Evaluation of Nutritional and Developmental Consequences and Renal Function of Children who Recovered from Hypernatremia

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Declaration

I hereby declare that the whole of the work now submitted as a thesis entitled, "Evaluation of Nutritional and Developmental Consequences and Renal Function of Children who Recovered from Hypernatremia" in the Institute of Nutrition and Food science, Dhaka University for the degree of Doctor of Philosophy (PhD) is the result of my own investigation. The thesis has not been concurrently submitted for any other degree.

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This is to certify that the thesis entitled, “Evaluation of Nutritional and Developmental Consequences and Renal Function of Children who Recovered from Hypernatremia” is an original work done by Sayeeda Huq under my supervision for the degree of Doctor of Philosophy (PhD). It contains no material previously published or written by any other person except, wherever due references have been acknowledgement. Moreover, it has not been submitted before for any other degree.

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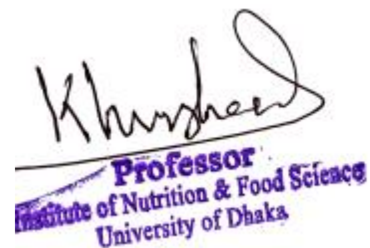

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Abstract

Background:

Hypernatremia (HN), defined as high sodium in the blood (≥145 µmol/L), is a serious complication of diarrheal diseases in children. However, clinical manifestations are usually observed in children in developing countries at the level of ≥150 µmol/L The primary cause of HN is excessive water loss relative to sodium loss. The resulting hyperosmolality can lead to neuronal cell shrinkage, causing brain injury, including widespread cerebral hemorrhage, thrombosis, subdural effusion, and permanent neurological deficits. Retrospective study conducted in icddr,b showed that 2.4-5.1% children with diarrhea had hypernatremia and case fatality ranges from 15-9%(Chisti et al., 2016).Deaths are often attributed to the severe effects of HN on the brain or to rapid rehydration, which can result in cerebral edema.

A prospective observational study was conducted at Dhaka Hospital of icddr,b from August 2013 to October 2015. In total, 259 children under five years old were enrolled. After treatment, 224 children were successfully discharged. The death rate was 13.5%, with neurological sequelae in 29.9%, acute kidney injury in 32.4%, and severe malnutrition in 44% of the children. However, post hypernatremia impact in long term on morbidity, nutritional status, cognitive development, and renal function is largely unknown. Therefore, it is imperative to evaluate nutritional status, growth, cognitive development, and renal function in long term among children recovered from hypernatremia.

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Methodology:

This Observational longitudinal study was conducted among children under five years of age who had hypernatremia and participated in the prospective observational study conducted from August 2013 to October 2015. The original study aimed to investigate neurologic complications and developmental consequences in children with hypernatremia. The sample size is based on 224 children who successfully recovered from the initial hypernatremia study. Accounting for a 25% attrition rate, the sample size was estimated to be 168. However, due to dropouts during follow-up, 143 children were successfully followed up in the present study. The study lasted from March 2016 to March 2017, and children were examined at the Dhaka Hospital of icddr, b.

All children were brought to Dhaka Hospital inpatient ward for a complete physical, nutritional, neurological, and cognitive assessment. A spot urine analysis was also performed to evaluate their kidney function. Upon arrival, each child's weight, height, and mid-upper arm circumference (MUAC) were measured using standard procedures. Data were collected using pre-designed and pre-tested Case Report Forms (CRFs), which included the child’s medical records, exact address, socio-demographic information, family status, living conditions, history of illness, and immunization status. Cognitive, motor and neuropsychological development were assessed by a trained psychologist using standard procedures. Two different tools were used depending on the child's age. The Bayley Scales of Infant Development-III (BSID-III) was used for children under 36 months, while the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) was used for children older than 36 months. Motor function was assessed using the Movement Assessment Battery for Children-II (MABC-II). A spot urine sample was collected from each child for

microscopic examination, and the protein-to-creatinine ratio was calculated to detect potential glomerular damage.

Results:

Of the 224 recovered hypernatremia children, 143 (64%) parents consented to participate in this study. The mean age of the children was 35 ± 8 months, and 59% were male. Mean± SD of weight and height of the study participants were 12.4 ±3.1 kg and 89.5 ±7.5 cm, respectively. Malnutrition was not significant in this study population. After stratified by two age groups, children aged up to 36 months and those older than 36 months, Median (IQR) of family income, 13000(10000,20000) vs. 11500 (8000,18000); maternal, 7(4,10) vs. 8(5,10); and paternal, 6(4, 9) vs. 8(1,10) education levels were comparable. Around 50% of the study children commonly presented with upper respiratory infections.

After 12 months of recovering from hypernatremia, half of the children had an increased protein-to- creatinine ratio. Children with mild hypernatremia were more likely to have raised urinary Pr/Cr ratio, though none presented with any evidence of urinary problems or glomerular damage. Eighty-six percent (86%) of the children from better socioeconomic status were less likely to have a high Pr/Cr ratio in comparison with their poorest counterparts (p=<0.001). Children under 36 months are twice more likely to have raised urinary Pr/Cr compared to those more than 36 months; 2.31(1.06, 5.02); p-0.035.

The mean cognitive score improved significantly at 12 months' post-recovery (86.1± 16.3; p=0.002), as well as the motor and language composite score; 83. ±15.7, and 80.9± 13.8 respectively. These developmental scores were similar between male and female participants.

However, 10% of the children showed poor cognitive performance (<69) after 12 months. After adjusting for age and weight-for-age Z-scores (WAZ), composite scores of cognitions and socioemotional domain of development showed a significant difference between baseline and end-line assessment (p=0.002 and p=0.013, respectively). On the other hand, after 12 months' children mostly presented with average IQ. The mean Movement Assessment score indicated that children are at risk of movement difficulties during the post-hypernatremia recovery period.

Conclusion: Long-term evaluation of children's nutritional status and renal function recovered from hypernatremia did not reveal any significant clinical abnormalities. However, developmental assessments indicated that most children exhibited average neurocognitive development and IQ. Further studies are required to validate the spot urine method against the gold standard 24-hour urine collection method for assessing proteinuria in post-hypernatremia children.

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List of Abbreviation

HN: Hypernatremia

SAM: Severe Acute Malnutrition

ORS: Oral Rehydration Solution

ECF: Extra Cellular Fluid

GI: Gastrointestinal

MRI: Magnetic Resonance and Imaging

MUAC: Mid Upper Arm Circumference

icddr, b: International Centre for Diarrheal Disease Research, Bangladesh

WAZ: Weight for Age Z

ANCOVA: Analysis of Co-Variance

Pr/Cr ratio: Protein creatinine ratio

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CHAPTER 1

Introduction

1.1.Sodium Homeostasis:

Sodium is an important electrolyte mainly found in extracellular fluid, which helps maintain fluid balance, blood pressure, nerve impulse conduction, and muscle contraction. Sodium homeostasis refers to the regulation of sodium levels in the body. The body regulates sodium levels through hormones that control the reabsorption of sodium in the kidneys, as well as through thirst mechanisms. Factors that stimulate sodium reabsorption include the renin-angiotensin-aldosterone system(ADH), and the sympathetic nervous system. Most of the body's sodium is located in the ECF, which is the most abundant cation. Accordingly, total body sodium is the principal determinant of ECF volume. The kidneys can compensate for any variations in sodium intake by increasing the excretion of sodium when there is sodium overload, and retaining sodium in the presence of sodium depletion to maintain normal ECF volume and plasma volume. When sodium intake and excretion balance is disturbed, any tendency for plasma sodium concentration to change is usually corrected by osmotic mechanisms that control water balance. As a result, disorders in sodium balance present chiefly as alterations in the ECF volume, resulting in hypovolemia or hypervolemia, rather than as an alteration in plasma sodium concentration. When serum sodium increases, it increases the solute load outside the cell, so water moves from inside to outside. Sodium levels are tightly controlled in a healthy individual by regulation of urine concentration and an intact thirst mechanism. Water homeostasis is maintained by balancing water intake and the combined water loss from renal excretion, respiratory, skin, and GI sources. Under normal conditions, water intake and losses are matched. The kidneys similarly adjust urine concentration to match salt intake and loss to maintain salt homeostasis.

In sodium homeostasis, it is important to understand how solutions affect water movement into and out of cells. The ability of an extracellular solution to make water move into or out of a cell by osmosis is known as its tonicity. If a cell is placed in a hypertonic solution, water will leave the cell and shrink. In an isotonic environment, there is no net water movement, so there is no change in the cell size. In a hypotonic environment, water will enter into the cell, and subsequently the cell will swell.

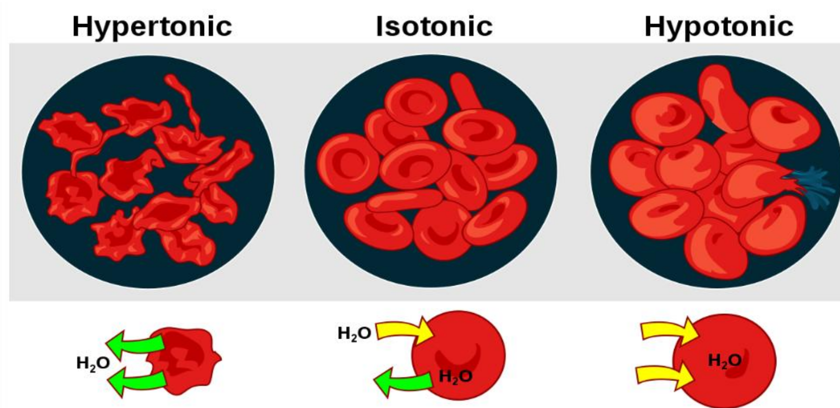

Figure 1: Osmoregulation and osmotic balance

1.2. Hypernatremia

1.2.1. Overview:

In clinical medicine, sodium is the most common and one of the most poorly understood electrolyte disorders among the different extracellular ions. Hypernatremia is a common electrolyte problem that is defined as a rise in serum sodium concentration to a value exceeding 145 µmol/L(Muhsin and Mount, 2016, Adrogué and Madias, 2000, Verbalis, 2012). It is strictly defined as a hyperosmolar condition caused by decreased total body water (TBW) relative to electrolyte content (Chumlea et al., 1999). Sodium concentration doesn't necessarily reflect the total amount

of sodium in the body but rather the amount of sodium relative to the amount of water in the body. However, manifestations are usually observed in children in developing countries at a level ≥150 µmol/L. HN usually occurs at extremes of age and in males and females equally. Hypernatremia prevalence in hospital patients has been reported at around 2 %, but in Intensive Care Unit (ICU) patients, its prevalence appears to range from 6 to 47 % (Lindner and Funk, 2013, Chand et al., 2022, Tauseef et al., 2021, Rugg et al., 2023, Rugg et al., 2021). Death can occur either due to the consequence of hypernatremia itself or as a result of complications during correction of dehydration.

1.2.2. Pathophysiology:

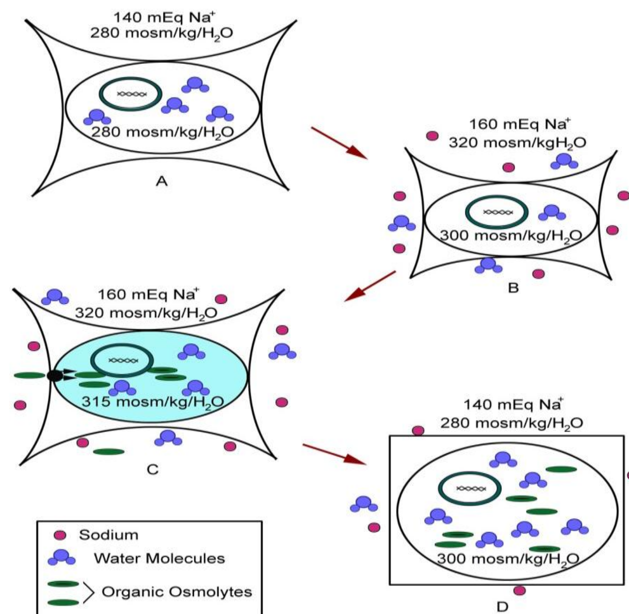

Figure 2: Pathophysiology. A: Normal cell. B: The cell responds to extracellular hypertonicity through passive osmosis C: Cellular response to extracellular hypertonicity resulting transport of osmolytes across the cell membrane, D: Extracellular hypertonicity rapid correction resulting movement of water into intracellular space, leading to cellular swelling, damage, and death.

Hypernatremia results from disequilibrium of sodium balance. The disorder is caused by a relative free water loss and salt loading. In Hypernatremia occurs, cells become dehydrated resulting from

extract of water from the cells. This is either due to increased osmotic load or burden of the body's free water deficit. Sodium, primarily an extracellular ion, is the primary factor of serum osmolarity. As a consequence of cells shrinkage and osmotic force cells respond by transport of electrolytrs through cell membrane This lead to generate intracellular organic solutes in an effort to restore cell volume and structural damage. If water replacement occurs faster than excretion or metabolism of accumulated solutes will lead to cerebral edema (figure 2). In the CNS, stretching of shrunken neurons and membrane potentials alteration lead to ineffective functioning. In severe shrinkage, stretching and rupture of bridging veins may cause intracranial hemorrhage (figure 3).

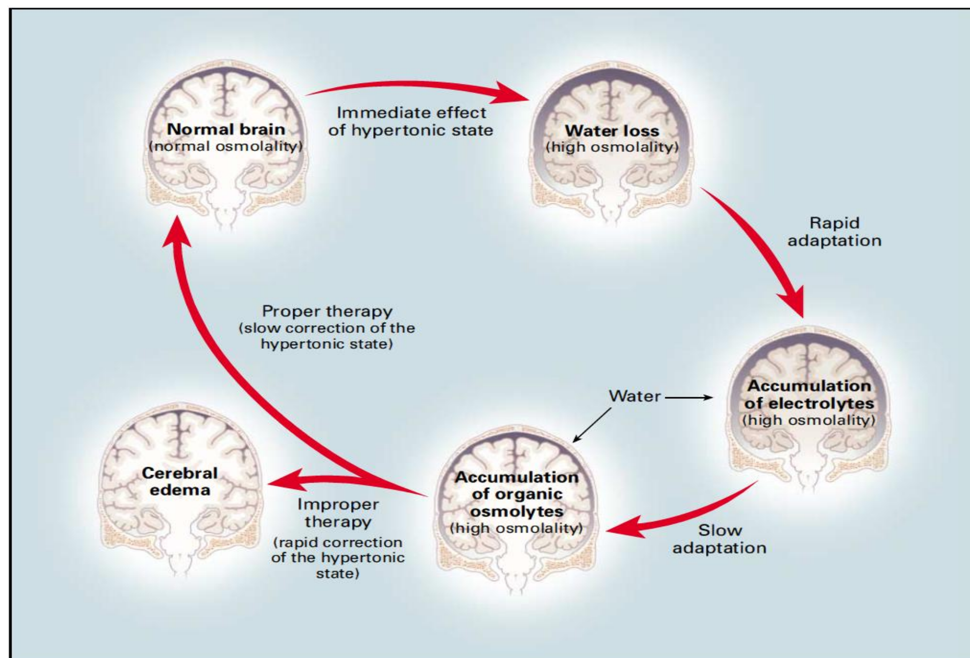

Figure 3: Effect of hypernatremia on CNS: Within minutes after the development of hypertonicity, loss of water from brain cells causes shrinkage of the brain and an increase in osmolality. Partial restitution of brain volume occurs within a few hours as electrolytes enter the brain cells (rapid adaptation) (Adrogué and Madias, 2000).

1.2.3 Etiology:

Nephrogenic and central diabetes insipidus is the classic cause of hypernatremia from a water deficit. HN develops in diabetes insipidus only if the patient does not have access to water or cannot drink adequately because of immaturity, neurogenic impairment, emesis or anorexia. Infants are at risk because of their inability to control their water intake. The other causes of a water deficit are typically secondary to an imbalance between losses and intake. Newborns, especially if premature, have high insensible losses. When HN occurs under conditions involving sodium and water deficits, the water deficit exceeds the sodium deficit due to inadequate water intake.

Hypernatremia concurs when water loss exceeds sodium loss, as in cases of diarrhea and vomiting; lack of water intake or no access to water -particularly in elderly individuals- contribute significantly to this condition. The sodium gain is mainly accidental, such as from salt ingestion, saltwater drowning and hypertonic saline infusion. In some cases, we found that hypernatremia arises from prepared feeding solutions administered excessively by caregivers. For example, caregivers provided concentrated ORS (oral rehydration solution) to infants, which increased their thirst and led to the administration of more ORS, creating a vicious cycle that worsens hypernatremia.

It is also important to note that during the winter season, rotavirus diarrhea is predominant among children under five years old. In rotavirus diarrhea, stool sodium loss is 37 µmol/L, whereas the ORS sodium is 75 µmol/L. Therefore, when caregivers gave more ORS, children developed

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hypernatremia. A study has revealed that the most common electrolyte disturbance in children with rotavirus diarrhea is hypernatremia (Gubbari, 2019).

There are also other causes listed in the table below:

Condition	Example	Pathophysiology	Volume status
Renal loss of water (i.e., osmotic diuresis)	Uncontrolled diabetes mellitus type II, chronic use of large doses of loop diuretics, diabetes insipidus	Free water loss	Hypovolemic usually; euvolemic in case of diabetes insipidus
Non-renal loss of water	Severe burn	Increased insensible water loss	Euvolemic and later hypovolemic
	Severe diarrhea	Water loss in excess of sodium loss	Hypovolemic
Deficit of free water intake	Infants, disabled patients, impaired mental status, inadequate breastfeeding	Impaired thirst mechanism, limited access to water	Hypovolemic
Excess of sodium (uncommon)	Accidental ingestion of large amounts of salt, infusion of large volumes of hypertonic saline or sodium bicarbonate	Sodium gain	Usually hypervolemic
Excess of mineralocorticoids (uncommon)	Cushing syndrome	Increase in serum cortisol leading to sodium and water retention	Usually hypervolemic

1.2.4. Clinical manifestation:

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms. In children with hypernatremic dehydration, water movement from the intracellular space to the extracellular space partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention only after experiencing more profound dehydration. Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated hypernatremic infant has a 'doughy' feel. Hypernatremia, even without dehydration, causes central nervous system symptoms. Some infants have a high-pitched cry and hyperpnoea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever. There is no apparent direct effect of hypernatremia on the body beyond the sequelae of dehydration, except on the brain. Brain cells are especially vulnerable to the development of complications related to hypernatremia because of the presence of abundant water channels in the brain (Robert and ST GEME, 2019). In diarrhea and vomiting (the most important conditions associated with HN in developing countries), where the loss of water may exceed that of electrolytes and can lead to an increase in the osmolarity of body fluids, there is the movement of water from the cells to the extracellular fluid compartment. This results in intracellular dehydration, subsequently causing brain shrinkage which predisposes the child to petechial brain hemorrhages. The development of hyperosmolality from the water loss in HN can lead to neuronal cell shrinkage and results in brain injury that includes widespread cerebral thrombosis, subdural effusion and permanent neurological deficit. The clinical manifestations of hypernatremia due to Central Nervous System (CNS) involvement include

excessive thirst, irritability, restlessness, lethargy, muscle twitching, spasticity, and hyperreflexia. Children with severe hypernatremia (plasma sodium concentration >170 µmol/L) may present with hyperthermia, delirium, seizures, and coma. Complications from HN usually arise from its inappropriate management including correction of hyperosmolality with rapid free water replacement often leading to cerebral edema(Conley, 1990, Paneth, 1980).

1.2.5. Management:

Management of hypernatremic dehydration is complex; improper and aggressive rehydration has been shown to result in a rapid fall in the osmolality of extracellular fluid due to rapid changes in the concentrations of serum sodium and other osmotically active substances, such as glucose. This results in higher intracellular osmolality relative to extracellular fluid, causing the movement of water into cerebral cells and leading to cerebral edema (Morris-Jones et al., 1967, Finberg et al., 1959, Banister et al., 1975). Frequent seizures may occur during fluid management. Recognition of these serious problems led to the development of low-solute infant formulas, which resulted in a decrease in the incidence of infantile hypertonic dehydration (Whaley and Walker-Smith, 1978, Sunderland and Emery, 1979, Manuel and Walker-Smith, 1980). Most studies indicate in the management of hypernatremia slow and gradual restoration of the deficit over a 24 to 48-hours, facilitating the slow return of serum sodium values to normal levels. Fluid therapy needs to be adjusted such that the decline of serum sodium does not exceed 10 µmol/L over 24 hours. Studies observed a significantly lower incidence of complications associated with oral correction of dehydration in hypernatremic children than those receiving intravenous rehydration in animal studies (Hogan et al., 1984, Rosenfeld et al., 1977). Isotonic saline is unsuitable for correcting hypernatremia, except in situations where extracellular fluid volume depletion causes significant

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hemodynamic compromise, such as shock. On the other hand, substitution by a hypo tonic fluid, particularly at higher infusion rates, could seriously overload the extracellular fluid compartment. Careful consideration of these management aspects can prevent complications (Pizarro et al., 1984).

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CHAPTER 2

Background

2.1. Literature review:

In developed countries, HN occurs more frequently among hospitalized patients as an iatrogenic condition and usually its complications arise from its inappropriate treatment (SNYDER et al., 1987, Palevsky et al., 1996). Anecdotal observations from Bangladesh suggest that ORS is perceived by some parents to be a 'treatment' for diarrhea. They do not realize that this is a remedy for dehydration and continue to give generous amounts of ORS. The condition can also be provoked by increased evaporative loss of water through the lungs, skin, and urine, especially in infants suffering from fever or tachypnea or residing in a dry environment. Because of their large surface area in relation to height or weight than adults, infants lose a relatively larger volume of water by evaporation and are particularly susceptible to hypernatremia. Aggressive rehydration result in a rapid fall in extracellular fluid osmolality and occasionally, a fall in the concentration of other osmotically active substances. Rapid rehydration resulted in excess water influx into cerebral cell, with the subsequent development of cerebral edema. Osmotic demyelination has also been reported. Survivors may have permanent neurologic complications, including hemiparesis, seizure disorders, and mental retardation (Jacobson and Bohn, 1993). Little is known, however, about the magnitude of this problem, particularly in developing countries. Hypernatremic dehydration has also been reported to occur due to inadequate breastfeeding (Cooper et al., 1995, Kaplan et al., 1998, Roddey et al., 1981) . Some of the reports go in favor of high sodium content in breast milk and postulate that hypernatremia can occur because of this high sodium content of breast milk (Kaplan et al., 1998, Chilton, 1995).

In a retrospective study done in the Dhaka Hospital of icddr,b between March 2001 and March 2002, 371 children (5.1%), with a median age of 5 months, had hypernatremia upon admission out

of a total of 7,212 patients admitted to the long-stay ward of the hospital (Chisti et al., 2016). This compares with a prevalence of 2% hypernatremia among patients (mostly adults) hospitalized in the US. Of the patients in the Dhaka study, 94% (median age 5 months) had a history of acute watery diarrhea, and 40% had malnutrition. The majority of the admissions for hypernatremia were in the winter months of December to March. Mild hypernatremia (less than 160 µmol/L) was present in 59% of the patients. The rest of the patients (41%) had moderate (serum sodium 160-169.9 µmol/L) or severe hypernatremia (≥170 µmol/L). Case fatality rates were 8.7%, 17.9% and 34.7% in patients with mild, moderate and severe hypernatremia, respectively. The overall CFR was 15.1%. Logistic regression analysis identified the following as risk factors for death in these patients with hypernatremic dehydration: serum sodium ≥170 µmol/L, bilateral pedal edema, hypoglycemia, and respiratory distress. Another retrospective analysis conducted in 2011 in the same hospital showed that 360 (2.4%) children under 15 years had hypernatremia upon admission among 15,219 admitted children in the long-stay ward and ICU of Dhaka Hospital of icddr,b between March 2009 and August 2011(Chisti et al., 2016). The overall case fatality rate was 19%. Retrospective analysis of children with hypernatremic dehydration demonstrates significant neurologic sequelae, including hypertonicity, developmental delay, seizures, cerebral thrombosis, and cerebral hemorrhage, despite appropriate rate of correction (Unal et al., 2008, Van Amerongen et al., 2001, Moritz and Ayus, 1999). Secondary complications such as acute renal failure and disseminated intravascular coagulation have also been reported in some patients(Robertson et al., 2007).

In low and middle-income countries (LMICs), over 250 million children under the age of five face the risk of not achieving their full developmental potential(Black et al., 2017, Lu et al., 2016, McCoy et al., 2016). Child development is a dynamic biological and psychological process

influenced by various environmental, familial, and societal factors. One of the key factors affecting development is the presence of childhood diseases such as diarrhea, which is often accompanied by severe dehydration. It can lead to acute symptoms such as confusion, headaches, and seizures(Terry, 1994, Shrimanker and Bhattarai, 2020). The first two years of life represent a critical period for brain development, and conditions such as hypernatremia, if left untreated or poorly managed, may have lasting effects on cognitive function. Previous studies have suggested a link between early childhood diarrhea and cognitive deficits that appear years later(Berkman et al., 2002, Niehaus et al., 2002). However, little research has specifically explored how hypernatremia, often resulting from improperly prepared oral rehydration salts or viral infections like rotavirus, impacts long-term cognitive and motor development (Paneth, 1980, Sahay and Sahay, 2014). In addition to its effects on neurodevelopment, hypernatremia is also associated with kidney dysfunction. Proteinuria (Pr/Cr ratio is greater than 0.2) is documented as an independent predictor for renal disease. Measuring protein in the urine is, therefore, one way to check the health of the kidneys. However, children may have only temporary proteinuria without any evidence of kidney disease. Increased urinary protein excretion is considered a valuable indicator for the initial detection and confirmation of renal disease as observed by Ruggenti and colleagues (Ruggenenti et al., 1998). The spot urine Pr/Cr ratio has a wide range of sensitivity and specificity ranging between 69% and 96%, and 41% and 97%, respectively (Price et al., 2005). Proteinuria, as well as hematuria, maybe the only early signs of renal disease ; membrano-proliferative glomerulonephritis, membranous nephropathy, post-infectious glomerulonephritis, IgA nephropathy and others.(Hajar et al., 2011). Proteinuria may induce renal insult through many pathways such as initiation of chemokines expression and complimentary activation which eventually lead to inflammatory cell infiltration and fibrogenesis (Abbate et al., 2006).

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2.2. Background research:

A prospective observational case-control study was recently conducted in the Dhaka Hospital of icddr,b, from August 2013 to October 2015. The objectives of that study were to investigate the neurological complications and developmental consequences of hypernatremia and to reduce the case fatality rate in children with hypernatremia by following an optimized management protocol. A total of 259 hypernatremic (serum sodium ≥150mmol/L) children under the age of five years were consecutively enrolled over 2 years and treated according to the standardized protocol adopted in icddr,b and followed up after 3 months from the date of discharge. In this study, 53 control children were selected from a similar age band suffering from diarrhea but who were normonatremic (serum sodium 135-145 µmol/L). This was done to gather background information on a same-age group of children with diarrhea. A complete neurological work-up was performed on admission, including fundoscopy, in order to evaluate surviving children for any neurological complications. As soon as the children recovered and were ready to be discharged from the hospital, a series of radiological examinations, including Magnetic Resonance Imaging (MRI) scans of the brain, were conducted to identify any possible intracerebral vessel rupture, hemorrhage, infarction, thrombosis, edema, or any residual effects of edema. Moreover, cognitive, motor and behavioral assessments were performed after recovery from HN in the Dhaka Hospital of icddr,b a day before discharge.

Among the hypernatremic cohort, 224 under-five children recovered from hypernatremia after optimized management. The mean age of the study children was about 7.9 months with a range from 1-33 months. A greater number of male children presented with mild hypernatremia than their female counterparts. The death rate was 13.5%, with neurological sequelae in 29.9% and severe malnutrition in 44% of the children. 81% were breastfed, but exclusive breastfeeding was

found in only 7% of the hypernatremic patients. Severe Hypernatremia (serum sodium>170mmol/l) was associated with common comorbidities, such as acute kidney injury, pneumonia and sepsis. Acute Kidney Injury and Sepsis were found to be potential risk factors among the hypernatremic children with abnormal MRI findings. Post hoc analysis showed that severe HN children were significantly associated with an increased incidence of acute kidney injury (p=0.02) and pneumonia (p=0.03). The study children were found to have a linear relationship between serum creatinine levels and increasing serum sodium. Among the cohort, 28% developed acute kidney injury. About half of these children required renal replacement therapy (dialysis). In this cohort, infants with AKI had an independent association with hypernatremia (odds ratio (OR) = 8.66, 95% confidence interval (CI) = 3.88–19.22) (Shahrin et al., 2020).

In this study, Magnetic Resonance Imaging (MRI) of the brain and Electroencephalogram (EEG) tests were performed on 204 children at the time of discharge. It was revealed that 66 hypernatremic children (32%) had abnormal MRI findings. A subsequent number of hypernatremic children (n=211) were also assessed for possible developmental delays (cognitive, language and motor functions) using the Bayley Scales of Infant and Toddler Development-third version (Bayley, 2006). The children's behavior during the Bayley-III assessment was rated on five 9-point scales using a modified version of the scales developed by Wolke(Wolke et al., 1990). Severely hypernatremic children had significantly lower scores on motor, fine motor and language development, as well as receptive and expressive communication, compared to mild and moderately hypernatremic children.

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CHAPTER 3

Longitudinal study

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3.1. Rationale:

It was previously unknown to what extent hypernatremia contributes to subsequent morbidities and physical development in the later stages of those children. Given the association between hypernatremia and both acute kidney injury and long-term cognitive impairments, it is critical to understand the full spectrum of its developmental consequences. Previous studies have shown an association between hypernatremia and acute kidney injury (Shahrin et al., 2020). Moreover, the role of hypernatremia in the progression of childhood growth, cognitive, and physical development over time has not been adequately studied. Therefore, we proposed to conduct a longitudinal study to follow developmental consequences, including motor, language, and cognitive development, growth, and renal damage among children who recovered from an episode of hypernatremia following acute watery diarrhea.

3.2. Research Question:

Is there any long-term consequence on nutritional growth, cognitive development and renal function among children who recovered from Hypernatremia?

3.3. Objectives:

3.3.1. General Objective:

Evaluate nutritional growth, cognitive developmental outcomes, and renal function of the children at around 12 months after recovering from hypernatremia

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3.3.2. Specific objectives:

1. Evaluate the long-term linear and ponderal growth of children who successfully recovered from hypernatremia by measuring their weight and length.

2. Assess the neuro-developmental aspects of the children at around 12 months after the date of discharge.

3. Evaluate renal function at around 12 months after discharge.

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CHAPTER 4

Methods and Materials

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4.1. Study design:

This study was an observational Longitudinal study

4.2. Study population:

The study participants were enrolled from a cohort of children under 5 years who were enrolled in a previous prospective observational study conducted from August 2013 to October 2015, and presented with hypernatremia (serum Na ≥150 µmol/l). Two hundred twenty-four (224) under-five children had recovered from hypernatremia in the previous study. Among these children we could perform cognitive test at the time of discharge on 211 children. In the present study we contacted parents of these children for follow up evaluation at around 12 months after discharge. However, 143 children could be available for follow up in the present study who were subsequently enrolled after consent from their parents or legal guardians.

4.3. Study setting:

This study was conducted in the inpatient unit of 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 pe-urban Dhaka, the capital city of Bangladesh.

4.4. Study duration:

The present longitudinal study was conducted from March 2016 to March 2017 in inpatient unit of Dhaka Hospital of icddr, b.

4.5. Inclusion criteria:

- Children who recovered from hypernatremia.
- Either sex
- Children who have complete 12 months after recovery from hypernatremia
- Informed consent given by the parent or legal guardian

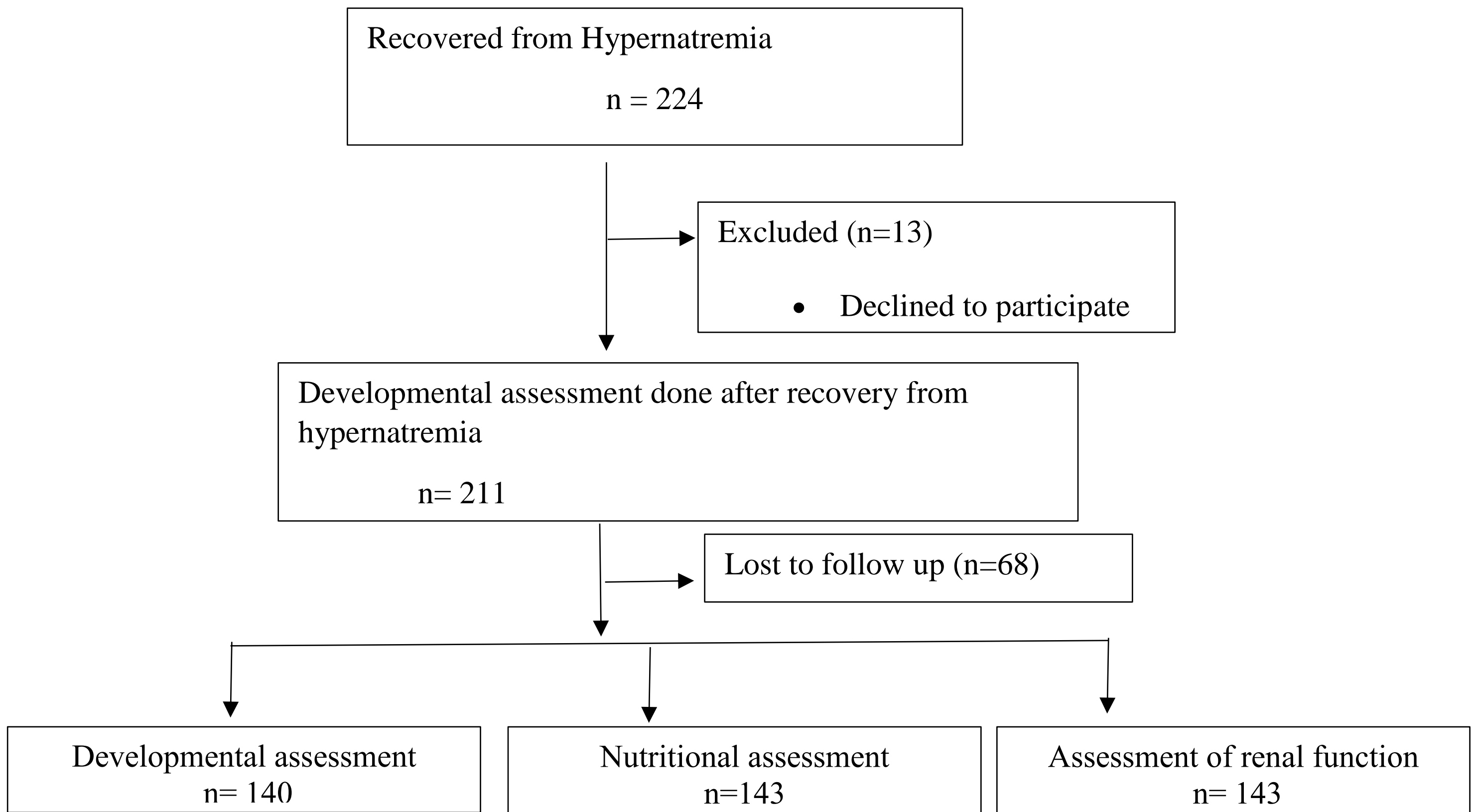
4.6. Exclusion criteria:

- Parent or legal guardian not agreed to provide informed consent

4.7. Sampling frame:

Sampling was based on the 224 who had successfully recovered and been discharged from hypernatremia in the parent hypernatremia study. Moreover, the developmental assessment was conducted among 211 of those discharged children from the hospital after recovery. Considering around 25% were lost to follow-up, the estimated sample size was 168. However, of the estimated 168 children, we were able to follow up with 143 children to assess nutritional status and renal function, and 140 children underwent developmental assessments.

Flow Chart:



4.8. Operational definition:

1. Hypernatremia (HN): Serum sodium level ≥150 µmol/l

- Mild Hypernatremia: serum sodium <160 µmol/l
- Moderate Hypernatremia : serum sodium 160-169.9 µmol/l
- Severe Hypernatremia : serum sodium ≥170 µmol/l

2. Long term impact of hypernatremia: 12 months after recovery from hypernatremia

3. Severe malnutrition: Any of the anthropometric indices such as WAZ (weight for age), WHZ (weight for height) and HAZ height for age) score <-3SD.

4. Severe Acute Malnutrition: Defined as the presence of odema of both feet or severe wasting (weight-for-height/length <-3SD or mid-upper arm circumference < 115 mm.

5. Underweight (assessed via weight-for-age): Weight-for-age is a composite index of height-for-age and weight-for-height that takes into account both wasting and stunting. Children whose weight-for age Z-score is below minus two standard deviations (−2 SD) from the median of the reference population are classified as underweight

6. Stunting (assessed via height-for-age): Height-for-age is a measure of growth faltering. Children whose height-for-age Z-score is below minus two standard deviations (−2 SD) from the median of the reference population are considered short for their age (stunted).

7.Wasting (assessed via weight-for-height): The weight-for-height index measures body mass in relation to body height or length and describes acute undernutrition. Children whose weight-for-height Z score is below minus two standard deviations (−2 SD) from the median of the reference population are considered thin (wasted).

4.9. Study activities:

In this study, we made a list of children who had been discharged after recovering from hypernatremia at around 12 months for follow-up evaluation. We invited the parents to attend Dhaka Hospital inpatient unit with their children. Afterward among those who came for follow up with proper documentation, we obtained informed consent from the parents or legal guardian after

describing the aim and procedure of the study. Subsequently, we conducted the full physical, nutritional, neurological and cognitive assessment. Additionally, we performed a spot urine analysis for evaluation of their kidney function.

4.9.1. Nutrition and morbidity assessment:

On arrival, each child's weight, height and mid-upper arm circumference (MUAC) were recorded using standard procedures. Pedal edema was assessed by pressing the dorsal surface of the feet for 3 seconds. Weight was measured using a digital scale with 2gm precision. Height was measured by stadiometre and length (for children less than two years old) by the infantometre (to nearest 1 mm), mid-upper arm circumference (MUAC) was measured using a standard MUAC measuring tape to the nearest 1 mm). Moreover, we measured the head circumference of all children according to standard pediatric guidelines. Using different anthropometric indices; height, weight, age and sex we calculated WAZ (weight for age Z score), WHZ (weight for Height Z score and HAZ (height for age Z score) according to WHO growth standard (M, 2007).

Other physical examinations were carried out according to standard pediatric practice. Data were collected on pre-designed and pre-tested Case Report Forms (CRF), which became part of the child's medical records. These contained the exact address, socio-demographic information including family status, living conditions, dietary history, history of illness, immunization status, and so on. Neuro-cognitive assessment was also carried out.

4.9.2. Developmental assessment

In Dhaka Hospital of icddr,b, the children were assessed for cognitive, motor and neuropsychological development using standard procedures by a trained Psychologist. Two different tools were used for 2 categories of age; up to36 months and >36months:

Children upto 36 months: The children's global Intelligence assessment by using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III).

Children between >36 months: Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) was used for testing IQ, motor function was assessed using Movement Assessment Battery for Children-II (MABC-II).

Bayley Scales of Infant and Toddler Development, third edition (Bayley-III):

Bayley Scales of Infant and Toddler Development- third edition (Bayley-III) (Bayley 2005) is a widely used tool for measuring the neurocognitive development of children in low-income settings. The tool has three major subsets: i) cognitive, ii) motor (fine and gross motor subtests) and iii) language (receptive and expressive language subtests) and one subtest for assessment of social-emotional behavior of children, from the mother's or primary caregiver's report. The fine motor subset measures eye/hand coordination and manipulation of small objects and the gross motor measures the large body complex movements like sitting, walking, jumping etc. The receptive communication subset measures the ability of the child to recognize sounds and understand 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 a series of developmental play tasks and takes 45-60 minutes to administer. Raw scores will be converted to norm-referenced standardized scores for the composite scale

(Bayley, 2006). Bayley-III had recently been used in Bangladeshi studies (Aboud et al. 2013, Singla et al. 2014). To establish validity of the subscales (cognitive, language and fine motor subsets) with age and other predictors researchers examined correlation. (Aboud et al., 2013).

Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)

The Wechsler Preschool and Primary Scale of Intelligence (Wechsler 2002) is a clinical instrument designed for assessing intelligence (cognitive ability) of children ages 2 years 6 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). 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 the 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-III had been previously used in Bangladesh after cultural modification (Aboud et al., 2013).

Movement Assessment Battery for Children (MABC-II)

The Movement Assessment Battery for Children (MABC) (Henderson et al., 1992) is a widely used tool for direct assessment of fine and gross motor skills of children above 36 months. The scale has three subscales: 1) manual dexterity (three items: posting coins, threading beads and drawing trial); 2) aiming and catching (two items: throwing a beanbag onto a mat and catching the beanbag); and 3) static and dynamic balance (three items: one leg balance, walking heels raised and jumping on mats). manual dexterity measures the child's fine motor skills involving hand and

finger manipulation, which is important for developing handwriting skills. The aiming and catching activities measure the child's hand-eye coordination through throw and catch activities. The balance activities evaluate the child's ability to coordinate the body in balancing tasks. The scores of the three subscales are summed to calculate a total score on the MABC. According to 'Traffic Light System" total test score is classified as the red, amber and green zone (Henderson et al., 1992). The MABC-II has not been validated in Bangladesh but has been used in a previous Bangladeshi study after piloting and cultural adaptation (Hamadani et al., 2013) Three subscales, e.g., threading the beads, catching the bean bag, and jumping over a cord, were slightly modified and administered to children aged 64 months.

4.9.3. Renal function assessment:

Protein- to- creatinine ratio of spot morning urine samples is a precise indicator of proteinuria. It is a reliable predictor of the progression of disease in patients with chronic nephropathies and represents a simple and inexpensive procedure for establishing severity of renal disease and prognosis. Spot urine sample was obtained from all children and a microscopic examination was performed for the detection of the Pr/Cr ratio for the detection of glomerular damage. Urine routine examination from morning spot samples was performed by an Automated urine analyzer (Sysmex UX-2000) and the underlying principles of the test in the analyzer was based on:

a) Photometry method to analyze the chemistry of urine
b) Refractometry method to analyze Specific Gravity
c) Flow Cytometry method to analyze urine sediments such as WBC (pus cells), RBC, epithelial cells, and fungi.

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Urine protein was measured photometrically in the automated chemistry analyzers of the Beckman Coulter AU series using reagents from the manufacturer. Urine creatinine was measured in the same analyzers with an enzymatic method using reagents from the same manufacturer. Urinary Pr/Cr ratio was calculated by Laboratory Information System (LIS) software using the following formula:

Total Protein: Creatinine ratio = Total Protein in g/L ÷ Creatinine in g/L

4.10. Data Analysis:

Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL) and STATA version 13. For dichotomous factors, a normal approximation test (Chi-square test) or Fisher's exact test was performed; for continuous variables, either a t-test or Mann-Whitney test was used. Multivariable techniques (e.g., logistic regression) were used to identify independent risk factors. Logistic regression analysis was done to model the relationship between a binary outcome and one or more predictor variables. Linear regression was performed to model the relationship between a quantitative outcome and one or more predictor variables. The mean difference of cognitive, motor, language scores 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. Nutritional assessments from the time of recovery to 12 months' follow-up were compared. The strength of association was determined by estimating odds ratios (OR) or standardized regression coefficients and their 95% confidence intervals (CI). p-values < 0.05 were considered statistically significant.

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4.11. Ethical Clearance:

Ethical approval was obtained from the Institutional Review Boards (IRB) of icddr,b. The study did not involve any invasive procedures like blood specimen collection. Data were collected by interviewing mothers using questionnaires and testing children through providing age-appropriate tasks. Before enrolment, signed informed consent was obtained from the parents/guardians of the children. The consent form was written in Bangla in a language and format that could be easily understood by the legal guardians of study subjects, even with little or no educational background. The consent form was read out to the legal guardian/parent of the study subject if he/she was unable to read. A signed consent or the left thumb impression was obtained from the care-giver/legal guardian/parent for the participation of the children in the study.

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CHAPTER 5

Results

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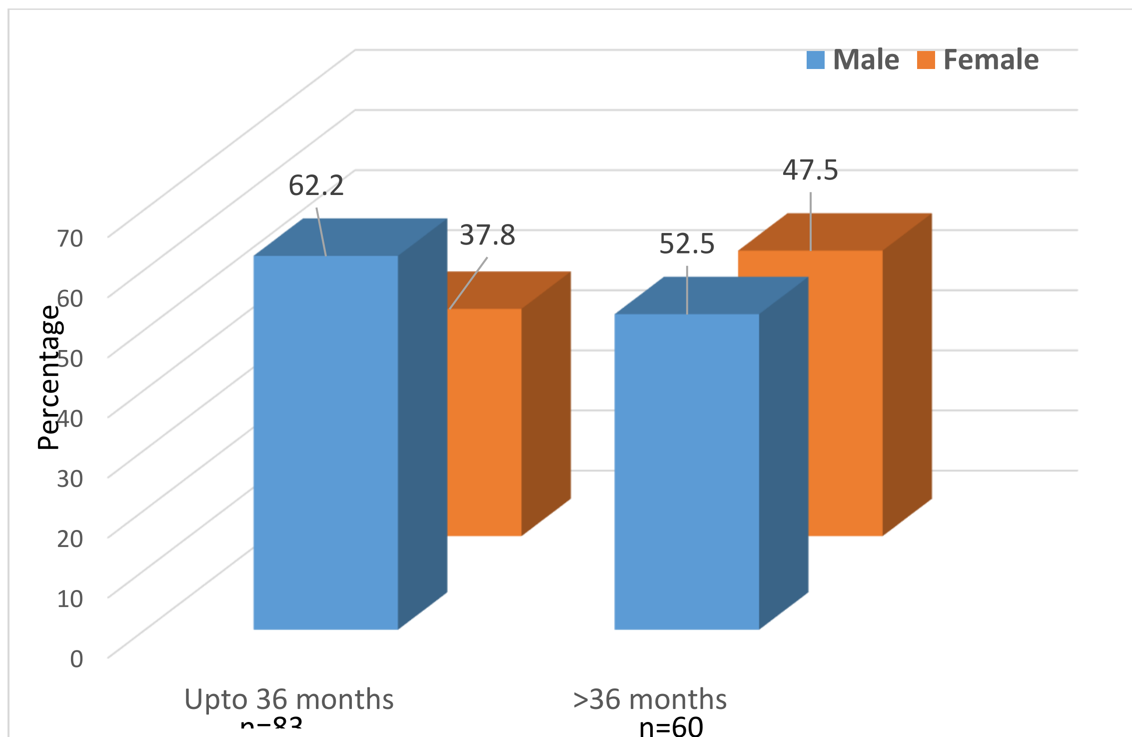
Among the 224 children recovered from hypernatremia (serum Na <150 µmol/l), 143 (64%) mothers gave consent to participate in this follow-up study. The rest of the children could not be traced out due to outmigration from the study area. During follow up phase developmental assessment tests were performed on the 140 participants between March 2016 and March 2017. More than half of the study children came from outside of Dhaka City. Forty percent (40%) belonged to poorer households, and about one-third were from low-income families. The mean age of the children at the baseline study (time of recovery) assessment was 7.9±4.5 months. After one year, during follow-up evaluation, the mean age was 34.6± 7.9 months. Baseline assessment showed that a greater number of male children had presented with hypernatremia than their female counterparts. At baseline, the mean weight and length were 6.6 ±2.0 kg and 66.2 ± 7.8 cm. The corresponding values at the 12-month follow up increased to 12.4 ±3 kg and 89.5± 7.5cm respectively. After stratifying the children in two age groups, 62.2% were male and 37.8% female among those up to 36 months (figure 4).

Figure 4: Distribution of study children in according to age and sex



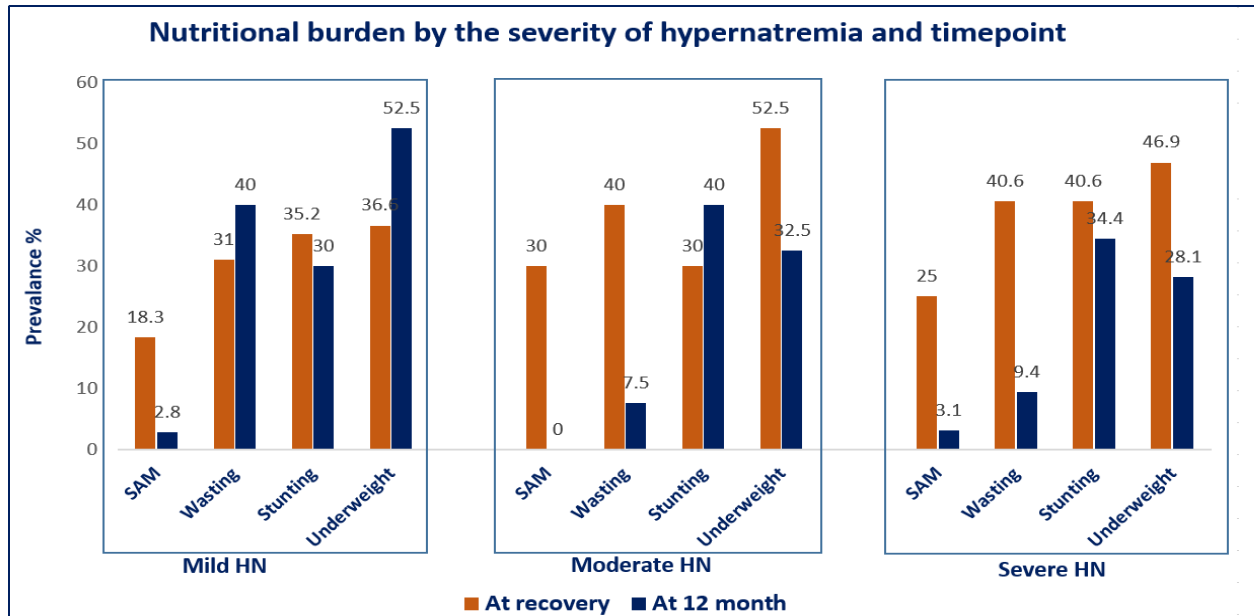
On the other hand, among children older than 36 months, 52.5% male and 47.5% female. 19.6% of study children had LBW. Anthropometric indices, parental education, asset quintile were comparable among different types of hypernatremia at the time of recovery. Post hoc analysis showed that severe hypernatremic 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). Severe acute malnutrition improved significantly at the follow-up visit in comparison to baseline (2% vs 23%). However, wasting and underweight prevalence increased among mild hypernatremic children compared to those with moderate to severe hypernatremia; while stunting increased among the moderate hypernatremic children at 12 months (Figure 5).

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

Parameter	Mild HN (n=110) Na= <160µmol/l	Moderate HN (n=58) Na=160-169.9µmol/l	Severe HN (n=43) Na= >170µmol/l	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
Anthropometry				
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
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)	

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

Figure 5: Nutrition Burden by Severity of hypernatremia at recovery and follow-up



Developmental assessments at the baseline (time of recovery) showed, 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 participants. However, cognitive scores were similar among children presenting with different severity levels (Table-2). Long-term developmental consequences differed across the three severity groups. After adjusting for age and weight for the age Z-score (WHZ), composite scores of cognitions and socioemotional domain of development showed a significant difference between baseline and end-line assessments (p=0.002 and p=0.013 respectively) (Table-3).

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

	Mild HN (n=110) Na= <160μmol/l	Moderate HN(n=58) Na=160-169.9μmol/l	Severe HN (n=43) Na= >170μmol/l	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

[a]Composite score; [b] Scaled score

Posthoc: ▼Mild vs Moderate and Mild vs Severe; *ANCOVA controlling for age and WAZ

Table 3. Developmental outcomes of the children on recovery and at 12 months follow up*

	At the time of recovery ; n=140	At 12 months 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

The multiple linear regression model for cognitive score showed that age was positively associated with cognitive score, with a coefficient of 0.44 (p = 0.025). WAZ also showed a significant positive association, with a coefficient of 2.23 (p = <0.001). Additionally, the severe hypernatremia group (reference: non-severe) had a significantly higher cognitive score, with a coefficient of 14.7 (p = 0.002). The model was adjusted for parents' education and study time points. (Table-4). At the 12-month follow-up, there were no significant differences in verbal (85.29 vs76.79 vs 78.39), performance (89.16 vs 81.00 vs 83.16) or full scale (86.07 vs 76.87 vs 79.53) IQ (Table-5). The Mean Movement Assessment score was 65.2 which indicated that children are at risk of movement difficulties during the post-hypernatremic recovery period.

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

*Group defined as hypernatremia group (mild, moderate and severe HN)

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

Measurement	Mild HN Na= <160µmol/l	Moderate HN Na=160-169.9µmol/l	Severe HN Na= >170µmol/l
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

Among the study participants, based on urinary Pr/Cr ratio ≥ 0.2 and < 0.2; 70 children were diagnosed with proteinuria and 73 children without proteinuria respectively. Bivariate analysis showed that family income and maternal education were comparable across the two groups. However, paternal education was higher among children with a normal Pr/Cr ratio. One third of the children presented with upper respiratory infections. Children from the poorest quintile were more likely to have proteinuria compared to their wealthier counterparts (Table-6). Although there is statistical difference in mean weight and length between two groups, mean WHZ (-0.43± 1.44 vs -0.54± 1.63; p=0.665), WAZ (, -1.11± 1.4 vs -1.05± 1.6; p=0.824) and LAZ score (-1.41± 1.39 vs -1.24± 1.58; p=0.490) were similar (Table-7). There was lack of associated urinary problem and glomerular damage among these children with high urinary Pr/Cr ratio. Proteinuria (Pr/Cr ≥0.2 gm/L) was comparable in different hypernatremic groups. After adjusting for potential co-variates like age, sex, malnutrition status, different forms of hypernatremia, and co-morbidities, regression analysis showed that 86% of the children from better socioeconomic status were less likely to have high Pr/Cr ratio in comparison to the poorest counterpart (p=<0.001). Children who had mild hypernatremia were more likely to have raised urinary Pr/Cr ratio although it was not statistically significant. Children below 36 months' age are 2 times more likely to have raised urinary Pr/Cr compared to those more than 36 months ; 2.31(1.06, 5.02); p-0.035. (Table-8).

Table 6: Sociodemographic characteristics of children with and without proteinuria

Parameter	Child with Proteinuria n=70	Child without Proteinuria n= 73	p-value
Sex; n (%)			
Male			
Upto 36 months	28 (71.8)	23 (50.0)	0.048
>36 months	11 (28.2)	23 (50.0)	
Female			
Upto 36 months	20 (64.5)	13 (48.1)	0.289*
>36 months	11 (35.5)	14 (51.9)	
Place of Residence n (%)			
Dhaka city	15 (21.4)	11 (15.3)	0.467
Within Dhaka district	11 (15.7)	16 (22.2)	
Outside Dhaka	44 (62.9)	45 (62.5)	
Any Co-morbidity	38 (55.1)	37 (51.4)	0.661
Mother's Education n (%)			
Illiterate	12 (17.1)	8 (11.0)	0.518
Up to Primary	19 (27.1)	19 (26.0)	
Above Primary	39 (55.7)	46 (63.0)	
Father's Education n (%)			
Illiterate	20 (28.6)	12 (16.4)	0.022*
Upto Primary	22 (31.4)	15 (20.5)	
Above Primary	28 (40.0)	46(63.0)	
Asset Quintile n (%)			
Poorest	23 (32.9)	6 (8.3)	<0.001*
Poorer	11 (15.7)	17 23.6)	
Middle	19 (27.1)	10 (27.1)	
Rich	7 (10.0)	21 (29.2)	
Richest	10 14.3)	18 (25.0)	

Table 7: Presenting characteristics of children with and without proteinuria

Parameter	Children with Proteinuria n-70	Children without Proteinuria n=73	p-value
Age (month)	32.9 ±7.9	36.2± 7.40	0.012
Weight in Kg	11.7 ± 3.5	12.8± 2.7	0.041*
Length in cm	87.1±9.2	90.9 ±7.4	0.006*
MUAC in cm	156.8 ±28.95	164.19 ±16.52	0.064
Weight for Height (WHZ) score	-0.43± 1.44	-0.54± 1.63	0.665
Weight for Age (WAZ) score	-1.11± 1.4	-1.05 ±1.6	0.824
Height for Age (HAZ) score	-1.41± 1.39	-1.24 ±1.58	0.490

All parameters are in Mean ±SD

Table 8: logistic regression to explore independent predictor of raised protein creatinine ratio in children who recovered from Hypernatremia

Parameter	Unadjusted		Adjusted	
	Odds ratio (95%CI)	p-value	Odds ratio (95% CI)	p-value
Hypernatremia				
Severe HN	Ref		Ref	
Mild HN	1.48 (0.82-2.68)	0.360	1.84(0.66-5.10)	0.243
Moderate HN	1.05 (0.41-2.68)	0.916	0.94 (0.31-2.85)	0.912
Age				
>36 months	Ref		Ref	
Upto 36 months	2.24 (1.13-4.44)	0.020*	2.31(1.06-5.02)	0.035*
Sex				
Male	Ref		Ref	
Female	1.35(0.69-2.65)	0.375	1.13(0.52-2.46)	0.756
Any form of malnutrition	1.14(0.59-2.21)	0.696	1.25(0.58-2.69)	0.562
Asset index				
Poorest	Ref		Ref	
Poorer	0.17(0.05-0.55)	0.003*	0.14(0.04-0.49)	0.002*
Middle	0.49(0.15-1.61)	0.244	0.45(0.13-1.59)	0.216
Rich	0.09(0.03-0.30)	<0.001*	0.06(0.02-0.24)	<0.001*
Richest	0.14(0.04-0.47)	0.001*	0.13(0.04-0.46)	0.001*

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CHAPTER 6

Discussion

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Diarrhea remains one of the major causes of childhood illness in Bangladesh. According to Bangladesh Demographic and Health Survey data revealed that the overall prevalence of diarrhea among children under-five is around 5%(Islam et al., 2023).In Bangladesh, late winter and early spring, rotavirus remains the leading diarrheal pathogen in infants and young children. Hypernatremia in diarrhea and are associated with life-threatening complications 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(Shahrin et al., 2020). The fecal loss of sodium in rotavirus diarrhea is often below 40 µmol/Whereas the concentration of sodium in the reduced osmolarity ORS in Bangladesh is 75 µmol/L Therefore, even prepared correctly, its use in an appropriate volume might contribute to the development of hypernatremia in children with rotavirus diarrhea (Chisti et al., 2016).Additionally, the lack of adequate knowledge about the ORS preparation and amount required ORS intake may significantly contribute for the development of hypernatremia (Nuzhat et al., 2025). Present study provides insight into the long-term nutritional, neurodevelopmental and renal outcomes in children who have recovered from hypernatremia, a condition commonly associated with diarrhea and dehydration. In terms of nutritional assessment, severe acute malnutrition declined substantially from the time of recovery from hypernatremia. However, other indices like wasting, stunting and underweight increased in mild hypernatremic children in comparison with their severe counterparts. Due to lack of food frequency data, it is difficult to predict the cause. There is lack of studies correlating post-hypernatremic nutritional deprivation. We found significant neurodevelopmental deficits in children with severe hypernatremia compared to those with mild or moderate hypernatremia, which aligns with prior research linking

serum sodium levels with cognitive function in both children and adults (Lee et al., 2021). While the exact mechanisms underlying the cognitive deficits associated with hypernatremia remain unclear, abnormalities in brain osmolyte levels during dehydration may play a role in disrupting normal cognitive development. The present study also suggests that cognitive deficits observed during the acute phase of hypernatremia tend to improve over time, with cognitive outcomes significantly better 12 months after the episode, indicating that the neurological impact of hypernatremia may be temporary. This contrasts with the findings of Boskabadi (Boskabadi et al., 2017), who observed long-term developmental delays in children without diarrhea. The differences may stem from variations in the antecedent causes of hypernatremia, as our study population primarily consisted of children with diarrhea.

Further analysis revealed that severe hypernatremia was associated with poor cognitive outcomes, with parental education level playing a role in the cognitive development of these children. Children whose mothers had higher levels of education tended to have better cognitive outcomes (Sania et al., 2019). In line with previous studies, we also found an association between malnutrition and poor cognition. However, our study did not detect a direct link between low birth weight and hypernatremia. This may be due to the relatively small number of low birth weight children in the study sample. For children over 36 months of age, there were no significant differences in IQ scores across mild, moderate, and severe hypernatremia groups, suggesting that any potential cognitive impact from abnormal sodium levels may not persist beyond the first few years of life. While our study was not designed to assess the long-term effects of hypernatremia beyond one year, it highlights the need for further research to determine whether these children experience lasting cognitive impairments as they age. In addition to neurodevelopmental outcomes, we also examined the renal effects of hypernatremia. Proteinuria, an early marker of

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kidney dysfunction, was found to be elevated in about half of the children during follow-up visits at 12 months' post-hypernatremia. This is an important finding, as increased urinary protein-to-creatinine (Pr/Cr) ratio is commonly used to detect early renal damage (Price et al., 2005). Interestingly, we found that children from lower socioeconomic backgrounds, as indicated by their asset index, were more likely to present with elevated Pr/Cr ratios, potentially due to increased exposure to unhygienic living conditions and urinary infections, which are common in underprivileged populations. This finding is consistent with other studies that link lower socioeconomic status to an increased risk of chronic kidney disease (CKD) (Shen et al., 2019). Although malnutrition is a known risk factor for CKD and can contribute to poor renal outcomes, our study did not identify it as a significant predictor of proteinuria. Conversely, children below 36 months were more likely to exhibit elevated Pr/Cr ratios, potentially indicating less mature kidney function. We also observed that 27% of children with proteinuria had a history of low birth weight, suggesting that LBW may be associated with smaller kidney size and poorer renal function, leading to higher protein-to-creatinine ratios. This observation is supported by previous research indicating that low birth weight is linked to micro proteinuria and may result from a low nephron count at birth (Yudkin et al., 1997). Despite these findings, our study did not find hypernatremia to be a direct predictor of proteinuria, which may be explained by the fact that the renal insufficiency in children with hypernatremia was likely transient and resolved once they became normonatremic. However, we did identify that children from poorer households, with low paternal literacy levels, and those with low birth weight were more likely to present with raised Pr/Cr ratios, suggesting that socioeconomic and early life factors can exacerbate renal vulnerability. One limitation of our study is the lack of serum creatinine measurements during follow-up visits to calculate glomerular filtration rate (GFR), which would have provided a more

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precise measure of renal function. Additionally, while spot urine analysis was useful in detecting proteinuria, it does not account for the diurnal variation of protein excretion, and further studies are needed to compare spot urine analysis with 24-hour urine collection to more accurately assess renal damage in children post-hypernatremia. Despite these limitations, our study underscores the value of urine analysis as an accessible tool for detecting early renal dysfunction in children recovering from hypernatremia. In conclusion, while our findings suggest that hypernatremia does not appear to be a long-term predictor of cognitive dysfunction or kidney disease, it highlights the complex interplay between socioeconomic factors, malnutrition, and renal health. Further research with larger sample sizes and long-term follow-up is necessary to better understand the full spectrum of developmental and renal consequences for children recovering from hypernatremia.

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CHAPTER 7

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7.1. Conclusion:

Long-term evaluation of the nutritional status revealed that, although prevalence of SAM decreased, other indices of malnutrition in some instances increased in the follow-up visit. Renal function of children recovered from hypernatremia did not reveal any significant clinical abnormalities. 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. However, the poor development appeared to be transient, with spontaneous recovery occurring in the long run.

7.2. Limitation:

We could not perform serum creatinine during the follow-up to calculate Glomerular Filtration Rate (GFR) to measure the extent of damage. As we included only recovered HN children with small sample size, we failed to conclude effect of hypernatremia on IQ levels. Due to small number of low birth weight/ severe malnourished children, we failed to find any association with cognitive function. Additionally, the lack of food frequency data made it difficult to correlate changes in anthropometric indices during the post hypernatremic follow up phase.

7.3. Strength:

Overall this study provides a snapshot of post hypernatremic clinical consequence. Moreover, this follow-up study provided us an overview of the long term impact of hypernatremia on nutrition, renal function and a developmental outcome of the children who have recovered from

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hypernatremia. This has significant clinical and public health implications.

7.4. Recommendation:

Studies are required to validate the spot urine method with the gold standard 24-hour urine method to assess proteinuria in post hypernatremic children. Large-scale studies are required to evaluate whether there is any association between developmental consequences and neurological sequelae among children suffering from hypernatremia to identify the effects on cognitive development.

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Chapter 8

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CHAPTER 9

Appendix

9.1. Consent Form

Protocol Title: Evaluation of Nutritional and Developmental Consequences and Renal Function of Children who Recovered from Hypernatremia

Investigator's name: Dr. Sayeeda Huq

Organization: icddr,b

Please feel free to ask any questions you may have about this study and the information given below. You will be given opportunity to ask questions and all questions will be answered. If you agree to our proposal of inclusion of your child in our study, we will provide you with a copy of this consent form.

Purpose of the research

Hypernatremia is a condition where blood salt level goes above normal to cause serious complications to children. Salt level in blood rises due to excess intake of saline or if the saline is not mixed properly during management of diarrhoeal illness. From our recently conducted study it was learned that 19% of these children developed some extent of brain lesion which result in some neurological problems and bad developmental outcomes. There is however, no systematic study which has either examined the long term effects of HN on nutrition, renal function and the central nervous system nor its effects on cognitive functions of children among the recovered children. The primary purpose of this study is to observe the long term nutritional and developmental consequences of children who have recovered from Hypernatremia. The findings of this study will assist in better understanding of long term effect of hypernatremia on nutrition,

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kidney function and neuro-developmental function, which in turn will help tin making recommendations and management plans for children who recover from hypernatemia.

Why invited to participate in the study?

One year ago your child was admitted in this hospital for management of increase level of salt in blood (hypernatremia). We are conducting the study on those children who were treated in our hospital for hypernatremia. As your child had increased salt level in blood we would like to examine your child's neurological, developmental and renal function This will help us to know about the long term effect of increase salt on nutrition, neuro-cognitive and renal function. Therefore, we request you for allowing us to include your child in our study.

Methods and procedures

- In order to assess the child's nutritional status, neurocognitive function, psychomotor development and renal function we will perform some examination and tests. These are noninvasive procedures therefore would not cause any harm to your child.

- . For the purpose of the study our research staff are going to ask you some question related to your child's illness. In addition, we will perform her/his thorough physical examination.

- We will ask you to collect urine once from your child for kidney function assessment.

. **Risk and benefits**

There is no major risk involved in the participation of your child in the study. Your child will be directly and indirectly benefited from participating in the study. The follow-up measures will help in early detection of any neurological problems and permit advising for appropriate precautions.

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Privacy, anonymity and confidentiality

We will keep all information collected from you/your child including the results of laboratory tests confidential, locked in a secure place under the responsibility of the principal investigator from icddr,b and the Ethical Review Committee (a group of experts which protects the interest of study participants) of icddr,b would have access to such information.

If you sign this form, you have given us permission to release information to authorized researchers and the safety committee. There is no expiration date to this permission. This information, like all of the information generated from this study, will be coded so it is unlikely that anyone will be able to trace it to you or your child.

Future use of information

In case of future use of the information collected from the study, the name or identity of your child would not be used in publishing the results of this study.

Right not to participate and withdraw

Your child's participation in the study is voluntary, and you are the sole authority to decide for and against your child's participation in this study. You would also be able to withdraw your child any time during the study. Refusal to take part in or withdrawal from the study will involve no penalty or loss of benefits.

Principle of compensation

You/your child will not receive any financial benefits for participating in the study. However, cost for all investigations and transport cost related to investigation during hospital stay will be borne by the investigator. We will provide food for you and your child during the hospital stay.

Moreover, during follow-up, we will compensate your wage loss at a rate of 500 Taka per day, and transport cost in relation to investigation will be borne by the investigator. The participant will also be provided the best possible, free treatment, for research related injuries, if any.

Answering your questions/ Contact persons

You will be able to ask us question about the illness and the study now, or at a later time and we would be happy to answer them. You should also be able to contact the principal investigator of this study personally at his office in this hospital or through telephone and the Committee Coordination Secretariat at the following address.

Principle Investigator:

Dr. Sayeeda Huq, Nutrition & Research Division, icddr,b , Mohakhali, Dhaka 1212, Phone no. 9827001--10 ; Extension 2358.

If you agree to our proposal of to enroll your child in our study, please indicate that by putting your signature or your left thumb impression at the specified space below

Thank you for your cooperation

____________________________________ ____________________

Signature or left thumb impression of Parent/ Guardian/ Attendant — Date

____________________________________ ____________________

Signature or left thumb impression of the witness — Date

____________________________________ ____________________

Signature of the PI or his/her representative — Date

9.2. Case Report Form

Evaluation of Nutritional and Developmental Consequences and Renal Function of Children who Recovered from Hypernatremia:

Completed By: Dr. …………………………………………………………………………. Sign Print	
Date of Follow up:	_ _ _ _ _ _ _ _ _ _ : _ _ Day Month Year Time (HH:MM 24 hour clock)
Specify Follow up	◯ Follow up ◯ Unscheduled visit
i. SOCIO-DEMOGRAPHIC HISTORY	
Residence:	◯ Within Dhaka City ◯ Withinin Dhaka District ◯ Outside Dhaka District
Distance of residence from Dhaka Hospital: _ _ _ KM	
Time to travel to Dhaka Hospital: _ _ : _ _ HH:MM	
Number of family members: _ _	
Number of children under five: _ _	
Number of rooms in home: _ _	
Family income last month: _ _ _ _ _ BDT	
Type of locality: ◯ Slum ◯ Non- slum ◯ Village ◯ Other, specify…………………	
Age of mother (in year): _ _	
Years of mother's formal education: _ _	
Mother's occpation:	0 Unemployed 0 Government Job 0 Petty Business 0 Hawker 0 NGO 0 Housewife 0 Day laborer 0 Housemaid 0 Garments worker 0 Other, specify…………………………..
Age of father (in year): _ _	
Years of father's formal education: _ _	

<table>
<tr><td>Father's occpation:</td><td colspan="3">0 Unemployed 0 Government Job
0 Petty Business 0 Hawker
0 NGO 0 Rickshaw puller
0 Day laborer 0 Other, specify…………………………..
0 Garments worker</td></tr>
<tr><td colspan="4">Does anybody smoke at home? ◯ Yes ◯ No</td></tr>
<tr><td colspan="4">ii. HOUSEHOLD ASSESTS:</td></tr>
<tr><td>Check all that apply:</td><td colspan="3">◯ Electricity ◯ Almirah/wardrobe
◯ Refrigerator ◯ Animal drawn cart
◯ Table ◯ Cows/buffalo
◯ Watch ◯ Radio
◯ Car or Truck ◯ Television
◯ Motorcycle/motor scooter/ tempo/ motor ◯ Chair
◯ Cot
◯ Bicycle ◯ Rickshaw/van
◯ Non-mobile telephone ◯ Goats/sheep
◯ Mobile telephone ◯ Poultry
◯ Boat with motor ◯ Other, specify …………………</td></tr>
<tr><td colspan="4">Cultivated land: Area – – – – – decimal</td></tr>
<tr><td colspan="4">Fallow land: Area – – – – – decimal</td></tr>
<tr><td colspan="4">Pond: Area – – – – – decimal</td></tr>
<tr><td colspan="4">Floor structure : ◯ Cemented ◯ Non-cemented</td></tr>
<tr><td colspan="4">Wall structure:
1. Brick 2. Bamboo fence 3. Ordinary tin ☐
4.Corrogated tin 5. Straw 6.Jute stick
7.Mixed 8.Mud 9.Other</td></tr>
<tr><td colspan="4">Roof structure:
1.Concrete/Pukka 2.Bamboo fence 3.Ordinary tin ☐
4.Corrogated tin 5. Straw 6. Polythene
7.Mixed 8.Mud 9.Other</td></tr>
<tr><td colspan="4">Source of Drinking water:
1.Tap 2.TW 3. Pond/River/Ditch ☐
4.1+2 5.1+3 6.2+3
7.1+2+3</td></tr>
<tr><td colspan="4">iii. CARE SEEKING BEHAVIOR (If no presenting illness skip to v)</td></tr>
<tr><td colspan="4">First symptoms:
☐ Cold/runny nose ☐ Diarrhea ☐ Fever ☐ Convulsion</td></tr>
</table>

☐ Cough	☐ Other specify	☐ NA
First consultation	◯ Qualified doctor ◯ Quack	◯ Homoeopath doctor or spiritual ◯ None
Prior hospitalization:	◯ Yes	◯ No
Reason for Delay : *Delay is > 48 hours	◯ No delay (if<48 hour since illness began)	
	◯ Financial constrain	
	◯ Cared for at home	
	◯ Under treatment of quack	
	◯ Under treatment of homeopath doctor or spiritual advisor	
	◯ Could not realize the problem	
	◯ Only caregiver, could not leave room	
	◯ Other, specify:_____________________________	
Illness Cost:	Medication _ _ _ _ BDT Hospitalization_ _ _ _ _ BDT Consultation _ _ _ _ _ BDT Lab investigation_ _ _ _BDT	Transportation _ _ _ __BDT Wage loss _ _ _ _ _BDT For mother or attendant_ _ _ _ _BDT Wage loss for father_ _ _ _ __BDT Food for child _ _ _ _ _ _ _BDT

iv. **HISTORY OF PRESENT ILLNESS**			
Diarrhea	☐ Watery	☐ Dysentery	☐ Persistent
Stools per day: _ _			
Diarrhea Began _ _ _ _ _ _ _ _ Day Month Yea r Time(HH:MM) _ _: _ _			
Vomiting :	◯ Yes	◯ No(skip to fever)	

Vomits per day: _ _
Vomiting Began: _ _ _ _ _ _ _ _ _ _:_ _ D ay Month Year Time(HH:MM)
Fever : ◯ Yes ◯ No (skip to cough)
Date and time Fever begin : – – – – – – – – – –:– – Day Month Year Time (HH:MM)
Cough: ◯ Yes ◯ No (skip to thirst)
Date and time Cough begin : – – – – – – – – – –:– – Day Month Year Time (HH:MM)
Thirst: ◯ Yes ◯ No (skip to drink)
Date and time Thirst begin : – – – – – – – – – –:– – Day Month Year Time (HH:MM)
Unable to drink : ◯ Yes ◯ No (skip to convulsion)
Date and time Unable to drink begin : – – – – – – – – – –:– – Day Month Year Time (HH:MM)
Convulsion : ◯ Yes ◯ No (skip to Mental Status)
Total number of Convulsions since onset of illness: – –
Total number of Convulsions in past 24 hours : – –
Type of convulsion : ☐ Generalized ☐ Focal
Durations of last convulsion : – – minutes
Mental Status : ◯ Normal ◯ Abnormal
Abnormality : ☐ Lethargic ☐ Irritable ☐ Unconcious
Duration of abnormality : – – hours
Hours since last urine passed : – – hours
Other Symptoms, Specify with duration:
v. HISTORY OF PAST ILLNESS
Any diarrohea of this child in last 7 days, other than this episode (1= Yes, 2= NO) ☐

Any diarrohea of this child in last 14 days, other than above episode (1= Yes, 2= NO)	
Any diarrohea of this child in last 1 month, other than above episode (1= Yes, 2= NO)	
Any cough/fever/sneezing/running nose/rapid resp./breathing difficulty/ear discharge/husky voice in last 14 days (1= Yes, 2= NO)	☐
Any other disease of this childin last 7 days (1= Yes, 2= NO)	☐
Any other disease of this childin last 14 days (1= Yes, 2= NO)	☐
Any other disease of this childin last 1 month (1= Yes, 2= NO)	☐

vi. FEEDING AND TREATMENT HISTORY
Vaccination Status : ◯ Fully immunized ◯ Partially immunized, up to date ◯ Partially immunized, not up to date ◯ None
Breast feeding history : ◯ Predominantly ◯ Partially ◯ Non breast feed ◯ NA
Date and time Of last feed : – – (Day) – – (Month) – – – – (Year) – – : – – Time (HH:MM)
ORS before admission : ◯ Yes ◯ No (skip to Clinical Evaluation)
ORS type : ☐ packet ☐ home made
If packet, specify ORS brand : ☐ Neosaline® ☐ ORSaline-N® ☐ Tasty Saline ☐ Other, specify……………..
Date and time Of first ORS intake : – – (Day) – – (Month) – – – – (Year) – – : – – Time (HH:MM)
Type of ORS : ☐ Glucose ☐ Sucrose ☐ Rice based
Number consumed : ----- -----
Volume of ORS consumed : – – – – ml
Volume of free water consumed : – – – – ml
ORS/ Water Preparation: ☐ Appropriately prepared ☐ Prepared with less water than indicated ☐ Prepared with more water than indicated
Boiled before preparation? ◯ Yes ◯ No

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vii. CLINICAL EVALUATION
Radial pulse imperceptible : ◯ Yes (skip to heart rate) ◯ No
Radial pulse volume : ◯ good ◯ low ◯ thready
Heart rate : _ _ _ beats/minute (if radial pulse imperceptible)
Rectal temperature : _ _ °C
SPO2 on room air : _ _ _
Respiratory rate : _ _ _ / minutes
Systolic blood pressure : _ _ _ (mm Hg)
Diastolic blood pressure : _ _ _ (mm Hg)
Associated Conditions : ☐ Sepsis ☐ Severe sepsis ☐ Septic shock ☐ Meningitis ☐ Pneumonia ☐ NA
Dehydration Status : ◯ No sign ◯ Some ◯ Severe ◯ NA
Lower Chest Wall in drawing: ◯ Yes ◯ No
Nasal Flaring : ◯ Yes ◯ No
Head Nodding : ◯ Yes ◯ No
Grunting respiration : ◯ Yes ◯ No
Pedal Edema : ◯ Yes ◯ No
Cyanosis : ◯ Central ◯ Peripheral ◯ None
Mental Status : ◯ Normal ◯ Abnormal
Abnormality: ☐ Lethargic ☐ Irritable ☐ Unconscious ☐ Convulsing
Type of Convulsion if Convulsion checked above : ◯ Generalized ◯ Focal
Planter Reflex : ◯ Flexor ◯ Extensor ◯ Exaggerated ◯ Equivocal
Knee Jerks : ◯ Normal ◯ Exaggerated ◯ Diminished
Admission Weight : – – : – – – kg

Admission Length : – – – : – – cm

MUAC : – – : – – cm

Conjunctival Hemorrhage : ○ Yes ○ No

Anisocoria : ○ Yes ○ No

Fontanels : ○ Normal ○ Bulge ○ Depressed

Skin Condition Doughy : ○ Yes ○ No

Fundoscopy Examination Findings :	
	Right Eye : ○ Normal ○ Hemorrhage ○ Edema ○ Others, specify
	Left Eye : ○ Normal ○ Hemorrhage ○ Edema ○ Others, specify

Level of Conciousness : ○ Normal ○ Abnormal

If Abnormal, severeity : ○ Mild; GCS ≥ 13 ○ Moderate; GCS 9-12 ○ Severe; GCS > 9

Neck Stiffness : ○ Yes ○ No

Kernigs sign : ○ Yes ○ No

Bulk of Muscles : ○ Normal (skip to tone of muscle) ○ Reduced

Location of Reduced Bulk of Muscle if checked above :

	Upper limb	Lower limb
Right	☐	☐
Left	☐	☐

Tone of Muscle : ○ Normal (skip to reflexs) ○ Abnormal

Location and type of Muscle tone if checked above :

	Hyper Upper Limb	Hyper Lower Limb	Hypo Upper Limb	Hypo Lower Limb
Right	☐	☐	☐	☐
Left	☐	☐	☐	☐

Reflexes : ○ Normal (skip to clonus) ○ Abnormal

Location of Exaggerated Reflex :

	Biceps	Triceps	Supinator	Knee	Ankle
Right	☐	☐	☐	☐	☐
Left	☐	☐	☐	☐	☐
	Biceps	Triceps	Supinator	Knee	Ankle

Location of Diminished Reflex:	Right	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐
Clonus :	◯ Present			◯ Absent		
Abdomen : ◯ Normal ◯ Distended; bowel sounds present ◯ Distended; bowel sounds absent						

Complete the Following Evaluation only for Children above 1 Year of Age :

Eyes If Abnormal:	◯ Normal Look (skip to corneal reflex) ◯ Abnormal Look ☐ Squint ☐ Nystagmus ☐ Ptosis
Corneal Reflex :	Right : ◯ Present ◯ Absent Left : ◯ Present ◯ Absent

Right Pupil

Size :	◯ Normal	◯ Dilated	◯ Constricted
Shape :	◯ Regular/Normal	◯ Irregular	
Reaction to Light :	◯ Reacting	◯ Not Reacting	

Left Pupil

Size :	◯ Normal	◯ Dilated	◯ Constricted
Shape :	◯ Regular/Normal	◯ Irregular	
Reaction to Light :	◯ Reacting	◯ Not Reacting	

Muscle Power		Grade 0	Grade I	Grade II	Grade III	Grade IV
	Right Upper Limb :	◯	◯	◯	◯	◯
	Right Lower Limb :	◯	◯	◯	◯	◯
	Left Upper Limb :	◯	◯	◯	◯	◯
	Left Lower Limb :	◯	◯	◯	◯	◯

Sensory Response : ◯ Intact ◯ Impaired

viii. Outcome

		◯ Usual discharge with Follow up
		◯ Referred

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		◯ Others
	Date : _ _ _ _ _ _ _ _ Day Month Year	
Sent for Further Consultation :	◯ Yes	◯ No

Assessment of cognitive & motor functions

1. **Bayley Scales of Infant Development (For children- age up 1 to 36 months)**

1.1= Cognitive

1.1.1= Cognitive raw score……………………………………………….(Score range 0-91)… ☐☐

1.1.2= Cognitive scaled score…………………………………………….(Score range 1-19)… ☐☐

1.1.3= Cognitive composite score………………………………………(Score range 55-145)… ☐☐☐

1.2= Language

1.2.1= Receptive communication raw score………………………………(Score range 0-49)…. ☐☐

1.2.2= Receptive communication scaled score……………………………(Score range 1-19)…. ☐☐

1.2.3= Expressive communication raw score……………………………..(Score range 0-48)… ☐☐

1.2.4= Expressive communication scaled score……………………………(Score range 1-19)…. ☐☐

1.2.5= Language total scaled score…………………………………………(Score range 2-38)… ☐☐

1.2.6= Language composite score…………………………………………..(Score range 45-155)… ☐☐☐

1.3= Motor

1.3.1= Fine motor raw score……………………………………………….(Score range 0-66)… ☐☐

1.3.2= Fine motor scaled score…………………………………………….(Score range 1-19)…. ☐☐

1.3.3= Gross motor raw score……………………………………………..(Score range 0-72)……. ☐☐

1.3.4= Gross motor scaled score…………………………………………..(Score range 1-19).. ☐☐

1.3.5= Motor total scaled score……………………………………………(Score range 2-38).. ☐☐

1.3.6= Motor composite score……………………………………………(Score range 45-155)…... ☐☐☐

1.4= Social-Emotional

1.4.1= Social-Emotional raw score……………………………………………(Score range 0-175)… ☐☐

1.4.2= Social-Emotional scaled score…………………………………………(Score range 1-19)…. ☐☐

1.4.3= Social-Emotional composite score…………………………………(Score range 55-145)… ☐☐☐

2.a. Wechler Preschool and Primary Scale of Intelligent -Third Edition : (For children Age 30 to 47 months)

2.1.1=Verbal sum of scaled score……………………………………………(Score range 2-38). ☐☐

2.1.2=Verbal composite score………………………………………………… (Score range 49-150) ☐☐☐

3.2.1=Performance **sum of** scaled score………………………………………… (Score range 3-38) ☐☐

3.2.2=Performance composite score…………………………………….......... (Score range 48-150) ☐☐☐

3.3.1=Full **sum of** scaled score……………………………………………… (Score range 7-86) ☐☐☐

3.3.2=Full composite score………………………………………………… (Score range 40-116) ☐☐☐

2.b. Wechler Preschool and Primary Scale of Intelligent-Third Edition: (For children Age >48 month)

3.1.1=Verbal sum of scaled score…………………………………………………(Score range 3-30) ☐☐

3.1.2=Verbal composite score………………………………………………(Score range 46-100)…. ☐☐☐

3.2.1=Performance sum of scaled Score………………………………………(Score range 3-30)…… ☐☐

3.2.2=Performance composite score…………………………………………(Score range 45-100)….. ☐☐☐

3.3.1=Processing Speed sum of scaled score……………………………………(Score range 2-38)…… ☐☐

3.3.2=Processing Speed composite score……………………………(Score range 46-150)….. ☐☐☐

3.4.1=Full sum of scaled score………………………………………(Score range 7-86)….. ☐☐☐

3.4.2=Full scale composite score……………………………………(Score range 40-116)…….

3. Movement Assessment Battery for Children- 2 (For children age >36 months)

3.1= Manual dexterity

3.1.1= Manual dexterity (Posting coins) Preferred hand Raw score…………(Score range 27+---<6)….

3.1.2= Manual dexterity (Posting coins) Non-Preferred hand Raw score……(Score range 31+---<8)….

3.1.3= Manual dexterity (Posting coins) Item SD score……………………..l..(Score range 1-19)…….

3.1.4= Manual dexterity (Threading beads) Raw score…………………..(Score range 122+--<17)..

3.1.5= Manual dexterity (Threading beads) Item SD score…………………(Score range 1-19)……

3.1.6= Manual dexterity (Drawing trail 1) Raw score………………………(Score range 18+--0)….

3.1.7= Manual dexterity (Drawing trail 1) Item SD score……………………(Score range 1-19)….

3.1.8= Manual dexterity (total) Component score……………………………(Score range <3—43+)..

3.1.9= Manual dexterity (total) Standard score ………………………………(Score range 1-19)….

3.2= Aiming and catching

3.2.1= Aiming and catching (Caching beanbag) Raw score……………………(Score range 0-10)…

3.2.2= Aiming and catching (Caching beanbag) Item SD score……………….(Score range 1-19)…..

3.2.3= Aiming and catching (Throwing bean bag onto mat) Raw score………..(Score range 0-10)…

3.2.4= Aiming and catching (Throwing bean bag onto mat) Item SD score……(Score range 1-19)….

3.2.5= Aiming and catching Component score……………………………..(Score range <6—33+)…

3.2.6= Aiming and catching Standard score……………………………………(Score range 1-19)…

3.3= Balance

3.3.1= Balance (One-leg balance best leg) Raw score…………………………(Score range 0-30)……

3.3.2= Balance (One-leg balance other leg) Raw score………………………..(Score range 0-30)…

3.3.3= Balance (One-leg balance) Item SD score………………………………(Score range 1-19)…

3.3.4= Balance (Walking heels raised) Raw score………………………………(Score range 0-15)…

3.3.5= Balance (Walking heels raised) Item SD score…………………………(Score range 1-19)…

3.3.6= Balance (Jumping on mat) Raw score……………………………………(Score range 0-5)……

3.3.7= Balance (Jumping on mat) Item SD score………………………………(Score range 1-19)……

3.3.8= Balance (total) Component score…………………………………..(Score range <8—44+)…….

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3.3.9= Balance (total) Standard score…………………………………………(Score range 1-19)…….. | | |

3.4= Total Test score……………………………………………………(Score range **<29—108+)..** | | | |

3.5= Standard score…………………………………………………………(Score range **1-19)………** | | |