

Metabolic alkalosis with multiple salt unbalance: an atypical onset of cystic fibrosis in a child

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Abstract

Dehydration with multiple salt abnormalities is frequently encountered in the paediatric emergency department, during acute illnesses complicated by loss of body fluids. Metabolic alkalosis is not a common finding in dehydrated children. The presence of unusual electrolyte unbalance, such as metabolic alkalosis, hyponatremia, hypochloremia and hypokalemia, without evidence of renal tubular defects, is named as pseudo-Bartter syndrome. It can occur in several clinical settings and, in infancy, it is described as a potential complication of cystic fibrosis. We report a case of pseudo-Bartter syndrome representing the onset of cystic fibrosis in childhood.

Keywords

Pseudo-Bartter syndrome, metabolic alkalosis, hyponatremia, cystic fibrosis, child.

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Introduction

Hyponatremic hypochloremic dehydration is a common finding during pediatric illnesses characterized with severe and rapid loss of fluids through the gastrointestinal tract. Hypokalemia could be commonly found in children affected with persistent vomiting, but the occurrence of important metabolic alkalosis is not so frequent [1]. Metabolic alkalosis associated to

hyponatremia, hypochloremia and hypokalemia all together can be found in Bartter syndrome, which is caused by renal salt wasting due to a mutation of Na-K-2Cl co-transporter (NKCC2) in the thick ascending limb of the loop of Henle. Classic Bartter syndrome is usually diagnosed during infancy and childhood: it has variable clinical manifestations, ranging from near-fatal volume depletion to mild muscle weakness. Similar electrolyte abnormalities could also be found in Gitelman syndrome, which is actually caused by a defect of thiazide-sensitive co-transporter (TSC) in the distal convoluted tubule: these patients are often diagnosed in adolescence or early adulthood and, importantly, they usually have reduced plasma levels of magnesium, too. [2]. Dated medical literature reported several cases of cystic fibrosis (CF) developing episodes of hyponatremic and hypochloremic dehydration associated to concomitant metabolic alkalosis and hypokalemia. Whenever this panel of electrolyte abnormalities is not associated to the aforementioned renal tubule defects, the clinical condition is defined as pseudo-Bartter syndrome (PBS): it is usually caused by an excessive loss of salts due to vomiting or insensitive perspiration in patients affected by CF. PBS has been prevalently described in infants, especially if breast-fed and during warmer months; moreover, acute gastrointestinal and/or respiratory diseases have been recognized as triggering factors of PBS in children with CF. However, especially in developed countries, physicians have not been used to see PBS as an onset of CF, thanks to the universal screening programs at birth and/or the precocious diagnosis after the onset of more typical respiratory and gastrointestinal symptoms [3, 4]. Here, we report a severe episode of acute metabolic alkalosis with multiple electrolyte unbalance in a previously healthy 9-year-old boy.

Patient's medical report

During the summer, a 9-year-old child from East Europe came to the attention of the Paediatric Emergency Department, as he was affected with a 2-day history of vomiting, abdominal pain and low-moderate fever. The patient had been in Italy for no longer than 2 weeks. No significant clinical clues were found, in addition to a condition of moderate dehydration due to persistent vomiting. Therefore, blood tests were carried out and, although the episodes of vomiting were not so many (2-4/day) and no diarrhea was reported, actually profound and multiple electrolyte abnormalities were recorded. Moreover, further concerns emerged from the information obtained by the parents: the child had a prolonged hospitalization in his home country at 3-4 months of age, because of a respiratory/pulmonary illness they were not able to define, unfortunately. After the placement of an intra-venous access, a fluid therapy with 0.9% NaCl solution was started immediately. However, biochemical analysis showed several and unexpected abnormalities, as represented in **Tab. 1**. Basically, the child had a significant metabolic alkalosis with severe hypokalemia, moderate hyponatremia and very low plasma chloride (t0, **Tab. 1**). Such an electrolyte perturbation resulted to be associated to a remarkable increase of blood ureic nitrogen and plasma creatinine, which was interpreted as pre-renal insufficiency due to severe dehydration. Liver function tests, blood count, coagulation panel and C-reactive protein were in the normal range; however, the plasma glucose was moderately elevated, but there was not glucose renal wasting.

Obviously, the child was admitted to the in-patient Paediatric Department in order to monitor the clinical condition, to perform further diagnostic investigations and to provide the necessary

Table 1. Biochemical parameters (temporal sequence).

	Unit	t0	t1 (4 h)	t2 (8 h)	t3 (16 h)	t4 (24 h)	t5 (72 h)	t6 (120 h)
Na	(meq/l)	127	128	126	133	134	137	140
K	(meq/l)	2.7	3.1	2.9	3.1	3.9	3.5	4.7
Cl	(meq/l)	73	77	82	92	99	103	106
Creatinine	(mg/dl)	1.13	0.96	0.80	0.65	0.64	0.6	0.55
BUN	(mg/dl)	121	119	112	75	49	34	13
Ph	-	7.55	7.68	7.52	7.63	7.46	7.45	7.37
CO ₂	(mmHg)	35	29	47	31	44	45	48
HCO ₃	(meq/l)	30.6	34.2	38.2	33.6	31.3	28	27.7

fluid therapy. Moderate amounts of KCl (no more than 1.5 meq/kg/die, in order to correct the severe hypokalemia associated to typical electrocardiographic abnormalities) were added to 0.9% NaCl solution. After 4 hours of fluid therapy, the biochemical parameters ameliorated (t1, **Tab. 1**), but the electrolyte balance worsened again 4 hours later (t2, **Tab. 1**). Therefore, radiological investigations to exclude bowel occlusion (with third-space fluid loss) were performed and, concomitantly, the load of potassium and fluid was implemented until reaching a volume of 3,000 ml/die of 0.9% NaCl solution, supplemented with a total of 80 meq of KCl (weight = 25.9 kg). This fluid and electrolyte management resulted in the improvement of all the biochemical parameters and of urine output after 8-16 hours (t3 and t4, **Tab. 1**); at that point, a maintenance fluid therapy was continued and the electrolyte balance was almost normalized after 48 hours, although a mild and persistent alkalosis was noticed (t5, **Tab. 1**). At 72 hours, the child was able to drink and eat appropriately by himself and the fluid therapy was stopped. At 120 hours (t6, **Tab. 1**), metabolic alkalosis completely solved, but the value of blood bicarbonates were still slightly elevated compared to normal range. Because of this unusual clinical course, further investigations were requested, in order to find any underlying diseases predisposing to those electrolyte disturbances. In particular, C3, C4, 25-OH-vitamin D, plasma PTH, urine cortisol and aldosterone/renin plasma levels, serum albumin and immunoglobulin were all normal. Finally, a sweat test was also performed and provided abnormal results (Cl⁻: 130 meq/l; n.v. < 40 meq/l), suggesting a diagnosis of CF. The genetic analysis was reported to be consistent with the diagnosis of CF, but that was performed in the country of provenience and the clinical record was not provided to us. Informed consent to publish the case report was obtained from the guardian of the individual described in the study.

Discussion

PBS is a clinical condition characterized with hyponatremia, hypochloremia, hypokalemia and metabolic alkalosis occurring without demonstrable defects of renal tubules. The differential diagnosis includes: cyclic vomiting, chloride-losing diarrhea, abuse of laxatives, diuretic abuse, continuous gastric drainage (without appropriate electrolyte replacement), pyloric stenosis and

CF. In all these pathological settings, with the exception of diuretic abuse, water and electrolyte losses are extra-renal and, thus, the chloride content of urine is low. The contrary occurs in Bartter syndrome, which is characterized with electrolyte renal wasting, because of a primitive tubular defect [4, 5]. CF is a genetic disease resulting from the mutation in the gene of CF trans-membrane conductance regulator (CFTR), encoding a chloride channel at the apical epithelial cell surface. Over 1,500 mutations have been described and those are classified in five classes, based on the type of qualitative and/or quantitative defect in the translated protein. Such a wide genotype heterogeneity was demonstrated to account for a significant variability in the clinical expression of the disease, involving lungs, gastrointestinal tract, liver and exocrine pancreas, as primary targets. Non-classical forms of CF include cases presenting during adolescence or adulthood, which are characterized with exocrine pancreatic sufficiency and mild, atypical or absent respiratory (e.g. chronic sinusitis, asthma) and gastrointestinal symptoms. They are estimated to be around 2% of affected patients [6-9].

Patients affected with CF are known to be prone to develop dehydration with salt loss and metabolic alkalosis: these episodes usually occur in regions with hot climate, due to salt wasting by sweating, and are timely recognized in CF patients. However, PBS seldom represents the onset or the main clinical feature of CF and, if so, it is mainly described in infants, especially below 1 year of age and during breast-feeding. Fustik et al. reported 17 cases out of 103 patients with CF: the episodes regarded infants from 2 to 6 months and no seasonal recurrence was found. Overclothing of infants during winter season and hot temperature in the summer time were factors promoting profuse sweating in CF patients and human milk, which has a low-salt content, was insufficient to compensate salt losses [5]. Another study by Yalçın et al. retrospectively reviewed 29 cases of PBS in children affected by CF, with a prevalence of 12% in their CF cohort. Most PBS cases were in children < 4-5 years of age with a known diagnosis of CF: older patients are likely to better compensate salt losses by greater salt intake. Basically, all the episodes of PBS were associated to vomiting or anorexia [4]. Interestingly, in our case, the age of presentation of PBS resulted to be older than usual, and the patient came to our attention without a previous

diagnosis of CF and no personal history of respiratory or gastrointestinal symptoms clearly suggesting CF was reported by the guardian.

Metabolic alkalosis with multiple electrolyte unbalance was the most important issue in our clinical case. As discussed, it was consistent with PBS and, considering that actually it is an uncommon metabolic abnormality in infancy and even more in childhood [10, 11], this finding prompted the diagnostic effort to look for any predisposing factor.

As the diagnosis of Bartter and Gitelman syndromes appeared to be quite unlikely, we considered the possibility of CF. Several studies described PBS in patients affected with CF and Bates et al. reported the case of a previously healthy 17-year-old man who was diagnosed with CF after the occurrence of metabolic alkalosis and hypokalemia [12, 13]. CF onset with PBS is very unusual, especially in childhood and later, and this event has been made even more unlikely since the neonatal screening was introduced in developed countries. However, this disease must be considered in the differential diagnosis of metabolic alkalosis with hypokalemia, particularly in patients coming from low-income foreign countries and whenever the personal history is not clear.

Conclusion

Patients with CF can develop a clinical condition characterized with hyponatremia, hypochloremia, hypokalemia and metabolic alkalosis, if they become dehydrated. Electrolyte abnormalities consistent with PBS must raise a suspicion for an underlying disease, such as CF, especially if the correction by fluid therapy is difficult. Nowadays, in developed countries, physicians encounter this clinical situation less frequently than in the past, as screening programs permit to diagnose CF early. However, atypical presentations of CF must be taken in account in patients coming from low-income foreign countries and whenever the personal history is not clear.

Declaration of interest

The Authors declare that they have no conflict of interest. This study received no funds.

References

1. Jospe N, Forbes G. Fluids and electrolytes: clinical aspects. *Pediatr Rev.* 1996;17(11):395-403.
2. Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndromes. *Am J Med Sci.* 2011;322(6):316-32.
3. Mauri S, Pedrolì G, Rùdeberg A, Laux-End R, Monotti R, Bianchetti MG. Acute metabolic alkalosis in cystic fibrosis: prospective study and review of the literature. *Miner Electrolyte Metab.* 1997;23(1):33-7.
4. Yalçın E, Kiper N, Doğru D, Özçelik U, Aslan AT. Clinical features and treatment approaches in cystic fibrosis with pseudo-Bartter syndrome. *Ann Trop Paediatr.* 2005;25(2):119-24.
5. Fustik S, Pop-Jordanova N, Slaveska N, Koceva S, Efreinov G. Metabolic alkalosis with hyponatremia in infants with cystic fibrosis. *Pediatr Int.* 2002;44(3):289-92.
6. Paranjape SM, Zeitlin PL. Atypical cystic fibrosis and CFTR-related diseases. *Clin Rev Allergy Immunol.* 2008;35(3):116-23.
7. Kerem E. Atypical CF and CF related diseases. *Paediatr Respir Rev.* 2006;7 Suppl 1:S144-6.
8. Bombieri C, Seia M, Castellani C. Genotypes and phenotypes in cystic fibrosis and cystic fibrosis transmembrane regulator-related disorders. *Semin Respir Crit Care Med.* 2015;36(2):180-93.
9. Marseglia GL, Caimmi S, Marseglia A, Poddighe D, Leone M, Caimmi D, Ciprandi G, Castellazzi AM. Rhinosinusitis and asthma. *Int J Immunopathol Pharmacol.* 2010;23(1 Suppl):29-31.
10. Poddighe D. Treatment of severe hypervolemic hyponatremia in a child with pneumonia. *Pediatr Emerg Care.* 2017;33(1):72.
11. Poddighe D. Common finding of mild hyponatremia in children evaluated at the Emergency Department and its correlation with plasma C-reactive protein values. *Minerva Pediatr.* 2016;68(3):173-6.
12. Zanolari Calderari M, Vigier RO, Bettinelli A, Bianchetti MG. Electrocardiographic QT prolongation and sudden death in renal hypokalemic alkalosis. *Nephron.* 2002;91(4):762-3.
13. Bates CM, Baum M, Quigley R. Cystic fibrosis presenting with hypokalemia and metabolic alkalosis in a previously healthy adolescent. *J Am Soc Nephrol.* 1997;8(2):352-5.