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Semilobar Holoprosencephaly in a Morgan Horse

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A 6½-month-old Morgan filly was examined because of a history of abnormal behavior, teeth grinding, hypothermia, and electrolyte disturbances when weaned. She was from a breeding farm with several other Morgan horses. The 11-year-old dam had been purchased the year before as a proven broodmare, which had several previous foals. Breeding, gestation, and birth of this foal were normal. She was raised with 4 other mares and their offspring on pasture with free access to shelter in an open barn. Supplementary feeding consisted of oats and timothy hay. The owners reported that the foal showed unusual behavior, such as lack of apprehension of people, lack of distress from maternal separation, and a higher activity level than other foals of the same age. The foal extensively chewed the dam's tail and mane, masticated oats slowly with rapid jaw movements without actually swallowing them, and ground her teeth. She frequently nibbled the handler's clothes without biting, ate pebbles, and played with the salt block in the paddock. At 4½ months of age, she was treated for suspected gastroduodenal ulcers and weaned. The referring veterinarian examined her 5 days after weaning because of dull demeanor and excessive teeth grinding. The foal was in thin body condition, hypothermic (37°C, 98.6°F), and tachycardic (60 beats per minute [bpm]) and had decreased borborygmi. Major abnormalities on serum biochemistry were severe hypernatremia (166 mmol/L; reference range 136–144 mmol/L) and hyperchloremia (128 mmol/L; reference range 94–104 mmol/L), azotemia (urea, 11.3 mmol/L; reference range 4.2–8.9 mmol/L), and hyperfibrinogenemia (5.2 g/L, reference range 1.6–2.9 g/L). The only abnormality on the CBC was hemoconcentration (PCV, 0.57 L/L; reference range 0.28–0.44 L/L). The foal was treated with penicillin procaine G[a] (20,000 IU/kg [9072 IU/lb] IM q12h) and rifampin[b] (5 mg/kg [2.7 mg/lb] PO q8h). The next day the tachycardia worsened (120 bpm) and the foal was estimated to be 5–8% dehydrated. IV fluid therapy with lactated Ringer solution[c] (LRS) was initiated, and the antibiotic was changed to ceftiofur[d] (2 mg/kg [0.91 mg/lb] IV q12h). The foal and dam were rejoined, and the foal's clinical status improved with resumption of nursing. Serial laboratory testing showed persistent hypernatremia (160 mmol/L) and hyperchloremia (123 mmol/L), azotemia (urea 11.3 mmol/L and creatinine 168 umol/L; reference range 80–130 μmol/L), hyperglycemia (8.7 mmol/L; reference range 3.7–6.7 mmol/L), high aspartate aminotranferase activity (662 U/L; reference range 259–595 U/L), and high creatine kinase (CK) activity (1,196 U/L; reference range 108–430 U/L). The foal's condition improved and IV fluids were discontinued. Ceftiofur administration was discontinued and trimethoprim-sulfamethoxazole[e] (25 mg/kg [11.3 mg/lb] PO q12h) was administered for 3 days. During the next month the foal was stable but the abnormal behavior persisted. She was weaned again, and within 5 days marked behavior changes such as circling, throwing the head around compulsively, and severe hind-end shivering recurred. At examination, the foal was dull, tachycardic (60 bpm), was hypothermic (33.6°C, 92.5°F), had dark red mucous membranes, and was estimated to be 5% dehydrated. Laboratory findings were similar to those of the previous tests except for high fibrinogen (7.1 g/L). The foal was again rejoined with the dam, treated with intramuscular penicillin, and referred.

At examination at the Ontario Veterinary College, the foal was 6½ months old, quiet but alert and responsive, and in moderate body condition (151 kg, 333 lb). Cranial nerve examination revealed normal mental status, but the pupils were enlarged and the pupillary reflex was delayed. Laboratory assessment showed the same abnormalities previously detected, including hypernatremia (151 mmol/L), hyperchloremia (112 mmol/L), hyperglycemia (7.6 mmol/L), high CK activity (526 U/L), high alkaline phosphatase activity (554 U/L; reference range 119–329 U/L), high glutamic dehydrogenase activity (21 U/L; reference range 1–7 U/L), high haptoglobin (1.91 g/L; reference range 0.1–1.7 g/L), hypobilirubinemia (total bilirubin, 13 umol/L; reference range 21–57 umol/L; free bilirubin, 11 umol/L; reference range 18–55 umol/L), hypercholesterolemia (3.18 mmol/L; reference range 1.70–2.70 mmol/L), and hyperfibrinogenemia (4.0 g/L). Food was withheld overnight to allow gastroscopy. Teeth grinding and excessive chewing, especially of the salt block, were noted. Overnight the foal also played with the water bucket for prolonged periods of time. The next morning she was lying in a sternal position. Stimulation to stand caused her to collapse into lateral recumbency with myoclonic spasms of the limbs and neck. Seizure activity recurred minutes later while she was repositioned into sternal recumbency. Serum ammonia levels were below limit of detection (10 mmol/L). Mild hypernatremia (147 mmol/L) and hyperchloremia (110 mmol/L)

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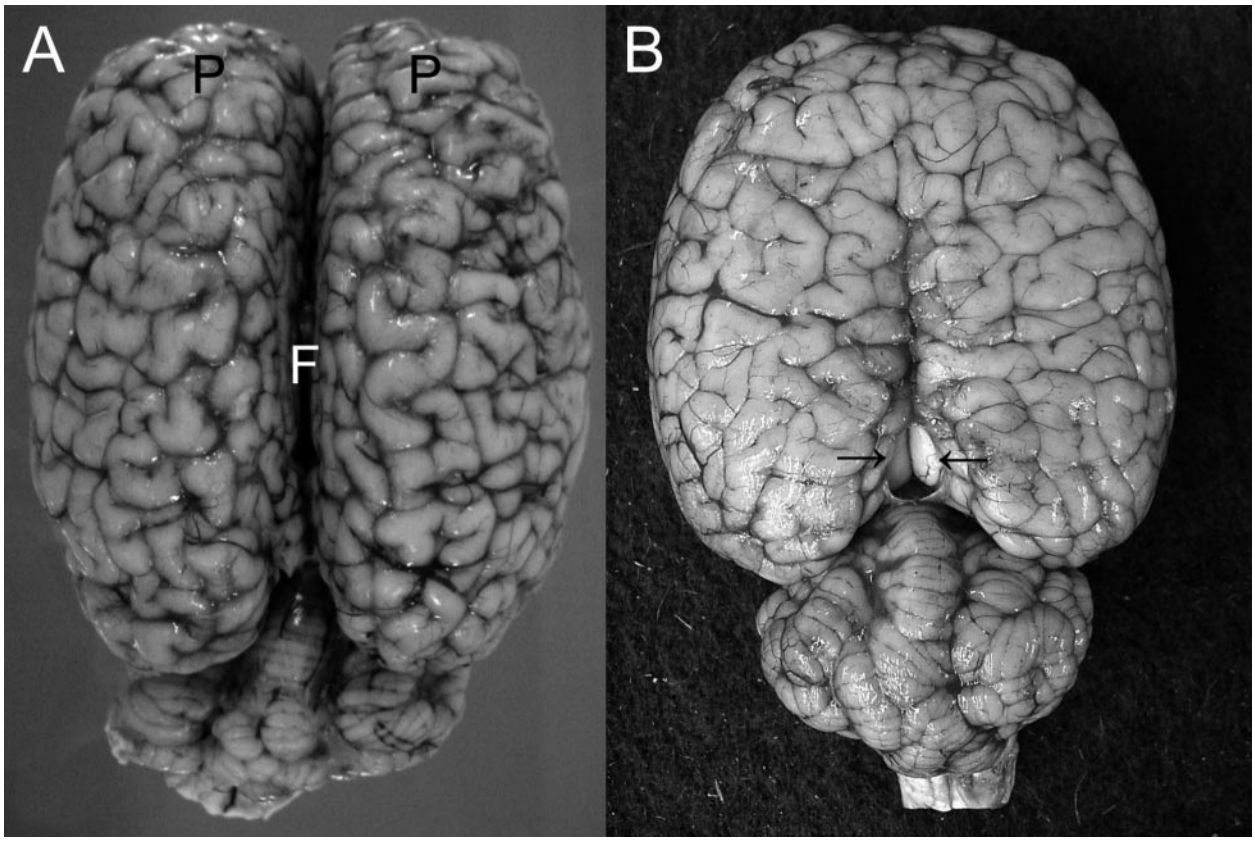

Fig 1. Dorsal aspect of the brain of a control horse **(A)** and the horse with semilobar holoprosencephaly **(B)**. **(A)** Longitudinal cerebral fissure (F); rostral poles of the cerebral hemispheres (P). **(B)** There is no separation of the rostral components of the cerebrum, which forms a single, noncleaved structure. The longitudinal cerebral fissure is absent on the rostral third of the brain and inconspicuous along the middle third of the brain. An interhemispheric cleft is on the caudal part of the brain at the level of the rostral colliculi (arrows), which are readily visible through this small space. There is also diffuse flattening of the cerebral gyri.

were present. Diazepam[f] (10 mg IV) was administered to decrease seizure activity and to allow placement of an IV catheter. Seizure activity recurred 5 minutes later. Unilateral intranasal oxygen (100%, 10 L/min) was administered to support oxygenation. A modified neurologic examination was performed with the foal in right lateral recumbency. She could be aroused but was unaware of her surroundings. Twice she attempted to assume sternal position. Her left eye was open and the pupil dilated with a normal response to bright light. Her right eye was closed, and when attempting to open it she started to struggle and show a rhythmic ventral nod of the head and neck, which progressed to a generalized tonic seizure with marked head ventroflexion. The neurologic examination could not be completed because of a postictal phase. The foal underwent more than 8 generalized seizures within 1 hour and was euthanized. Cerebrospinal fluid (CSF) was sampled from the atlantooccipital space, and urine was obtained by catheterization within 5 minutes of euthanasia. The CSF was xanthochromic and slightly cloudy and had an increased nucleated cell count (0.006×10^9/L; reference range 0–0.005×10^9/L) and red blood cell count (1.68×10^9/L; reference range 0–0.320×10^9/L). Differential count of the CSF (200 cells) revealed 3% neutrophils, 39% lymphocytes, 46% mononuclear cells, and 12% macrophages consistent with normal CSF with iatrogenic hemorrhage.[1] No abnormalities were noted on urinalysis.

At postmortem examination the dorsal surface of the brain was diffusely flattened. The brain was easily removed after the optic nerves were sectioned because there were no olfactory bulbs to free from the cribiform plate. The longitudinal cerebral fissure was absent on the rostral third of the brain and inconspicuous along the middle third of the brain (Fig 1). An interhemispheric cleft measuring approximately 2 cm in diameter was on the caudal part of the brain at the level of the rostral colliculi, which were readily visible through this small space. No separation of the rostral components of the cerebrum was noted. Instead, they formed a single, noncleaved, flat structure. The cerebral gyri were flattened over the entire dorsal surface of the brain. The olfactory bulbs and olfactory peduncles were absent (olfactory aplasia) (Fig 2). The lateral rhinal sulcus and adjacent gray matter of the olfactory peduncles were continuous from one piriform lobe to the other across the midline rostral to the optic chiasm. The brain was fixed in totum for approximately 1 week in a single jar with approximately 20 vol of 10% formalin. No other tissues were fixed in the glass container so as to avoid compression artifacts on the brain. After this period, the fixed brain was cut transversely at approximately 5-mm intervals. Rostral

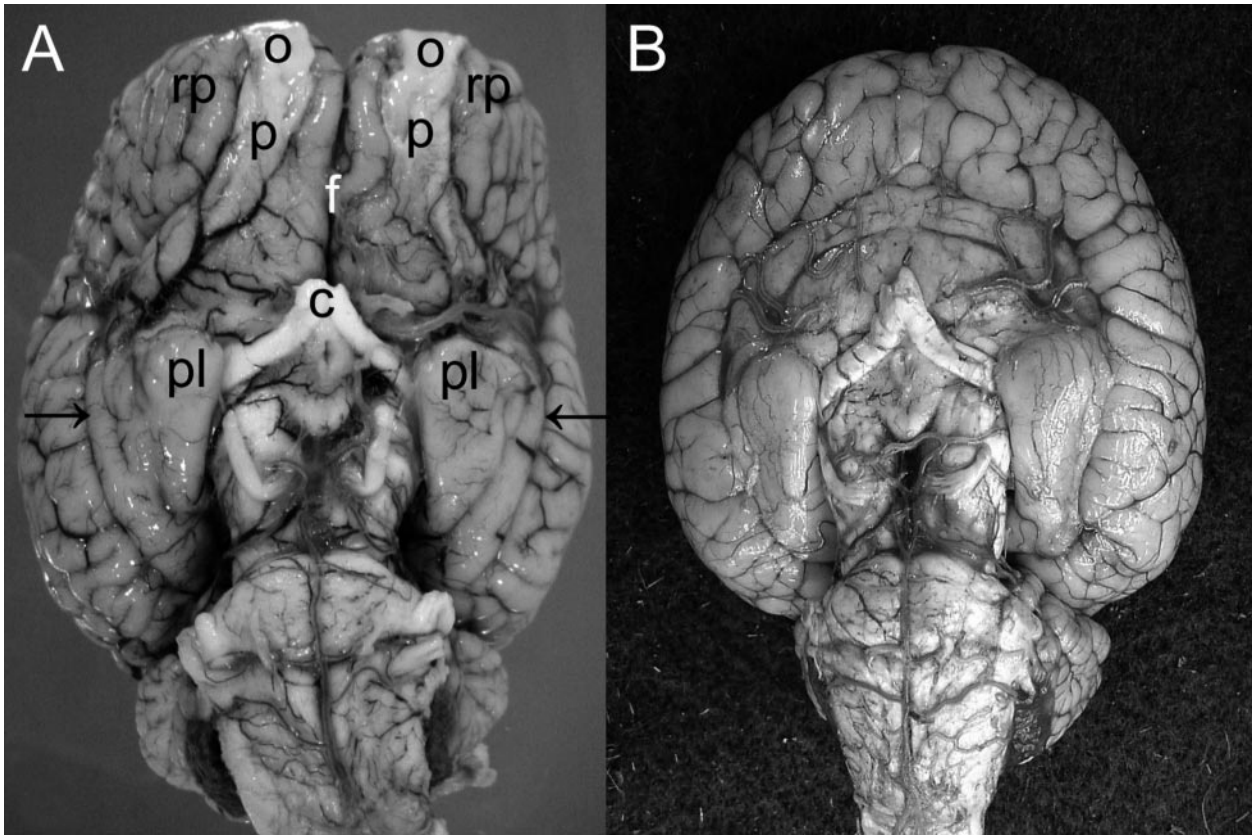

Fig 2. Ventral aspect of the brain of a control horse **(A)** and the horse with semilobar holoprosencephaly **(B)**. **(A)** Olfactory bulbs (o); olfactory peduncles (p); lateral rhinal sulci (arrows); piriform lobes (pl); optic chiasm (c); longitudinal cerebral fissure (f); rostral poles of the cerebral hemispheres (rp). **(B)** The olfactory bulbs as well as the olfactory peduncles are absent (olfactory aplasia). The lateral rhinal sulcus and adjacent gray matter of the olfactory peduncles are continuous from one piriform lobe to the other across the midline rostral to the optic chiasm. Separation of the rostral components of the cerebrum is absent and forms a single, noncleaved structure as seen in Figure 1.

transverse sections of the brain showed no evidence of separation in the cerebrum (Fig 3). In the first 3 transverse sections, the right and left cerebral cortical surfaces were continuous without any longitudinal cerebral fissure. The longitudinal cerebral fissure was first identified at the fourth serial section of the forebrain. From this level caudally, a longitudinal cerebral fissure was present along the midline of the brain. Rostrally, the lateral ventricles did not extend into the nonseparated portion of the cerebrum and were continuous with each other to the level of the caudate nuclei. Caudally, the lateral ventricles were separate in each temporal and occipital lobe. Dorsally, no septum pellucidum was between the ventricles (Fig 4). The remainder of the ventricular septum was normal. The caudate nuclei on each side were formed ventrally. No gross lesions were identified in the brainstem and cerebellum. The cribriform plates of the ethmoid bone were absent (Fig 5). Multiple postmortem radiographs of the skull (ventrodorsal, dorsoventral, and right and left lateral views) did not reveal abnormalities. Multiple transverse sections of the head from the level of the frontal sinuses rostrally to the level of the nostrils did not show gross changes. No other craniofacial malformations were identified at postmortem examination. No morphologic changes were identified in the pituitary gland and adrenal glands compared with those of a foal of the same age and sex. No histologic changes were identified in multiple sections of brain. The diagnosis was semilobar holoprosencephaly.

Holoprosencephaly (HPE) is a disorder of forebrain development characterized by failure of the brain to separate into hemispheres during early development.[2] HPE is the most common anomaly of the face and brain in humans and a significant cause of abortion, with a prevalence of 40 in 10,000 pregnancies.[2] The condition has been reported in humans, cattle,[3] sheep,[4] pigs,[5] monkeys,[6] and recently dogs.[7]

Semilobar HPE in this foal was diagnosed by the original classification system that includes alobar, semilobar, and lobar forms of HPE.[8] In the present foal, the abnormalities of the skull were restricted to the absence of the cribriform plates of the ethmoid bone.

Interference with forebrain development and ventral patterning of the most rostral part of the neural plate is the main feature of HPE.[2] Most human cases are considered sporadic, although predisposing factors and genetic etiologies have been identified. Diabetes mellitus in women is a recognized risk factor.[9] Identified teratogens include ethyl alcohol, retinoic acid, cigarette smoking, and steroid alkaloids.[4,10] In sheep, ingestion of the steroid alkaloids of the desert corn lily (*Veratrum californicum*) during early ges-

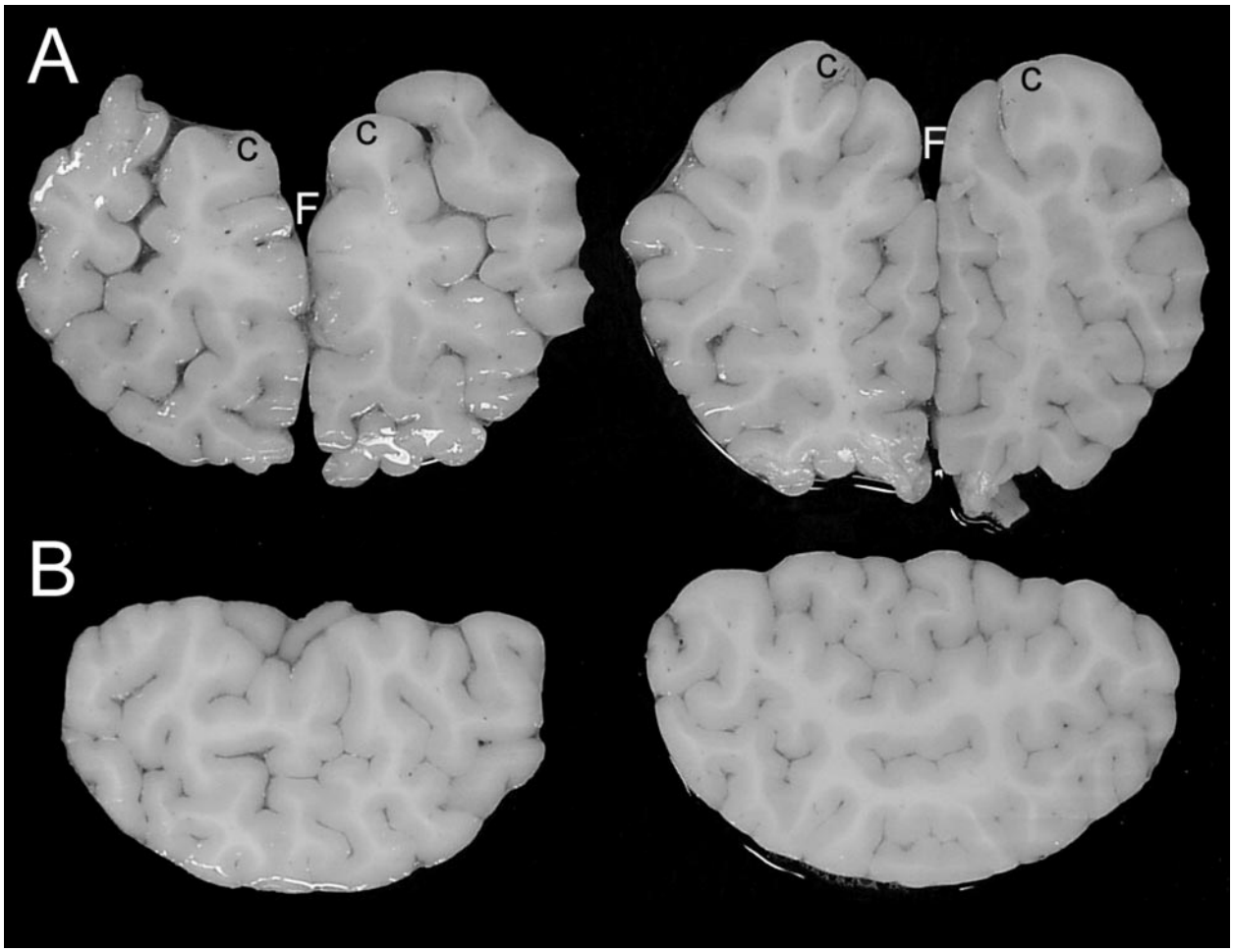

Fig 3. Rostral transverse sections of the brain of a control horse **(A)** and the horse with semilobar holoprosencephaly **(B)**. **(A)** Longitudinal cerebral fissure (F); right and left cerebral cortical surfaces (c). **(B)** No evidence of separation is in the cerebrum. The right and the left cerebral cortical surfaces are continuous with each other. The longitudinal cerebral fissure is absent.

tation is thought to induce HPE accompanied by cyclopean malformation.[4] The mechanism of action is postulated to be interference with the response to sonic hedgehog (SHH) stimuli that is important in ventral patterning of the neural plate.[11] Less than 15% of human cases of HPE are attributed to monogenetic mutations such as SHH genes.[11] Familial predisposition because of dominant inheritance with reduced penetrance, polygenetic inheritance, or undetermined monogenic inheritance has been reported.[11,12] The cause of HPE in the foal reported here could not be determined. Hereditary disorders such as congenital nuclear cataracts,[13] neuroaxonal dystrophy of the accessory cuneate nucleus,[14] and persistent hyperammonemia[15] have been suggested to occur more often in Morgan horses because of a common single origin by the founding stallion, ''Figure'' (1789–1821).[16] However, no historical familiar predisposition was identified in this foal, and genetic studies of the foal, dam, or stallion were not performed. Reporting of similar cases in this breed might warrant future genetic investigation.

The clinical findings in this foal included lack of apprehension, hyperactivity, pica, teeth grinding, excessive nibbling, and abnormal temperature regulation. Depressed demeanor, dehydration, hypernatremia, and hyperchloremia were noted postweaning. Although the reference ranges provided were derived from mature Standardbred horses,[g] serum sodium and chloride concentrations are similar in adult and neonatal horses.[17] However, serum glucose is typically higher in foals than in adult horses and may therefore be normal for a foal of this age.[17] Hypernatremia and hyperchloremia have been noted in dogs with HPE[7] and are very common in humans with HPE.[18] Nonseparation of hypothalamic nuclei, referred to as hypothalamic nonseparation, is the cause in humans, and the severity correlates with the degree of nonseparation.[18] Nonseparation of the hypothalamus likely interferes with the normal development of thermostats and osmostats and other thirst-regulating mechanisms of the hypothalamus. Clinical deterioration and peak electrolyte abnormalities were closely correlated with weaning. The foal likely was able to maintain normal hydration status and homeostasis as long as she received mare's milk, but when weaned she did not have appropriate thirst sensation and became dehydrated with hypodipsic hypernatremia and hyperchloremia. This is similar to the sin-

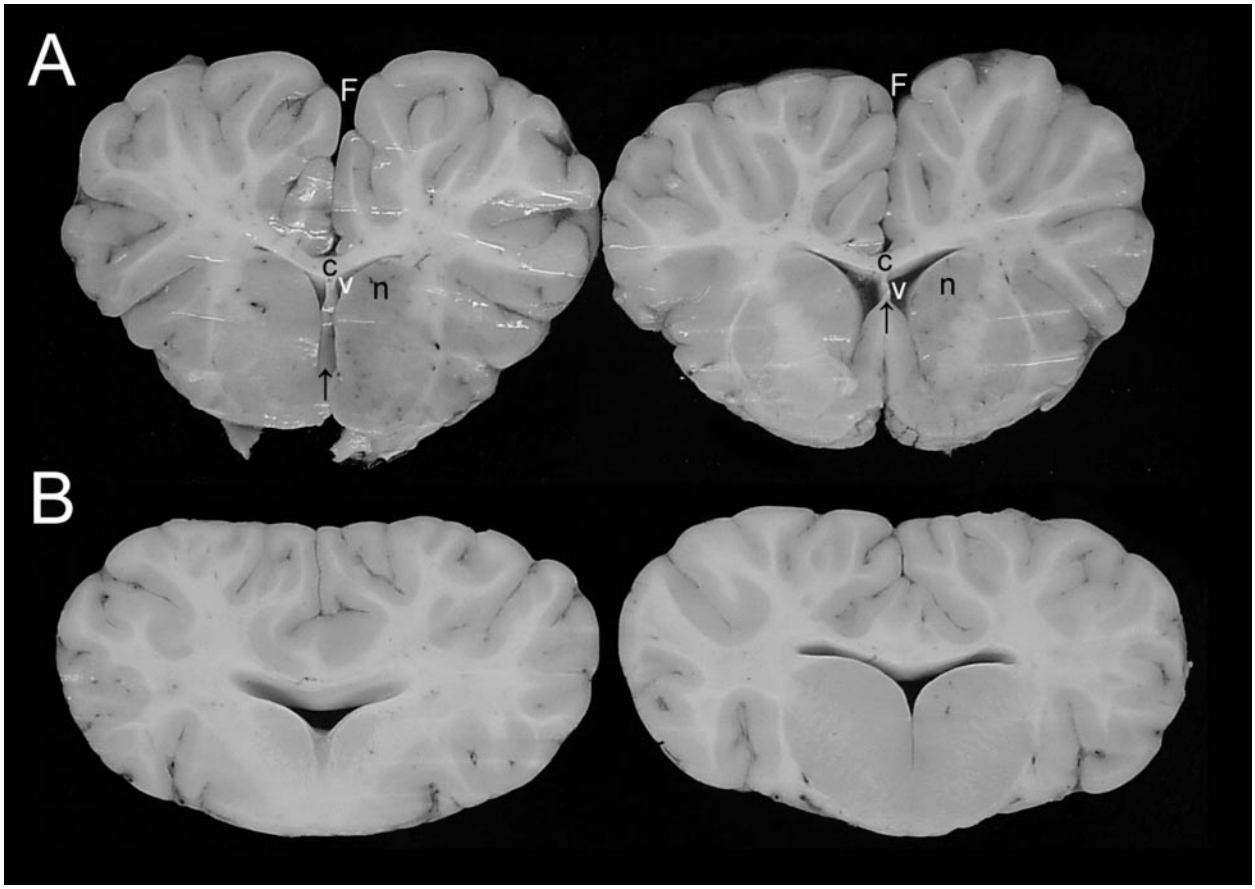

Fig 4. Rostral transverse sections of the brain of a control horse **(A)** and the horse with semilobar holoprosencephaly **(B)**. **(A)** Longitudinal cerebral fissure (F); corpus callosum (c); lateral ventricles (v); caudate nuclei (n); septum pellucidum (arrows). **(B)** A partial longitudinal cerebral fissure is present along the midline of the brain and does not meet the corpus callosum. The lateral ventricles do not extend into the nonseparated portion of the cerebrum and are continuous with each other over the caudate nuclei. No septum pellucidum is between the ventricles. The caudate nuclei on each side of the brain are continuous ventrally.

gle report of lobar HPE–hypodipsic hypernatremia in a dog that maintained normal electrolyte homeostasis only if water was mixed with food.[7] The cause of the electrolyte abnormalities is likely lack or malfunction of hypothalamic osmostats. In turn, this results in inappropriate stimulation of antidiuretic hormone release from the pituitary gland and an imbalance between renal water conservation mechanisms and blood sodium concentration.

Normal brain size or microcephaly has been reported in humans with HPE.[18] Normal brain size in humans is often relative and related to hydrocephalus caused by a dorsal cyst.[18] Locomotion of this foal appeared normal, although the limited time of hospitalization combined with rapid deterioration did not allow thorough gait evaluation. This is in contrast to findings in humans, where mobility and upper-extremity function is often severely affected.[18] This may reflect differences in the neuroanatomic pathways controlling locomotion in horses and humans. Minimal cerebral regulation is applied in equine locomotion, whereas human locomotion is largely regulated by the cerebral cortex. Hyperactivity, as exhibited in this foal, was likely caused by the abnormal cerebral cortices, which in children has been associated with attention deficit hyperactivity disorder.[19] Jaw muscle twitching, the so-called chewing-gum fits, are commonly observed in neonatal foals with cerebral disorders.[20] The oral proprioceptive deficits noted in this foal were likely caused by disturbances in similar regions of the cerebral cortex. Seizures commonly occur in humans with HPE,[18] and difficult-to-control seizures correlate with cortical malformations.[18] The owner of this foal noted seizure-like activity on 1 occasion before presentation at our hospital. Electrolyte measurements at the time of seizure activity in the hospital revealed only minor electrolyte abnormalities. Blood pressure and serum glucose were not measured, and it is possible that hypoglycemia caused by withholding feed overnight, with or without hypotension, predisposed the foal to seizures.

Footnotes

[a] Depocillin, Intervet Canada Ltd, Whitby, ON, Canada
[b] Rifadin, Aventis Pharma Inc, Laval, QC, Canada
[c] Lactated Ringer's Injection, Baxter Corporation, Mississauga, ON, Canada
[d] Excenel, Pharmacia Animal Health, Orangeville, ON, Canada

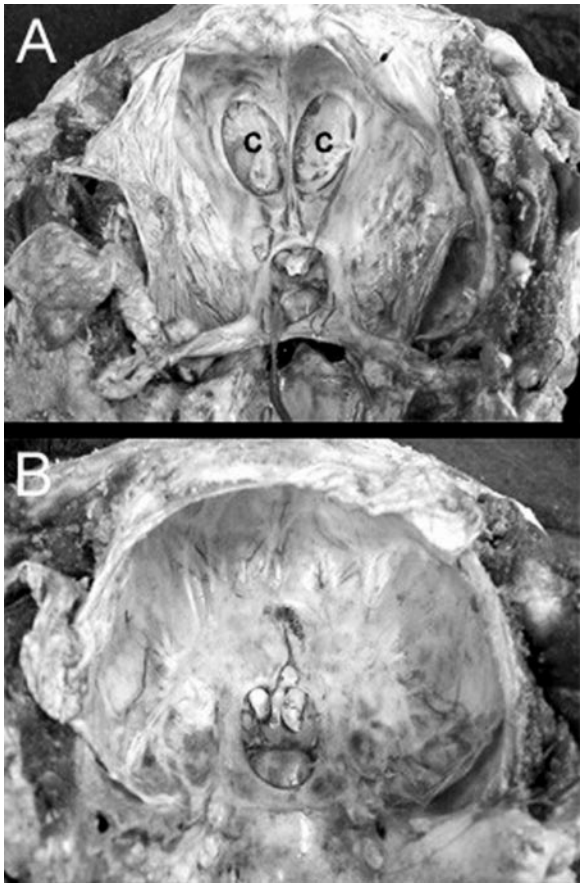

Fig 5. Cranial cavity of a control horse **(A)** and the horse with holoprosencephaly **(B)**. **(A)** Cribriform plates of the ethmoid bone (c). **(B)** The cribriform plates of the ethmoid bone are absent.

[e] Novo-Trimel DS, Novopharm, Toronto, ON, Canada
[f] Diazepam, SABEX 2002 Inc, Boucherville, QC, Canada
[g] Animal Health Laboratory, University of Guelph, Guelph, ON, Canada

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