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STANDARD ARTICLE

Presumed Neuroglycopenia Caused by Severe Hypoglycemia in Horses

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Background: Neuroglycopenia refers to a shortage of glucose in the brain resulting in neuronal dysfunction and death if left untreated. Presumed neuroglycopenia has not been described in horses.

Objective: To report neurological signs in horses with presumed neuroglycopenia as the result of severe hypoglycemia.

Animals: Ninety horses (hours to 28 years of age) diagnosed with hypoglycemia (blood glucose concentration < 75 mg/dL [< 4.2 mmol/L]).

Methods: Retrospective study. Electronic medical records were searched. Signalment, history, complaint, clinical signs, laboratory findings including CSF analysis, electroencephalogram, clinical or definitive diagnosis, and outcome were recorded. Kruskal-Wallis analysis of variance and logistic regression were used to investigate association between blood glucose concentration and data extracted. Statistical significance was set at $P < 0.05$.

Results: Thirty-eight and 52 horses had mild (50-74 mg/dL [2.8-4.1 mmol/L]), and severe hypoglycemia (< 50 mg/dL [< 2.8 mmol/L]), respectively. Most common causes of hypoglycemia included liver and gastrointestinal (40%) disease, sepsis (33%), neoplasia (7%), and insulin-induced (4%). Most common neurologic deficits included obtundation (100%), seizures (42%), and disorientation (22%). CSF-glucose was severely low (mean 2.5 mg/dL [0.1 mmol/L], median 0 mg/dL). Paroxysmal discharges in support of seizures were identified in the occipital (visual) and parietal (closest to temporal-auditory) cortical regions upon EEG examination (8/8 horses).

Conclusions and clinical importance: Neuroglycopenia is presumed to occur in horses as the result of severe hypoglycemia. Subclinical seizures, and intermittent blindness and deafness of cortical origin can occur. Severe altered state of consciousness and seizures can be observed at a blood glucose cut-off value of < 42 mg/dL (< 2.3 mmol/L).

KEYWORDS

Cerebrum, glucose, obtundation, paroxysms, seizures

1 | INTRODUCTION

Neuroglycopenia is a term that refers to a shortage of glucose in the brain resulting in alteration of neuronal function.[1,2] One of the most common causes of neuroglycopenia is hypoglycemia.[2] In human medicine, hypoglycemia is usually defined by a blood glucose (BG) concentration below 70 mg/dL (< 3.9 mmol/L).[3] Neurogenic (autonomic) and neuroglycopenic symptoms occur in humans with hypoglycemia.[4–6] Neurogenic symptoms result from the physiologic response to hypoglycemia by the autonomous nervous system.[4] These include tremors, palpitations, anxiety, sweating, tachycardia, hunger, and paresthesias.[4] Neuroglycopenic symptoms are related to

Abbreviations: BG, blood glucose; CSF, cerebrospinal fluid; CSF-G, CSF glucose; ECG, electrocardiogram; EEG, electroencephalogram; IGF, insulin growth factor; NE, neonatal encephalopathy; NICTH, non-islet cell tumor-induced hypoglycemia

deprivation or profound low glucose concentration in the brain, which manifest as confusion, sensation of warmth, blurred speech, fatigue, cognitive failure, seizures, coma, and death if unattended.[3,4] During the early stage of neuroglycopenia, cortical dysfunction might only be recognized through a systematic cognitive testing.[5,7] Cerebral cortical dysfunction has been recorded when BG concentration is 36 mg/dL (2 mmol/L) or less in humans and rats.[1,2] At that low glucose level, brain glucose concentration was reported to be close to zero.[1,2] Measurement of glucose concentration in cerebrospinal fluid (CSF) might aid to investigate glucose concentration in the brain.[8,9] Low glucose concentration in CSF is termed hypoglycorrhachia and is most commonly associated with infection (mainly bacterial meningitis) but other causes such as stroke, malignancy, neurosarcoidosis, and severe hypoglycemia are associated with low CSF glucose concentrations.[10,11]

The effects of hypoglycemia on brain function through electroencephalography (EEG) have been studied in patients with and without insulin dependent diabetes.[2,12,13] Through the collection of serial blood samples, it was determined that blood glucose concentration above 54 mg/dL (3 mmol/L) did not cause alterations in EEG activity.[2] Cortical neuronal dysfunction was shown as an abrupt decrease in alpha activity with a concomitant increase in theta activity at a median blood glucose concentration of 36 mg/dL (2 mmol/L).[2] Further, changes in EEG activity appear and disappear within a narrow range of blood glucose concentrations.[2] However, there is variability among individuals manifesting neurologic dysfunction and EEG alterations associated with hypoglycemia.[14] In addition to hypoglycemia, alterations in glucose transport, metabolism, and storage of glycogen can cause or contribute to low glucose concentrations in the brain.[9,15] Hypoglycemia has been reported in horses and defined as a BG concentration below 75 mg/dL (< 4.2 mmol/L).[16,17] Although seizures associated with hypoglycemia have been sporadically reported in veterinary medicine, comprehensive clinical descriptions of the effects of hypoglycemia on neurologic findings, documentation of hypoglycorrhachia and presumed neuroglycopenia and its associated electroencephalographic findings have not been reported in horses.[18–21] Further, there are no studies correlating low glucose concentrations in blood and CSF in equine medicine.[22,23] Therefore, the objective of the study was to report neurological signs in horses with severe hypoglycemia. Furthermore, glucose concentration in CSF and EEG findings were reported when available. Our testing hypothesis was that hypoglycorrhachia and presumed neuroglycopenia manifested as severe neurologic dysfunction occur in horses with severe hypoglycemia.

2 | MATERIALS AND METHODS

2.1 | Animals

Electronic medical records from the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California at Davis were searched using the words hypoglycemia, disorientation, insulin, obtundation, stupor, coma, and seizures from the years 2000 to 2018. Medical records were reviewed for the evaluation and definition of state of consciousness, described as quiet, lethargic or obtunded (dull but responsive to stimuli [e.g. non-painful tactile, visual, auditory]), stupor (recumbent horse requiring strong painful stimuli for any cortical response [perception or awareness, not reflex] to occur), and coma (lack of any cortical response regardless of intensity of stimuli). Horses of any breed, sex, and age with documented hypoglycemia at admission or at any time (if intermittent, recurrent, or as the result of insulin therapy) during hospitalization were considered for the study. For this study, hypoglycemia was defined as a BG concentration below 75 mg/dL (< 4.2 mmol/L), and severe hypoglycemia below 50 mg/dL (< 2.8 mmol/L). Signalment, presenting complaint, physical and laboratory parameters, clinical or definitive diagnosis, and outcome were recorded. When available, glucose concentration in cerebrospinal fluid (CSF) was recorded. Measurement of CSF-glucose was done within 5 minutes after collection.

2.2 | Electroencephalography

An EEG to assess cortical activity during hypoglycemia was also recorded if available. The examination consisted of an electroencephalogram, electrooculogram (EOG), electrocardiogram (ECG), and respiratory monitoring. A Nihon Kohden digital wireless EEG system (Neurofax Wireless Input 1000A, Nihon Kohden America Inc., Foothill Ranch, CA) with integrated video was used to obtain all standard EEG, EOG, and ECG recordings. Electrode nomenclature and placement was based from a modified human 10-20 system and described in horses previously.[24,25] Needle electrodes were placed subcutaneously in the scalp of horses for the recording of the EEG as described elsewhere.[25] In brief, subcutaneous needle electrodes were placed in the prefrontal (2 electrodes), frontal (3), central (3), parietal (3) and occipital (2) regions. Additional electrodes included 1 that served as a ground (between the 2 prefrontal electrodes, 1 in the intercanthus region and 1 at the base of each ear to evaluate for ear movement artifacts on the EEG. Concurrently, an electrooculogram (2 subcutaneous electrodes per eye, 1 each in the upper and lower eyelids), electromyogram (2 subcutaneous electrodes located in the splenius muscle), and electrocardiogram (1 subcutaneous electrode in the region of the left heart base and 1 at the left heart apex) were also performed. A bipolar montage (rostral to caudal and transverse) was used with sensitivities set for recording as described.[24,25] Thirty to forty minutes of EEG recordings were obtained. The data obtained was thoroughly examined from EEG tracings and simultaneous video of the horse under study. The EEG study was approved by an animal care and use protocol from our institution and clients consented to perform an EEG.

2.3 | Statistical Analysis

Descriptive statistics are presented as mean, standard deviation, median, and range. To assess if neurologic status (e.g. state of consciousness, seizures), clinical diagnosis (e.g. sepsis, liver disease, and others), and outcome (survival vs non-survival) were associated with serum glucose concentration, Kruskal-Wallis analysis of variance was performed. Linear regression was used to evaluate the correlation between blood and CSF-glucose. Logistic regression was used to evaluate the association between BG concentration and clinical signs (mental status, seizures); models were verified to be linear in the log

odds of clinical sign occurrence. Receiver operating characteristic curve analysis was performed to determine the cut-off for blood glucose concentration that maximized the percentages of correctly classified cases with mild and severe neurologic signs. Statistical significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Horses

Ninety horses had hypoglycemia (BG 0-74 mg/dL [0-4.1 mmol/L]) at admission or intermittently during hospitalization. Based on age, the following groups were identified: 1) neonatal foals defined as foals up to 10 days of age (N = 35), 2) foals 11 days to one-month (N = 4), 3) horses over one month up to 1-year (N = 4), and 4) adult horses, older than 1 year (N = 47). The population in this study consisted of various breeds including Quarter horses and related breeds (N = 33), American miniature horse (N = 17), Thoroughbred (N = 12), Arabian (N = 8), Warmblood (N = 4), Pony (N = 4), Draft (N = 3), Morgan (N =3), Andalusian (N = 2), and others (N = 1, each: Tennessee Walker, Standardbred, Mustang, and Selle Francais). There were 48 females, 17 geldings, and 25 intact males.

3.2 | Signalment by Age Group

Group 1: Neonatal foals were of Quarter horse (N = 16), Thoroughbred (N = 6), American Miniature (N= 3), Pony and Draft (N = 2 each), and other (N = 1 each, Morgan, Tennessee Walker) breeds. There were 18 fillies and 17 colts. The mean and median age was 15 and 12 hours, respectively (SD 7 h, range 3 to 36 h). Group 2: Foals 11 days to one month old were of Quarter Horse (N = 3), and Andalusian (N = 1). There were 2 fillies and 2 colts. The mean and median age was 14.8 and 13 days, respectively (SD 4.3 d, range 12 to 21 d). Group 3: Horses over one month up to 1 year of age were of Quarter Horse (N = 2), and Arabian and American Miniature (N = 1 each) breeds. There was one female and 3 colts. The mean and median age was 6.3 and 6.5 months, respectively (SD 4.3 m, range 2 to 10 m). Group 4: Horses older than 1 year of age were of American Miniature (N = 13), Quarter Horse and related breeds (N = 12), Thoroughbred (N = 6), Arabian (N = 5), Warmblood, Morgan, and Pony (N = 2 each), and Draft, Andalusian, Standardbred, Mustang, and Selle Francais (N = 1 each) breeds. There were 28 females, 17 geldings, and 3 intact males. The mean and median age was 12.7 and 11 years old, respectively (SD 7.5 y, range 1.4 to 28 y).

3.3 | Glucose Concentration

For this section, glucose concentration will be reported as mg/dL. Of 90 horses with hypoglycemia, 38 had mild hypoglycemia (mean BG 62.5 [SD 7.4], median 63 [range 50-74] mg/dL), and 52 had severe hypoglycemia (mean 27.3 [SD 15.9], median 31 [range 0-49] mg/dL) (Table 1). There were 13 and 22 neonatal foals with mild (mean 61.3 [SD 7.7], median 63 [range 51-74] mg/dL) and severe (mean 23.5 [SD 15.8], median 18 [range 0-44] mg/dL) hypoglycemia, respectively. One foal less than a month of age had a BG concentration of

TABLE 1 Disease process and glucose concentration (blood, CSF). N = number of horses, NE = neonatal encephalopathy, hyper-TG = hypertriglyceridemia, other = other disease processes, BG = blood glucose concentration, CSF-G = cerebrospinal fluid glucose concentration, SD = standard deviation, md = median, IMM = immune-mediated myositis

AGE GROUP	SEPSIS (N)	NE (N)	LIVER DISEASE (N)	HYPER-TG (N)	GI (N)	NEOPLASIA (N)	OTHER (N)	BG (Mean, SD) mg/dL	BG (Md, range) mg/dL	Hypoglycemia (N)	CSF-G (Mean, SD) mg/dL	CSF-G (Md, range) mg/dL
NEONATES (N = 35)	25	6	2	0	0	0	EHV1 = 2	38.6 (22.2)	41 (0-74)	Mild N = 12 Severe N = 23	1.9 (3.5) N = 9	0 (0-10) N = 9
> 10 DAYS - 1 MONTH (N = 4)	2	0	2	0	0	0	0	25.8 (32.6)	15.5 (0-72)	Mild N = 1 Severe N = 3	0 N = 1	0 N = 1
> 1 MONTH - 1 YEAR (N = 4)	1	0	1	0	1	0	IMM = 1	61.5 (9.5)	51 (60-70)	Mild N = 4	NA	NA
> 1 - 28 YEARS (N = 47)	2	0	15	8	15	7	0	46.4 (19.3)	46 (7-73)	Mild N = 21 Severe N = 26	3.9 (5.9) N = 10	0 (0-12) N = 10
TOTAL (N = 90)	30	6	20	8	16	7	3	50.7 (16.2)	45 (0-74)	Mild N = 38 Severe N = 52	2.5 (4.4) N = 20	0 (0-12) N = 20

[Correction added after first online publication 31 August 2018: in Table 1 formatting has been updated.]

72 mg/dL; and 3 foals had 0, 6, and 25 mg/dL each. Four older horses up to a year of age had mild hypoglycemia (51, 56, 69, and 70 mg/dL). There were 21 and 26 adult horses with mild (mean 64.3 [SD 6.5], median 67 [range 50-73] mg/dL) and severe (mean 33.1 [SD 14], median 36 [range 7-49] mg/dL) hypoglycemia, respectively. See Table 1 for further details on BG by age group. Glucose concentration was measured in CSF collected from the atlanto-occipital cisterna in 20 horses (neonatal foals = 9 [mean 1.9 mg/dL, SD 3.5], non-neonatal foals = 1 [0 mg/dL], and adults = 10 [mean 3.9 mg/dL, SD 5.9]) (Table 1). In these horses, CSF glucose concentration (mean 2.5 [SD 4.4], median 0 [range 0-12] mg/dL) was markedly lower (P <0.001) than that of BG concentration (mean 14.6 [SD 15.5], median 12 [range 0-63] mg/dL). A correlation (R = 0.81, P < 0.0001) between low BG and CSF-glucose concentration was found. Cytology (clear transparent, total protein < 100 mg/dL, total nucleated cells < 3/uL, proportion of small and large mononuclear cells within reference range, and absence of neutrophils, eosinophils and basophils) and other biochemical parameters (electrolytes, creatine kinase[26]) in CSF were within reference range. Lactate in CSF was measured in 10 horses and had a mean of 2 mmol/L with a range from 1.2 to 4 mmol/L (reference range ≤ 2 mmol/L). These 10 horses had a systemic lactate within reference range (≤ 2 mmol/L). There was no evidence of bacteria in CSF.

3.4 | Clinical Diagnosis

Causes associated with hypoglycemia included sepsis (N = 30/90 horses), liver disease (N = 20/90), gastrointestinal disease (colic, colitis, N = 16/90), hypertriglyceridemia (triglycerides 237-1415 mg/dL, reference 9–41 mg/dL for adult horses) not secondary to GI or liver disease (N = 8/47 adults), neoplasia (N =7/47 adults), neonatal encephalopathy (N = 6/35), and others (N = 3/90) (Table 1). Three others consisted of 2 neonatal foals tested positive for EHV1, and a 2-month old filly was diagnosed with immune-mediated myositis. The most common diseases in these horses by age group are presented in Table 1. In brief, the most common cause associated with hypoglycemia in neonatal foals was sepsis (N = 25/35). Seven of these 25 foals had concurrent neonatal encephalopathy. Neonatal encephalopathy was presumed based on the development of altered neurological status in foals 24 to 48 hours of age with no other apparent underlying cause, and history of dystocia or rapid birth (< 20 minutes). Pathogens identified on blood culture included *Enterococcus sp.*, *Actinobacillus sp.*, *E. coli*, and *Proteus vulgaris*. In adult horses, the most common disorders associated with hypoglycemia included liver and gastrointestinal disease (N = 15/47, each), and hypertriglyceridemia (N = 8/47) secondary to other causes (anorexia from respiratory and renal disease, endocrinopathies). These 8 horses with hypertriglyceridemia were of American Miniature breed, and in 4 had severe hypoglycemia and seizures were presumed to be induced by the administration of insulin therapy since dextrose administration corrected hypoglycemia and prevented further seizures. Liver disease included failure due to cirrhosis of undetermined cause (N = 6/47 adults), pyrrolizidine alkaloid toxicosis (N = 4/47 adults), cholangiohepatitis (N = 2, one young and adult horse), acute hepatitis (N = 2/47 adults), Tyzzer's (N = 2 non-neonatal foals), and hepatic lipidosis (N = 1 adult horse). Seven adult horses (mean age 13 years, range 4 to 22 years old) were diagnosed with neoplasia or presumed neoplasia and intermittent episodes of hypoglycemia. Identified neoplasia included renal undifferentiated carcinoma (N = 2 horses, BG 13 and 40 mg/dL each), renal tubular carcinoma with GI carcinomatosis (BG 35 mg/dL), hemangiosarcoma (BG 51 mg/dL), and lymphoma (BG 56 mg/dL). The 2 remaining horses had masses suspected to be neoplasia based on ultrasound examination appearance (heterogeneous echogenicity, absence of a wall-off cavitary mass containing fluid). Blood glucose in these 2 horses was 37 and 46 mg/dL, respectively. Five adult horses had sepsis. One horse had disseminated *Corynebacterium pseudotuberculosis* infection, and one other had *Klebsiella sp.* pneumonia. There was no significant association between BG concentration and clinical diagnosis (probability 0.0891).

3.5 | Neurologic Status

Reported neurological signs included altered state of consciousness (N = 90/90), seizures (N = 38), disorientation (N = 20), intermittent blindness (N = 12), and intermittent deafness (N = 10). Blindness was observed as a lack of menace, bumping into objects and become startled upon being touched. Deafness was identified as lack of response or reaction to loud sound and being startled when approached. These abnormalities were not always associated with altered state of consciousness. State of consciousness was described as quiet, lethargic or mildly obtunded (N = 24), severe obtundation (N = 61), stupor (N = 4), and coma (N = 1). Neurological signs were defined as mild (quiet, lethargic, or mildly obtunded) or severe (severe obtundation, stupor, or coma, and seizures) (Figure 1). Overall, for all age groups combined, BG was significantly different between animals showing mild and those with severe neurological signs (P = 0.0001, Figure 1). Blood glucose was inversely related to the probability of developing abnormal mental status: for every 10 mg/dL (0.6 mmol/L) increase in glucose,

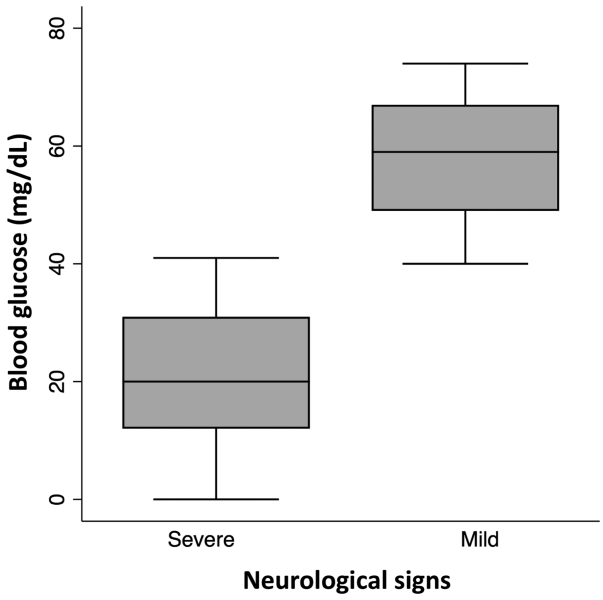

FIGURE 1 Blood Glucose concentration (mg/dL) in association with severity of neurological signs. Mild (quiet, lethargic, or mildly obtunded) or severe (severe obtundation, stupor, or coma, and seizures) neurological signs

the odds of abnormal mental status declined approximately 33% (odds ratio of 0.656, 95% confidence interval = 0.473-0.909, P = 0.011). Blood glucose was inversely related to the probability of developing seizures: for every 10 mg/dL (0.6 mmol/L) increase in glucose, the odds of developing seizures declined by approximately one-half (odds ratio = 0.525, 95% confidence interval = 0.398-0.693, P < 0.001). For neonates and horses older than 1 year of age, BG was significantly different between animals showing mild versus severe neurological signs (P = 0.005 and P = 0.0011, respectively). A cut-off value of < 42 mg/dL (< 2.3 mmol/L) correctly classified 100% of severely affected neurologic cases and 96% of mildly affected cases, establishing a total correct classification of 98% of all cases. The area under the receiver operating characteristic curve was 0.997 (95% confidence interval of 99.1-100%). Of the 38 horses in which seizures were reported, 81.6% (N = 31/38: neonates N = 17/23, non-neonates N = 2/2, adults N = 12/12) had severe hypoglycemia. Seven of 12 horses with intermittent blindness also had intermittent deafness. Six horses also had other metabolic abnormalities that could have contributed to the altered neurologic status such as hyperammonemia (N = 3: neonate = 1 [183 μg/dL], adults = 3, blood ammonia 70, 460 and 1217 μg/dL, respectively; reference 5-59 μg/dL) and hypernatremia (N = 2 neonates, sodium 156 and 183 mmol/L; reference 131-144 mmol/L). One adult horse with mild hypoglycemia had collapsing episodes and hypocalcemia (Ca^{++} 0.63 mmol/L, reference ≥ 1.2 mmol/L). Recumbence was reported in 33 horses: neonates = 25, non-neonates = 1, < 1 y = 1, adults = 6 horses.

3.6 | Electroencephalogram

Eight horses had an EEG performed while standing: 6 horses under sedation (detomidine hydrochloride 0.01 mg/kg IV) and 2 unsedated because of severe obtundation. These 8 horses had a mean BG of 29.6 mg/dL (range from 0 to 46 mg/dL). For illustration, the EEG recording from a 5-year-old Thoroughbred filly with intermittent seizures, blindness and deafness diagnosed with renal tubular carcinoma is presented on Figure 2 (A-F). The EEG demonstrated paroxysmal activity consisting of sharp waves (70-200 milliseconds), and spikes (<70 ms) and waves supportive of seizure activity (Figure 2B-D). Paroxysmal activity was also observed in the absence of obvious clinical manifestations of seizures and preceded clinical manifestations (Figure 2C). Paroxysmal activity was observed in the occipital and parietal cortical regions in all 8 horses, and in the frontal region in 5 horses. Paroxysmal activity was more profound and first observed in the occipital cortical region. These EEG alterations became generalized if hypoglycemia was not treated promptly (Figures 2E-F). Electroencephalographic activity in the mare presented in the figures returned to normal upon resuming IV dextrose administration (not shown). Five of 8 horses had a CSF-glucose concentration of 0 mg/dL.

3.7 | Outcome

The overall hospital mortality rate for these 90 horses was 48% (euthanasia = 28/90, died = 15/90 horses) (Table 2). Mortality appeared to be higher in foals less than a one month of age (N = 20/39, 51.3%) than older foals and adults. By group, the case fatality rate was 51, 50, 0, and 49% for the neonatal, non-neonatal foals, ≤ 1 year, and adult horses, respectively (Table 2). The overall fatality rate was 34 and 58% for horses with mild and severe hypoglycemia, respectively (Table 2). However, a significant association between BG concentration and outcome was not identified. Macroscopic postmortem evaluation of the brain was available for 10 horses and did not reveal alterations. Histological evaluation of the brain was not available.

4 | DISCUSSION

This study reports horses with presumed neuroglycopenia based on the presence of neurological signs such as altered state of consciousness, seizures, disorientation, and intermittent blindness and deafness; along with hypoglycemia which in 57% of horses was profound. Furthermore, CSF glucose concentration was severely low and likely reflecting glucose concentration in the brain as reported in human medicine.[9] Paroxysmal activity in support of seizures in the parietal and occipital cortical region was seen in all horses on which an EEG was performed. Therefore, this study also highlights the importance of performing an EEG examination for the investigation of paroxysmal activity in support of seizures even in the absence of clinical manifestations.

Disorders causing hypoglycemia include those resulting in increased glucose utilization and/or decreased glucose production, altered metabolism, transport and storage.[17] Examples of conditions resulting in hypoglycemia in horses include sepsis, endotoxemia, liver failure, illnesses impairing neonatal foals from nursing, and glycogenosis such as glycogen branching enzyme deficiency in neonatal Quarter Horses.[16,17,27–29] Starvation and severe malnutrition are less common causes of hypoglycemia. Delayed serum or plasma separation from blood cells and hyperlipemia can result in falsely low BG concentration. Although hypoglycemia has been reported in equids of various ages; neurological signs have been scarcely described.[16,17]

Neurogenic signs such as those described in humans with mild hypoglycemia were rarely documented here.[4,30] Observations of tremors, palpitations, anxiety, sweating and others might have been overlooked, difficult to interpret, or simply not reported in the medical record. Early clinical manifestations of severe hypoglycemia in humans include cognitive dysfunction.[2,5] It has been reported that cognitive function deteriorates in most diabetic patients at a BG concentration of about 54 mg/dL (3 mmol/L) at which most patients are unaware of hypoglycemia.[2,5] Cognitive dysfunction in horses might be difficult to assess and interpret. Instead, alterations in behavior such as disorientation might have been an early manifestation of presumed neuroglycopenia. Although glucose concentration in the brain was not measured to define neuroglycopenia in our study; 100% of the horses in which a CSF sample was collected (N = 20/20) had severe hypoglycorrhachia. The report of intermittent blindness and deafness in a few horses here was likely a manifestation of abnormal cortical activity since these signs were intermittent and coincided with paroxysmal activity based on EEG examination. However, alterations in the state of consciousness can also result in intermittent lack of clinical response to a menace and sound (clap) test. Neuroelectrodiagnostics

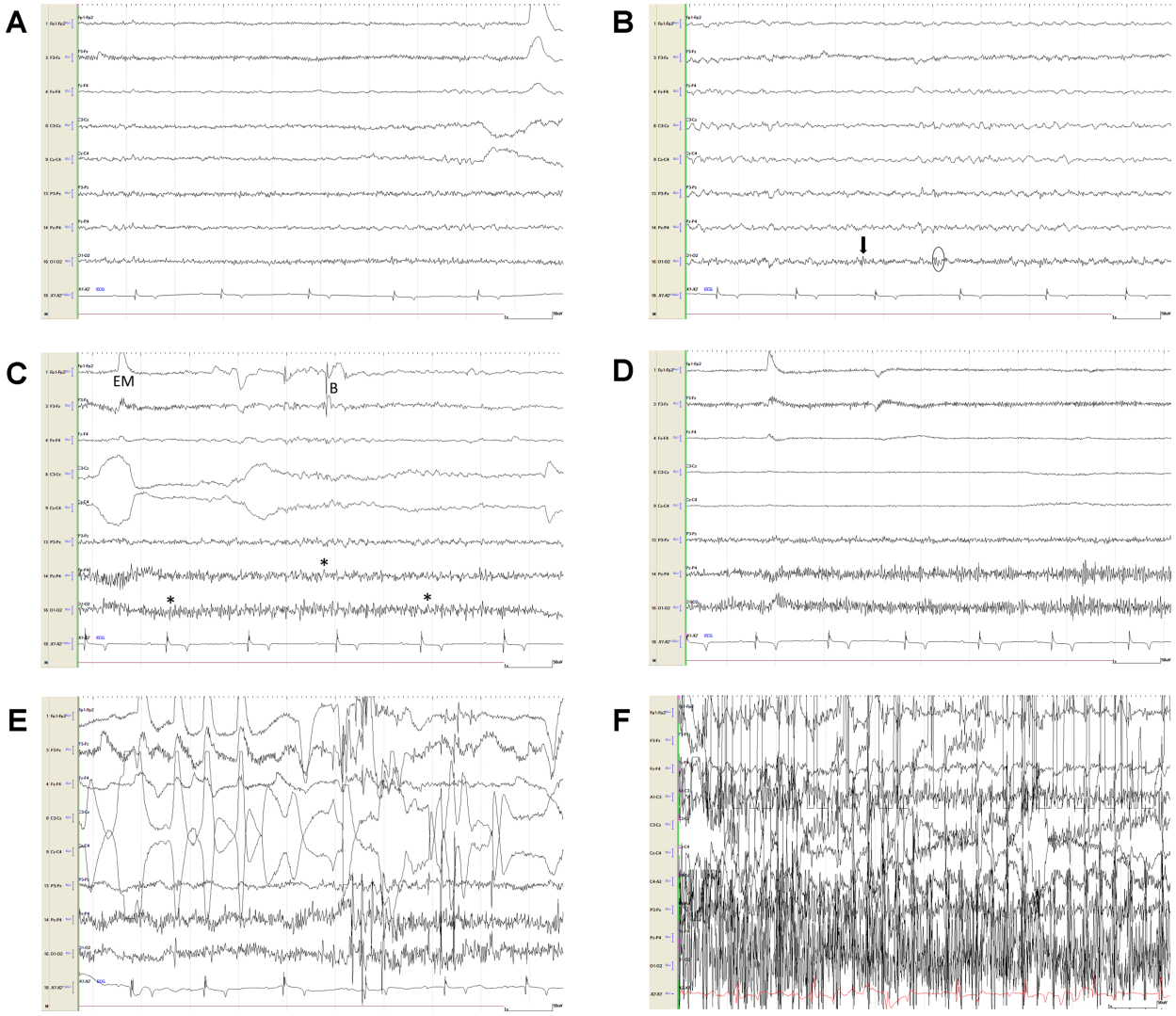

FIGURE 2 Electroencephalogram and simultaneous video recording of a 5-year-old Thoroughbred mare with renal tubular carcinoma. The following figures depict EEG recordings of this filly at various stages of blood glucose manipulation during dextrose infusion. For all figures: odd numbers represent left side, even numbers represent right side, FP = frontal polar, F = frontal, C = central, P = parietal, O = occipital, z = midline, A = auricular, X2-X3 = ECG. Bar = 1 second, 50 microvolts. Note different scale for ECG. Figure 2A. Baseline EEG recording while the mare was on IV dextrose administration. Heart rate = 30 bpm. Blood glucose concentration at the time of this recording was 83 mg/dL. Figure 2B. Electroencephalogram showing slowing of waves throughout this epoch of 10 seconds. This recording was made within 1 minute of discontinuing IV dextrose administration. Note sharp wave (arrow), spike and wave (oval) on occipital cortical region (O1-O2 channel) following cessation of IV dextrose drip. Heart rate = 36 bpm. Figure 2C. Electroencephalogram showing multiple spikes and waves (throughout O1-O2) and sharp waves (*) noted on occipital and parietal region. No IV dextrose administered during this 10 second epoch. Frontal polar channel is picking up eye movement artifacts: eye movement (EM) and blink (B). Heart rate = 36 bpm. Figure 2D. Note increased paroxysmal discharges in occipital and parietal regions. No IV dextrose administration during this recording. Heart rate = 42 bpm. Blood glucose concentration at the time of this recording was 44 mg/dL. Figure 2E. Electroencephalogram showing paroxysmal activity mixed with movement artifact as the filly is having a clinical seizure manifested as facial twitching and eye rolling. Blood glucose during this recording was 23 mg/dL. Heart rate = 36 bpm. Figure 2F. Electroencephalogram during seizures. Note spread of paroxysmal activity, movement, and loss of electrodes. Note irregular ECG activity. After this recording, IV dextrose administration was resumed and EEG activity returned to normal

such as visual and auditory evoked potentials were not performed in these horses to further investigate the origin of those abnormalities. Furthermore, intermittent blindness and deafness could be subtle and not readily apparent unless a thorough and careful neurologic examination is performed at various times. Therefore, more horses with these signs could have been missed. More severe clinical manifestations of neuroglycopenia as those reported in humans (e.g. seizures, coma)[4] are more readily apparent than subtle abnormalities to the clinician dealing with non-human species. In this study, 80.6% of the horses with seizures had severe hypoglycemia. A BG concentration cut-off value of 42 mg/dL (2.3 mmol/L) was associated with the development of severe neurologic dysfunction (severe alteration of the state of consciousness and seizures, and severe hypoglycorrhachia (CSF-glucose mean 2.5 mg/dL [0.1 mmol/L]). Recumbence at admission was reported here in 39% of the horses of which the majority were neonatal foals (N = 25/33). However, these foals also had other disorders that could have resulted in recumbence (e.g. sepsis, NE, severe liver disease).[31–33] Recurrent hypoglycemic episodes can lead to blunting of mild

TABLE 2 Outcome. N = horses, EU = euthanasia

AGE GROUP	Mild Hypoglycemia	Severe Hypoglycemia	TOTAL HORSES (N)
NEONATES	**N = 12/35**	**N = 23/35**	**N = 35**
OUTCOME	Alive = 7 EU = 3 Died = 2	Alive = 10 EU = 5 Died = 8	Alive = 17 EU = 8 Died = 10
FATALITY RATE (%)	42	57	51
> 10 DAYS - 1 MONTH	**N = 1/4**	**N = 3/4**	**N = 4**
OUTCOME	EU = 1	Alive 2 Died = 1	Alive = 2 EU = 1 Died = 1
FATALITY RATE (%)	100	33	50
> 1 MONTH - 1 YEAR	**N = 0/4**	**N = 0/4**	**N = 4**
OUTCOME	Alive = 4	NA	Alive = 4
FATALITY RATE (%)	0	NA	0
> 1 - 28 YEARS	**N = 21/47**	**N = 26/47**	**N = 47**
OUTCOME	Alive = 14 EU = 7	Alive = 10 EU = 12 Died = 4	Alive = 24 EU = 19 Died = 4
FATALITY RATE (%)	33	62	49
ALL HORSES	**N = 38/90**	**N = 52/90**	**N = 90**
OVERALL OUTCOME	Alive = 25 EU = 11 Died = 2	Alive = 22 EU = 17 Died = 13	Alive = 47 EU = 28 Died = 15
FATALITY RATE (%)	34	58	48

symptoms in people resulting in hypoglycemia unawareness and risk of progressing to neuroglycopenic symptoms.[14,34] In veterinary medicine, mild hypoglycemic clinical manifestations might be more difficult to recognize and therefore missed. Furthermore, other disease processes can result in similar non-specific clinical signs.

Hypoglycemia is a leading cause of neurological signs and sequelae in infants with severe metabolic or infectious diseases.[35] Cortical white matter hemorrhage, basal nuclei and thalamic injury, and infarction in areas of the middle cerebral artery resulting in neurologic symptoms and later neurodevelopmental impairment have been documented in up to 94% of newborn infants with hypoglycemia.[36,37] This injury has been dependent on duration and severity of hypoglycemia.[36] Reference ranges for blood glucose concentration in neonatal foals have been reportedly higher than older foals and adult horses.[17,38] The reference range of blood glucose concentration for neonatal foals at our institution is reported to be from 118 to 207 mg/dL (6.6 to 11.5 mmol/L). Glucose concentration in CSF can be similar or slightly lower to that of BG in healthy adult horses; but it could range from 40 to 70 mg/dL (2.2 to 3.9 mmol/L).[22,23] Neonatal and non-neonatal foals CSF glucose ranges from 65 to 110 mg/dL (3.6 to 6.2 mmol/L).[39] Although it is unknown at what level of hypoglycemia neonatal foals develop clinical manifestations; the authors decided to follow Hollis definition of hypoglycemia (< 75 mg/dL [< 4.2 mmol/L]) for this study.[16] Hypoglycemia has been reported to occur in 29% of critically ill neonatal foals.[16] This is because neonatal foals are born with very low fat and glycogen stores, therefore any illness that interferes with getting adequate nutrition can result in hypoglycemia.[40] Hypoglycemia in neonatal foals was associated with nonsurvival to hospital discharge.[16] Furthermore, extreme hypoglycemia defined as blood glucose below 50 mg/dL (< 2.8 mmol/L) was associated with sepsis, a positive blood culture and nonsurvival compared to animals with higher blood glucose concentrations.[17] In the current study, the majority of neonatal foals were diagnosed with sepsis (N = 25/35), of which 17 had severe hypoglycemia. Thirteen (57%) of 23 foals with severe hypoglycemia died or were euthanized. Similar to other reports, foals from our study with severe liver disease such as those with Tizzer's developed severe hypoglycemia.[33,41]

Hypoglycemia is less common in adult horses compared to neonatal foals and has been associated with liver failure, abdominal disease, critical illness, and neoplasia (hepatic and renal).[17,18,42] In our study, the most common causes associated with hypoglycemia in adult horses included liver and gastrointestinal disease (33% each), followed by hypertriglyceridemia (18%). Hypoglycemia is the most common adverse effect of insulin treatment in humans with type 1 diabetes and insulin-dependent type 2 diabetes.[43,44] Hypoglycemia and seizures as the result of insulin therapy were also observed in our study (N = 4/8) and corrected with IV dextrose administration and adjustment of insulin therapy. Renal adenocarcinoma, renal anaplastic carcinoma, papillary renal adenoma, hepatocellular carcinoma, cholangiocarcinoma, peritoneal mesothelioma, and gastrointestinal stromal tumor have been associated with hypoglycemia and presumed to be associated with the release of insulin growth-like factor.[17,18,42,45–49] In these horses, BG concentration was usually low ranging from 13 to 65 mg/dL (0.7 to 3.6 mmol/L). Descriptions of altered mentation and seizures were not always reported.[18] In our horses, intermittent to persistent hypoglycemia ranging from 13 to 56 mg/dL (0.7 to 3.1 mmol/L) was observed. All of these horses had neurologic abnormalities (obtundation N = 6/7, seizures N = 4/7). Possible causes for hypoglycemia in these horses could have included intermittent or persistent secretion of insulin growth-like factor by non-islet cell tumors (non-islet cell tumor-induced hypoglycemia [NICTH]) and paraneoplastic hypoglycemia as described in humans.[50–53] Concentrations of insulin-growth factors I and II for the documentation of NICTH was not performed in these horses.[53]

Electroencephalography reflects the metabolic state of the brain.[3] Hypoglycemic episodes have been associated with EEG changes that could serve as predictors of severe hypoglycemia in humans.[54,55] The earliest abnormalities reported in mice included an increase in the power of the delta and theta band relative to the power in the alpha band.[3] Reported EEG alterations include a decrease in alpha frequencies and an increase in delta frequencies following with gradual aggravation in EEG alterations as hypoglycemia progresses.[55] Alpha/theta ratio is a sensitive parameter for detecting changes in EEG during hypoglycemia.[55] Paroxysmal discharges supportive of epileptic activity consist of sharp waves (70-200 milliseconds) and spikes (< 70 ms) and waves.[56] These discharges were observed in some horses despite the lack of obvious clinical manifestations of seizures supporting subclinical paroxysmal (epileptic) activity. However, altered behavior and mentation could be manifestations of paroxysmal activity. As an example, one mare on which an IV dextrose infusion was discontinued, paroxysmal activity was observed prior to any clinical

manifestations of seizures (Figure 2). Continuous EEG recording in this mare showed an increase in paroxysmal activity that became generalized. Concurrently, the mare developed clinical manifestations of seizure activity which subsided when IV dextrose infusion was resumed. In humans, a topographic maximum of slow frequencies is found in the frontal cortex at glucose levels of 50 to 60 mg/dL.[2,55] During more profound hypoglycemia (30 to 50 mg/dL [1.7 to 2.8 mmol/L]) there is a shift toward the posterior parts of the brain, and overall changes in the EEG are more pronounced in the parietal-occipital and temporal regions at blood glucose levels of 36 mg/dL (2 mmol/L).[2,55] Generalized slowing is followed by spikes as the severity of hypoglycemia worsens.[3] Alterations of the EEG during hypoglycemia might not be identical in all patients but tend to be reproducible in each patient.[57] Similarly, EEG alterations in this study included slow frequencies mainly in the occipital and parietal cortical areas in all horses (N = 8/8) and in some horses (N = 5/8) slowing in the frontal cortex was also observed. Alterations in the occipital (visual cortex) and parietal (closest region to temporal-auditory cortex) cortical function observed on EEG might explain the observed intermittent blindness and deafness in these horses. Furthermore, blindness, deafness, and EEG alterations appeared to resolve upon IV dextrose administration (e.g. Mare in Figure 2). These 8 horses had severe hypoglycemia (BG mean 29.6 [1.6 mmol/L], SD 17.6 mg/dL [1 mmol/L]). Generalized slowing on EEG was followed by spikes as hypoglycemia worsened. Five of these 8 horses had a CSF-glucose of 0 mg/dL.

In conclusion, presumed neuroglycopenia manifested as severe altered state of consciousness and seizures can occur in horses with severe hypoglycemia. Disorientation and intermittent blindness and deafness of cortical origin sometimes occurred. Hypoglycemia was more common in neonatal foals than in older foals and adults, and commonly associated with sepsis. In adult horses, severe liver and/or gastrointestinal disease were the most common causes of hypoglycemia. Neoplasia must be considered as a possible cause of intermittent hypoglycemia in adult horses. Caution must be taken when administering insulin therapy to avoid insulin-induced hypoglycemia. A blood glucose concentration cut-off value of < 42 mg/dL (< 2.3 mmol/L) was associated with severe neurologic dysfunction and hypoglycorrhachia in support of presumed neuroglycopenia. Hypoglycemia-induced EEG alterations were observed in the occipital and parietal cortical regions in horses with severe hypoglycemia. These EEG alterations became more generalized if hypoglycemia was not treated promptly. This study also highlights the importance of performing EEG for the investigation of abnormal cortical activity such as epileptic discharges despite the lack of obvious clinical manifestations. Future studies should include postmortem evaluation of the brain to document tissue glucose concentration, and type, extent, and severity of neuronal injury as the result of severe hypoglycemia.

[Correction added after first online publication 31 August 2018: Last sentence removed.]

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CONFLICTS OF INTEREST DECLARATION

Authors declare no conflict of interest

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label used of antimicrobials

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved animal use and care protocol by UCD and owner consent.

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