Acid-base disturbances in dehydrated patients with cystic fibrosis : four case reports with review of literature

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Abstract

Most episodes of vomiting, reduced intake and diarrhoea in children can be evaluated and treated without additional tests. However, when the degree of clinical dehydration is not in line with the patient's medical history, other diagnoses should be suspected. In the presence of a hyponatraemic hypochloraemic metabolic alkalosis, cystic fibrosis (CF) should be included in the differential diagnosis, especially if there is failure to thrive even in the absence of respiratory symptoms. Furthermore, young patients diagnosed with CF have a higher risk for an acute electrolyte decompensation caused by increased salt and fluid losses. We present 4 paediatric cases to raise the awareness of electrolyte disturbances in CF patients. (Acta gastroenterol. belg., **2020**, 83, **315-318**).

Key words : Hyponatraemic hypochloraemic alkalosis, cystic fibrosis, dehydration, electrolyte disturbances, pseudo-Bartter.

Introduction

Vomiting, diarrhoea and reduced oral intake in small children induces a high dehydration risk due to increased insensible water losses as a result of their high body surface to body weight ratio (1). Furthermore, the diminished renal concentrating capacity limits their compensating capacities. Faced with dehydration, children will typically develop a metabolic acidosis. As in adults, dehydration activates the renin-angiotensin-aldosterone system (RAAS) to increase sodium and water retention (Fig. 1). Physicians will mainly evaluate dehydrated children through a thorough history and physical examination. Most episodes of vomiting and diarrhoea are self-limiting and have an infectious origin. Laboratory testing is not indicated in mild cases without underlying pathology (1). However, inconstancies in the medical and current history as well as clinical appearance might warrant further investigations. Ph and serum electrolytes, eventually associated with urinary electrolytes in case of unexplained electrolyte abnormalities, are among the most frequent measured parameters.

The following cases illustrate the need of a high level of suspicion for CF in children presenting with hyponatraemic, hypochloraemic metabolic alkalosis, and on the other hand increased awareness of electrolyte disturbances in known CF patients with a history of decreased intake. The laboratory results of all cases are summarised in table 1.

Case 1

A 6.5-month-old girl presented during summer with increasing food refusal. She was breastfed and introduction of solid foods failed repeatedly. Originally her weight curve followed the -2 standard deviations (SD) with length on -1 SD. She had no previous medical history of note. Clinical examination revealed an alert baby with sunken fontanel and deep-set eyes and stable vital parameters (pulse 110/min, oxygen saturation 96%, blood pressure 100/45 mmHg, temperature 36.8°C). Her body weight was 4.85 kg (-4.3 SD). Laboratory results are mentioned in table 1. The association of failure to thrive with hyponatraemic, hypochloraemic metabolic alkalosis prompted the diagnosis of CF. A sweat test revealed an elevated sweat Cl- of 74 mmol/L. A normal faecal elastase (> 500 µg/g) indicated pancreatic sufficiency.

Case 2

A 7-month-old boy was seen in July because of decreased oral intake with weight loss, without vomiting, diarrhoea or fever. He was known with excessive crying, the indication for a 24h oesophageal pH-monitoring which was normal. Physical examination only revealed deep-set eyes. His body weight was 6.54 kg (-1.9 SD), which was according to the parents 6.88 kg (-1.2 SD) one month before. Blood results showed hyponatraemia (133 mmol/L) and hypochloraemia (83 mmol/L) which were corrected with 24h intravenous (IV) rehydration with NaCl 0.9%.

One month later the history repeated itself (weight 6.51 kg (-2.3 SD)). Blood results are available in table 1. Again, the combination of failure to thrive with the repeated electrolyte disturbances led to the diagnosis of CF (sweat Cl^- : 97.1 mmol/L). The faecal elastase (< 5 µg/g) indicated pancreatic insufficiency.

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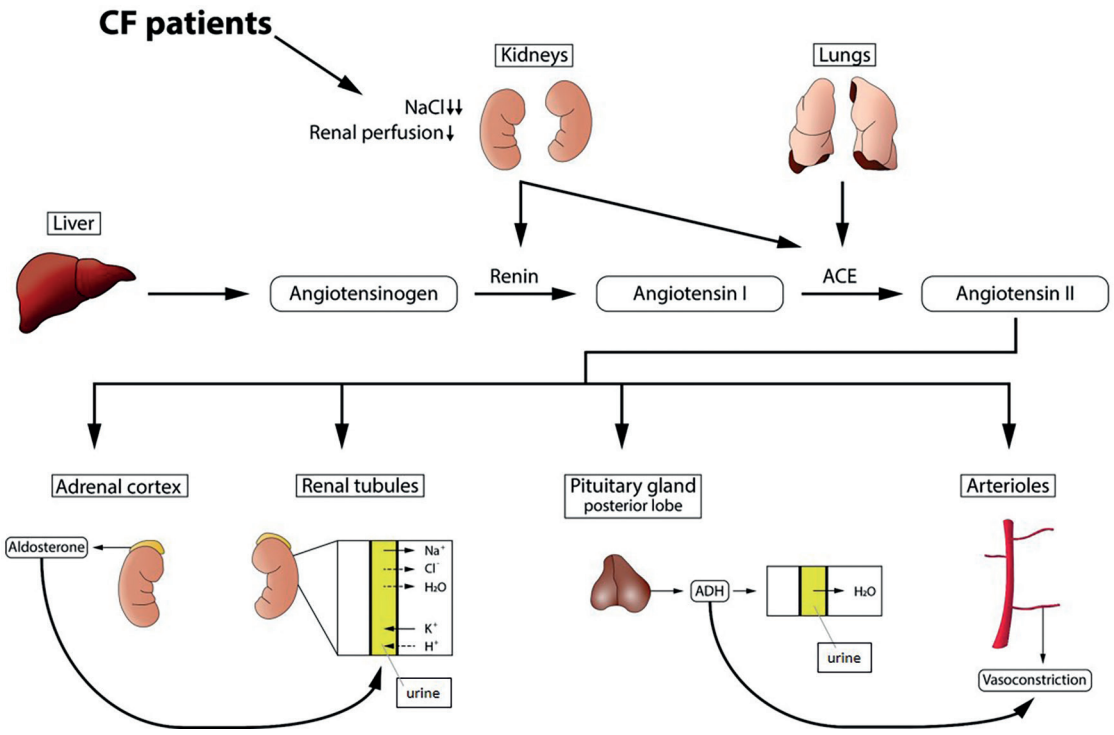

Fig. 1. — The renin-angiotensin-aldosterone system (RAAS). In CF patients, increased sweat NaCl concentration and dehydration stimulate the kidneys to produce renin, which converts angiotensinogen to angiotensin I. This is converted to angiotensin II by ACE secreted by kidneys and lungs. Angiotensin II affects multiple organs : the adrenal cortex increases aldosterone production, which stimulates the reabsorption of NaCl and H_2O in the renal tubules in exchange for K^+ and H^+ ; this process is also directly stimulated in the renal tubules by angiotensin II ; the posterior lobe of the pituitary gland stimulates ADH production, which increases H_2O reabsorption and stimulates vasoconstriction in arterioles ; this vasoconstriction is also stimulated directly by angiotensin II. CF : cystic fibrosis ; ACE : angiotensine converting enzyme ; ADH : antidiuretic hormone.

Table 1. — **Overview of the laboratory results of all cases**

Case	Blood results						Urine results			Calculated		
	Ph	PCO_2	$[HC0_3^-]$	$[Na^+]$	$[K^+]$	$[Cl^-]$	$[Na^+]$	$[K^+]$	[Cl-]	FE Na	FE Cl	Anion gap
1	7,55	39,8	34,8	124	3,2	72	<20	48	<20	0,07	0,1	17,2
2	7,54	45,9	39	133	2,78	78	<20	57,5	<20	0,13	0,2	16
3			23,1	129	4,2	82	<20	43	<20	0,025	0,03	23,9
4	7,49	40,4	30,2	134	4,1	79	<20	91	<20	0,13	0,2	24,8
nl values	7,35-7,45	32-45 mmol/L	22-26 mmol/L	136-145 mmol/L	3,6-4,8 mmol/L	98-107 mmol/L	mmol/L	mmol/L	mmol/L	0,5- %	0,5- %	10-14

Case 3

In July, a 7-year-old boy, known with CF and pancreatic insufficiency, complained of obstipation associated with vomiting for one day without fever. Since a few days the fluid intake was reduced and a weight loss of 1.5 kg was reported. Physical examination showed no signs of dehydration nor other abnormalities. Laboratory results (table 1) prompted the need for IV rehydration with initiation of salt supplementation. After two days he was discharged from the hospital with a salt supplement (3 X 500mg/day).

Case 4

A 16-month-old girl, known with CF and pancreatic insufficiency, consulted because of reduced alertness and fainting. She had a reduced intake for one day and vomited twice. She had a slightly elevated temperature (38°C). Urinary output was decreased and she was constipated. There were signs of moderate dehydration : reduced alertness, deep-set eyes, sunken fontanel and a decreased skin turgor. Blood tests displayed in table 1. She was rehydrated with ORS per nasogastric tube (50 ml/kg over 6h). Oral salt supplements were started on discharge (3x 250 mg/day).

Discussion

Metabolic alkalosis is uncommon in children. It is caused by excessive hydrogen losses due to vomiting (pyloric stenosis, ...), tubular dysfunction with increased renal bicarbonate reabsorption and potassium depletion (hyperaldosteronism, Cushing syndrome, Bartter's syn-

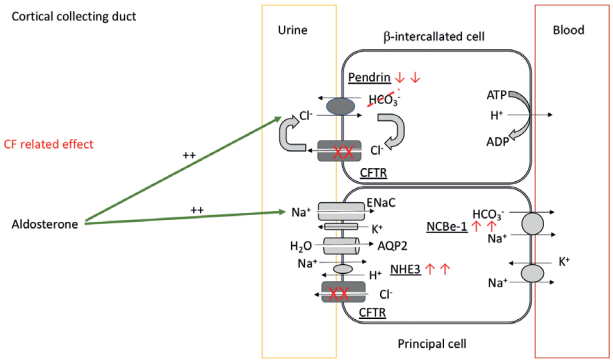

Fig. 2. — The effect of aldosterone on the cortical collecting duct, ion channels and the interference of cystic fibrosis. Aldosterone will stimulate Na^+ absorption from the urine through epithelial Na^+ channels (ENaC) and K^+ will be excreted. Water will be absorbed through aquaporins (AQP) opening under influence of antidiuretic hormone secreted by the pituitary gland. In CF Pendrin displays a decreased membrane expression and an increased cytoplasmatic localisation. The Na^+/H^+ exchanger (NHE3) have an aberrant induction in the apical membrane of the principal cells and Na^+/HCO_3^- exchanger (NBCe-1) on the basolateral membrane. Figure adapted from Yamazaki and Varasteh Kia (9,10).

drome, potassium-losing diuretics, ...) or contraction of the extracellular fluid volume. Loop diuretics inhibit the Na+/K+/2Cl- cotransporter responsible for 25% of the Na+ reabsorption. Thiazide inhibit the Na+-Cl- cotransporter in the distal tubule responsible for 5% of the Na+ reabsorption. Both will result in hypovolemia and activation of the RAAS leading to a mineralocorticoid driven Na+/K+, H+ exchange in the collecting duct. This results in alkalosis and hypokalaemia.

Metabolic alkalosis is the presenting sign in 16.5% of CF patients before the age of 12 months, possibly accompanied by symptoms as failure to thrive, vomiting, food refusal, lethargy and dehydration (2). Several infants have a history of repeated electrolyte disturbances before the diagnosis of CF is made (2-6). Hyponatremia was present at diagnosis in 95% of new CF diagnoses (6). Although infants are more prone to this condition, adults with CF can present with the same clinical picture also known as pseudo-Bartter syndrome (7).

The pathogenesis is attributable to the primary defect in the CF transmembrane conductance regulator gene, resulting in increased sweat chloride and sodium concentration (8). Since infant feeding contains only a low sodium concentration (± 20mg/100ml), nutrition will not cover the sodium required to maintain a steady state (5,6). Hypovolemia in infants with CF will activate their RAAS (Fig. 1), resulting in increased water and sodium retention in both proximal and distal tubule. Aldosterone induces transcription and activation of the epithelial Na^+ channel through the mineralocorticoid receptor, resulting in increased Na^+/H^+-exchange and increased urinary potassium losses (Fig. 2) (9). In normal circumstances aldosterone also increases the pendrin expression. Pendrin is a Cl^-/ HCO_3^- exchanger located in the β-intercalated cells of the cortical collecting duct which plays an important role in volume as well as acid-base homeostasis (10). Recent research focussing on the CF-mice kidneys revealed a decreased ability to excrete HCO_3^- in case of salt depletion and dehydration which was attributed to reduced pendrin expression (10) (Fig. 2).

The volume as well as acid-base homeostasis in CF is already significantly challenged in basal conditions. Each situation leading to a minor increase of fluid and/or salt losses either through sweat (fever, high ambient temperature, exercise), respiratory exacerbation, vomiting or decreased intake will cause further decompensation (2,11). Depletion of body stores as well as the inability to correct acid/base imbalance, leads to the observed hyponatraemic, hypochloraemic metabolic alkalosis eventually associated with hypokalaemia. Since electrolyte disturbances often develop slowly over time, dehydration is not always clinically prominent (5).

The clinical picture in infants is dominated by poor weight gain or even weight loss and anorexia, whilst other symptoms of CF may be absent. This entity is not always recognized timely since 27% of CF children have a former history of alkalosis (2). Patients at risk are younger and often had previous episodes (2). However, also older patients with CF are at risk since they have the tendency to underestimate their fluid losses, especially during exercise (12,13). The "ad libitum" fluid replacement after a 3%-dehydration-inducing exercise was 40% lower in CF patients compared to controls (13). Even with comparable dehydration, CF patients displayed less changes in serum osmolality compared to controls (14). The isotonic dehydration could explain the difference in ad libitum fluid intakes although the feeling of thirst was rated equally as in controls (14).

The long-term clinical impact is not yet studied. However, it is well documented that salt-losing tubulopathies are associated with failure to thrive and growth retardation. Hence, chronic electrolyte disturbances in patients with CF might also impair weight gain and growth (5). Furthermore, mucus plugging as a result of dehydration could increase, and alkalosis might lead to CO_2 retention (6). Therefore, these electrolyte abnormalities could accentuate acute hypercapnic respiratory failure in the end stage of the disease (15).

In order to prevent decompensation, correct estimation of salt and fluid homeostasis is necessary. Estimation of salt (NaCl) depletion is not straightforward. Hyponatremia is a late sign of more Na^+ than water deficit. The urinary Na^+ concentration is influenced by urinary flow and is therefore imprecise. Urinary sodium/creatinine ratio offers the potential to be less diuresis-dependent in the individual patient, but since creatinine is muscle mass dependent, which might be lower in CF patients, it has some disadvantages in cohort-studies. Fractional Na^+ excretion appears to be the best way to estimate Na^+ handling in the body, but requires paired blood and urinary samples. A study in 10 newly diagnosed

CF infants demonstrated a good correlation between fractional Na^+ excretion and urinary Na^+ /creatinine ratio (15). The target fractional Na^+ excretion of 0.5-1.5% corresponded to a urinary Na^+ /creatinine ratio range of 17-52 mmol/mmol. By regular urinary check, Na^+ intake could easily be adapted to sodium excretion avoiding both under- and over-supplementation.

Acute decompensations should be handled depending on the degree of dehydration, with IV 0,9% NaCl with K^+ (10-20 mmol/500ml) or oral rehydration using a modified HCO_3^- depleted ORS solution containing 6g/L NaCl, 1,5 g/L KCl and 111 mmol/L Glucose (16). Half of the fluid should be given within the first 8 hours (1). Supplemental salt intake adapted to the circumstances (temperature, exercise, season, ...) should be advised as prevention. Nutritional guidelines, vary from ⅛-¼ tablespoon of table salt (not exceeding 4 mEq/kg/d) until the age of two to 1-3 mmol/kg/d NaCl during the first 6 months (17,18). The Western diet is assumed to contain enough salt to compensate for the needs in older children and adults with CF (17). However, increased sodium concentration in rehydration fluid induced an increased fluid intake in sporting CF children (19). Since literature on the topic of salt supplementation in CF as well as on CF disease evolution is scarce, and guidelines are based on case reports and small studies, larger studies are needed to sustain current practice.

Conclusion

Metabolic alkalosis with hyponatremia, hypochloraemia and hypokalaemia is rather uncommon in infants. In the absence of obvious causes (vomiting, diarrhoea, drugs), a first clinical symptom of cystic fibrosis should be taken in consideration. In known CF patients, one must be also aware of dehydration and electrolyte disorders during episodes of negative sodium balance. This implicates that salt supplementation is often necessary, but should be adapted to the season and the nutritional intake. Monitoring of urinary electrolyte levels is mandatory in order to adjust supplemental salt intake.

Conflict of interest

None of the authors have a conflict of interest to declare concerning this article.

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