

Hypernatremia and Acute Kidney Injury in Exclusive Breast Fed Babies-Time to Reconsider!

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ABSTRACT

Introduction: Hypernatremia in breast fed babies is not very commonly reported. But incidence seems to be increasing. Exact pathophysiology is not clear but hypothesised to be due to relative lactation failure in early postnatal period especially in primiparous mothers, and it can be severe enough to cause life threatening complication like Acute Kidney Injury (AKI) which is even less reported. Moreover, clinical presentation can be misleading even in presence of severe AKI. Presence of other co-morbidities further adds to the problems and may lead to adverse outcome.

Aim: To study clinical presentation, severity and outcome in hypernatremic term breast fed young infants who develop AKI.

Materials and Methods: This was a retrospective study in which data analysis of all consecutively admitted young infants, ≤ 2 months age, who had hypernatremia as well as deranged kidney functions in last six months, was done. AKI was assessed by neonatal RIFLE criteria. Analysis was done by student's t-test or Fischer-exact test or one-way ANOVA (multiple groups) or non-parametric test as applicable. Pearson correlation

coefficient was used to analyse correlation between groups. Statistical analysis of data was done using SPSS version 21.0.

Results: Sixteen babies were included. Majority i.e., 81% (13/16 in each group) were born to primiparous women and were on exclusive breast feeding; 75% babies presented with poor oral acceptance and 56% with fever. Other complaints were lethargy, poor urine output and excessive crying. An 80% of the babies had severe AKI (AKI stage III). A total of 31% (5 out of 16) died. Mean serum sodium was 165 ± 8.4 mEq/L with range of 156-183 mEq/L. Median creatinine value was 2.4 mg/dL. Presence of sepsis, requirement of mechanical ventilation, vasopressors, high mean values of blood urea and serum creatinine ($p < 0.05$) were significantly associated with poorer outcome.

Conclusion: Hypernatremia is severe enough to cause AKI in exclusive breast fed babies which is not uncommon and is difficult to recognize clinically. Presence of other co-morbidities like sepsis portends poorer outcome. High index of suspicion in all babies specially without predisposing factors may lead to early diagnosis and timely management.

Keywords: Diagnosis, Kidney function, Sepsis

INTRODUCTION

Exclusive Breast Feeding (EBF) the recommended national policy for first six months of life due to obvious advantages. But inability to initiate or maintain sufficient breastfeeding in postnatal period may cause many problems. One of the less recognised but serious problem is hypernatremic dehydration, which can result in life threatening complications like seizures, intracranial haemorrhage, vascular thrombosis and even death as reported in individual case reports and series [1-8]. Although there is paucity of data, hypernatremic dehydration is increasingly reported in breast fed infants in recent studies [9-15]. Some even have reported hypernatremic dehydration to be more common in exclusively breast fed babies compared to those on mixed feeding [14]. It is hypothesized that the main predisposing factors include problems with maternal breast milk synthesis, difficulty with breast milk removal, and low daily breast milk intake [16]. One of the rare but potentially serious complications in these infants is AKI which is primarily due to hypernatremic dehydration and can be life-threatening if not detected and managed early.

There are very few studies, that too mainly case reports, mentioning renal failure with deranged kidney functions in breast fed babies with hypernatremic dehydration [8,9,15-19]. This study was done on the clinical data of young infants who were admitted with hypernatremia with AKI and to study their clinical presentation, course and outcome were studied.

MATERIALS AND METHODS

Retrospective analysis of case records was done over a period of six months. Study was conducted in Department of Paediatrics and

neonatal unit of a tertiary care centre in Northern India. Approval and clearance from Head of the Institute as well as ethical committee for same was taken to conduct the study. Duration of study of six months was empirically chosen from November 2017 to April 2018 as there was clustering of cases during this period and was based on analysis of clinical records. Consecutive babies ≤ 2 months of age requiring admission during above mentioned duration in paediatric or neonatal ward with documented hypernatremia and deranged kidney functions were included. Babies with known congenital anomaly of kidneys, Diabetes Insipidus and hypernatremia without documented rise in serum creatinine were excluded from study.

Sixteen young infants met inclusion criteria and their medical records were analysed for clinical presentation, course and outcome. Parameters analysed were age of presentation, type of feeding, birth weight, admission weight, presenting complaints, evidence of sepsis, parity of mother, place of delivery (home/hospital), urine output, serum sodium at admission, blood urea and serum creatinine on admission, treatment modality (conservative with fluid therapy/Renal replacement therapy), time taken to normalize serum sodium, creatinine and clinical outcome along with duration of stay.

Definition of hypernatremia: Serum sodium > 145 mEq/L.

Exclusive breast feeding: Only breast milk but including vitamin supplements and Oral Rehydration Solution (ORS).

Sepsis was defined as a clinical syndrome characterised by signs and symptoms of infection (systemic inflammatory response syndrome) with or without accompanying bacteremia [20].

Data of young infants requiring admission having documented hyponatremia as well as deranged kidney function test with or without oligo-anuria were studied. Blood sample at the time of admission was taken for sepsis screen, biochemical parameters including serum sodium, blood urea and serum creatinine. Serum sodium, potassium and blood urea was analysed by Beckman Coulter AU480 chemistry analyser. Serum creatinine level was measured on fully automated chemistry analyser (Siemens ADVIA 2400) using commercially available kit. Urine output was monitored by catheterisation for accurate measurement. AKI staging was done by neonatal RIFLE criteria [21]. Fluid correction for dehydration (if present) and hyponatremia was done as per standard protocol. Empirical parental antibiotics started as per hospital protocol. Vasopressors and renal replacement therapy (peritoneal dialysis) was done when required and standard management protocol followed till outcome (improvement with discharge or death) in all cases.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel sheet for analysis. Quantitative data were represented by Mean, Median and Range wherever applicable, qualitative data by percentage. Analysis of outcome with various clinico-laboratory factors was done by student's t-test or Fischer-exact test or one way ANOVA (multiple groups) or non-parametric test (Mann-Whitney U test) as applicable to find p-value. The p-value less than <0.05 was taken as significant. Spearman rank correlation and Pearson correlation coefficient was used to analyse correlation between serum sodium levels and various clinico-laboratory factors. SPSS version 21.0 was used to analyse data.

RESULTS

Sixteen included young infants who fulfilled admission criteria had equal sex distribution. Median age at admission was 10.5 days ranging from 3-30 days, with only three (19%) being more than 28 days but they were also within one month of age (30 days each). Majority (94%) were delivered in hospital and were born to primiparous females (81%). Out of 16 young infants, 13 (81%) were

Variable	Number (%)
Age (days)	
Median	10.5
Range	3-30
Sex	
Male	8 (50.0)
Female	8 (50.0)
Place of delivery	
Home	1 (6.3)
Hospital	15 (93.7)
Parity	
Primi	13 (81.2)
Multi	3 (18.8)
Birth weight (Kg)	
Mean±SD	3.02±0.44
95% CI	2.78-3.26
Exclusive breastfeeding	
Yes	13 (81.2)
No	3 (18.8)

[Table/Fig-1]: Demographic profile of the cases.

on exclusive breast feeding whereas three were on mixed feeding [Table/Fig-1].

Most common presenting complaint was decreased feeding observed in 75% (12) young infants followed by fever which was

present in 56% (9). Two babies had history of seizures at admission, however during subsequent course seizures occurred in 10 more babies, so that 75% (12) of all had seizures. Complaint of decreased urine output was in around 30% (5) babies but after admission on monitoring oliguria (<1 mL/kg/hr) was observed in all (15) babies except one. Majority of the young infants i.e., 75% (12) had stage III AKI as per neonatal RIFLE criteria with 12.5% each with stage II and I. Sepsis screen was positive in 31% (5) babies. Mechanical ventilation and vasopressor support was required in 31% (5) and 37% (6) babies respectively. Out of 16 young infants

Variable	Number (%)
Presenting Symptoms	
Seizures*	2 (12.5)
Decreased oral acceptance	12 (75)
Fever	9 (56.3)
Decreased urine output	5 (31.3)
Lethargy	3 (18.8)
Excessive crying	1 (6.3)
Diarrhoea	1 (6.3)
Vomiting	1 (6.3)
AKI staging	
Stage I: At Risk	2 (12.5)
Stage II: Injury	2 (12.5)
Stage III: Failure	12 (75.0)
Seizures	
Present	12 (75.0)
Absent	4 (25.0)
Septicaemia	
Present	5 (31.2)
Absent	11 (68.8)
Received mechanical ventilation	
Yes	5 (31.2)
No	11 (68.8)
Vasopressor use	
Yes	6 (37.5)
No	10 (62.5)
Outcome	
Discharged	11 (68.8)
Died	5 (31.2)

[Table/Fig-2]: Distribution of the cases according to clinical parameters.
*Seizures before admission

described, mortality was observed in 31% (5) babies and were same who required mechanical ventilation and had positive sepsis screen [Table/Fig-2].

Urine output in included cases ranged from 0-1 mL/kg/hr and mean of 0.44 mL/kg/hr with only one baby having value more than 1 mL/kg/hr, whereas rest all of the babies (15) documented to have oliguria. Blood urea ranged from 63 mg/dL to 779 mg/dL with median value of 199.5 mg/dL. Serum creatinine ranged from 0.6 to 9 mg/dL with median value of 2.4 mg/dL. Serum sodium values were observed to range from 156 mEq/L to as high as 183 meq/L with mean value being 165.9±8.40 mEq/L [Table/Fig-3].

On comparing various clinico-laboratory characteristics among babies who died and survived (clinical outcome), it was observed that use of vasopressor, presence of septicaemia, requirement of mechanical ventilation, levels of blood urea and serum creatinine on admission were significantly associated with adverse clinical outcome. Out of six babies requiring one or more vasopressors, five (83%) died, whereas no death among other 10 (100% survival) babies who did not require vasopressors (p=0.00). Similarly, 80% (4)

Variable	Mean±SD
Urine output (mL/kg/hr)	
Mean±SD	0.44±0.34
Blood urea (mg/dL)	
Median	199.5
Range	63-779
Serum creatinine (mg/dL)	
Median	2.4
Range	0.6-9.0
Serum sodium (mEq/L)	
Mean±SD	165.88±8.40

[Table/Fig-3]: Clinical and biochemical parameters among cases.

died out of 5 babies diagnosed with septicaemia compared to 9% (1) mortality among 11 babies without septicaemia ($p < 0.05$). Median blood urea value was 373 mg/dL in babies who died compared to 184.6 mg/dL among survivors and difference was statistically significant ($p < 0.05$). Also, median serum creatinine values in babies who died was 6.3 mg/dL compared to 1.6 mg/dL among survivors and difference was statistically significant ($p = 0.013$). Other parameters like age at presentation, gender, parity of mother, place of delivery, seizures, requirement of Renal Replacement Therapy (RRT) by Peritoneal dialysis, type of feeding did not vary statistically

	Outcome			p-value
	Survived (n=11)	Died (n=5)	Total (n=16)	
Age (days)				
Mean (SD)	14.6 (10.7)	8.0 (3.1)	12.6 (9.4)	0.082*
Sex				
Male {n (%)}	5 (62.5)	3 (37.5)	8 (100.0)	1.00*
Female {n (%)}	6 (75.0)	2 (25.0)	8 (100.0)	
Place of delivery				
Home {n (%)}	0 (0.0)	1 (100.0)	1 (100.0)	0.313*
Hospital {n (%)}	11 (73.3)	4 (26.7)	15 (100.0)	
Parity				
Primi {n (%)}	9 (69.2)	4 (30.8)	13 (100.0)	1.00*
Multi {n (%)}	2 (66.7)	1 (33.3)	3 (100.0)	
Birth weight				
Mean (SD)	3.1 (0.3)	2.7 (0.6)	3.0 (0.4)	0.089#
Weight change (%)				
Mean (SD)	12.3 (14.2)	17.0 (6.1)	13.8 (12.3)	0.791*
Exclusive breastfeeding				
Yes {n (%)}	10 (76.9)	3 (23.1)	13 (100.0)	0.214*
No {n (%)}	1 (33.3)	2 (66.7)	3 (100.0)	
Seizures				
Present {n (%)}	7 (58.3)	5 (41.7)	12 (100.0)	0.245*
Absent {n (%)}	4 (100.0)	0 (0.0)	4 (100.0)	
Vasopressor use				
Yes {n (%)}	1 (16.7)	5 (83.3)	6 (100.0)	0.000*
No {n (%)}	10 (100.0)	0 (0.0)	10 (100.0)	
RRT (PD)				
Yes {n (%)}	2 (66.7)	1 (33.3)	3 (100.0)	1.00*
No {n (%)}	9 (69.2)	4 (30.8)	13 (100.0)	
Septicaemia				
Present {n (%)}	1 (20.0)	4 (80.0)	5 (100.0)	0.013*
Absent {n (%)}	10 (90.9)	1 (9.1)	11 (100.0)	
Mechanical ventilation				
Yes {n (%)}	0 (0.0)	5 (100.0)	5 (100.0)	0.000*
No {n (%)}	11 (100.0)	0 (0.0)	11 (100.0)	

Serum Sodium (mEq/L)				
Mean (SD)	163.3 (7.3)	171.6 (8.7)	165.9 (8.4)	0.065*
Blood Urea (mg/dL)				
Median (Range)	184.6 (63-353)	373 (183-779)	199.5 (63-779)	0.038**
Serum creatinine (mg/dL)				
Median (Range)	1.6 (0.6-5.7)	6.3 (1.8-8.98)	2.4 (0.6-9.0)	0.013**

[Table/Fig-4]: Comparison between clinical outcome (discharge/death) and clinico-laboratory characteristics among cases.

*t-test, *Fisher's-Exact Test, **Mann-Whitney U test, RRT: Renal replacement therapy; PD: Peritoneal dialysis

between those who survived or died. Mean serum sodium level was high among those who died (172 mEq/L) compared to survivors (163 mEq/L), although the difference was statistically not significant [Table/Fig-4].

There was no statistically significant difference in levels of serum sodium depending on type of feeding, presence of seizures, requirement of vasopressors, RRT as well as mechanical ventilation. In babies with septicaemia, although mean values of serum sodium

	Serum Sodium Level (mEq/L) Mean (SD)		p-value*	
Exclusive Breast Feeding (EBF)	EBF (n=13)	Non-EBF (n=3)	0.964	
	165.9 (9.4)	165.7 (1.5)		
Seizures	Present (n=12)	Absent (n=4)	0.128	
	167.8 (8.9)	160.3 (2.9)		
Vasopressor	Received (n=6)	Not received (n=10)	0.267	
	169.0 (10.1)	164.0 (7.2)		
RRT	Received (n=3)	Not received (n=13)	0.485	
	162.7 (3.1)	166.6 (9.2)		
Septicaemia	Present (n=5)	Absent (n=11)	0.055	
	171.8 (8.5)	163.2 (7.3)		
Mechanical ventilation	Received (n=5)	Not received (n=11)	0.065	
	171.6 (8.7)	163.3 (7.3)		
Outcome	Discharged alive (n=11)	Died (n=5)	0.065	
	163.3 (7.3)	171.6 (8.7)		
Stage of AKI	I (n=2)	II (n=2)	III (n=12)	0.163**
	160.5(3.5)	157.0 (1.4)	168.2 (8.4)	
	Spearman Rank Correlation			
Serum creatinine	0.414		0.110#	
Urine output	Pearson Correlation		0.358#	
	0.246			

[Table/Fig-5]: Association between serum sodium levels and clinico-laboratory parameters among cases.

RRT: Renal replacement therapy; *t-test **One-way ANOVA #Correlation

were comparatively high than those without (171.6 mEq/L vs 163.2 mEq/L), but difference was not significant. Similar observation was seen for stage of AKI ($p = 0.163$). Also, serum sodium levels did not significantly correlate with urine output and serum creatinine levels [Table/Fig-5].

DISCUSSION

Sixteen consecutive babies meeting inclusion criteria (hyponatremia as well as AKI) during study period were included in the series. Median age at presentation was 10.5 days similar to observations in various studies [17,22]. Some studies have reported lesser age at presentation (3-6 days) [9, 12, 14, 19]. However, most of these studies were related to age for presentation for hyponatremia whereas in this study, babies had established AKI along with hyponatremia.

Majority i.e., 81% (13/16) were born to primiparous women and were (81%) on exclusive breast feeding similar to studies who have recently observed increasing reports of hypernatremia in exclusively breast fed babies born to primiparous females [9-15,18,19]. Basiratnia M et al., observed incidence of hypernatremia to be more in exclusively breast fed babies (9.3%) compared to the babies on mixed feeding (2.7%) [14]. It seems that incidence of hypernatremia in term or near term exclusively fed babies is much higher than previously thought and clinically difficult to recognize as although 73% of infants had $\geq 10\%$ weight loss in various studies, dehydration was noted rarely in the medical records, because infants with hypernatremic dehydration have better-preserved extracellular volume [23,24]. Exact reason for developing hypernatremia in term babies is not known but most commonly hypothesized to be inadequate breast milk in initial days.

In the present study, most common presentation was poor oral acceptance (75%), followed by fever (56%). Other presenting problems were decreased urine output and lethargy (31% and 19% respectively). A 12.5% (2/16) had seizures before admission but during hospital course majority i.e., 75% (12/16) of babies developed seizures. In a very similar study by Yildiz N et al., who did retrospective analysis of 15 breast fed newborns with hypernatremia and severe AKI requiring acute Peritoneal Dialysis (PD), mean age was 11.9 \pm 9 days as in our study, also oligo-anuria was present in all cases [17]. Moritz ML et al., in their retrospective analysis of breast fed babies with hypernatremia (n=70) found that besides jaundice which was most common manifestation, other presenting complaints mimicked sepsis, like poor oral intake (61%), fever and lethargy. In their study, decreased urine output was observed in 36% cases; however, acute renal failure was documented in only one baby with serum creatinine of 2 mg/dL [9]. In systematic review by Lavagno C et al., out of 1485 breast fed babies with hypernatremia, besides weight loss >10%, poor oral acceptance was most commonly seen manifestation in 46% (469/1029) babies followed by jaundice and poor hydration (44% and 45% respectively). Fever was observed in 37% (319/853) cases. Other manifestation being decreased urine output, lethargy and irritability. AKI was documented in 64% cases (119/186) [15]. Others also had similar observations suggesting that one of the reasons for under diagnosis of hypernatremia in breast fed newborns may be due to their presentation with presumed sepsis e.g., poor oral acceptance, fever, lethargy, irritability, seizures etc., [9,12,15,19].

Seventy five percent (12/16) cases had severe AKI (stage III) with 12.5% each with stage II and I respectively based on neonatal RIFLE criteria [21]. AKI in newborns and young infant age group is not very common and most of the available studies are in specific population like perinatal asphyxia, low birth weight, septicaemia or post cardiac surgery etc., which are more susceptible groups [25-27]. Great variability of incidence in various studies may depend on different criteria for AKI taken with reported incidence of around 20% when along with serum creatinine, urine output was taken to diagnose AKI, compared to 6.3% when only serum creatinine was taken as criteria for AKI [28,29]. In this study, on monitoring oligo-anuria was observed in all babies except one and mean urine output was 0.44 mL/kg/hr. Blood urea values were significantly elevated with median of 199.5 mg/dL, so was serum creatinine which ranged from 0.6-9 mg/dL with median value of 2.4 mg/dL. Serum sodium levels ranged from 156-183 mEq/L with mean value of 165.9 \pm 8.4 mEq/L. Oligo-anuria with established AKI has been reported in very few studies, mainly in form of case reports and series but criteria and severity of AKI was not clearly defined [8,9,12,15-19]. In this study, PD was done in three babies out of which two survived. Overall, out of 16 young infants, 31% (5) died which is higher than reported mortality of 1-5% by various authors [15,18]. However, most of these studies had variable degree of hypernatremia without AKI.

Historically, acute hypernatremic dehydration is reported to have high mortality (45%) [30]. In study very similar to ours by Yildiz N et al., with severe hypernatremia with kidney dysfunction requiring PD, reported mortality was 26.7% (5/15). Also, majority of newborns presenting with renal failure and hypernatremia were on EBF with no other predisposing factors similar to observation made in our study [17]. Ours being a tertiary care centre, severe cases in delayed stages are referred as highlighted by higher mean values of serum sodium, creatinine and also later age of presentation. Also, to look for factors associated with increased mortality it was observed that presence of sepsis (4 out of 5) with p=0.013, requirement of mechanical ventilation (5 out of 5) with p=0.0, higher mean blood urea levels (398.6 mg/dL in those who died vs 183.7% in survived babies) with p=0.019 and higher mean values of serum creatinine (5.8 mg/dL vs 2.1 mg/dL) with p=0.003 significantly contribute to increased risk of mortality. Yildiz N et al., also had similar observations with highest mortality seen in babies requiring mechanical ventilation and sepsis, highlighting the role of severity and other co-morbidities in outcome of such cases [17].

Although serum sodium values were high in babies who died (171.6 mEq/L vs 163.3 mEq/L), difference was statistically not significant similar to observation made by Yildiz N et al., [17]. In our analysis to see association of serum sodium levels with various clinico-laboratory parameters like presence of seizures (p=0.12), requirement of vasopressors (p=0.26), PD (p=0.48), mechanical ventilation (p=0.065) and stage of AKI (p=0.16) along with urine output (r=-0.246, p=0.358) and serum creatinine (r=-.414, p=0.110), no significant association was found with any of the characteristics (p>0.05). Previous studies have correlated serum sodium values with weight loss, age at presentation, maternal age and degree of hyperbilirubinemia but not with the factors mentioned in our series [9,19].

This is one of the few studies reporting severe complication of hypernatremia in term normal babies with majority on exclusive breast feeds and no predisposing factors. Over a small period of six months, we could find 16 babies with hypernatremia with AKI which in most cases was severe whereas most of previous studies done reported mild to moderate hypernatremia. Also, unlike other studies criteria and severity of AKI was defined in this series. Major limitation of the study lies in small sample size and being a retrospective analysis, chances of missed cases are high.

CONCLUSION

Hypernatremia in term exclusively breast fed babies is more common than thought and most of the babies present with no or minimal dehydration and features mimicking sepsis and if not diagnosed and treated early can lead to kidney injury and failure. Therefore, it is important to have high index of suspicion for this complication in all breast fed babies. There is strong need to further study this phenomenon prospectively in large group of breast fed babies with no other predisposing factors and to prevent this devastating complication.

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