Patients included were those admitted with acute neurological presentation like seizure disorders, altered level of consciousness including drowsiness and coma, irritability, cranial nerve palsies, headache and disorientation (in older patients).

A control group included 75 children (43 boys and 32 girls) visiting the out-patient department for minor illnesses like upper respiratory tract infections, abdominal pain, and those who were attending for vaccination.

Venous blood was drawn on admission; serum was separated and kept frozen until the time of analysis. Urine samples were collected in the early morning and stored at -20^0 C until analyzed.

Statistical Analysis:

Data were expressed as (mean ± SD). Statistical analysis was performed using one way analysis of variance (ANOVA) and Chi-square (X^2) test, p-values less than 0.05 were considered as significant.

RESULT

The mean age was 33.7 ± 28 months for the patient group and 32.9 ± 28.4 for the control group. Forty-four of the patient group (58.6%) and 43 of the control group (57.3%) were males.

Nineteen (25.3%) patients with acute CNS diseases were admitted to the hospital because of meningoencephalitis, 17 (22.6%) with febrile convulsion and the rest because of acute bacterial meningitis 8 (10.6%), partially treated meningitis 10 (13.3%), epilepsy 10 (2 presented with status epilepticus and 8 with non-febrile fit), acute ataxia 4 (5.3%), intracranial abscess 4 (5.3%), intracranial hemorrhage 2 (2.6%) and one patient with tuberculous meningitis (see Table1).

Table 1: Characters of Patients with Acute CNS Diseases

Diagnosis	Patients		Sex	
	N	%	M	F
a. CNS infection				
1. Acute bacterial meningitis	8	10.6	5	3
2. Meningoencephalitis	19	25.3	11	8
3. Tuberculous meningitis	1	1.3	1	-
4. Partially treated meningitis	10	13.3	6	4
b. Intracranial diseases				
1. Abscess	4	5.3	3	1
2. Hemorrhage	2	2.6	2	-
c. Others				
1. Febrile convulsion	17	22.6	9	8
2. Epilepsy	10	13.3	6	4
3. Acute Ataxia	4	5.3	1	3

Table 2 shows 8 pediatric patients (10.7%) with acute CNS diseases had hyponatremia according to the diagnostic criteria; SIADH was diagnosed in 3 patients, and another 2 patients showed evidence of CSW. In the remaining 3 patients the clinical and laboratory data were insufficient for further classification. The highest frequency of hyponatremia was found in patients with infection of CNS (4 out of 38; 10.5%) including: acute meningitis (bacterial and tuberculous), partially treated meningitis and meningoencephalitis; and in 3 out of 6 patients (50%) with intracranial diseases (abscess and hemorrhage).

Table 2: Frequency and Causes of Hyponatremia among Patients with Acute CNS Diseases

Diagnosis	N	Hyponatremia			
		SIADH	CSW	Unknown origin	Total
a. CNS infection					
1. Acute bacterial meningitis	8	1	-	-	1
2. Meningoencephalitis	19	-	-	2	2
3. Tuberculous meningitis	1	1	-	-	1
4. Partially treated meningitis	10	-	-	-	-
b. Intracranial diseases					
1. Abscess	4	-	1	-	1
2. Hemorrhage	2	1	1	-	2
c. Others					
1. Febrile convulsion	17	-	-	-	-
2. Epilepsy	10	-	-	1	1
3. Acute Ataxia	4	-	-	-	-
Total	75	3	2	3	8

The results of biochemical investigations for the 150 children included in the study (patients and controls) are presented in Table 3. It reveals significantly lower values in the mean serum level of glucose, sodium and osmolality, whereas significantly higher values in the mean urine urea and osmolality levels in patients with acute CNS diseases compared to controls. No significant difference in the mean serum levels was found.

Table 3: Biochemical Values (mean ± SD) in Patients with CNS Diseases and Controls without CNS Disease

Parameters	Patients N = (75)	Controls N = (75)	p-value
S. glucose (mmol/1)	3.9 ± 0.78	4.2±1.1	< 0.05
S. urea (mmol/1)	2.8 ± 0.94	2.8 ± 0.95	NS
S. Na (mEq /1)	130 ± 3.1	136.9 ± 3.5	<0.05
S. K (mmol/1)	3.8 ± 0.63	3.8 ± 0.54	NS
S. Osmolality (mOsmol/1)	277 ± 3.3	288 ± 6.6	<0.05
U. Na/Cr (mEq/1)	18.5 ± 3.8	15.4 ± 3.5	NS
U. glucose (mmol/1)	0.85 ± 0.23	0.96 ± 0.24	NS
U. urea (mmol/1)	62.6 ± 31	37.8 ± 16.1	0.001
U. K (mmol/1)	9.4 ± 8.1	7.8 ± 3.1	NS
U. Osmolality (mOsmol/1)	115.6 ± 73.9	82 ± 16.8	0.001

All the biochemical parameters estimated for patients with acute CNS diseases with and without hyponatremia are presented in Table 4. It shows that the mean serum level of glucose, sodium and osmolality were significantly lower, while the mean urinary level of sodium/creatinine ratio, urea and osmolality were significantly higher in the hyponatremic patients compared to patients without hyponatremia.

Table 4: Biochemical Values (mean ± SD) in Patients with Acute CNS Disease with or without Hyponatremia

Parameters	Patients with acute CNS diseases		
	With hyponatremia N = (8)	Without hyponatremia N = (67)	p-value
S. glucose (mmol/1)	3.9 ± 0.7	4.3±1.1	<0.05
S. urea (mmol/1)	2.9 ± 1.06	2.8 ± 0.94	NS
S. Na (mEq /1)	127.7 ± 1.9	136.5 ± 2.3	0.01
S. K (mmol/1)	4 ± 0.85	3.8 ± 0.6	NS
S. Osmolality (mOsmol/1)	261 ± 5.4	281 ± 4.1	0.01
U. Na/Cr (mEq/1)	69.7 ± 50	12.6 ± 4.3	0.01
U. glucose (mmol/1)	0.84 ± 0.14	0.86 ± 0.16	NS
U. urea (mmol/1)	86.5 ± 47.7	59.3 ± 27.6	0.01
U. K (mmol/1)	9.21 ± 7.14	8.9 ± 5.4	NS
U. Osmolality (mOsmol/1)	257 ± 153.9	98.2 ± 16.9	0.01

The biochemical values in hyponatremic patients of different causes (SIADH, CSW and hyponatremia due to unknown causes) were also evaluated. It was demonstrated that there were highly significant differences ($p<0.01$) in the mean urine sodium and osmolality among the three groups of hyponatremia; patients with SIADH had the highest values (see Table 5). There was also a statistically significant difference ($p<0.05$) in the mean serum glucose level between CSW group and hyponatremia due to unknown origin. In addition, serum urea level was significantly higher ($p<0.05$) in patients with CSW compared to those with SIADH. Serum osmolality and urine were significantly different among the three groups of hyponatremia.

Table 5: Biochemical Values (mean ± SD) in Hyponatremic Patients in Relation to Differential Diagnosis

Parameters	Causes of Hyponatremia			p-value
	SIADH N = (3)	CSW N = (2)	Unknown origin N = (3)	
S. glucose (mmol/1)	4.1 ± 1.05	3.2 ± 0.9	5.03 ± 1.5*	<0.05
S. urea (mmol/1)	1.9 ± 1	3.8 ± 1**	3.2 ± 0.28	<0.05
S. Na (mEq/1)	125.6 ± 0.57	128 ± 0	129 ± 0.57	NS
S. K (mmol/1)	3.6 ± 0.21	3.7 ± 0.26	4.6 ± 1.3	NS
S. Osmolality (mOsmol/1)	253 ± 1.6	261 ± 2.2	279 ± 4.3	<0.05
U. Na/Cr (mEq/1)	115 ± 8.1	90 ± 7.07	50.9 ± 3.6	0.01
U. glucose (mmol/1)	0.88 ± 0.11	0.96 ± 0.19	0.73 ± 0.12	NS
U. urea (mmol/1)	126.3 ± 45.9	81 ± 34.32	50.3 ± 30	<0.05
U. K (mmol/1)	9 ± 0.8	8 ± 0.7	7.3 ± 0.17	NS
U. Osmolality (mOsmol/1)	400.6 ± 70.1	277.9 ± 10	114.9 ± 3	0.01

* P < 0.05 between patients with CSW and Hyponatremia of unknown cause

** P <0.05 between patients with SIADH and CSW

DISCUSSION

Hyponatremia is the most common electrolyte abnormality seen in general hospital patients, with an incidence of about 1% in USA[2,9].

In the current study, hyponatremia was detected in 10.7% of patients with acute cerebral insult. This percentage is comparable to the result of another study from Germany which recorded hyponatremia in 10.3 % of children with acute CNS insults[6]. The present study included 38 patients with acute bacterial meningitis, partially treated meningitis, tuberculous meningitis and meningoencephalitis; hyponatremia was detected in 4 (10.5%) patients. In comparison with other studies, Bussmann et al reported hyponatremia in 2 out of 23 (8.7%) patients with acute bacterial meningitis, partially treated meningitis and tuberculous meningitis, while Von-vigier et al described hyponatremia in 97 out of 300 (32.3%) patients with CNS infection[6,10]. The difference in percentage of hyponatremia among different studies may be related to the difference in both numbers of patients and diagnostic criteria.

This study included one patient with tuberculous meningitis who had hyponatremia due to SIADH. This is similar to Bussmann et al who reported one patient with tuberculous

meningitis who had hyponatremia due to SIADH[6]. While Rapoport et al described a salt losing state as a possible cause for hyponatremia in patients with tuberculous meningitis[11].

We found hyponatremia in three patients (37.5%), which was caused by SIADH (acute bacterial meningitis, tuberculous meningitis and intracranial hemorrhage) and in 2 out of 8 (25%) cases due to CSW (intracranial abscess and intracranial hemorrhage). In the remaining 3 (37.5%) patients, the clinical and laboratory data were insufficient for further classification and the cause of hyponatremia was unknown.

In comparison with other studies, Bussmann et al reported SIADH in 7 out of 20 (35%) hyponatremic patients and CSW in 9 out of 20 (45%) and in 4 patients the diagnosis was unknown because of insufficient clinical and laboratory data[6]. Narotam et al reported increased percentage of CSW with evidence of dehydration as a cause of hyponatremia and postulated that increased atrial natriuretic peptide (ANP) may be the cause of this condition[12].

This study demonstrated that patients with acute CNS diseases have significantly lower levels of serum sodium, osmolality and glucose compared to the control group, while patients with acute CNS diseases have significantly higher levels of urea and osmolality compared to the control group. This is similar to Bussmann et al and Von-vigier et al who demonstrated low serum levels of sodium and osmolality and high urine osmolality in patients with acute CNS diseases relative to the control and no significant change in serum potassium level between the two groups. However, these studies did not reveal any relationship between patients and controls regarding serum glucose and urine urea[6,10].

Most hyponatremic disorders are associated with hypoosmolality[13]. The fall in the levels of serum osmolality indicates excess total body water relative to body solutes[14]. The counteractive mechanism to volume expansion is urine sodium loss via an increased glomerular filtration and decreased proximal tubular sodium reabsorption[15].

The serum levels of glucose, sodium and osmolality in patients with hyponatremia were significantly lower compared to the non hyponatremic patients while the urinary levels of Na/Cr ratio, urea, and osmolality, were significantly higher in patients with hyponatremia compared to patients without hyponatremia. Serum urea and potassium showed no significant changes in hyponatremic patients compared to patients without hyponatremia. Although similar findings were reported by Bussmann et al, other studies reported low serum urea in hyponatremic patients[6,16].

Hyponatremia patients in this study were discharged without adverse consequence. Arrangement for long- term follow up for neurological sequelae was not possible. In a study performed in USA it was found that 3.7% of patients had neurological sequelae and 12% of them ultimately died, although they reported that the prognosis appears to be more clearly related to the underlying medical disorder rather than to the hyponatremic state or its correction[16].

CONCLUSION

From this study, we may conclude that hyponatremia was not uncommon in patients with acute CNS insult as it was detected in 10.7% of these patients. The findings of the

study suggest that CSW develops at least as frequently as SIADH in children with acute CNS disease. Thus, it is recommended that serum sodium should be monitored routinely for all patients with acute or chronic central nervous system diseases, especially those on drugs or those needing intravenous fluids to avoid iatrogenic hyponatremia. Serial measurements are also needed after a baseline measurement on admission.

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