Case Report

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Transient diabetes mellitus in a neonatal Thoroughbred foal

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Abstract

Objective – To describe the clinical presentation, treatment, and outcome of a neonatal foal diagnosed with transient Type 1 diabetes mellitus.

Case Summary – A 3-day-old Thoroughbred foal presented with a 24-hour history of diarrhea and depression. Coronavirus particles were observed in the feces via electron microscopy. During hospitalization the foal developed hyperglycemia concomitantly with low insulin concentration and an adequate response to exogenous insulin therapy supported a diagnosis of Type 1 diabetes mellitus. The foal required SC insulin for 26 days, but developed complications associated with insulin therapy that resolved with appropriate care. On follow up assessment the foal was found to be a healthy euglycemic animal with normal insulin concentration at 11 months of age.

New or Unique Information Provided – To our knowledge this is the first report of Type 1 diabetes in this age group and the first report of transient neonatal diabetes mellitus in horses. Type 1 diabetes mellitus should be considered a differential diagnosis for hyperglycemia in equine neonates and that it can be transient and managed successfully.

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A 3-day-old Thoroughbred male foal presented with a 24-hour history of diarrhea and depression. The foal was born from a multiparous healthy mare. Pregnancy was of normal duration; delivery was vaginal, unassisted, and normal as judged by the farm manager. Previous foals from the mare had been healthy. The foal was clinically normal for the first 48 hours of life when it developed diarrhea. The referring veterinarian administered ceftiofur sodium, flunixin meglumine, metronidazole, clioquinol, IV immunoglobulins concentrate, and 3 L of IV fluids (lactated Ringer's solution [LRS]). There were no other sick animals on the farm at the time but there had been neonates with clostridial diarrhea in the past.

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On presentation to the University of Illinois Veterinary Teaching Hospital, the foal was ambulatory, mildly depressed, and responsive. Temperature was 38.1°C (100.6°F). Respiratory rate was 60/min with normal respiratory pattern and sounds ausculted in the trachea and thorax bilaterally. Heart rate was 100/min with regular rhythm and no murmurs. Mucous membranes were pink and moist with a capillary refill time of 2 seconds. The external umbilicus was normal to palpation. Pulses palpated at the greater metatarsal and median arteries were mildy weak. There was a small cool hematoma on the left jugular vein. Eyes and eyelids were normal and increased synovial effusion was not appreciated in any joints. The ribs palpated normally, the foal had normal suckle reflex, was witnessed to nurse normally, presented moderate carpi valgi, was sound at the walk, and had no difficulty rising. The angular limb deformity could be partially corrected manually and resolved progressively without surgical intervention. Feces were watery to slightly mucoid.

Initial CBC showed mild anemia (PCV 26.5%; reference interval 32–53%), leukopenia (5.18×10^9/L; reference interval $5.5 - 12 \times 10^9$/L) characterized by a mild left shift (0.16×10^9/L; reference interval $< 0.1 \times 10^9$/L), and lymphopenia (0.41×10^9/L; reference interval

$1.5 - 5.0 \times 10^9$/L). Rare toxic neutrophils and Dohle bodies were seen and fibrinogen was mildly increased 14.7 μmol/L (500 mg/dL) (reference interval 2.94–11.76 μmol/L) (100–400 mg/dL).

Serum chemistry showed normal renal values, hyponatremia (125 mmol/L; reference interval 137–148 mmol/L), hyperglycemia (14.26 mmol/L [257 mg/dL]; reference interval 3.94–5.55 mmol/L [71–100 mg/dL]), mildly decreased HCO_3 (24.8 mmol/dL; reference interval 28–38 mmol/L), mildly increased anion gap (15.7 mmol/L; reference interval 5–15 mmol/L), and increased creatine kinase at 3136 U/L (reference interval 120–350 U/L).

Urine specific gravity was high (1.030). A urinalysis was not obtained. Immunoglobulin G concentration was measured via a membrane based ELISA[a] and was >800 mg/dL.

A fecal sample was submitted for *Clostridium difficile* toxins A and B ELISA, anaerobic culture for detection of *Clostridium perfringens*, electron microscopy for detection of rotavirus and coronavirus particles, fecal flotation, and acid fast staining. Three samples from 3 consecutive days were submitted for *Salmonella* culture and PCR. Testing was negative with exception of electron microscopy where coronavirus particles were observed. *Eimeria* (0.6 eggs/g) and strongyles (28.4 egg/g) were detected in a Wisconsin double sugar flotation and were of uncertain significance. Blood was obtained in a sterile fashion from the IV catheter immediately after placement and aerobic and anaerobic culture yielded no growth.

The foal was given 2.5 L of LRS[b] IV over the first 2 hours of hospitalization as fluid deficits were considered to be approximately 5% and the estimated weight 50 kg. A high specific gravity in a foal usually suggests dehydration with intact renal tubular function; although in this case glucosuria was likely a component of the increase in the specific gravity. After the initial fluid therapy the foal was given boluses of LRS (500 mL, IV, q 4 h) until renal values and plasma electrolytes were rechecked after 20 hours. Physical examinations, PCV, and total plasma protein measurements were performed every 6 hours. Fluid therapy was then adjusted to provide maintenance requirements and to balance losses through the feces while considering milk intake. The amount (500–750 mL, q 3–6 h) and type of fluids were chosen based on the plasma electrolytes, hydration, and acid-base status. Fluids were supplemented with sodium bicarbonate or sodium chloride. The supplementation was mainly due to hyponatremia that was likely caused by a combination of losses due to diarrhea and hyperosmolar hyponatremia due to the hyperglycemia. Sodium concentration increased slowly and was 134 mEq/L on Day 9 of hospitalization. Fluid therapy was continued for 12 days after which the diarrhea resolved and fluids were discontinued.

Metronidazole[c] (15 mg/kg, PO, q 8 h) therapy was initiated at admission due to the diarrhea and the history of clostridial infections in the farm. Based on the clinical and clinico-pathological findings broad-spectrum antimicrobial therapy was not indicated.

Omeprazole[d] (4 mg/kg, PO, q 24 h) was administered. The umbilicus was dipped with 0.5% chlorhexidine[e] every 6 hours initially. Oral vitamin E[f] (20 U/kg, PO, q 24 h) and vitamin E/selenium[g] injection (1.36 IU of vitamin E and 0.05 mg/kg of selenium IM twice) were administered. Nutritional myodegeneration was considered unlikely but was a differential diagnosis for the increased creatine kinase. There was no history of nutritional myodegeneration in this farm.

The glycemia, monitored every 6 hours, increased progressively over the first 24 hours of hospitalization to values over 27.75 mmol/L (500 mg/dL). Triglyceride (TGC) concentration was 6.52 mmol/L (577 mg/dL) on Day 4 (reference interval <2.26 mmol/L [<200 mg/dL]), 4.1 mmol/L (363 mg/dL) on Day 5, 7.33 mmol/L (649 mg/dL) on Day 6, 2.06 mmol/L (183 mg/dL) on Day 8, 4.4 mmol/L (390 mg/dL) on Day 11, and 1.13 mmol/L (100 mg/dL) on Day 12. Insulin concentration measured from a sample collected on Day 5, before insulin administration was begun, was low (8.05 pmol/L [1.16 μU/mL]) despite a BG of 28.96 mmol/L (522 mg/dL). Amylase and lipase measured on Day 11, as markers of pancreatic injury, were <3 U/L (reference interval 14–35 U/L) and 24 U/L (reference interval 23–87 U/L), respectively. Two abdominal ultrasounds performed during the first week of hospitalization showed no significant abnormalities.

Administration of enteral nutrition (milk replacer = 2% cow's milk, no glucose added) was started due to hyperlipemia on Day 4 of hospitalization and continued until Day 7.

Because of the continuing and worsening hyperglycemia (Figure 1), Protamine Zinc Insulin[h] (PZI) was administered SC (12–24 U, 0.2–0.4 U/kg) starting on Day 6. The hyperglycemia was controlled with the above-mentioned dose of PZI (Figure 1). The SC injections of PZI were administered twice a day initially and the intervals were prolonged progressively to maintain a controlled glycemia.

One week after presentation, the CBC showed a decreased PCV (23.3%; reference interval 32–53%), normal WBC count, normal fibrinogen (8.82 μmol/L [300 mg/dL]) and lymphopenia (0.8×10^9/L).

To further characterize insulin sensitivity and investigate if response to regular insulin would be more predictable, regular insulin[i] (15 U, approx 0.25 U/kg, IV) was administered on Day 9 and glycemia measured

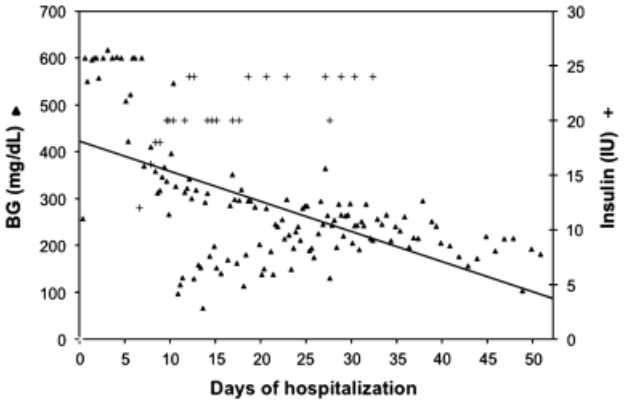

Figure 1: Glycemia and insulin administration during hospitalization. Glycemia was measured initially every 6 hours and the frequency was decreased progressively.

hourly. It was thought that obtaining a glucose curve could help guide and monitor the effects of therapy. Blood glucose was 20.92 mmol/L (377 mg/dL) when the insulin was administered. The foal developed labored breathing and an increased temperature 39.2°C (102.6°F) almost immediately after the insulin was given. The BG decreased to 9.6 mmol/L (173 mg/dL) 1 hour after insulin administration, to 5.21 mmol/L (94 mg/dL) 2 hours after insulin administration, and increased progressively after that. The foal was given flunixin meglumine[j] (1.1 mg/kg, IV once) and monitored closely. The fever and increased respiratory rate persisted for 6 hours. The adverse reaction occurred previous to the lowest concentration of glucose and persisted for longer than the drop in BG. Therefore it was considered unlikely that the increased temperature and respiratory effort was due to changes in glycemia and an adverse reaction to regular insulin was suspected. Subsequently the foal was reverted back to PZI therapy and regular insulin was discontinued as a treatment option. The interval between PZI treatments was gradually prolonged, as it took longer for the blood glucose to rise subsequent to each insulin administration. Insulin therapy was discontinued after Day 31 of hospitalization.

On Day 14 of hospitalization the foal developed a severe thrombophlebitis of the right jugular vein and septic arthritis of the right hip on Day 26. *Staphylococcus aureus* was isolated from an aspirate from the vein and synovial fluid of the coxofemoral joint. Cloramphenicol[k] (50 mg/kg, PO, q 6 h) was given to treat the phlebitis. The phlebitis improved after local therapy, drainage, and antimicrobials. The arthritis resolved after several joint lavages (needle and arthroscopic), intraarticular antimicrobial (amikacin,[l] 250 mg), and systemic antimicrobial therapy (chloramphenicol and later clarithromycin[m] 7.5 mg/kg, PO, q 12 h and rifampin[n] 5 mg/kg, PO, q 12 h). Systemic anti-inflammatories (flunixin meglumine 1.1 mg/kg, PO, q 12 h or ketoprofen[o] 2.2 mg/kg, IV or IM, q 24 h) were also administered. The foal was discharged after 54 days of hospitalization. The glycemia had ranged from 5.71 to 10.65 mmol/L (103–192 mg/dL) during the last week of hospitalization and no insulin had been administered for 3 weeks.

The foal remained clinically normal in the farm and represented at 8 months of age due to diarrhea and pneumonia. The weanling was treated successfully and discharged after 10 days of hospitalization. At that time glycemias measured were 6.66 mmol/L (120 mg/dL) on the day of presentation, 7.05 mmol/L (127 mg/dL) on Day 5 of hospitalization, and 6.99 mmol/L (126 mg/dL) on the day of discharge (Day 10). The foal was sound and the right jugular vein had recanalized. At 11 months of age the foal was healthy and BG and insulin were normal[1] (6.21 mmol/L [112 mg/dL] and 31.18 pmol/L [4.49 μU/mL], respectively).

Hyperglycemia can be caused by stress, glucocorticoids, α2-agonists, or dextrose administration.[2] Typically, sepsis is considered to cause hypoglycemia although in some instances it can cause hyperglycemia as the endocrine balance of septic patients can be characterized by a shift in the balance between insulin and its counterregulatory hormones (elevation in glucagon, epinephrine, and cortisol) favoring the latter.[3] Diabetes mellitus and pituitary pars intermedia dysfunction cause hyperglycemia but have not been described in equine neonates. Hyperglycemia in sick neonates is not well understood but has been related with insufficient insulin secretion, failure of insulin to suppress hepatic gluconeogenesis, or insulin resistance of peripheral tissues.[4]

Regular insulin can be administered as a constant rate infusion (CRI) or may be provided as SC or IV injections. Initial infusion rates of 0.0133 IU/kg/h and increasing by 0.002 IU/kg/h every 6 hours until blood glucose concentrations return to normal have been described.[4] For repeated injections the reported dosage is 0.1 to 0.5 IU/kg of regular insulin given SC or IV[2,4] or PZI 0.15–0.3 IU/kg SC, every 12 hours.[5] In this case the insulin therapy was designed with the goal to control the glycemia and extend progressively the interval of administration so the foal could have a regimen that did not require intensive management. A CRI of insulin, to more accurately control the glycemia, could have been planned but the foal was bright alert and nursing and a CRI would have not allowed the foal to remain with the mare continuously; furthermore prolonged intensive care was not an option financially.

Hyperlipemia is a pathophysiological response to negative energy balance resulting in mobilization of fat.[6] The disease is most common in pony and minia-

ture breeds and has been occasionally reported in neonates.[7] Insulin insensitivity has been described in animals with hyperlipemia[5] and glucose challenge tests may reveal glucose intolerance.[6] Lack of inhibition or insensitivity to insulin can cause increased release of FFA by tissue hormone-sensitive lipase. Insulin stimulates lipoprotein lipase, and decreases in reuptake of VLDL by peripheral tissues in animals with insulin insensitivity predispose to hyperlipemia.[2] The foal was hyperlipemic on Days 4 and 6 of hospitalization. At the time TGCs were measured the foal was nursing ad libitum and this may have influenced the wide fluctuations in the TGC's plasma concentration. Coincidentally, with initiation of milk supplementation, the TGC's plasma concentration decreased. It is possible that decreased secretion of insulin was affecting hormone sensitive lipase inhibition, lipoprotein lipase activity, hepatic metabolism, and thus caused increased TGC concentration.

The insulin concentration in normal foals from birth to 7 days of age is $13.5 \pm 1.5\,\mu U/mL$.[8,9] Therefore the insulin concentration in this foal before supplementation was low and inappropriate for the glycemia. Low insulin concentrations accompanying hyperglycemia and an adequate response to exogenous insulin supports a diagnosis of Type 1 diabetes mellitus. To our knowledge Type 1 diabetes mellitus has been reported in the scientific literature in adult horses[10] but never in a neonate. Additional insulin concentration measurements would have been informative to characterize the progression of the disease. These were not obtained due to monetary constraints.

Neonatal diabetes mellitus (NDM) is defined in the human literature as diabetes that presents during the first 6 months of life.[11] The majority of cases present with intrauterine growth retardation, failure to thrive, decreased SC fat, low or undetectable C-peptide levels, and is of genetic origin in 90% of the cases. Neonatal diabetes is rare (1 case per 300,000–500,000 human births)[11] and 2 main groups are recognized: transient NDM and permanent NDM, which differ in the duration of insulin dependence.[12] A high percentage of children with transient NDM relapse and develop Type 2 diabetes years after the initial hyperglycemic period.[11]

Hyperosmolarity, dehydration, and ketone bodies production can cause clinical signs in hyperglycemic individuals. The severity is typically proportional to the degree and duration of the hyperglycemia.[13] Serious consequences of uncontrolled hyperglycemia include hyperosmolar hyperglycemic nonketotic syndrome and diabetic ketoacidosis.[14] It has been speculated that ketone-producing pathways are relatively unimportant in the horse[15] and diabetic ketoacidosis may therefore be less likely in diabetic horses. The fact that the horse was treated with IV fluids, the hyperglycemia was not prolonged, and diabetes was Type 1 could have prevented nonketotic syndrome or other severe signs.

The presenting complaint in this case was diarrhea. Coronavirus particles were identified in the feces via electron microscopy. Coronavirus has been identified as a cause of pancreatic damage in other species.[16,17] Viruses may cause direct damage to the pancreas or induce autoimmunity via several mechanisms. There may be an infection of the pancreas, local damage, and activation of bystander T cells, or immunological cross-reactivity (molecular mimicry)[18] although the diabetogenic process is unproven.[19] We hypothesize that the coronavirus may have resulted in both the diarrhea and subsequent pancreatic injury in this foal, resulting in transient diabetes mellitus, which resolved as the injury to the pancreas resolved over a period of several weeks. Even though markers of pancreatic injury were normal, they were measured several days after the speculated insult. We are also unaware of the sensitivity of clinicopathologic tests (or sonography) to demonstrate pancreatic injury in horses. Therefore we consider that pancreatic damage due to coronavirus infection is a plausible hypothesis.

In summary, this is the first reported case of transient NDM in a foal. Diabetes mellitus should be considered in the differential diagnosis of hyperglycemia in neonates. The foal required SC insulin therapy for 26 days. The foal developed complications that resolved with appropriate care and was a healthy animal with normal glycemia and insulin concentration at 11 months of age.

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Footnotes

[a] SNAP® Foal IgG, IDEXX Laboratories Inc, Westbrook, ME.
[b] Lactated Ringers solution, Abbott Animal Health 200, Abbott Park, IL.
[c] Flagyl®, Pfizer Inc, New York, NY.
[d] Gastrogard®; Merial LCC, Duluth, GA.
[e] Clorhexidine 2% solution, Agri Laboratories Ltd, St Joseph, MO.
[f] Vitamin E capsules 400 IU, Walgreen Co, Deerfield, IL.
[g] E-Se®, Schering-Plough Animal Health Corp, Union, NJ.
[h] PZI-Vet®, IDEXX Laboratories Inc.
[i] Humulin R®, Eli Lilly and Company, Indianapolis, IN.
[j] Viceton®, Bimeda Inc, Le Sueur, MN.
[k] Amiglyde-V®, Fort Dodge Animal Health, Princeton, NJ.
[l] Byaxin®, Abbott Laboratories, North Chicago, IL.
[m] Rifadin®, Sanofi-aventis U.S. LLC, Bridgewater, NJ.
[n] Flunixamine®, Fort Dodge Laboratories, Fort Dodge, IA.
[o] Ketofen®, Fort Dodge Animal Health Livestock Division, Overland Park, KS.

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