Hyponatremia and metabolic alkalosis in a foal with gastroesophageal reflux: a case report

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ABSTRACT: A foal with a history of diarrhea and fever was presented to the Equine Clinic of the University of Cordoba for acute onset of abundant serous nasal discharge. On endoscopic examination the oesophagus was found to be atonic and ulcerated, the cardia was permanently open and the stomach showed extensive ulceration. In addition, the nasal discharge was identified to have a gastric origin (gastroesophageal reflux). The electrolyte and acid-base profiles showed marked hyponatremia (99 mEq/l) and metabolic alkalosis (pH = 7.46, Strong Ion Difference = 50 mEq/l). The foal was also uremic (plasma creatinine = 12.6 mg/dl). Although the foal experienced an improvement in its hydroelectrolytic status after treatment with 7.5% NaCl for 36 h, the owner requested euthanasia. The foal described here developed severe hyponatremia and hyposmolarity but, contrary to most reported cases, showed metabolic alkalosis instead of metabolic acidosis. Another interesting feature of this case is the lack of overt neurologic signs in the face of extreme hyposmolarity. The paucity of neurologic signs in this foal may have been influenced by slow instauration of hyponatremia, concurrent azotemia, or acid-base status.

Keywords: foal; hyponatremia; hyposmolality; metabolic alkalosis

Hyponatremia is one of the most common electrolyte derangements in ill foals and is frequently related to uroperitoneum (Behr et al., 1981; Richardson and Kohn, 1983; Morley and Desnoyer, 1992; Kablack et al., 2000), diarrhea (Lakritz et al., 1992; Wong et al., 2007) or renal disease (Zicker et al., 1990; Ramirez et al., 1998). Other less common causes of hyponatremia include excessive sweating, rhabdomyolisis, administration of hypotonic fluids and adrenal insufficiency (Couetil and Hoffman, 1998; Wong et al., 2007). Moreover, transient pseudohypoaldosteronism secondary to urinary tract disorders has been recently described as a cause of hyponatremia in foals (Arroyo et al., 2008). In addition to the loss of sodium, these conditions are characterized by volume depletion that results in increased ADH secretion. Excess ADH leads to water retention and results in hyposmolality as a consequence of an excess of water in relation to solute (Sterns et al., 1994).

Severe hyponatremia (< 122 mEq/l) is usually associated with neurological signs characterized by generalized encephalopathy. The symptoms directly attributable to hyponatremia are induced by hypoosmolality. As the blood osmotic pressure falls, an osmolal gradient is created across the blood brain barrier resulting in water movement into the brain and cerebral oedema. The degree of cerebral overhydration appears to correlate with the severity of the symptoms. Reported clinical signs of acute hyponatremia in horses include blindness, intention tremors, hypermetria, seizures, hyperesthesia, disorientation, head pressing, nystagmus, and incoordination of motor activity (Wong et al., 2007).

Gastroesophageal reflux is infrequent in horses. Due to the species' small gastric capacity and relative inability to vomit, clinical signs of colic are often found before an important loss of gastric fluids takes place (Heidmann et al., 2004). Gastroesophageal reflux disease due to incompe-

tence of the gastroesophageal junction has been described in adult horses (Shannon et al., 2004). In foals, gastroesophageal reflux is generally associated with gastric ulcer syndrome, and it is related to oesophageal (oesophagitis, oesophageal ulceration, megaoesophagus) or pyloric (pyloric outflow obstruction) complications (Murray, 2002; Shannon et al., 2004).

Case description

A 3-month-old male Anglo-Arab foal with a 1-month history of diarrhea and fever was referred to the Equine Clinic of the University of Cordoba (Spain). The foal had been treated by the referring veterinarian with antibiotics (gentamicin and metronidazol) and antiinflammatories (flunixin-meglumine). Response to treatment had been partial and inconsistent. The foal developed nasal discharge 24 hours prior to referral to the University Clinic.

On presentation the foal showed copious serous nasal discharge, mild depression and loose faeces. Physical examination revealed a fair body condition (body score 4/9), moderate dehydration, normal gut sounds, and slightly increased respiratory sounds.

The following abnormalities were detected in the initial CBC and blood biochemistry: severe hyponatremia (99 mmol/l; reference range, 134–142 mmol/l) and hypochloremia (55 mmol/l; reference range, 95–103 mmol/l), hyperkalemia (6 mmol/l; reference range, 3–5 mmol/l), increased bicarbonate (32 mmol/l; reference range, 22–29 mmol/l), and alkalemia (pH: 7.46; reference range, 7.34–7.43). Abnormalities in calculated parameters included a marked decrease in effective osmolality (203 mOsmol/kg; reference range, 265–290 mOsmol/kg) and an increase in strong ion difference [SID = Na + K – Cl = 50 mmol/l; reference range, 35–45]. Other biochemical abnormalities included hyperfibrinogenemia (700 mg/dl; reference range, 150–300 mg/dl), increased creatinine (12.6 mg/dl; reference range, 1–2 mg/dl) and BUN (241 mg/dl; reference range, 15–35 mg/dl) (Table 1). Electrolyte and acid-base parameters were measured with a Ciba-Corning 800 gasometer (Bayer Diagnostics, Barcelona, Spain). Spectrophotometry (Vettest 8008, Idexx Laboratories, Inc. Maine, USA) was used for additional biochemical measurements.

Table 1. Electrolyte values and acid-base balance at admission (0 h) and after (36 h) intensive fluid therapy

	0 h	36 h
Osmolality (mOsmol/kg)	203	239
Na (mmol/l)	99	117
Cl (mmol/l)	55	82
K (mmol/l)	6	4
HCO_3 (mmol/l)	32	23
AG (mmol/l)	12	12
pH	7.46	7.39
pCO2 (mmHg)	45	38
SID (mmol/l)	50	39
Atot (mEq/l)	14.5	13.7

AG = anion gap (Na – Cl + HCO_3)
SID = strong ion difference (Na + K – Cl)
Atot = total weak acid concentration (0.21 × total protein) (Stampfli et al., 1999).

Ultrasonographic examination of the thorax revealed pleural irregularities and altered areas within lung parenchyma consistent with small pneumonic foci. No abnormalities were detected in an abdominal ultrasonography. Radiographs of the thorax revealed a markedly distended oesophagus. Endoscopic examination of the upper respiratory tract did not show any abnormalities but endoscopy of the oesophagus and stomach revealed an atonic oesophagus that was ulcerated in its caudal portion, a permanently opened cardia and extensive gastric ulceration (Figure 1). In addition, the nasal discharge was identified to have a gastric origin (gastroesophageal reflux) by direct visualization of the fluid refluxing from the stomach and through the oesophagus.

Abdominocentesis yielded a normal appearing fluid with leucocytes = 5 400/µl (reference range 0–10 000), total proteins = 11 g/l (reference range 0–40 g/l), and peritoneal/serum creatinine = 1.05 (normal value ≤ 2).

Abnormalities detected in the urinalysis included proteinuria, pyuria and isosthenuria (specific gravity = 1.012; reference range, 1.020–1.050). Electrolyte fractional excretions were: FE_{Na} = 0.14% (reference range, 0.02–1%), FE_{Cl} = 0.16% (reference range, 0.04–1.6%) and FE_K = 4.54% (reference range, 15–65%).

Based on these findings a diagnosis of gastric ulcer syndrome, reflux oesophagitis and renal in-

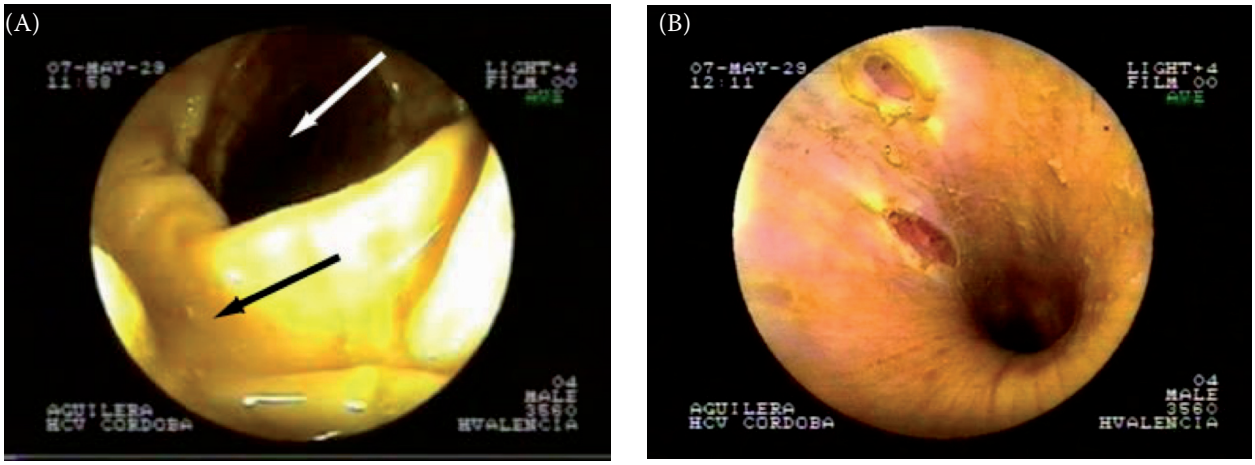

Figure 1. Endoscopic images of the oesophagus showing. (A) a distended cardia (white arrow) and gastroesophageal reflux (black arrow), and (B) oesophageal ulcers

sufficiency was made. Initial treatment consisted in fluid therapy (Ringer Lactate + 7.5% NaCl) and anti-ulcer therapy (Ranitidine-Zantac, GlaxoSmithKline, S.A., Madrid – 1.5 mg/kg *i.v.* q 8 h). Fluid rate was adjusted by frequent measurement of electrolyte concentrations. Care was taken to prevent an excessively rapid sodium correction and thus the rate of 7.5% NaCl administration was adjusted to avoid an elevation of serum sodium that exceeded 1 mmol/l/h (Cluitmans and Menders, 1990; Wong et al., 2007).

The foal experienced a significant improvement in his hydration and electrolyte status over the next 36 h (Table 1 and Figure 2). However, due to the severity of the gastroesophageal lesions and the persistence of azotemia after 36 hours of intensive fluid therapy (creatinine = 10.9 mg/dl, BUN = 215 mg/dl), the owner requested euthanasia.

At necropsy, the gross findings confirmed severe dilation and ulceration of the oesophagus, extensive gastric ulceration and small pneumonic foci. Histopathology of the kidney revealed acute tubu-

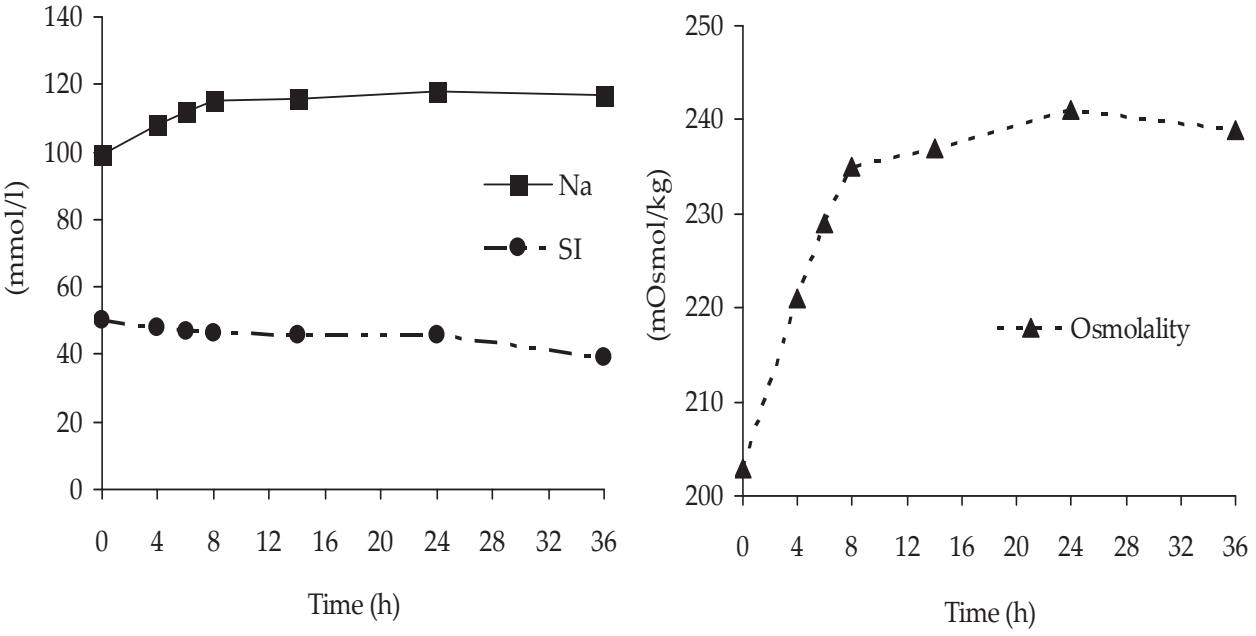

Figure 2. Changes in plasma effective osmolality [2Na (mmol/l) + glucose (mg/dl)/18], sodium, and strong ion difference (SID = Na + K – Cl) over the hospitalization period

lar necrosis and interstitial nephritis. The adrenal glands showed signs of hyperplasia (vessels lined by several layers of large columnar cells) in the *zona glomerulosa*.

DISCUSSION

In this foal uroperitoneum was the first differential diagnosis, because hyponatremia was accompanied by hypochloremia, hyperkalemia and azotemia. However, it was ruled out by the normal abdominal ultrasonography (lack of excessive peritoneal fluid and normal appearance of the bladder and urogenital tract). In addition, the peritoneal/serum creatinine ratio, which is considered to be a useful and reliable laboratory parameter in the antemortem diagnosis of a ruptured bladder (Genetzky and Hagemoser, 1985; Kablack et al., 2000), was normal.

Azotemia reflected both hypovolemia as well as renal injury (possibly drug-related nephrotoxicity), which was documented in the *post mortem*. However, in this case the fractional excretion of sodium was not increased, which could reflect active tubular attempts to maintain water and sodium. Therefore, the contribution of renal disease to hyponatremia in this foal does not seem to be relevant.

This foal did not present with frank diarrhea and during his hospitalization period soft faeces without watery diarrhea was noted. Diarrhea may have been more severe over the period of illness prior to the foal's presentation at the hospital and in this way contributed to some degree to the hyponatremia documented on arrival.

An important and unusual finding in this case was the copious gastroesophageal reflux, associated with atonicity of the cardia and the oesophagus, which may have represented an important factor in the electrolyte losses. The ability of this foal to release gastric pressure through spontaneous reflux may have minimized the signs of colic. Gastric ulcer syndrome in this foal was likely multifactorial and associated to chronic stress from chronic diseases (diarrhea/pneumonia), decreased mucosal blood flow secondary to hypovolemia, azotemia and the ulcerogenic potential of previous treatments (flunixin meglumine).

In cases like this, in which the plasma Na : K ratio is very low, adrenal insufficiency has to be included in the differential diagnosis (Couetil and Hoffman, 1998). Adrenal insufficiency can be associated with septicemia and enteritis in neonatal foals (Couetil and Hoffman, 1998). Although adrenal hormones were not measured, the histologic appearance of the adrenal glands (hyperplasia of the *zona glomerulosa*) does not point towards a diagnosis of hypoaldosteronism in this foal.

Hyponatremia is commonly associated with metabolic acidosis, but here we report a foal with gastroesophageal reflux that developed severe hyponatremia and instead of acidosis showed alkalosis. An acid-base analysis using the comprehensive physicochemical approach first described by Stewart demonstrated that alkalosis was due to the increase in strong ion difference (SID) (Lindinger, 2004). It is unusual to find an increase in SID in a hyponatremic animal. In this case, although hyperkalemia represented a minor contribution to the elevated SID, the increase in SID was mostly due to the severe hypochloremia exhibited by the foal. In horses, hypochloremia is characteristic of diseases that course with gastroesophageal reflux, like pyloric stenosis (Heidmann et al., 2004) or spontaneous regurgitation (Laing and Hutchins, 1992). Volume depletion also contributes to perpetuate metabolic alkalosis through renal mechanisms that involve an increase in sodium reabsorption with concurrent chloride depletion, bicarbonate reabsorption is increased to dissipate, the electrical gradient (Rose, 1989). This scenario is common in canines with pyloric obstructions (Bellenger et al., 1990) and results in similar changes of metabolic alkalosis and hypochloridemia. These changes also develop in ruminants with abomasal displacement (Fubini et al., 1991). Thus, in this foal loss of gastric fluids through regurgitation and the associated volume depletion seem to be the most likely cause of hypochloremia and metabolic alkalosis.

It could be argued that the small pneumonic lesions present in this foal may have contributed to acid-base imbalance. The slight respiratory acidosis (PCO_2 = 45 mmHg) detected on presentation seems to be a compensatory mechanism and not a primary disorder, as demonstrated by the rapid decrease in PCO_2 (to 38 mmHg) after fluid replacement (Table 1).

This foal did not develop significant neurologic deficits as has been reported previously with hyponatremia (Zicker et al., 1990; Lakritz et al., 1992; Wong et al., 2007). In this case neurological signs were minimal (mild depression) even though hyponatremia and hyposmolality were extreme at

presentation (Na = 99 mmol/l and effective osmolality= 203 mOsmol/kg).

The lack of neurological signs in this foal may relate to a gradual onset of hyponatremia, as well as concurrent renal disease and acid-base abnormalities. Neurologic signs have been reported to be less prominent in cases in which hyponatremia develops slowly over a prolonged period (Wong et al., 2007). In the foal described here, the instauration of hyponatremia was most likely acute and related to the onset of gastroesophageal reflux (24 h). However, since no sodium values had been recorded prior to admission the possibility of a long-standing hyponatremia cannot be ruled out.

Renal disease results in increases in blood urea nitrogen and this metabolite exerts an important influence on plasma osmolality (osmolality = 2Na (mmol/l) + glucose (mg/dl)/18 + BUN (mg/dl)/2.8). However, urea is an ineffective osmolite and does not influence water distribution changes (urea, in contrast to sodium, readily crosses the cell membrane and osmotic equilibrium is reached by urea entry into cells rather than by water movement out of cells). Thus, although the elevated BUN in this foal contributed to increase plasma osmolality, effective osmolality (2Na (mmol/l) + glucose (mg/dl)/18), which is the relevant parameter to consider, was still very low in this case. Although theoretically an elevation in BUN should not influence the osmolal gradient across the blood-brain barrier, the role of azotemia on water movement in the brain is quite complex. Several studies in rats and humans have found that increments in urea protect the brain against the neurologic sequelae (myelinolysis) that can result after rapid correction of hyponatremia (Van Reeth and Decaux, 1989; Soupart and Decaux, 1996; Soupart et al., 2000; Decaux, 2001; Soupart et al., 2007). The mechanisms involved in the protective role of urea are not clear but they seem to be related to the ability of this metabolite to "buffer" rapid changes in osmolality across the blood-brain barrier and limit water movement (Oo et al., 2003).

Finally, the fact that, contrary to previous reports (Zicker et al., 1990; Lakritz et al., 1992; Wong et al., 2007) this case exhibited metabolic alkalosis instead of acidosis may also have influenced the severity of neurologic signs. In humans, metabolic acidosis is known to be associated with changes in mental status (Aldemir et al., 2001). In previous reports of hyponatremic foals with neurologic signs, hyponatremia was accompanied by metabolic acidosis (Lakritz et al., 1992; Wong et al., 2007). Since our foal did not develop acidosis, we hypothesize that metabolic acidosis may influence the severity of the neurologic signs that have been reported in hyponatremic and acidotic foals.

In conclusion, this case report describes a foal with an uncommon clinical presentation and with massive gastroesophageal reflux that resulted in severe metabolic alkalosis with hyponatremia without overt neurologic signs. The lack of neurologic signs in this foal could be related to the concurrent renal disease or to metabolic alkalosis, which is an uncommon finding in hyponatremic individuals.

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