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Case Report

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Severe Unexpected Hyponatremia in an Infant With Cystic Fibrosis Carriership

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Abstract

This report describes the development of severe hyponatremia in a 4-month-old infant, with known carriership of cystic fibrosis (CF; heterozygous delta F508 cystic fibrosis transmembrane conductance regulator (CFTR) mutation), in the course of a coronavirus disease 2019 (COVID-19) infection with mild respiratory symptoms and a urinary tract infection. Laboratory investigations were performed in the outpatient clinic because of persistent loss of appetite, fussiness and mild weight loss after a recent antibiotically treated urinary tract infection. The results showed severe hyponatremia of 115 mmol/L, mild hypokalemia of 3.0 mmol/L, with normal renal function, without other biochemical signs of dehydration and neither signs of fluid retention. Urinary fractional sodium excretion was extremely low, indicative of adequate renal sodium retention in the hyponatremic state. We hypothesize that the combination of disturbed extrarenal salt losses due to CF carriership, together with loss of appetite, relatively low sodium content of breastmilk and possibly COVID-19-associated mild syndrome of inappropriate antidiuretic hormone secretion (SIADH), resulted in the severe hyponatremia that was found in this infant. We believe it is important to report the findings in the current case to underscore the intricate balance of sodium homeostasis in the fully breastfed older infant and the alertness for checking sodium levels during infections/illness in heterozygote CF patients, as was previously reported in literature. In conclusion, this report describes the development of severe unexpected hyponatremia in the course of a mild infectious period in a fully breastfed 4-month-old infant with known CF carriership and underscores the importance of measuring sodium levels with low threshold during infections in CF carriers.

Keywords: Hyponatremia; Cystic fibrosis carriership; Pediatrics; COVID-19; Breast milk

Introduction

Hyponatremia, marked as a sodium level < 135 mmol/L, is a common electrolyte imbalance in the inhospital pediatric population. Sodium homeostasis is essential for maintaining intravascular volume and is tightly linked to water balance. Plasma water volume is regulated mainly by the secretion of antidiuretic hormone (ADH) and by the thirst mechanism (central and peripheral osmoreceptors). Renal sodium and water homeostasis are hormonally regulated by both ADH and aldosterone [1].

Two biological mechanisms can alter the sodium balance and hydromineral homeostasis. The first is largely determined by the intake of sodium chloride (NaCl), which accumulates in the extracellular space and leads to the displacement of water from the cell to the extracellular space, producing cell dehydration. In this situation, the appetite for sodium is inhibited and its excretion is increased (natriuresis), while the intake of water is enhanced and the excretion of fluid is reduced (ADH). Conversely, a reduction in extracellular fluid (ECF) osmolality (hyponatremia) leads to the inhibition of water intake and promotion of diuresis, increasing the appetite for sodium and suppressing natriuresis [2]. The second mechanism results from the loss of intravascular fluid (hypovolemia), one of the components of ECF. Diarrhea, vomiting, hemorrhages, sweating, renal disease and cardiovascular disorders can be accompanied by the loss of intravascular volume. Hypovolemia triggers compensatory behavioral and physiological reactions to conserve sodium and body fluids. These include thirst and appetite for sodium (osmoreceptors), as well as antidiuretic and antinatriuretic responses to retain water and sodium. Conversely, ECF hypervolemia reduces the intake of water and sodium and increases diuresis and natriuresis [2]. In this respect, it is important to realize that sodium and water intake in the fully breastfed infant is solely dependent on the quantity and composition of mother's milk and that previous studies have shown that sodium content of breast milk decreases rapidly in the first 3 days after birth, and then more slowly. After the first week, the daily variation of sodium concentration in the breast milk is minimal with reported ranges mainly between 3.5 and 6.8 mmol/L depending on postnatal age [3, 4].

Based on the above-described physiological mechanisms, the differential diagnosis of hyponatremia can be roughly classified into ECF tonicity/fluid overload states (e.g., syndrome of inappropriate antidiuretic hormone secretion (SIADH)) and causes related to sodium losses, which can be renal and extrarenal (gastrointestinal, pulmonary, skin). Symptoms can be lethargy, nausea, loss of appetite, muscle cramps and convulsions. Symptoms occur most often when the hyponatremia has developed in a short period of time or if the sodium level is severely low [5]. In the current case report, we describe a

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previously healthy, fully breastfed 4-month-old infant with known cystic fibrosis (CF) carriership and mild bilateral hydronephrosis that presented with a mildly symptomatic, but unexpected severe hyponatremia of 115 mmol/L, probably multifactorial (as will be described further) and aggravated by his underlying CF carriership. Slow correction of sodium deficit and correction of suspected mild fluid deficit resulted in gradual and uncomplicated restoration of serum sodium level and disappearance of symptoms. We believe it is important to report the current case to underscore the alertness for checking sodium levels with low threshold during infections/illness in heterozygote CF patients, especially in infants, as was previously mentioned in literature [6].

Case Report

A 4-month-old male infant, previously known with CF carriership and mild bilateral hydronephrosis (with absent reflux assessed by voiding urethrogram), was evaluated in the outpatient pediatric clinic because of not drinking well and fussiness while he received solely breastfeeding. These symptoms were preceded by a period of mild respiratory symptoms and urinary tract infection accompanied by 1 day with fever, caused by *Citrobacter koseri*, for which oral antibiotics were given. During the week before presentation, his intake had already been problematic. He was allowed to drink small amounts of water from the bottle because of his decreased intake and mother's fear for dehydration. He had not been vomiting and had no diarrhea nor fever. He was still being treated with oral antibiotics (amoxicillin/clavulanic acid) because of the urinary tract infection. Urinalysis was repeated, which did not show signs of a recurrent urinary tract infection and a repeated ultrasound did not show aggravation of his mild hydronephrosis. Laboratory investigations showed a severe hyponatremia of 115 mmol/L, a mild hypokalemia of 3.0 mmol/L, and a hypochloremic metabolic alkalosis, with otherwise normal findings regarding renal function, infectious parameters and hormonal status (Table 1).

His complete medical history did not show additional explanatory findings for the severe hyponatremia. The mother went through a COVID-19 infection with uncomplicated course in the first trimester of pregnancy. The infant was born term at a gestational age of 37 weeks and 5 days, with a birthweight of 3,650 g (p88) by cesarean section because of failure of labor progression. There was meconium-stained amniotic fluid. His Apgar scores were 9, 7 and 8 after respectively 1, 5 and 10 min. Postpartum there was respiratory distress for which he was admitted on the neonatology department with the diagnosis of transient tachypnea of the newborn, and received continuous positive airway pressure (CPAP) a couple of hours after birth. The next day he was discharged from the hospital.

During pregnancy, bilateral pyelectasia was seen in the fetus. Ultrasounds of the kidneys were performed postnatally, 1 month and 3 months after birth and confirmed a stable mild bilateral pyelectasia. A voiding cystourethrogram in a later stage showed no signs of vesicoureteral reflux. The working diagnosis for these findings was a mild ureteropelvic junction obstruction, for which three-monthly follow-up by ultrasound during the first year of life was planned.

Table 1. Laboratory Results at Presentation

Laboratory investigation	Results
Serum	
Sodium	115 mmol/L
Potassium	3.0 mmol/L
Calcium	2.81 mmol/L
Phosphate	1.80 mmol/L
Chloride	77 mmol/L
Urea	2.50 mmol/L
Creatinin	14 µmol/L
Osmolality	254 mOsmol/kg
Blood gas capillary	
pH	7.48
pCO_2	6.0 kPa
Bicarbonate	33.2 mmol/L
Base excess	8.6 mmol/L
Sodium	122 mmol/L
Potassium	2.82 mmol/L
Chloride	76 mmol/L
Glucose	5.4 mmol/L
Hemoglobin	8.2 mmol/L
Trombocytes	6.7×10^9/L
Leucocytes	6.7×10^9/L
TSH	3.45 mU/L
T4, free	23.8 pmol/L
Cortisol	1,221.9 nmol/L
Albumin	42 g/L
CRP	< 4 mg/L
Urine	
Creatinin	1.9 mmol/L
Sodium	< 10 mmol/L
Specific gravity	1.006 kg/L
pH	6.0
Protein	Negative
Glucose	Negative
Ketones	Negative
Nitrite	Negative
Blood	Negative
Leukocytes esterase	Negative

CRP: C-reactive protein; TSH: thyroid-stimulating hormone.

The family history revealed a healthy mother of 35 years old, who was then gravida 3, para 2, and carrier of the CFTR gene mutation (delta F508). The father was also carrier of a

Table 2. Sodium, Potassium and Chloride Levels During Admission

	14-07-2022 (3 PM)	15-07-2022 (4 AM)	15-07-2022 (11 AM)	15-07-2022 (8 PM)	16-07-2022 (8 AM)	17-7-2022 (8 AM)	18-7-2022 (8 AM)	27-7-2022*
Sodium (mmol/L)	115	122	121	124	128	131	135	138
Potassium (mmol/L)	3.0	2.82	4.03	3.42	3.31	4.2	5.64	4.79
Chloride (mmol/L)	77	76	78	81	84	99	104	105

*Two days after discontinuing suppletion.

CFTR gene mutation (164G>A) with unclear clinical relevance. Both were asymptomatic. Parents were not consanguineous. Because of the CFTR mutation carriership in both parents, a genetic screening was performed in the newborn shortly after birth and showed heterozygosity for the same CFTR mutation as his mother (delta F508), but the mutation of father was not transmitted. He had a healthy older brother of 4 years old, who was not tested for CF gene mutations.

On physical examination on the day of the severe hyponatremia, a well grown child was seen without signs of respiratory distress and he seemed well circulated. His weight was 7.5 kg (+1.6 standard deviation (SD); 8 days earlier 7.8 kg, length 65 cm (+1.1 SD), head circumference 44 cm (+2 SD), heart rate (HR) 144/min, blood pressure (BP) 85/63 mm Hg and a temperature of 37 °C. A full physical examination showed a well-circulated child with normal capillary refill, warm extremities and well palpable peripheral pulses. There were no signs of dyspnea and auscultation of heart and lungs was normal. His abdomen was soft and he did not have hepatosplenomegaly. The skin did not show any abnormalities. His neurological examination was normal. An alert, happy and well-developed child was seen. His tone was normal and he moved his extremities symmetrical.

The initial differential diagnoses consisted of a pseudohyponatremia or laboratory artefact, a more severe intake problem than previously recognized, renal or unknown extrarenal sodium losses, hyponatremic-hypertension syndrome (BP was within normal range for his age), pseudohypoaldosteronism during urinary tract infection (although potassium levels not increased) or SIADH.

First, a laboratorial artefact and pseudohyponatremia was ruled out by the clinical chemist. Further laboratory and urinary investigations were performed to determine the cause of the hyponatremia. An associated hypochloremia of 76 mmol/L and a hypokalemia of 3.0 mmol/L were found (Table 1). The serum osmolality was 254 mOsmol/kg in line with the severe hyponatremia. His creatinine and urea nitrogen levels were normal (Table 1). A capillary blood gas showed high bicarbonate of 33.2 mmol/L with a pH of 7.48, a CO_2 of 6.0 kPa and a base excess of 8.6 mmol/L, consistent with a hypochloremic metabolic alkalosis. There was no use of diuretics. His cortisol and glucose levels and thyroid functions were normal. His urine sodium level showed a low value of < 10 mmol/L, resulting in a fractional excreation of sodium that was adequately very low (< 0.06%), thus ruling out renal saltwasting as the underlying cause. Urine-specific gravity was normal, indicative of normal urine osmolality, which was not supportive of SIADH as the underlying cause of hyponatremia. Because of a mild cough and two family members that were recently tested positive for COVID-19, a polymerase chain reaction (PCR) for COVID-19 was done and turned out to be positive, but with a high cycle threshold (CT) value, indicative of resolving infection (CT value 27.39). A sweat test was considered unnecessary because of the genetically proven heterozygosity for the delta F508 mutation and is technically not possible in Curacao Medical Center.

Based on the medical history, the physical examination with only slight weight loss and the laboratory findings including additional breastmilk investigations (as described below), it was hypothesized that the hyponatremia in this specific case, was possibly due to a combination of multiple causes: 1) hyponatremic dehydration due to decreased fluid intake; 2) relative low sodium intake with complete breastfeeding; 3) possible slightly lower sodium content in breastmilk of mother with CF carriership; 4) increased extrarenal sodium and chloride loss during illness due to CF carriership; and 5) possibly COVID-19-associated mild SIADH.

Because of the severe hyponatremia of 115 mmol/L and associated risks of neurological complications when correcting too fast, he was admitted on the pediatric ward. The sodium and water deficits were calculated and were orally supplemented in a period of 48 h, whereafter normal sodium intake was guaranteed. Correction proceeded gradually (Table 2) and without complications and soon after admittance his symptoms of loss of appetite and fussiness disappeared. He was discharged 4 days after admission with a normalized sodium level of 135 mmol/L, with continued oral sodium suppletion 1 mmol/kg/day for a few days more and recommendations to start additional infant feedings besides breastfeeding (fruits and vegetables). After discontinuing the suppletion, his sodium level remained within normal ranges. It is noteworthy to mention that this patient was re-admitted at the age of 8 months with respiratory distress and less oral intake due to an adenovirus infection. At that time, he kept his sodium levels within the normal range.

Additional laboratory investigations

In an attempt to explore the possibility of low sodium content of the mother's breastmilk in this individual situation, after permission was obtained, the sodium and chloride contents in three portions of pumped breastmilk of the mother were measured in the clinical chemistry laboratory of our hospital. Sodium and chloride levels were compared with voluntarily obtained breastmilk portions of two breastfeeding mothers

Table 3. Sodium and Chloride Content in Breast Milk of Mother of Infant in This Case, Two Healthy Controls and in Literature Reported Ranges

	Sodium (mmol/L)	Chloride (mmol/L)
Case		
Sample 1	3.4	3.7
Sample 2	4.2	3.6
Sample 3	5.2	4
Control 1		
Sample 1	6.1	5.4
Sample 2	6.4	4.8
Control 2		
Sample 1	8.6	7.1
Stallings et al [4]		
0 - 6 months	6.0 mmol/L (95% CI 5.1 - 6.8)	
7 - 12 months	4.8 mmol/L (95% CI 3.5 - 6.2)	
Turck et al [7]		11.3

Case shows sodium and chloride levels in breast milk of patient's mother, measured in three different samples. Control 1 shows sodium and chloride levels in breast milk of a 2-month-old baby, fully breastfed, measured in two different samples. Control 2 shows sodium and chloride levels in breast milk of an 8-month-old baby, measured in one sample. Literature shows sodium and chloride levels in breast milk in Stallings et al [4] and Turck et al [7]. CI: confidence interval.

with healthy infants of 2 and 8 months old and were also compared with reported levels in the literature. Table 3 shows the results of these comparisons and shows a mildly lower sodium content in the breastmilk of the mother of the infant discussed in this report compared to the two voluntary controls and the levels reported in literature in the 0 - 6 months age group [4, 7].

Discussion

This report describes the unexpected finding of severe hyponatremia (115 mmol/L) in a 4-month-old previously healthy infant with known CF carriership in the course of a urinary tract infection treated with oral antibiotics and COVID-19 infection with mild respiratory symptoms, which led to decreased intake. The hyponatremia was accompanied by a mild hypokalemia (3.0 mmol/L) and a hypochloremic metabolic alkalosis. Renal saltwasting was excluded and renal function was normal. Due to the relatively mild clinical symptoms at presentation, we suspect the occurrence of a slow and gradual decrease in sodium concentration in the days, maybe the week before presentation when the intake was significantly decreased during urinary tract infection in combination with mild respiratory symptoms due to COVID-19, in this fully breastfed infant. The finding of a low serum osmolality indicated a hypotonic hyponatremia. A further classification of hyponatremia can be made based on the volume status of the patient [1]. Clinically the infant seemed euvolemic, but he did have a 3.8% weight loss and loss of appetite, thus, a hypovolemic hypotonic hyponatremia was suspected. The additional findings of metabolic alkalosis and mild hypokalemia could be consistent with volume depletion associated hyperaldosteronism; however, the severity of the hyponatremia does not support this hypothesis. Furthermore, transient pseudohypoaldosteronism which has shown to be associated with urinary tract infections [8] could also cause severe hyponatremia; however, in that scenario a hyperkalemia would be expected, while this infant showed hypokalemia. There was also no history of gastrointestinal losses and renal saltwasting was ruled out by the finding of a very low fractional excretion of sodium. Additionally, the normal urinary specific gravity at presentation was not supportive for SIADH as the main underlying cause for the hyponatremia. His normal BP ruled out a hyponatremic-hypertension syndrome and other hormonal causes for hyponatremia (glucose, cortisol and thyroid function) were measured and found to be normal. Taking into account the above findings, we concluded that the hyponatremia in the reported case was possibly due to a combination of mainly fluid- and salt intake disturbances in a fully breastfed infant with prolonged decreased appetite during an infectious period, possibly aggravated by both his own and the mothers' CF carriership with relatively low sodium content of the breastmilk compared to literature and two voluntary controls. The three samples of breastmilk of mother were tested for sodium level and showed a mean of 4.3 mmol/L. Normal values of sodium level in breast milk show a mean of 6.0 mmol/L (95% confidence interval (CI) 5.1 - 6.8) for infants 0 - 6 months and 4.8 mmol/L (95% CI 3.5 - 6.2) for 7 - 12 months [4]. Based on the above measurements, it could be speculated that the breastmilk of the mother in this patient showed a relatively low sodium level for the age compared to that in literature, as well as the levels of the controls measured in our laboratory. However, other case reports show normal sodium values in breast milk in mothers with CF and breastfeeding is not contraindicated in CF patients [9-12].

Increased sodium and chloride imbalance during illness due to CF carriership has been previously described [6]. In patients with homozygous CF, electrolyte imbalances such as hyponatremia, hypochloremia, hypokalemia and metabolic alkalosis have been described more often [13, 14]. This was almost always associated with an often clinically inapparent fluid volume depletion. The electrolyte imbalances were associated with respiratory infections, excessive sweating, increased body temperature, failure to thrive, heat exposure and volume depletion [14]. The excessive sweat production in CF patients contains an abnormally high salt content and thereby explains the chloride and sodium depletion. Farrell et al reported in 1996 that heterozygous CF patients do have a mildly but significantly higher chloride level in the sweat than healthy subjects [15]. A carriership of CF has long been considered as asymptomatic without increased health risk. However, Miller et al showed recently in a large cohort that CF carriers are at increased risk for almost all CF-related conditions, including electrolyte imbalances and dehydration [6].

Last but not least, although not supported by urinalysis, COVID-19-associated mild SIADH cannot be ruled out. It has been reported that the causes of hyponatremia in COVID-19

are multifactorial. It may be due to increased gastrointestinal loss (diarrhea, vomiting), decreased oral intake, or SIADH. It can be hypervolemic, euvolemic, or hypovolemic hyponatremia. Reported rates of hyponatremia have been up to 50% of the hospitalized COVID-19 adult patients in the United States [16, 17].

In conclusion, the working diagnosis of the severe hyponatremia in the reported case was most probably multifactorial causes aggravating each other, starting with the underlying CFTR mutation carriership, together with the trigger of a urinary tract infection, closely followed or combined by a COVID-19 infection (with possible mild SIADH) and prolonged loss of appetite with associated fluid and salt depletion together with relatively low sodium content in the breastmilk. Of interest, his older brother was diagnosed with a severe hypotonic dehydration at the age of 5 months, secondary to a *Bordetella pertussis* infection. He showed a sodium level of 123 mmol/L and a chloride of 73 mmol/L. These levels normalized after rehydration. He was not genetically tested, but CF heterozygosity could very well be possible. We state that every physician should be aware of the higher risk of electrolyte disturbances in patients with carriership of CF and should perform low-threshold electrolyte testing, even with mild symptoms.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent has been obtained by the parents of the patient.

Author Contributions

Simone de Milliano was responsible for writing the first draft and tables and incorporating revisions. Dr. Farah A.Falix reviewed the manuscript and approved the final version. Dr. Nasser E. Ajubi was responsible for the analysis of the breast milk and approved the final version.

Data Availability

The authors declare that data supporting the findings of this case report are available within the article.

Abbreviations

ADH: antidiuretic hormone; BP: blood pressure; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CPAP: continuous positive airway pressure; CT: cycle threshold; ECF: extracellular fluid; HR: heart rate; NaCl: sodium chloride; PCR: polymerase chain reaction; SIADH: syndrome of inappropriate antidiuretic hormone secretion

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