Association between hyponatremia and neurological dysfunction in hospitalized foals

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Abstract

Objective: Hyponatremia and rapid correction of hyponatremia can lead to neurological abnormalities. The objective of the study was to determine whether plasma sodium concentrations (Na^+) and speed of correction of hyponatremia are significantly associated with neurological abnormalities in foals.

Design: Retrospective cohort study 2012-2016

Setting: Equine hospital

Animals: 109 foals less than 6 months old with hyponatremia (Na^+ concentration ≤125mmol/L)

Interventions: Case records were reviewed for any foal with hyponatremia. Clinicopathological findings, presence or absence of neurological signs on the day of the lowest Na^+ concentration measured and also the following 5 days, diagnosis and outcome were recorded and changes in Na^+ concentration per hour were calculated for up to 5 subsequent days. Logistic regression was used to assess the association between presence or absence of neurological signs, Na^+ concentration, other known risk factors for neurological dysfunction in foals and possible confounders.

Measurements and Main Results: In the final multivariable model only Na^+ (OR 0.86; 95% CI 0.79-0.95; p=0.002) and BUN concentrations (OR 1.04; 95% CI 1.02-1.06; p=0.001) were significantly associated with neurological signs. Changes in Na^+ concentrations per hour were not associated with neurological signs on any day after the lowest Na^+ concentration had been measured (p=0.18-0.82) and development of new neurological signs following correction of hyponatremia were not reported in any foal.

Conclusions: Na^+ concentrations were associated with the development of neurological signs in hyponatremic foals. Increased BUN concentrations might contribute to neurological dysfunction but further studies are necessary to confirm or refute these findings.

List of abbreviations:

AG: Anion gap

95% CI: 95% confidence interval

Ca^{2+}: Total plasma calcium concentration

Cl^-: Plasma chloride concentration

cOsmol: Calculated plasma osmolality

efOsmol: Effective plasma osmolality

K^+: Plasma potassium concentration

Na^+: Plasma sodium concentration

OR: Odds ratio

PAS: Perinatal asphyxiation syndrome

SIRS: Systemic inflammatory response syndrome

SID: Strong ion difference

TCO_2: Total carbon dioxide concentration

Introduction

Mild hyponatremia is frequently observed in foals presenting with a variety of disorders including enterocolitis, uroperitoneum, renal disease, rhabdomyolysis, pneumonia, perinatal asphyxiation syndrome (PAS), and sepsis with intestinal disease being the most common cause of hyponatremia in foals.[1-5] Hyponatremic encephalopathy is a relatively infrequent complication that occurs secondary to changes in the plasma osmolality and subsequent development of cerebral edema.[6] The presence of neurological complications depends on the severity of the hyponatremia and the time over which the abnormality develops. In critically ill foals, several metabolic abnormalities with the potential to influence neurological function often co-exist, making it difficult for the clinician to identify the most important abnormalities. Apart from plasma sodium concentrations (Na^+), hypoglycemia, hyperkalemia, hypocalcemia,

systemic inflammatory response syndrome (SIRS), and sepsis have all been implicated.[7] A further complicating factor is that rapid correction of chronic hyponatremia can lead to osmotic demyelination syndrome with lasting neurological impairment or even death, as described in the literature in other species.[8] Although not described in the literature, isolated anecdotal reports in foals exist and most clinicians endeavour to correct asymptomatic hyponatremia of chronic or unknown duration gradually. Current guidelines for human patients recommend limiting the increase of Na^+ concentrations to <0.5-1.0mmol/L/h or <10mmol/L/day, regardless of chronicity.[8, 9] Apart from case reports and small case series,[1, 2, 10] only one study has described hyponatremic encephalopathy in 11 foals.[6] In this study, the influence of other concomitant electrolyte and glucose abnormalities was not taken into consideration, probably at least in part due to the small number of cases. Currently, there is no information available whether any concurrent abnormalities might interact with Na^+ concentrations, either decreasing or increasing the likelihood of neurological dysfunction. In addition, apart from anecdotal reports, there is no information available about how speed of correction of hyponatremia influences neurological symptoms in foals.

The study therefore tested the hypothesis that Na^+ concentrations and speed of correction of hyponatremia are significantly associated with neurological abnormalities in foals.

Material and Methods

The Clinical Research Ethics Board of the Royal Veterinary College granted ethical approval for this study. Inclusion criteria for the study were the presence of hyponatremia (sodium concentration of ≤125mmol/L)[8, 9] in foals less than 6 months of age at any stage during hospitalization.

Medical records from Hagyard Equine Medical Institute in Lexington, Kentucky, USA from 2012-2016 were reviewed for foals matching the inclusion criteria. Data collected from patient records included signalment, presenting complaint, clinicopathologic findings, final diagnosis and outcome. The date of the lowest Na^+ concentration was identified and neurological status and laboratory parameters for this date and up to 5 subsequent days were recorded. The time when sodium concentrations had been measured were recorded as stated on the print out of the laboratory results sheet and the change of the Na^+ concentration per hour from one measurement to the next was calculated. Whenever available, changes over 24h were calculated. Measurements were routinely performed within 30min of blood collection. Strong ion difference (SID = Na^+ + plasma potassium (K^+) – plasma chloride (Cl^-) concentrations), anion gap (AG = $Na^+ + K^+ – Cl^-$ - total carbon dioxide (TCO_2)),[11] calculated plasma osmolality (cOsmol = $2Na^+$ (mmol/L) + glucose (mg/dL)/18 + BUN (mg/dL)/2.8) and effective plasma osmolality (efOsmol = 2Na (mmol/L) + glucose (mg/dL)/18) were calculated.

Based on clinical signs recorded on the day of blood collection, foals were categorized as neurologically normal or abnormal. In addition, their neurological status was subsequently assessed and recorded each day for up to 5 days. The following clinical signs were considered neurologically abnormal: obtundation, ataxia, presence of cranial nerve deficits, hyperreactivity, needing assistance to stand and recumbency (if the foal had been able to rise and stand before development of signs and other reasons such as orthopaedic disease or colic had been excluded), protruding tongue, continuous chewing motions, decreased suckle reflex (if normal prior to the development of clinical signs) and partial or generalized seizure activity. Foals showing neurological signs during the first 24h of life were excluded. Presence or absence of SIRS was assessed as previously described[12] on the day of the lowest recorded Na^+ concentration. In brief, presence or absence of 6 criteria (fever or hypothermia; tachycardia;

tachypnea; leucocytosis, leucopenia or >5% band cells; hyperlactatemia and hypoglycaemia) was noted with different cut off points being used for 3 different age groups (<3 days old; 4-14 days old; 15 days – 6 months old).[12] Sepsis was defined as foals with either a positive blood culture or presence of SIRS and a documented infection. A documented infection was defined as a positive microbiological culture or cytological evidence of bacteria from a physiologically sterile body site. The final diagnosis was listed as recorded by the clinician in charge of the case; in several animals, multiple diagnoses were recorded. Foals with a diagnosis of head trauma, suspicion of toxicity or infectious meningitis were excluded. The neurological outcome was classified as normal at discharge, improved but residual abnormalities, unchanged abnormalities and worsened abnormalities. The overall outcome was categorized as discharged from hospital, euthanized, or died.

Statistical Analysis

Data were analysed using a commercially available software program (IBM SPSS Statistics 22). Continuous data were expressed as mean ± standard deviation or median and range (minimum to maximum) and categorical data were presented as numbers and percentages. Normality of the data was assessed using the Shapiro-Wilk test. A Mann Whitney U test (all continuous data were not normally distributed) was used to investigate an association between presence or absence of neurological signs and SID, AG, cOsmol and efOsmol. In addition, the association between outcome and Na^+ concentration on admission and the lowest Na^+ concentration during hospitalization was tested. A χ^2 test Exact test (categorical data) was used to investigate the association between outcome and presence or absence of neurological signs.

Logistic regression was used to assess the association between presence or absence of neurological signs, plasma Na^+ concentration, and possible confounding factors (age, gender,

diagnosis, blood glucose, K^+, Cl^-, TCO_2, total plasma calcium (Ca^{2+}), blood urea nitrogen (BUN) and creatinine concentrations and presence or absence of SIRS and sepsis) on the day the lowest plasma Na^+ concentration was measured. Only factors with a p-value <0.1 in the univariable analysis were assessed in the multivariable analysis using backward elimination procedure. As Na^+ concentration is the main determinant of cOsmol and efOsmol, and Na^+, Cl^- , K^+ and TCO_2 concentrations are used to calculate SID and AG, none of the calculated values were included into the multifactorial analysis. Results of the final multivariable logistic regression analysis were displayed as odds ratio (OR) and 95% confidence interval (95% CI). Statistical significance was set at $p \leq 0.05$ for all analyses.

Results

Revision of medical records identified 114 foals that matched the inclusion criteria. Five foals <24h of age were excluded as the neurological signs were consistent with PAS and 109 foals were included in the final study. This constituted approximately 3.6% of foals of that age that presented to the hospital. The predominant breed was Thoroughbred (n=78), two foals were Standardbreds and in 29 foal the breed was not recorded. Comparison with the overall hospital population, which consists to 75-80% of Thoroughbreds, was difficult to the large number of foals without recorded breed. Of the 109 foals, 43% (n=47/109) were males, 37% (n=40/109) were females and in 20% (n=22/109) gender was not recorded. The median age at admission was 7 days (range 0-180 days). Most foals had multiple presenting complaints with the most common presenting complaint being diarrhea (37%, n=40/109), followed by lethargy and inappetence (15%, n=16/109) and colic or abdominal distension (13%, n=14/109). Neurological signs apart from depression were noted in 4 foals prior to admission; all consisting of seizure activity.

Colitis/enterocolitis was the most common diagnosis (45%, n=49/109), followed by pneumonia (10%, n=11/109), a clinical diagnosis of sepsis (9%, n=10/109; only one of these met the study criteria for sepsis), uroperitoneum (8%, n=9/109), renal disease (5%, n=5/109), meconium impaction (4%, n=4/109), perinatal asphyxia syndrome (3%, n=3/109), immune-mediated hemolytic anemia/neonatal isoerythrolysis (3%, n=3/109) and 22/109 foals (20%) with other conditions. Some foals had multiple diagnoses. Thirty foals were classified as having SIRS; however, only 9 foals had plasma lactate concentrations recorded on the relevant day while 10 foals had no white blood cell count measured at this time point. Blood cultures were performed in 41 foals; 41% (n=17/41) were positive. Overall, 27 foals were considered septic according to the study's definition.

In 77 (71%) foals the lowest Na^+ concentration was measured on admission while in 32 (29%) foals the lowest concentration was documented during hospitalisation. Two foals presented with Na+ concentrations ≤100mmol/L, thirteen with concentrations >100 and ≤110mmol/L, fifteen with concentrations >110 and ≤115mmol/L, thirty with concentrations >115 and ≤120mmol/L and fifty-four with concentrations >120 and ≤125mmol/L. Electrolyte concentrations in neurologically normal and abnormal foals are displayed in Table 1. In 66% (n=72/109) of foals no neurological abnormalities were recorded. Twenty-two percent (n=24/109) presented with neurological signs on admission and 12% (n=13/109) developed neurological signs during hospitalisation (total 34% n=37/109). Colitis/enterocolitis was also the most common diagnosis in foals with neurological signs (n=19), followed by a clinical diagnosis of sepsis (n=5), renal disease (n=4), uroperitoneum (n=1), pneumonia (n=1) and other conditions (n=7). Most foals showed more than one neurological abnormality. In decreasing frequency, the following neurological signs were recorded: obtundation (n=10), ataxia (n=10), generalized seizure-like activity (n=10), partial seizure-like activity (n=9),

decreased suckle reflex (n=7), hyperreactivity (n=5), central blindness (n=4), a head tilt (n=2), opisthotonus (n=2), continuous chewing/tongue movement (n=2), grimacing (n=2), circling (n=1), head pressing (n=1) and one foal was comatose. By the time of discharge/death, 25/37 foals were reportedly neurologically normal (68%; 14 discharged from the hospital; 8 euthanized; 3 died), 6 had neurologically improved (16%; all discharged from the hospital with normal Na^+ concentrations), one was neurologically unchanged (2%; died) and in 5 the neurological status had worsened (14%; 3 euthanized, 2 died). Four of these 5 cases had Na^+ concentrations of ≥125mmol/L at the time of death/euthanasia while in one foal only a minimal increase from 118 to 119mmol/L over 24h was recorded before it died. The maximal recorded increase in Na^+ concentration was 1.75mmol/L/h in one foals and <0.5mmol/L/h for all others. Overall 67% (n=73/109) of foals were discharged, 23% (n=25/109) were euthanized and 10% (n=11/109) died.

In a univariable analysis, neurological signs were significantly associated with Na^+ concentrations (OR 0.85; 95% CI 0.78-0.92; $p<0.001$; Figure 1). Factors assessed in the multivariable model ($p<0.1$) were age, Cl^-, K^+, TCO_2, BUN and creatinine concentrations. Gender, diagnosis, total Ca^{2+} and glucose concentration and presence or absence of SIRS and sepsis and diagnosis were not included ($p>0.1$). In the final multivariable model only Na^+ (OR 0.86; 95% CI 0.79-0.95; $p=0.002$) and BUN concentrations (OR 1.04; 95% CI 1.02-1.06; $p=0.001$) were significantly associated with neurological signs.

Changes in Na^+ concentrations per hour were not associated with neurological signs on any day after the lowest Na^+ concentration had been measured ($p=0.18$-0.82) and development of new neurological signs following correction of hyponatremia were not reported in any foal.

On the day of the lowest Na^+ concentration, SID and cOsmol were not significantly different between foals with neurological signs (SID: 38mmol/L (21-56mmol/L); cOsmol: 257mOsmol/kg (228-309mOsmol/kg)) and those without (SID: 37mmol/L (21-51mmol/L); p=0.53; cOsmol: 260mOsmol/kg (224-286mOsmol/kg); p=0.62). In contrast, efOsmol and AG were significantly different between foals with neurological signs (efOsmol: 240mOsmol/kg (192-264mOsmol/kg); AG: 19mmol/L (6.3-41mmol/L)) compared to those without (efOsmol: 252mOsmol/kg (214-264mOsmol/kg) p<0.001; AG: 13mmol/L (-6-39mmol/L); p<0.001).

Neither admission, nor the lowest Na^+ concentration measured during hospitalization were associated with outcome (admission Na^+ concentration non-survivors: 120mmol/L (105-150mmol/L) versus survivors 123mmol/L (96-149mmol/L), p=0.85; lowest Na^+ concentration non-survivors 119mmol/L (105-125mmol/L) versus survivors 122mmol/L (94-125mmol/L), p=0.39). In contrast, presence of neurological signs in hyponatremic foals at any stage during hospitalization was associated with outcome (Table 2).

Discussion

Results of this study corroborate and expand findings of the few previous studies conducted on hyponatremia in foals. As expected, Na^+ concentrations were significantly associated with signs of neurological dysfunction in the multivariable analysis. In people, iso- and hypertonic hyponatremia can occur secondary to severe hyperglycemia, pseudohyponatremia and mannitol use[8] but those conditions are rarely encountered in horses. In foals, most cases of hyponatremia are likely to be accompanied by hypotonicity as Na^+ concentrations and associated anions are the largest determinants of efOsmol. This assumption was supported by the fact that calculated efOsmol was significantly lower in foals with neurological signs

compared to those without. Ideally, efOsmol is measured, rather than calculated, but in most clinical situation good correlation between both can be assumed.[13] Exceptions are cases with the presence of unidentified osmoles which remain undetected unless osmolality is measured.[14] This has anecdotally been reported in neonatal foals but the frequency of the condition and its effects on the foal still remain to be determined. The development of neurological signs does not only depend on the degree of hyponatremia and hypotonicity but also on the speed with which it develops. The more rapidly hyponatremia ensues, the more likely it is that neurological complications will arise. The duration of hyponatremia also determines how an animal responds to treatment. While acute hyponatremia (<48h duration) can be corrected relatively quickly, fast correction of chronic hyponatremia carries a risk of osmotic demyelination.[8] Unfortunately, information about duration of the condition is difficult to accurately establish in clinical cases, even in human patients, and more so in a retrospective study. Due to this uncertainty current recommendations are to treat chronic and acute hyponatremia equally conservatively if Na^+ concentration are <120mmol/L. In symptomatic cases, an increase of 4-8mmol/L (approximately 5% increase in Na^+ concentration) over the first 6h of therapy often alleviates clinical signs and further increases should not exceed a total of 10mmol/L/d.[8, 15] In cases with no neurological symptoms, a gradual increase by 10% per day should be targeted. The average correction rate in this study was at most time points <0.5mmol/L/h, indicating that clinicians are well aware of the issue of rapid correction of Na^+ concentrations and aimed to avoid any possible complications. In this study, no case of osmotic demyelination was documented or suspected, despite increases in Na^+ concentrations of up to 8.3mmol/L/h in individual animals. However, these large changes occurred in animals in which measurements were taken relatively closely to each other and the total change over 24h was often not known. In addition, the duration of hyponatremia was not known this cannot be taken as indication that a gradual increase of the Na^+ concentrations is not necessary in foals. In addition, foals were

only followed until discharge and any signs that might have occurred later were not recorded. Due to the rarity of osmotic demyelination, it will be very difficult to establish the risk in foals in a prospective study and in the absence of species-specific recommendations, following guidelines for human patients might be advisable.

Interestingly, results of the study suggest that high BUN concentrations were associated with the development of hyponatremic encephalopathy. Possible reasons might include a direct effect of BUN on the brain or BUN acting as a marker of renal insufficiency. It is also possible that, although statistically associated with neurological signs, the BUN concentration has no causal effect on neurological dysfunction. Uremic encephalopathy is well reported in people with acute or chronic renal failure and has been described in horses.[16-18] Symptoms are thought to be caused by a number of uremic neurotoxins, largely derived from protein and amino acid metabolism such as urea guanidines, uric acid, polypetides and other substrates that are able to cross the blood brain barrier. Only 14% of foals with neurological signs presented with diseases directly relating to the urinary system. However, 79% of foals with neurological signs also had increased BUN concentrations largely secondary to hypovolemia or, less commonly, placental insufficiency in neonates. In 2 case series, all foals with hyponatremic encephalopathy were diagnosed with renal disease[1, 6] highlighting the possibility that either BUN or other unidentified metabolites usually cleared by the kidney contribute to the development of hyponatremic encephalopathy. The differences in primary disease processes might be explained by different inclusion criteria and different geographical locations. In contrast to blood glucose, BUN concentrations are not included in the calculation of efOsmol. Urea transporters facilitate diffusion across systemic capillaries and most cell membranes nearly as rapidly as water, rendering the molecule osmotically ineffective.[19] In contrast to other cell membranes, the blood brain barrier has a reflection coefficient of 0.5 for BUN, allowing it to

act as osmotic agent.[19] It also acts as a diuretic, increasing renal excretion of free water, which in turn increases Na^+ concentrations. One would therefore assume that increased BUN concentrations, if solely acting as an osmotic substance, would counteract the development of neurological signs rather than fostering it. In fact, BUN has been suggested as treatment for eu- or hypervolemic hyponatremia as it might have cytoprotective and osmoprotective properties. By creating an osmotic gradient across the blood brain barrier, it promotes water efflux from the brain.[19] An additional benefit of treatment with BUN is that overcorrection of hyponatremia resulted in significantly lower neurological impairment and mortality than the other treatment options.[20] Indeed, in people, a protective effect of increased BUN concentrations against the development of osmotic demyelination following rapid correction of hyponatremia has been described.[19, 20] Part of this effect might be based on a substantially enhanced re-uptake of organic osmoles into the brain, particularly myoinositol, which has been demonstrated in uremic animal models.[19, 21, 22] It seems therefore more likely that either BUN or unidentified metabolites act as neurotoxins, enhancing the effect of hyponatremia.

Surprisingly, blood glucose concentrations had no effect on the development of neurological signs. In foals, severe hypoglycemia has been most commonly associated with neurological signs and seizure-like activity presumed to be due to neuronal energy depletion. Only one foal in this study had severe hypoglycemia (1.4mmol/L; 26mg/dL) and this foal showed no neurological signs. Interestingly, in a recent study in severely hypoglycemic calves (blood glucose concentrations <2.0mmol/L; <36mg/dL), only 10% displayed neurological symptoms, highlighting that neurological complications associated with low glucose concentrations are probably rare and mainly occur with extreme hypoglycaemia.[23] Severe hyperglycemia can also lead to neurological complications secondary to hyperosmolarity and cellular dehydration. However, hyperglycemia of the required severity is rarely observed in horses and the highest

glucose concentration measured in this study was 20.8mmol/L; 374mg/dL. The absence of cases with extremely low or high glucose values probably explains the lack of an association with neurological symptoms. Although glucose concentrations influence efOsmol, the contribution is comparatively low and largely negligible in comparison to Na^+ concentrations.

Different to studies in people and cats and dogs, but in accordance with another study on hyponatremia in foals, Na^+ concentrations were not associated with outcome.[6, 24, 25] It has frequently been assumed that marked deviations from the tightly regulated normal Na^+ concentrations are a marker of disease severity, rather than a direct contributor to mortality.[25] However, recent studies in critically ill people have identified dysnatremias as independent predictors of mortality[24, 26] and a study in cats and dogs found a linear association between the magnitude of hyponatremia and case fatality. Only hyponatremic foals were included in the study, as was the case in Collins' study,[6] and a comparison with normonatremic animals could therefore not be conducted. It is possible that comparison with a normonatremic group would have identified an influence on outcome. Further investigations in foals might therefore be warranted.

In contrast, outcome was associated with the presence of neurological signs. This is in line with studies in people where hyponatremia complicated by hyponatremic encephalopathy is associated with a poor outcome.[27] This is interesting as neurological signs resolved or improved in 84% of foals, coinciding with increases in the Na^+ concentrations, yet 44% of the foals in which neurological signs resolved still died or were euthanized. This could suggest that hyponatremia and associated neurological signs are a reflection of disease severity. While correction of hyponatremia might alleviate neurological signs, the underlying disease process can still prove to be fatal. In contrast to people, no widely accepted disease severity scores are

available in horses although scores for prediction of sepsis and prognosis have been reported for neonatal foals.[28-30] A disease severity score would have been useful to assess whether the degree of hyponatremia correlates with disease severity. No correlation between neurological signs and presence of SIRS or sepsis was found. This is similar to people, where inflammation or infection do not seem to be significant risk factors for development of hyponatremic encephalopathy.[27] However, the number of foals with SIRS might have been underestimated in this study due to missing data, and an association cannot be categorically excluded.

As in any retrospective study, there are several limitations. The classification of presence or absence of neurological signs and their description relied on notes made in the clinical records. It is possible, that subtle abnormalities were not recorded and that interpretation of clinical signs differed between clinicians. Foals were also only followed to discharge from the hospital and any neurological signs occurring after this time point would not have been accounted for. In neonatal foals, several disease processes can cause similar clinical signs. Particularly PAS is often associated with neurological dysfunction ranging from lack of coordination, poor tongue control and absent suckle reflexes to generalized seizure-like activity. Every effort was made to exclude foals that presented with signs consistent with PAS by only including animals that were normal at birth and developed neurological signs during the disease process. Unfortunately, measures of arterial oxygenation and pH and were not available for the majority of foals and could therefore not be included in the multivariable analysis. Hypoxic brain damage in human patients is most commonly encountered in the form of hypoxic-ischemic encephalopathy in neonates or following cardiac arrest. In both conditions, ischemia plays a vital part in the pathophysiology.[31, 32] Animal models suggest that 0-8% inhaled oxygen, corresponding approximately to a PaO_2 of <40mmHg, produce some degree of neurological dysfunction if perfusion remains normal.[33] As foals with PAS and neurological signs were

ruled out and respiratory disease was only documented in 1 case with neurological signs, it is unlikely that hypoxia was the reason for the observed neurological signs. However, a contributing role cannot be excluded and ideally measurements of PaO_2 would have been included. Intra- and extracellular pH can significantly influence neurological function[34] and would ideally have been included as well. However, even a single brief episode of seizure-like activity can cause severe acidosis and hyperlactatemia and therefore cause and effect would have been difficult to differentiate in foals with neurological signs.[35] Due to the retrospective nature, the volume status (hypo-, normo-, or hypervolemic) could not be assessed and any effect this might have on symptoms was therefore not accounted for.

In conclusion, Na^+ and BUN concentration are significantly associated with neurological function. Further studies are needed to establish the role of BUN in hyponatremia.

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Figure legend:

Figure 1: Median and interquartile range of lowest sodium (Na^+) concentration measured during hospitalization grouped by presence or absence of neurological signs at the same time point. There was a statistically significant association between presence of neurological signs and Na^+ concentration in a univariable logistic regression analysis (OR 0.85; 95% CI 0.78-0.92; $p<0.001$).

Table 1: Comparison of clinicopathological parameters between foals < 6 months old with hyponatremia (≤125mmol/L) with and without neurological abnormalities on the day the lowest sodium concentration was measured and on up to four subsequent days.

	Day of lowest Na concentration		Day 1 after lowest Na concentration		Day 2 after lowest Na concentration		Day 3 after lowest Na concentration		Day 4 after lowest Na concentration	
Neurological signs	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Na^+ concentration (mmol/L)	116 (94-124); n=37	123 (109-125); n=72	118 (102-134); n=26	128 (106-142); n=78	120 (104-140); n=16	133 (106-149); n=61	127 (108-164); n=11	132 (113-144); n=33	129 (121-167); n=7	134 (125-148); n=23
Effective osmolality (mOsmol/kg)	240 (192-264); n=30	252 (214-264); n=68	254 (193-298); n=25	263 (228-291); n=53	252 (209-286); n=16	273 (237-292); n=45	262 (214-288); n=11	268 (249-296); n=34	258 (226-297); n=6	276 (257-289); n=21
Δ Na^+ (mmol/L/h)	NA	NA	0.27 (0-1.75); n=26	0.45 (0-8.3); n=78	0.22 (-0.21-1.65); n=16	0.25 (-0.2-4.1): n=61	0.32 (0-1.1); n=11	0.18 (-0.69-1.16); n=33	1.22 (0.08-2.36); n=7	0.04 (-0.13-0.37); n=23
K^+ concentration (mmol/L)	4.2 (1.3-7.7); n=37	4 (2.1-6.9); n=72	4.1 (1.3-7.1); n=26	3.9 (2.0-6.2); n=78	3.5 (1.8-7.4); n=16	3.6 (1.9-5.3); n=61	3.4 (2.3-5.5); n=11	3.8 (1.81-5.2); n=33	3.5 (1.9-5.2); n=7	3.9 (2.5-5.9); n=23
Cl^- concentration (mmol/L)	82 (63-101); n=37	89 (74-106); n=72	87 (72-101); n=26	93 (72-108); n=78	88 (73-105); n=16	97 (74-114); n=61	87 (763-108); n=11	97 (82-107); n=43	89 (71-110); n=7	97 (85-113); n=23
TCO_2 concentration (mmol/L)	18 (7-34); n=37	23 (11-35); n=72	21 (7-41); n=26	26 (11-34); n=74	22 (10-33); n=16	25 (12-35); n=61	18 (7-34); n=11	26 (14-32); n=33	18 (7-34); n=7	28 (5.1-35); n=21
BUN concentration (mmol/L; mg/dL)	18 (5-85); 49 (14-237); n=32	8 (3-41); 22 (7-114); n=64	14 (4-44); 39 (10-123); n=25	6 (2-33); 18 (6-93); n=51	13 (3-36); 37 (9-102); n=16	6 (2-71); 16 (5-199); n=45	10 (3-39); 29 (9-110); n=11	5 (1-29); 15 (4-82); n=33	10 (6-39); 27 (18-110); n=6	5 (1-17); 13 (3-48); n=21
Creatinine concentration (umol/L; mg/dL)	389 (80-2131); 4.4 (0.9-24.1); n=34	150 (80-2043); 1.7 (0.9-23.1); n=70	407 (97-2131); 4.6	133 (62-2617); 1.5	274 (88-2104); 3.1	115 (62-1061); 1.3	221 (71-2096); 2.5	115(62-1645); 1.3	283 (80-725); 3.2	124 (62-937); 1.4

			(1.1-24.1); n=26	(0.7-29.6); n=69	(1.0-23.8); n=16	(0.7-12.0); n=55	(0.8-23.7); n=11	(0.7-18.6); n=33	(0.9-8.2); n=7	(0.7-10.6); n=22

* Changes over 24h could not always be calculated due to lacking data and the time between measurements varied between 1-24h

Table 2: Association between presence and absence of neurological signs and survival to discharge from the hospital in foals < 6 months old with hyponatremia (≤125mmol/L). Statistical significance was set at a p-value of <0.5.

	Non-survivors	Survivors	Total
No neurological signs present	19	53	72
Neurological signs present	17	20	37
Total	36	73	109
P-value			0.034