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Original paper

Clinical Manifestations of Hyponatremia and Hypernatremia in Under-Five Diarrheal Children in a Diarrhea Hospital

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ABSTRACT

Objective: To study clinical manifestations and outcome of hyponatremia and hypernatremia in children with diarrhea.

Method: We compared children aged 0–59 months hospitalized from 1 January to 31 December 2013 with hyponatremia (serum sodium <130 mmol/l), hypernatremia (serum sodium >150 mmol/l) and normonatremia (serum sodium 135–145 mmol/l).

Results: The case fatality was significantly higher among the children with hypernatremia and hyponatremia than normonatremia. A logistic regression analysis adjusting for potential confounders revealed that children with hyponatremia are more likely to have convulsions, have severe acute malnutrition and be of older age compared with children with normal serum sodium. Children with hypernatremia are more likely to have convulsions and dehydration than normonatremic children (for all $p < 0.05$).

Conclusion: Early diagnosis and prompt management of hypo- and hypernatremia by identifying simple clinical predicting factors of these two conditions in diarrheal children <5 years of age is critically important to prevent deaths in such children, especially in resource-limited settings.

KEYWORDS: children, deaths, diarrhea, hypernatremia, hyponatremia

INTRODUCTION

Diarrheal disease is the second leading cause of death and accounts for nearly 9% of 6.3 million global deaths in children <5 years of age, and 6% of deaths in children <5 years of age in Bangladesh [1]. Most of these deaths are associated with diarrheal complications and/or associated problems [2, 3]. A standardized management protocol for severe malnutrition, a common problem associated with diarrhea, was implemented in our hospital in 1996. This management

protocol reduced the death rate among severely malnourished children by 47% [2]. Despite this achievement, hyponatremia (serum sodium <130 mmol/l) and hypernatremia (serum sodium >150 mmol/l), two main complications of diarrhea, are still important causes of death both in well-nourished and malnourished children [3, 4]. Moreover, globally hyponatremia and hypernatremia are also considered as common problems in children with diarrhea [5]. They are known to contribute to morbidity and often other morbid conditions including seizures and encephalopathy [4].

Clinical manifestations of hyponatremia include lethargy, disorientation and depressed motor reflexes, which often overlap with manifestations of hypernatremia [6]. Severe hypernatremia (>170 mmol/l) may present with hyperthermia, seizures and coma [7]. If not identified early and managed properly, children may develop neurological sequelae [8]. Owing to a wide range of overlapping manifestations, hyponatremia and hypernatremia are often underdiagnosed, and timely intervention is delayed [8].

Children with malnutrition and diarrhea are more prone to develop hyponatremia and have a higher mortality rate [4]. On the other hand, most studies revealed that hypernatremia occurs primarily in dehydration associated with diarrhea [9, 10]. Improperly prepared oral rehydration salt (ORS) solution, excessive intake of the same and rotaviral infection are thought to be the major causes of hypernatremia in diarrhea and are associated with life-threatening complications [9]. Thirty years ago, the consequences of hyponatremia and hypernatremia with acute diarrhea were evaluated in Bangladesh [5], which reported a high-case fatality rate with hyponatremia (>10%). A correlation of malnutrition and dehydration was also demonstrated [5]. However, there is an obvious change in the trend of the consequences of these two fatal conditions. Since the earlier study, no further research on the pattern of hyponatremia and hypernatremia has been undertaken in this specialized setting of diarrhea and malnutrition. Our study aimed to evaluate the associated factors of hyponatremia and hypernatremia and outline the characteristics of such children in the setting of diarrheal disease.

MATERIALS AND METHODS

Study site and population

This study was conducted in the Dhaka hospital of International Centre for Diarrheal Disease Research, Bangladesh (icddr,b). This is the largest diarrheal treatment center in the world, providing care and treatment to >140,000 patients of all ages annually. Patients often come with diarrheal illnesses and/or other associated problems, including pneumonia, malnutrition, sepsis and electrolyte abnormalities. In the year 2013, the total number of children <5 years of age admitted was 98,506; those who had serum electrolytes measured during hospitalization were included in our study, and their medical data were extracted from the hospital electronic medical record system. The majority of the care seekers were from a poor socioeconomic background and lived in urban and pre-urban Dhaka. Care is provided by a professional team, which includes junior and consultant physicians, nurses, counselors and dietary workers in a multidisciplinary approach. Patients were treated according to the written protocolized hospital management plan for severe acute malnutrition (SAM), and treatment for hyponatremia and hypernatremia was provided when required [11, 12]. During hospitalization, all treatment is provided free of cost, which includes drugs, food, laboratory investigations and other logistic support.

Study design

This study was an unmatched retrospective medical record analysis with a case control design. We studied children of either sex, aged 0–59 months, who attended the Dhaka hospital during 1 January to 31 December 2013, and had serum electrolytes measured during hospitalization. Patients' medical records were stored in a computerized hospital management system, which is access guarded. The data were collected anonymously, and children were organized into three groups: normonatremia (serum sodium 135–145 mmol/l), hyponatremia (serum sodium <130 mmol/l) or hypernatremia (serum sodium >150 mmol/l). Children with hyponatremia and hypernatremia were compared separately from normonatremic children.

Data management and analysis

All data were entered into a database (SPSS version 17.0; Chicago, IL, USA). Differences in proportions were compared by the Chi-square test or Fisher-Exact test, as appropriate. Differences in means were compared by *t*-test (for normally distributed data), and differences in medians were compared by Mann–Whitney test (for data that were not normally distributed). *p*-values <0.05 were considered statistically significant. Strength of association was determined by calculating odds ratios and their 95% confidence intervals. In univariate models, characteristics analyzed included age, diarrhea after admission, fever on arrival, convulsion on presentation, no rehydration fluid intake before hospitalization, abnormal mentation (either lethargic or irritable), dehydration on arrival, edema, association of SAM, association of sepsis, development of septic shock, association of pneumonia and death in hospital. Finally, we performed logistic regression analysis to identify characteristics that were significantly associated with hyponatremia and hypernatremia after adjusting for the covariates. In the regression model, characteristics that were significantly associated with hyponatremia or hypernatremia by univariate analyses were considered as independent variables, whereas hyponatremia and hypernatremia acted as dependent variables in two different models.

Ethical approval statement

The study (protocol number: PR-14063) was approved by icddr,b's Research Review and Ethical Review Committees. All the data collected were kept confidential.

RESULTS

We reviewed 1224 medical records of children admitted from January to December 2013 who fulfilled our inclusion criteria. Of these children, 693 (56.6%) were normonatremic, 292 (23.8%) were hyponatremic and rest 239 children (19.5%) were hypernatremic. Mean serum sodium levels among children with normonatremia, hyponatremia and hypernatremia were 138.7 ± 2.8, 125.8 ± 4.2 and 165.2 ± 13.4, respectively.

The median ages of children with normonatremia, hyponatremia and hypernatremia with their differences are shown in Table 1. The case-fatality rate was significantly higher among both the groups of hyponatremia and hypernatremia compared with normonatremia group (Fig. 1). In univariate analyses, children with hyponatremia more often presented at an older age, with convulsion, abnormal mental status, dehydration, SAM, septic shock and pneumonia. Similarly, children with hypernatremia more often presented with fever, convulsion, abnormal mental status, dehydration, septic shock and pneumonia. Distribution of diarrhea, no rehydration fluid intake at home, edema and sepsis among the groups were statistically insignificant (Table 1).

In logistic regression analyses, after adjusting for likely confounders (Table 2), children with hyponatremia were significantly more likely to present at an older age, with convulsion, and SAM (Table 2). For children with hypernatremia, the significant associations found after logistic regression analysis were convulsion and dehydration (Table 3).

DISCUSSION

Our study evaluates children suffering from hyponatremia and hypernatremia, which are serious complications of diarrhea in developing countries with a high burden of diarrhea and malnutrition [4, 5]. Thirty years ago, Samadi *et al.* [5] described the consequences of hyponatremia and hypernatremia in children with diarrhea in Bangladesh. Hyponatremia was associated with a high case fatality rate of $>10\%$, whereas hypernatremia-associated deaths were only 1.2%. Our study suggests that the scenario has now changed, with case fatality in hypernatremia being 12% and in hyponatremia only 5%. Malnourished children are typically hyponatremic despite having excess total body sodium because of an intracellular shift of sodium related to an inefficient Na^+/K^+ pump [13]. During states of volume depletion, using fluids containing large quantities of sodium may lead to a high mortality rate [5]. In view of this fact, World Health Organization has revised the formulation of standard rehydration salt (ORS) with a new low-sodium-containing ORS (the hypo-osmolar ORS) for the past two decades, which may have an

Table 1. Comparison of baseline characteristics among the under-five children with normonatremia, hyponatremia and hypernatremia on admission

Characteristics	All patients $n = 1224$ n (%)	Normonatremia 693 (56.62%)	Hyponatremia 292 (23.86%)	Hypernatremia 239 (19.53%)	Normo vs. hypo OR (95% CI) p-value	Normo vs. hyper OR (95% CI) p-value
Age in months (median, IQR)		7.0 (4,12)	11.0 (4.3, 24)	7.0 (4,10)	–	–
					<0.001	0.1
Diarrhea during hospitalization	1088 (88)	610 (88)	269 (92)	209 (87)	1.59 (0.96–2.66)	0.95 (0.59–1.52)
					0.58	0.81
Fever during admission	491 (40)	260 (38)	119 (41)	112 (47)	1.15 (0.86–1.53)	1.47 (1.08–2.00)
					0.34	0.01
Convulsion during admission	275 (22)	62 (9)	119 (41)	94 (39)	3.15 (2.13–4.66)	6.60 (4.49–9.70)
					<0.001	<0.001
No rehydration fluid intake before hospitalization	229 (19)	137 (20)	51 (18)	41 (17)	0.86 (0.59–1.24)	0.84 (0.56–1.26)
					0.40	0.37
Abnormal mental status (lethargic or irritable)	609 (50)	307 (44)	171 (59)	131 (55)	1.78 (1.33–2.37)	1.53 (1.12–2.07)
					<0.001	<0.001
Dehydration on arrival (some or severe sign)	760 (62)	398 (57)	198 (68)	164 (69)	1.56 (1.16–2.10)	1.62 (1.17–2.24)
					<0.001	<0.001
Edema	13 (1)	6 (1)	6 (2)	1 (1)	2.40 (0.68–8.47)	0.48 (0.02–4.03)
					0.12	0.49
Association of SAM (>-3 WLZ)	192 (16)	92 (13)	66 (23)	34 (14)	1.91 (1.32–2.75)	1.00 (0.69–1.69)
					<0.001	0.71
Association of sepsis	89 (6)	51 (7)	25 (9)	13 (5)	1.18 (0.69–1.99)	0.72 (0.37–1.40)
						0.31
Development of septic shock	56 (5)	12 (1)	17 (6)	27 (11)	3.51 (1.57–7.93)	7.23 (3.44–15.40)
					<0.001	<0.001
Association of pneumonia	345 (28)	193 (27)	61 (21)	91 (38)	0.68 (0.49–0.96)	1.59 (1.16–2.20)
					0.02	0.003
Death in hospital	56 (5)	12 (2)	15 (5)	29 (12)	3.07 (1.34–7.09)	7.84 (3.77–16.57)
					0.005	<0.001

Note. Figures represent n (%), unless specified. OR = odds ratio; CI = confidence interval; IQR = interquartile range.
Legend: SAM = severe acute malnutrition; WLZ = weight for length Z-score.

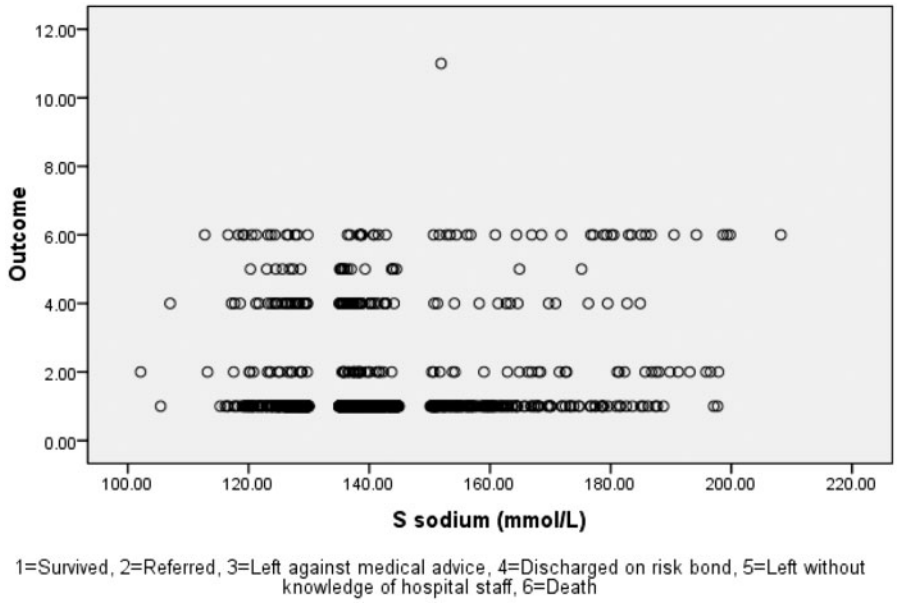

Fig. 1. Association of death with different levels of serum sodium.

Table 2. Independent predictors of hyponatremia in under-five diarrheal patients

Predictors	Unadjusted		Adjusted	
	OR (95%CI)	*p*	OR (95% CI)	*p*
Age	–	<0.001	**1.05 (1.04–1.06)**	**<0.001**
Convulsion	3.15 (2.13–4.66)	<0.001	**2.86 (1.91–4.29)**	**<0.001**
Presence of SAM	1.91 (1.32–2.75)	<0.001	**2.32 (1.58–3.41)**	**<0.001**
Abnormal mental status	1.78 (1.33–2.37)	<0.001	1.35 (0.9–1.88)	0.08
Presence of dehydration	1.56 (1.16–2.10)	<0.001	1.24 (0.88–1.75)	0.22

Note. Exclusion variables: Septic shock and pneumonia variables were excluded from the regression model, as in 2/2 table, one cell value was 0. Adjustment variables: Abnormal mental status and presence of dehydration.

Table 3. Independent predictors of hypernatremia in under-five diarrheal patients

Predictors	Unadjusted		Adjusted	
	OR (95%CI)	*p*	OR (95% CI)	*p*
Convulsion	6.60 (4.49–9.70)	<0.001	**6.94 (4.74–10.15)**	**<0.001**
Presence of dehydration	1.62 (1.17–2.24)	<0.001	**1.84 (1.28–2.66)**	**0.001**
Abnormal mental status	1.53 (1.12–2.07)	<0.001	1.10 (0.77–1.57)	0.59
Fever on admission	1.47 (1.08–2.00)	0.01	1.19 (0.86–1.66)	0.30

Note. Exclusion variables: Association of pneumonia variable were excluded from the regression model, as in 2/2 table, one cell value was 1. Adjustment variables: Abnormal mental status and fever on admission.

impact in reducing the mortality related with volume overload in hyponatremic children [14]. There has been a reduction in the incidence of invasive diarrhea owing to Shigellosis in Bangladesh, which could have resulted in a reduced prevalence of hyponatremia. This may have an impact in reduced mortality from hyponatremia [15]. Moreover, diagnosis of hypernatremia is still underestimated by the clinicians owing to lack of overt clinical signs of dehydration in hypernatremia children [16].

The prevalence of hypernatremia among hospitalized patients has been reported to be 2.5–12%, while mortality rates vary between 24% and 60% [17, 18]. Death can occur either owing to the consequence of hypernatremia itself or as a result of complications during correction of dehydration [18]. In our study, case fatality associated with hypernatremia seems to be increasing compared with previous reports [5]. Several factors may contribute to the situation, such as change in the etiology of diarrhea [19] and the concept of preparation of ORS solution for managing dehydration [20]. This is an important aspect to reduce diarrhea-related deaths and further research, particularly qualitative, needs to be undertaken.

We observe a significant association between serum sodium concentration and abnormal mental status that includes lethargy, irritability or convulsions. Most importantly, commonly associated conditions of hypernatremia in developing countries such as diarrhea and vomiting cause excess loss of water that may exceed electrolyte loss and lead to an increase in the osmolarity of body fluids. As a result, there is movement of water from the cells to the extracellular fluid compartment. This results in intracellular dehydration, subsequently resulting in brain shrinkage, which predisposes the child to petechial brain hemorrhages that may manifest convulsion [16]. Alternatively, convulsion in hyponatremia occurs owing to brain cell swelling as a result of Na^+ deficit in the extracellular fluid compartment, which is sufficient to lead to a devastating neurological outcome [21]. From our study, it can be postulated that convulsion on presentation can be used as a screening tool for sodium disorders, and should be managed immediately to prevent future neurological complications.

Our study describes an association between hyponatremia with SAM and pneumonia. A number of studies have reported the association of hyponatremia with SAM [22, 23]. Children with pneumonia may often present with syndrome of inappropriate Antidiuretic Hormone (ADH) secretion resulting in hyponatremia. Moreover, co-existence of pneumonia and hyponatremia often occurs in SAM children with minimum clinical manifestation of pneumonia owing to poor inflammatory response and hypokalemia in SAM children [24–26].

We observed the association of dehydration with hypernatremia. Clinical signs such as restlessness and thirst are common signs of dehydration and hypernatremia. This may have led to an association of dehydration with hypernatremia [6, 7, 27].

The main limitation of this study is the retrospective nature of the study that may restrain interpretation of information. Moreover, the data on rehydration fluid used at home could not be retrieved, which could contribute more to the findings. Finally, this report reflects the experience of just one urban hospital that primarily provides care for children with diarrheal disease and so this may not be generalizable to all patients admitted elsewhere.

In conclusion, both hyponatremia and hypernatremia are common diarrheal-associated complications in developing countries that have high-case fatality. The findings of our study have significant clinical importance to generate future research hypotheses for targeted identification of hyponatremia and hypernatremia and early interventions to reduce diarrhea-related deaths in developing countries.

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