LONG-TERM DEVELOPMENTAL ASSESSMENT OF CHILDREN RECOVERED FROM HYPERNATREMIA

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ABSTRACT

Purpose: Imbalances in sodium result in acute neurologic symptoms such as seizures and impaired mental status. Studies investigating the long-term consequences of hypernatremia on cognitive, motor, and language development in children are limited. The aim of this study was to assess the long-term impact of hypernatremia on children's cognitive, motor, and language development. **Methodology:**It was an observational study conducted from March 2016 to March 2017 in Dhaka Hospital of icddr,b. In this study,211 children with acute watery diarrhea accompanied with hypernatremia (serum sodium level ≥150 mmol/L) who had already been enrolled in a previous observational study were prospectively followed for one year.The objective was to investigate if there are any long term neurologic and developmental consequences of hypernatremia in those children.

Physical, cognitive, motor, and language development as well as expressive or receptive expression of the children were assessed using a standard tool at the time of discharge (Baseline) and 12 months after discharge (End line). We also assessed IQ in a subgroup of children > 36 months (n=57) using the Wechsler Preschool and Primary Scale of Intelligence in parallel. **Results:** Among the 211 participants, developmental assessment on motor, cognitive, and language development test was done on 140 (66.3%) children. The mean age of the children at the time of discharge from the hospital (baseline) was 7.9±4.5 months. Compared to mild (serum Na 150 mmol/L to less than 160 mmol/L), and moderately (serum Na 160 mmol/L to 169 mmol/L) hypernatremia, children with severe hypernatremia (serum sodium >170mmol/L) significantly had lower mean scores on the motor, fine motor, and language development score at baseline after adjusting age and weight for the age z score. Although there was an improvement in motor, language, and socioemotional scores, significant improvement was only observed with cognitive function at the end line (p=0.002). In Mmultiple regression after adjusting for potential confounders such as levels of hypernatremia, parents' education, age of the child, and WAZ, these factors were showed significantly associated with the cognitive function of children. There was no difference in mean IQ level performed at the end-line among the children with different level of hypernatremia (mild, moderate or severe). **Conclusion:** Children with hypernatremia had poor developmental scores in cognitive, motor, language, and socio-emotional domains at the time of recovery from hypernatremia. However, other than cognitive score, there was no significant improvement in motor or language development at 12 months in children recovering from hypernatremia. Further studies are therefore warranted to reveal any association of motor or language deficit with neurological deficit in those children beyond 12 months.

KEYWORDS: Hypernatremia, children, developmental assessment

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Introduction

Child development takes place as an ongoing biological and psychological process influenced by the environment, caregivers, community, and society. More than 250 million children under the age of 5 in low and middle-income countries (LMICs) are at risk of not attaining their full development potential (Black et al., 2017, Lu et al., 2016, McCoy et al., 2016). Sodium is one of the major extracellular electrolytes, which is important in maintaining extracellular fluid volume and potentials across cell membranes (Shrimanker and Bhattarai, 2020, Terry, 1994). Imbalances in sodium concentrations have been recognized to manifest as headaches, confusion, nausea, and restlessness. The rapid changes in sodium concentrations result in acute neurologic symptoms such as seizures and impaired mental status (Terry, 1994, Sahay and Sahay, 2014). Improperly prepared oral rehydration salt (ORS) solution, excessive intake of the same, and Rota viral infection are thought to be the major causes of hypernatremia in diarrhea and are associated with life-threatening complications (Paneth, 1980).

Only a few studies have addressed the relationship between serum sodium levels and cognitive function; however, the definition of cognitive function appears to vary among different studies. In addition, studies only examine single domains of cognitive function, or assess multiple domains grouped as a single variable. Previous studies addressing the relationship between serum sodium levels and cognitive function are limited. Within the past several years, important research has linked early childhood diarrhea, with cognitive deficits several years later (Berkman et al., 2002, Niehaus et al., 2002). This association is attributed to the concept that the first two years of life represent a critical period in brain development, and that if severe diarrhea causes its characteristic dehydration and nutrient loss during this time, permanent effects on cognitive function may result. Although these studies demonstrated impaired cognitive deficit later in life, the role of disease, malnutrition, and social environment on such deficit has not been investigated. To our knowledge, there has been no well-controlled study that has examined the long-term effects of hypernatremia on the cognitive functions of children. Therefore, we propose to conduct a longitudinal study to follow developmental consequences, including motor, language and cognitive development among children who recovered from an episode of hypernatremia complicating acute watery diarrhea.

Materials and Methods

Study design

The study was an observational study conducted in Dhaka hospital of International Centre for Diarrheal Disease Research, Bangladesh (icddr,b).from March 2016 to March 2017.

Study subject

The study participants were enrolled in a cohort of under 5 years' diarrheal children who were enrolled in a prospective observational study conducted from August 2013 to October 2015 presented with hypernatremia. Hypernatremic children were stratified as having mild hypernatremia (serum Na 150 mmol/L to less than 160 mmol/L), moderate hypernatremia (serum Na 160 mmol/L to 169 mmol/L) and severe hypernatremia (serum Na ≥ 170 mmol/L).

Study settings

This study was conducted in the Dhaka Hospital, icddr,b. Dhaka Hospital of the icddr,b provides care to around 150,000 patients per year of all ages with diarrhea, with or without complications or comorbidities. Diarrhea is the presenting problem in all patients admitted to icddr,b, however, features of acute lower respiratory tract infections and severe malnutrition are also commonly seen as comorbidities. The vast majority of the patients come from poor socioeconomic backgrounds in urban and peri-urban Dhaka, the capital city of Bangladesh.

Study activities

We followed a cohort of 211 children who presented with hypernatremia (serum sodium >150 mmol/l) and who had already been enrolled in a previous observational study. The objective was to investigate if there are any long term neurologic and developmental consequences of hypernatremia in those children.

All of the participants received standard care for diarrhea mediated hypernatremia management, aiming to reduce the case fatality rate among children admitted with hypernatremia and diarrhea employing an optimized management protocol based on consensus. After 1 day of recovery from acute illness, they were subjected to a full physical, neurological, nutritional and cognitive assessment (Baseline assessment) and discharged for home. All of them were brought back to Dhaka hospital after 1 year to follow-up the assessments (End line assessment)

Procedure for Developmental assessment

The cognitive, motor and neuropsychological assessments were done at in a Dhaka Hospital in a quiet room simulation of a home environment and conducted by trained Psychologists using standard validated procedures. For children up to 36 months. Global Intelligence assessment was measured using the Bayley Scales of Infant Development-III (BSID-III) (Bayley, 2006). For children >36 months old, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) used for testing IQ.

Tools for assessing development

The BSID-III is a gold-standard observational measure of development for children aged less than 42 months. The tool measures development by direct observation across five subscales: cognition, receptive and expressive language, and fine and gross motor skills (Albers and Grieve, 2007). Bayley third editions have been the instruments of choice for many nutrition and child development studies in developing countries. The tool has three major subsets: i) cognitive, ii) motor (fine and gross motor subtests) and ii) language (receptive and expressive language subtests) and one subtest social-emotional behavior of children, from the mother's or primary caregiver's report. The fine motor subset measures the motor control skills of the hands and fingers like grasping and drawing, and the gross motor measures the complex movements of the large body like sitting, walking, jumping etc. The receptive communication subset measures the ability of the child to recognize sounds and understanding spoken words and directions, while the expressive communication scale measures the ability of the child to communicate through sounds, gestures, facial expressions or words (simple or difficult) and also assesses how they can combine words into phrases, sentences and paragraphs. The scale consists of series of developmental play tasks and takes 45-60 minutes to administer. BSID-III has been used in Bangladeshi studies after validation of cognitive, language and fine motor subsets (Aboud et al., 2013, Singla et al., 2014). The scores of urban and rural children (<15 months) in Bangladesh were within the normal range with good inter-observer reliability and short term test retest stability (Aboud et al., 2013).

Trained assessors administered the five Bayley-III subscales for assessment of cognitive, receptive communication, expressive communication, fine motor, gross motor. Each test subscale yields a total raw score based on the number of items passed; the raw score is then converted to a scaled score based on normative data. Each scaled score has a mean of 10 and a standard deviation (SD) of 3. The scaled scores for the five subscales are then converted to composite scores as follows: the cognitive composite score (based on the cognitive scaled score), the language composite score (combination of receptive and expressive communication scaled scores), and the motor composite score (combination of fine and gross motor scaled scores). Composite scores are derived from the scaled scores using normative test data; each composite score has a normative mean value of 100 (the developmental quotient mean) and a SD of 15 quotient points. The mean and SD for the Bayley-III composite scores are identical to those of the Bayley-II, although the latter included only mental and motor developmental indexes (Anderson et al., 2010, Spittle et al., 2010, Danzer et al., 2010).

Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) (Wechsler, 2002) was used to measure the IQ of children. WPPSI-III is a clinical instrument designed for assessing the intelligence (cognitive ability) of children ages 2 years and 6 months through 7 years and 3 months (Wechsler, 1967). It has five subscales: i) verbal IQ (VIQ), ii) Performance IQ (PIQ), iii) Full scale IQ (FSIQ), iv) processing speed quotient (PSQ) and v) general language composite (GLC). In the present study, we performed only VIQ, PIQ, FSIQ at 12 months' follow-up. The age range has been divided into two age bands: a) 2:6-3:11 and b) 4:0-7:3 with different subset batteries. There are four composite scores for the lower age band as VIQ, PIQ, FSIQ and GLC while there are five composite scores for the upper age band as VIQ, PIQ, FSIQ. Raw scores of verbal (information, vocabulary, and comprehension), performance (block design, matrix reasoning, and picture concepts), and processing speed (coding) subtests will be used in unconverted form as well as in converted form to scaled scores, the sum of which will be used to calculate the full scale IQ. WPPSI has been previously used in Bangladesh after cultural modification (Aboud et al., 2013).

Ethical consideration

The study was approved by the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of icddr,b. Before enrollment, signed informed consent was obtained from the parents or guardians of the children. The consent form was written in Bangla in a simple language that was easily understood by the legal guardians even with little or no educational background. The consent form was read out to the parent or guardian if he or she was unable to read it. Signed consent or a left thumb impression was obtained from them for the participation of their children in the study.

Data Management and Analysis

Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL) and STATA version 13. For dichotomous factors, a normal approximation test (Chi squared test) or Fisher's exact test used; for continuous variables, either a t-test or Mann-Whitney test was used. Multivariable techniques (e.g., logistic regression) was used to identify independent risk factors. Logistic regression analysis was used to model the relationship between a binary outcome and one or more predictor variables. Linear regression was used to model the relationship between a quantitative outcome and one or more predictor variables. The strength of the association was determined by estimating odds ratios (OR) or standardized regression coefficients and their 95% confidence intervals (CI). P-values < 0.05 was considered statistically significant.

Mean difference of cognitive, motor, language score and socio-emotional scores controlling for age and other confounders (maternal age and education, nutritional status etc.) were analyzed using ANCOVA comparing between different hypernatremic groups (mild, moderate or severe). Multiple regression was used to model the relationship between developmental scores (dependent variable) and one or more confounders (independent variables) among different hypernatremic groups. Standardized regression coefficients and 95% confidence intervals was used to determine the strength of the association.

Result

Among the 211 participants,28% (60 participants) could not be traced out because of outmigration from the study area. The developmental assessment tests were performed on the remaining 66% (140 participants) one year after discharge between March 2016 and March 2017.

About one-third of the children belonged to poorer households. Mean age of the children at the baseline assessment was 7.9±4.5 months. The mean and SD of children after 1 year at the time of endline evaluation was 34.6± 7.88 months. A greater number of male children presented with mild hypernatremia than their female counterparts (Table-1). At baseline the mean weight and length were 6.6 ±2.0 kg and 66.2 ± 7.8 cm. The corresponding values at the endline were. 12.4 ±3 kg and 89.5± 7.5cm. Post hoc analysis showed that severe hypernatremic children were significantly associated with an increased incidence of co-morbidities like acute kidney injury (p=0.02) and pneumonia (p =0.03);(Table-1).

Table 1. Sociodemographic characteristics study children at the time of recovery from hypernatremia (HN).

Parameter	Mild HN (n=110)	Moderate HN (n=58)	Severe HN (n=43)	p- value
Sex; n(%)				
Male	68 (61.8)	41 (70.7)	24 (55.8)	0.288
Female	42 (38.2)	17 (29.3)	19 (44.2)	0.288
Low Birth Weight	18 (16.4)	10 (17.2)	7 (16.3)	0.979
Anthopometry				
Length/Height (Mean±SD)	65.9±8.0	66.4±7.5	67.0±7.8	0.713
Weight (Mean±SD)	6.7±2.3	6.5±1.8	6.6±1.9	0.714
WAZ (Mean±SD)	-1.86±1.84	-2.30±1.5	-2.22±1.75	0.240
HAZ (Mean±SD)	-1.48±1.80	-1.56±1.57	-1.45±2.04	0.944
WHZ (Mean±SD)	-1.18±1.97	-1.78±1.68	-1.71±1.33	0.071
Place of Residence n(%)				
Dhaka city	27 (24.6)	9 (15.5)	7 (16.3)	0.285
Within Dhaka district	23 (20.9)	8 (13.8)	7 (16.3)	
Outside Dhaka	60 (54.6)	41 (70.7)	29 (67.4)	
Co-morbidity				
Acute kidney infection (AKI)*	20 (18.2)	14 (24.1)	17 (39.5)	0.021▼
Pneumonia	34 (30.9)	19 (32.8)	23 (53.5)	0.027✦
Sepsis	8 (7.3)	7 (12.1)	5 (11.6)	0.497
Maternal Age	22 (20,28)	25 (20, 27)	23 (20,25)	0.816
Mother's Education n(%)				
Illiterate	15 (13.6)	9 (15.5)	8 (18.6)	0.599
Up to Primary	29 (26.4)	14 (24.1)	15 (34.9)	
Above Primary	66 (60.0)	35 (60.3)	20 (46.5)	
Father's Education n(%)				
Illiterate	26 (23.6)	17 (29.3)	13 (30.2)	0.862
Upto Primary	25 (22.7)	14 (24.1)	10 (23.3)	
Above Primary	59 (53.6)	27 (46.6)	20 (46.5)	
Asset Quintile n(%)				
Poorest	20 (18.2)	15 (25.9)	2 (4.7)	0.232
Poorer	19 (17.3)	11 (19.0)	10 (23.3)	
Middle	21 (19.1)	10 (17.2)	10 (23.3)	
Rich	24 (21.8)	10 (17.2)	13 (30.2)	
Richest	26 (23.6)	12 (20.7)	8 (18.6)	
Income (BDT, in K) (Median, IQR)	12 (8, 20)	10 (7, 20)	10 (7, 15)	0.401

*Posthoc: ▼ Mild vs Moderate; ✦ Mild vs Severe and Moderate vs Severe HN

At the baseline, children with severe hypernatremia had significantly lower scores on motor (p=0.01), fine motor and language development (p=0.01), receptive communication (p=0.04) and expressive communication (p=0.01) compared to mild and moderately hypernatremic participant.. However, cognitive scores were comparable among children presenting with different severity levels (Table-2).

Table 2. Developmental outcomes of the hypernatremia children based on the level of hypernatremia at recovery.*

	Mild HN (n=110)	**Moderate HN(n=58)**	**Severe HN (n=43)**	p-value
Cognitive[a]	86±16	89±15	83±18	0.066
Motor [a]	84±15	87±14	79±16	0.008▼
Fine motor[b]	7.6±2.7	8.3±2.5	7.2±2.9	0.045
Gross motor[b]	7.2±2.8	7.4±2.8	5.7±3.3	0.007✦
Language[a]	81±14	84±13	76±13	0.009▼
Receptive communication[b]	6.2±2.6	6.6±2.4	5.5±2.6	0.044▼
Expressive communication[b]	7.4±2.7	7.9±2.5	6.4±2.5	0.015▼
Socio-emotional[a]	95±14	95±14	96±13	0.842

Posthoc: ▼Mild vs Moderate and Mild vs Severe; *ANCOVA controlling for age and WAZ
[a]Composite score; [b] Scaled score

Long-term developmental consequences differed in three severity groups of hypernatremia. After adjusting for age and weight for the age Z-score (WHZ), composite scores of cognition and socioemotional domain of development showed a significant difference between baseline and end line assessment (p=0.002 and p=0.013 respectively) (Table: -3). In multiple regression, after adjusting for potential confounders such as severity of hypernatremia, parents' education, age, WAZ was significantly associated with cognition (Table-4). At the end line, there were no difference in verbal (85.29 vs76.79 vs 78.39), performance (89.16 vs 81.00 vs 83.16) and full scale (86.07 vs 76.87 vs 79.53) IQ levels among the children with three different severity categories of hypernatremia (mild, moderate or severe) (Table-5).

Table 3. Developmental outcomes of the case children on enrollment and after 12 months*.

	At the time of discharge n=140	At follow-up n=140	**p-value**
	Mean±SD		
Cognitive[a]	83.0±10.1	86.1±16.3	0.002*
Motor [a]	82.8±9.7	83.3±15.7	0.071
Fine motor[b]	7.1±1.7	7.6±2.8	0.118
Gross motor[b]	7.1±2.1	6.8±3.1	0.108
Language[a]	85.8±9.7	80.9±13.8	0.953
Receptive communication[b]	7.4±1.7	6.1±2.5	0.799
Expressive communication[b]	7.7±1.8	7.4±2.7	0.963
Socio-emotional[a]	100.3±6.9	93.9±13.1	0.013*

*ANCOVA controlling for age and WAZ**;** [a]Composite score; [b] Scaled score

Table 4. Multiple regression analysis predicting cognitive, motor and language score.

	COGNITIVE		MOTOR		LANGUAGE	
	B (95%CI)	P	B (95%CI)	P	B (95%CI)	P
Age	0.44 (0.05, 23.8)	0.025	0.31 (-0.07, 0.69)	0.113	0.22 (-0.13, 0.56)	0.22
WAZ	2.23 (1.13, 3.55)	<0.001	1.41 (0.21, 2.61)	0.022	0.73 (-0.37, 1.82)	0.192
Group	14.7 (5.6, 23.8)	0.002	8.20 (-0.71, 17.1)	0.071	0.18 (-7.92, 8.29)	0.964
R^2	0.11		0.07		0.08	

WAZ: Weight-for-age z score; Study time point: after 12 mon Follow up=0, At discharge=1
Model for cognitive score: step 1: age of the child entered, step 2: mother's education, father's education, WAZ offered, step 3: Study time point and types of HN entered
Model for motor score: step 1: age of the child entered, step 2: mother's education, WAZ offered, step 3: Study time point and types of HN entered
Model for language score: step 1: age of the child entered, step 2: mother's education, WAZ offered, step 3: Study time point and types of HN entered

Table 5. Distribution of IQ scores at follow up in children > 36 months based on level of hypernatremia.

Measurement	Mild HN	Moderate HN	Severe HN
Verbal IQ	85.29± 13.64	89.16±11.17	86.07±13.95
Performance IQ	76.79 ±11.71	81.00± 9.38	76.87 ±9.93
Full scale IQ	78.39 ±13.45	83.16± 10.67	79.53 ±11.63

Discussion

Our study, demonstrated a significant neurodevelopmental deficit in participants with severe hypernatremia in comparison to those with mild or moderate hypernatremia. The findings corroborates well with that of a cross sectional study conducted by Lee at al demonstrating association of serum sodium levels with cognitive function in elderly (Lee et al., 2021). mainly in the elderly population with low sodium level (β=4.25, SE=1.83, p=0.027).. The mechanism of the association between cognitive deficit and hypernatremia remains unclear. However, abnormalities in brain osmolyte levels might have played a role in cognitive development. The present study also revealed decreased cognitive outcome as observed during acute phase of diarrhea improves around 12 months after the episode indicating that the hypernatremic lesion occurred is temporary and recovers well with the progression of age. Although these complications decrease with the increase in age trajectory. The findings of the present study differ with that of Boskabadi et al.who has observed adverse effect child development over a period of 24 months. in children with no diarrheal illness (Boskabadi et al., 2017). The difference may be attributed to the antecedent causes of hypernatremia as the population of the present study had diarrheal illness. . Our study also showed that severe hypernatremic children had poor cognitive outcomes in comparison with mild to moderate hypernatremia. Parental education level may be a contributing factor for poor cognition in these children with severe hypernatremia. Study revealed that children's mothers with secondary schooling had 0.14 SD (95% CI 0.05-0.24) higher cognitive scores in comparison to children whose mothers had primary education only (Sania et al., 2019). Hypernatremia has also been associated with poor cognitive outcomes in underweight children. Systematic review revealed an association of malnutrition and poor cognition. The poor cognition as reported in this review may be attributed to reduction of intrauterine neurodevelopmental trajectory interrupted, as myelination and formation of synapse (Counsell and Boardman, 2005). The present study did not reveal any association between low birth weight and hypernatremia. Probable cause of not getting an association might be related to the small number of low birth weight children (about one-third) studied in present study.

This study found that mean IQ level among children more than 36 months' age were comparable with mild, moderate and severe hypernatremia, indicating that abnormalities in sodium level possibly did not exert any adverse effect afterward on the intelligent score. The present study was not designed to see the cognitive effects of hypernatremia in children long-term beyond 1 year. However, further study is warranted with a larger sample to confirm whether hypernatremia leads to any effect on IQ level or cognitive function long-term beyond one year in children presenting with diarrhea complicating with hypernatremia.

Conclusion

Children with hypernatremia had poor developmental scores in all domains of child development (cognitive, motor, language and socio-emotional) following the recovery of the illness. The poor development appears to be transient and spontaneous recovery takes place in the long run. Further large-scale studies are required to evaluate if there is any association between developmental consequences and neurological sequelae among children suffering from hypernatremia.

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