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Case Report

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Catecholamine Metabolism in a Shetland Pony with Suspected Pheochromocytoma and Pituitary Pars Intermedia Dysfunction

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Key words: Endocrine tumor; Horse; Norepinephrine; Normetanephrine.

The two main physiologic components of the response to a stressor are mediated by the hypothalamus–pituitary–adrenocortical (HPA) axis and by the locus coeruleus/norepinephrine (LC/NE) autonomic nervous system. These responses result, respectively, in increases in cortisol and catecholamine concentrations in plasma.[1] Excessive secretion of catecholamines can occur because of neoplasia of the chromaffin cells of the adrenal medulla, a so-called pheochromocytoma. In this report, we describe a pony with an adrenal mass and clinical signs suggestive of pheochromocytoma in which measurements of catecholamines and their metabolites were performed in vivo.

Case History

A 27-year-old Shetland pony mare weighing 205 kg was presented for evaluation of acute colic poorly responsive to metamizole (dipyrone). The mare had been examined for laminitis 6 years previously and received corrective shoeing regularly. Clinical signs consistent with an active pheochromocytoma, such as excessive sweating, tachycardia, or excitement had not been observed before presentation.

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Abbreviations:

ACTH	adrenocorticotropic hormone
CBC	complete blood count
CRI	constant rate infusion
HPA	hypothalamus–pituitary–adrenocortical
HPLC	high-performance liquid chromatography
LC/NE	locus coeruleus/norepinephrine
MAP	mean arterial pressure
NIBP	noninvasive blood pressure
PCV	packed cell volume
PPID	pituitary pars intermedia dysfunction

Clinical Findings and Treatment

Upon presentation, the mare was lethargic, moderately painful, tachycardic (80/min), tachypneic (80/min), and rectal temperature was increased (39.7°C). The mare showed diffuse hypertrichosis, pale mucous membranes, and prolonged capillary refill time. A rectal examination, limited because of the size of the pony, was unremarkable, and no reflux was obtained after nasogastric intubation. A transcutaneous abdominal ultrasound examination identified a large amount of anechoic swirling free fluid (Fig 1) and an approximately 15 × 20 × 20 cm heterogeneous mass cranioventral to the left kidney (Fig 2). Differential diagnoses for the abdominal mass included hematoma,

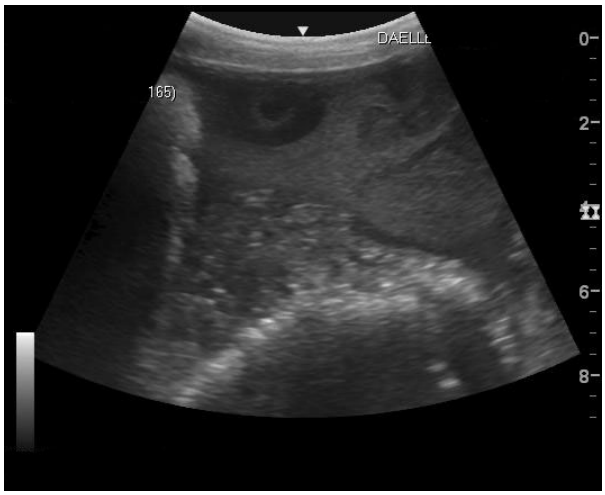

Fig 1. Transabdominal sonogram of the ventral abdomen using a 5-MHz convex probe in a cranio-caudal orientation showing large amounts of echoic swirling free fluid within the abdominal cavity (depth of the display: 10 cm). Cranial is to the left.

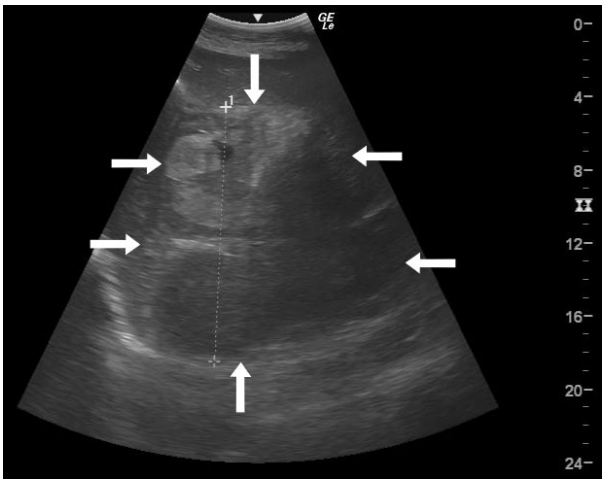

Fig 2. Transabdominal sonogram of the left paralumbar fossa using a 5-MHz convex ultrasound probe in a ventro-dorsal orientation showing a large heterogenous mass cranioventral to the left kidney (depth of the display: 24 cm). Dorsal is to the left.

granuloma, or neoplasia originating from the adrenal gland. No association with kidneys, lymph nodes, spleen, intestine, or ovaries was visible, and these were considered less likely origins. Hemoabdomen was confirmed by abdominocentesis that yielded red fluid with a total protein concentration of 60 g/L (reference interval [RI], 0–20 g/L), a leukocyte count of 6.8×10^9/L (RI, 0–5×10^9/L), a PCV of 34% (RI, 0%), a lactate concentration of 14.6 mmol/L (RI, 0–2 mmol/L), and an absence of platelets. Microscopic examination of peritoneal fluid disclosed no further abnormalities.

An initial CBC indicated a normal hematocrit (38%; RI, 31–47%) and leukocytosis (12.3×10^9/L; RI, 5.3–10.3×10^9/L) characterized by neutrophilia (8.1×10^9/L; RI, 2.5–6×10^9/L) and monocytosis (0.9×10^9/L; RI, 0.04–0.45×10^9/L). Abnormalities of the biochemistry profile included severe hyperglycemia (384 mg/dL; RI, 50.5–90.1 mg/dL), hyperlactatemia (16 mmol/L; RI, 0–2 mmol/L), hypoproteinemia (53.1 g/L; RI, 54–73 g/L), hypoalbuminemia (18.6 g/L; RI, 32.2–39.9 g/L), hyperlipidemia (triglycerides, 513 mg/dL; RI, 7.1–33.6 mg/dL), and increases in BUN (22.4 mg/dL; RI, 9.3–18.6 mg/dL), CK (3328 IU/L; RI, 0–262 IU/L), GGT (45 IU/L; RI, 11–26 IU/L), and GLDH (51 IU/L; RI, 0–14 IU/L). An electrocardiogram (ECG) showed unifocal ventricular tachycardia (Fig 3). Noninvasive blood pressure (NIBP) monitored on several occasions over the middle coccygeal artery using an oscillometric monitor[a] remained normal to mildly low. Mean NIBP noncorrected to heart level was 62–79 mmHg (reference, 88 ± 14 mmHg).[2] An echocardiogram performed when the pony was hemodynamically normal several days after presentation to the hospital disclosed no abnormalities. Anti-Müllerian hormone concentration (<0.01 ng/mL; RI, <2 ng/mL), measured to rule out a granulosa cell tumor of the left ovary, also was normal.

A secreting pheochromocytoma was suspected because of the presence of mass cranial to the left kidney, abdominal pain, hemoperitoneum, ventricular tachycardia, severe hyperglycemia, and severe hyperlactatemia. Initial treatment was aimed at hemodynamic stabilization. Analgesia was provided because of persistent signs of abdominal pain, and antibiotics were administered to prevent septic peritonitis. Treatment consisted of IV lactated Ringer's solution[b] (100 mL/kg/d), metamizole[c] (45 mg/kg IV once), flunixin meglumine[d] (1.1 mg/kg IV q12 h), and cefquinome[e] (1 mg/kg

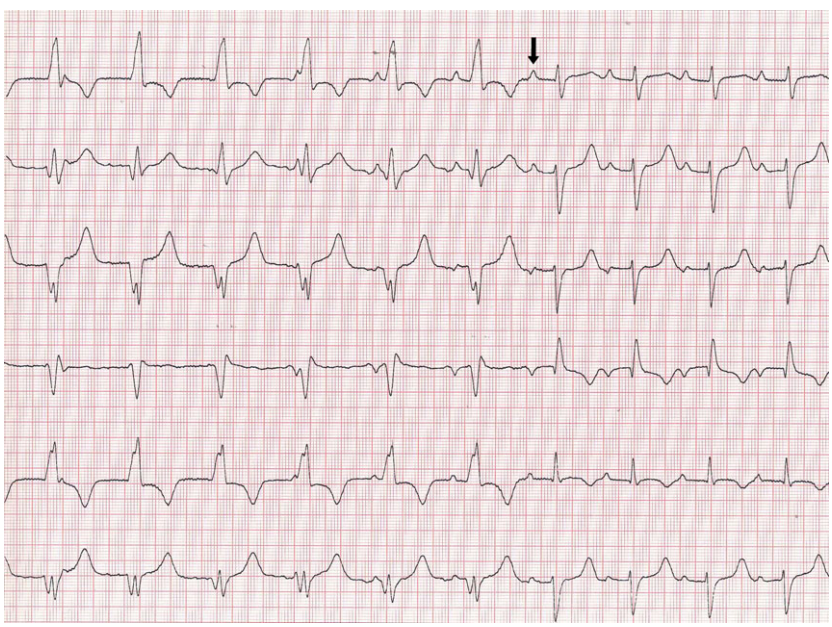

Fig 3. ECG shows uniform ventricular tachycardia (first 6 complexes) followed by sinus tachycardia. Lead I is a base-apex lead, and the rest are nonconventional leads. Paper speed is 10 mm/s.

IV q12 h). The ventricular tachycardia was treated with magnesium sulfate[f] (12.5 g IV once over 25 minutes) diluted in 1L of 0.9% NaCl[g] and lidocaine[h] (1.3 mg/kg IV over 15 minutes, followed by 0.05 mg/kg/min as a constant rate infusion [CRI]). After the initial simultaneous administration of magnesium sulfate and lidocaine, the rhythm changed to sinus tachycardia (76–140/min). Propranolol[i] (0.78 mg/kg PO once) was given because of concern about the catecholamine effect on cardiac β-receptors and tranexamic acid[j] (5 mg/kg IV once) was administered because of its antifibrinolytic effects. Protamine zinc insulin[k] (0.1 IU/kg SQ once) followed by an IV CRI of regular insulin[l] (0.01–0.02 IU/kg/h) was given and blood glucose concentration returned to normal within 12 hours. The mare remained lethargic and anorexic for 24 hours after the initial treatment was started. After 3 days of supportive treatment, the mare was in good general condition and eating well. All treatments were stopped after 3 days of hospitalization except for antibiotics and anti-inflammatory medications which were given for a total of 5 days.

Because of hypertrichosis and the history of chronic laminitis, ACTH plasma concentration was measured 6 days after the acute episode of colic. The ACTH concentration was increased (104 pg/mL; RI, <28 pg/mL in April),[3] and therapy with pergolide[m] (2.5 μg/kg PO q24h) was initiated.

Plasma and urine samples were collected simultaneously for the measurement of catecholamines and metanephrines as previously described in dogs.[4] Seven days were allowed after the last dose of propranolol to avoid false positives. Plasma from 3 hospitalized Shetland pony mares, aged 4–9 years, and urine from 1 pony were used as controls. Reasons for hospitalization of the other ponies were colon impaction and gastric ulcers, colon impaction and retained fetal membranes, and uterine prolapse after parturition, respectively. The mares were recovering from their diseases, and not severely ill at the time of sampling. Creatinine concentrations were measured in plasma and nonacidified urine, and urinalysis showed no abnormalities. Plasma samples were collected in chilled heparin tubes, centrifuged at 4°C, and stored at −80°C protected from light. Ten milliliters of urine was placed in a plain silicone-coated tube containing 280 μL of 20% HCl. Urinary pH was measured using pH indicator stripes (range of pH, 1-6), and HCl was added to achieve a pH ≤2 as needed for proper analysis. Samples were shipped on dry ice and thawed immediately before analysis.

Plasma norepinephrine and epinephrine, plasma free and total normetanephrine and metanephrine were determined by high-performance liquid chromatography (HPLC) tandem mass spectrometry.[5–7] Urinary norepinephrine, epinephrine, total normetanephrine, and total metanephrine were quantified by HPLC with amperometric detection as separate compounds.[6,8] The results are expressed as a ratio to urinary creatinine concentrations. Samples were treated with sulfatase (sul) and glucuronidase (glu) for the analysis of total metanephrine and normetanephrine.

The pony with suspected pheochromocytoma had higher plasma norepinephrine (11.92 nM vs. 0.61, 1.12, and 1.15 nM), total normetanephrine (3.82 nM vs. 0.93, 1.02 and 0.84 nM [sul] and 19.24 nM vs. 3.94, 3.84 and 5.58 nM [glu]), and free normetanephrine (3.29 nM vs. 0.73, 0.72 and 0.66 nM) concentrations than the 3 control ponies. Furthermore, urinary norepinephrine (69.2 nEq/mEq [nmol/mmol] vs. 3.1 nEq/mEq [nmol/mmol]) and normetanephrine (76.2 nEq/mEq [nmol/mmol] vs. 13.4 nEq/mEq [nmol/mmol] [sul] and 384.9 nEq/mEq [nmol/mmol] vs. 48.9 nEq/mEq [nmol/mmol] [glu]) measurements were higher in the diseased animal than in the control pony. All the results are given in Table 1.

The pony was clinically normal after 1 week of hospitalization. An abdominal sonogram identified no free abdominal fluid at that time. The mass had decreased in size (measuring $10 \times 15 \times 15$ cm approximately) and showed a hyperechoic outer layer with a hypoechoic fluid-filled area interpreted as a reorganizing hematoma. Transrectal ultrasound examination of the left adrenal gland was considered but not performed because of concerns about manipulation leading to an adrenergic crisis. Because of the lack of medical therapy available for treatment of pheochromocytoma, surgical removal of the adrenal mass was planned and advanced imaging scheduled to prepare for the surgical procedure. To decrease the potential risk of catecholamine release during general anesthesia, phenoxybenzamine[n] (dosing protocol: 0.2 mg/kg PO q24h twice, then 0.3 mg/kg PO q12h for 2 days, then 0.4 mg/kg PO q12h for 3 days, then 0.5 mg/kg PO q12h for 8 days) was administered. During the treatment, heart rate remained normal (40–44/min) and mean noncorrected NIBP decreased initially (50 mmHg) and then stabilized at approximately 66 mmHg. No other adverse effects were observed.

Two weeks later, the pony was presented again for further diagnostic investigations under general anesthesia. A balanced electrolyte solution (2 mL/kg/h) was given for 12 hours before anesthesia, and phenoxybenzamine therapy was discontinued the evening before the intervention.

The pony was premedicated with dexmedetomidine[o] (3.5 μg/kg IV) and levo-methadone[p] (0.05 mg/kg IV), and anesthesia was induced with diazepam[q] (0.1 mg/kg IV), propofol[r] (2 mg/kg IV), and thiopental[s] (0.25 mg/kg IV). Anesthesia was maintained with isoflurane[t] in 100% oxygen and lidocaine[u] (1.8 mg/kg/h IV). Mean arterial pressure >60 mmHg, assessed by NIBP measurement at the base of the tail, was achieved using lactated Ringer's solution[b] (10 mL/kg/h), dobutamine[v] (0.2–4 μg/kg/min), and norepinephrine[w] (0.1–0.5 μg/kg/min). Heart rate ranged between 36 and 51/min. The mare recovered without incident.

Computed tomography (CT) of the abdomen was performed using a 16-slice spiral computed tomography scanner. Images were acquired with 120 kV and 270 mAs. Postcontrast images were acquired after administration of 80 mL nonionic iodinated (300 mg/mL) contrast medium. A space-occupying lesion was identified craniomedially to the left kidney, with a cavitary medial

Table 1. Results of plasma (P-) catecholamines and plasma total and free metanephrines and urinary (U-) catecholamines, metanephrines to creatinine ratios, vanillyl mandelic acid, and homovanillic acid to creatinine ratios in a pony with suspected pheochromocytoma (PC) and controls (C1, C2, C3).

Parameter	PC	C1	C2	C3
P-dopamine (nmol/L)	0.18	0.10	0.04	0.10
P-epinephrine (nmol/L)	0.15	1.03	1.13	0.46
P-norepinephrine (nmol/L)	11.62	0.61	1.12	1.15
P-total metanephrine (nmol/L) [sulfatase-treated]	0.16	0.97	0.42	0.31
P-total metanephrine (nmol/L) [glucuronidase-treated]	1.17	5.94	2.41	2.12
P-free metanephrine (nmol/L)	0.16	0.94	0.26	0.25
P-total normetanephrine (nmol/L) [sulfatase-treated]	3.82	0.93	1.02	0.84
P-total normetanephrine (nmol/L) [glucuronidase-treated]	19.24	3.94	3.84	5.58
P-free normetanephrine (nmol/L)	3.29	0.73	0.72	0.66
P-total methoxytyramine (nmol/L) [sulfatase-treated]	0.01	0.05	0.08	0.02
P-total methoxytyramine (nmol/L) [glucuronidase-treated]	7.32	7.77	7.15	6.08
P-free methoxytyramine (nmol/L)	0.02	0.10	0.10	0.06
U-dopamine: creatinine (nmol/mmol)	20.9	11.6		
U-epinephrine: creatinine (nmol/mmol)	1.6	2.1		
U-norepinephrine: creatinine (nmol/mmol)	69.2	3.1		
U-metanephrine: creatinine (nmol/mmol) [sulfatase-treated]	4	12.2		
U-metanephrine: creatinine (nmol/mmol) [glucuronidase-treated]	23.1	63.3		
U-normetanephrine: creatinine (nmol/mmol) [sulfatase-treated]	76.2	13.4		
U-normetanephrine: creatinine (nmol/mmol) [glucuronidase-treated]	384.9	48.9		
U-vanillyl mandelic acid: creatinine (μmol/mmol)	1.82	0		
U-homovanillic acid: creatinine (μmol/mmol)	10.4	1.82		

part of 7 cm in diameter with a hypodense center (pre- and postcontrast approximately 30 Hounsfield Units [HU]) and a contrast-enhancing peripheral ring (precontrast, 33 HU; postcontrast, 97 HU). The laterocaudal part of the lesion was slightly heterogenous and ill-defined with a diameter of 6 cm. On the right side, a homogenous, soft tissue-attenuating and mildly contrast-enhancing lesion (precontrast, 63 HU; postcontrast, 97 HU) with a diameter of approximately 6 cm was identified craniomedially to the right kidney (Fig 4). Both mass lesions were suspected to be adrenal glands. Although exact sizes for adrenal glands of horses on CT are not reported in the veterinary literature, left adrenal glands have been measured using transrectal ultrasound and the mean diameter (±SD) did not exceed 0.89 ± 0.18 cm.[9] Furthermore, adrenal glands are anatomically described as small, flattened organs with a size of approximately 9–10 cm long, 3–4 cm wide, and approximately 1.5 cm or more in thickness.[10] Assuming that adrenal glands usually have about the same size and would be expected to be even smaller in a pony, we assumed that both were enlarged in the patient. The cavitary lesion of the left adrenal mass was suspected to be a hematoma in regression or a cystic pheochromocytoma.[11] Differential diagnosis for the enlarged right adrenal gland included adrenal hyperplasia, adenoma, adenocarcinoma, or pheochromocytoma. Because of the presence of bilateral masses, surgery was not considered and the pony was discharged with pergolide as the only treatment. The owner reported that the mare had not had signs of disease during the 12 months after discharge.

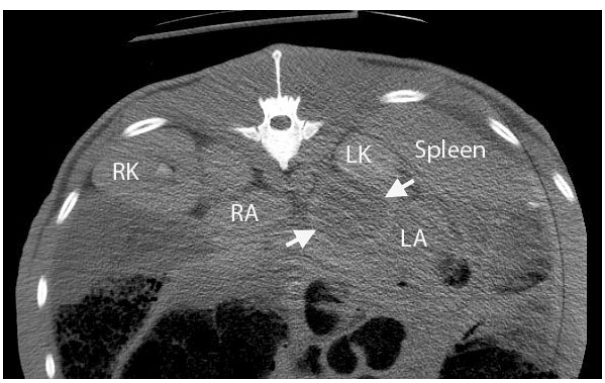

Fig 4. Transverse postcontrast CT image of the abdomen at the level of the cranial pole of the left kidney (LK), which is located medially to the spleen. The left adrenal gland (LA) is soft tissue attenuating at its lateral aspect with a cavitary mediodorsal part (white arrows). Medially to the right kidney (RK), the soft tissue attenuating right adrenal gland (RA) is visible.

To the best of our knowledge, this is the first report of an antemortem diagnosis of pheochromocytoma in an equid using analysis of plasma and urinary catecholamines and metabolites. Diagnosis and management followed the standard of care in small animals and humans with suspected pheochromocytomas, and such an approach has been mentioned in previous reports in horses.[12] The biochemical test of choice for pheochromocytomas in human medicine is measurement of plasma or 24-hour urinary fractioned metanephrines in addition to CT or magnetic resonance imaging.[13] Collection of urine during 24 hours is impractical in horses, and determination of plasma and urinary metanephrine and normetanephrine is considered appropriate for the differentiation of dogs with pheochromocytomas from those with hypercortisolism,

nonadrenal diseases, and healthy controls.[4] Pheochromocytoma is considered highly probable in humans with plasma concentrations of normetanephrines and metanephrines >4 times the reference concentration.[14] In the case presented here, these criteria were met for plasma norepinephrine and normetanephrines, urinary norepinephrine, and normetanephrine-to-creatinine ratio. Norepinephrine seemed to be the most markedly increased catecholamine, which agrees with reports in affected dogs.[4]

Extrapolation of conclusions from other species should be performed with caution, and results of total metanephrine and normetanephrine show a remarkable difference between horses and other species because catecholamine metabolites are mostly glucuroconjugated and not sulfoconjugated.[1,4] Methoxythyramine, a catecholamine metabolite, also is glucuroconjugated in horses.[15] We presented the individual control results rather than an average because only 3 animals were used for comparison. Preliminary data can be used to define the sample size needed to establish a reference range. Data obtained from an appropriate sized control population should be checked for normality, and reference ranges established based on the 95% confidence interval. A larger number of horses with pheochromocytomas will need to be compared to healthy controls to confirm that patterns described in small animals and humans are followed by horses with pheochromocytomas. It is a limitation of the diagnosis in this case that the comparison was made with a small group of hospitalized ponies and that the absolute concentrations and ratios were somewhat lower than those commonly described in dogs and people with pheochromocytomas.[4,14] Nevertheless, the large differences between the case and controls support the diagnosis in these species. Differences in laboratory methods complicate direct comparison of the results among studies, and reliable reference ranges are not available for horses.

Horses with laminitis or colic have been shown to have increased serum norepinephrine concentrations compared to controls.[16] This might have been a confounding factor; however, signs of laminitis or colic were not present at the time of sampling. It is a major limitation that the diagnosis of pheochromocytoma was not confirmed histopathologically and assessment using radionuclide imaging modalities was not performed.

Pheochromocytomas in horses can be suspected clinically and confirmed postmortem or during exploratory laparotomy.[11,17,18] Pheochromocytomas often are asymptomatic and often are found incidentally during necropsy in horses. If clinical signs are present, colic is the most common presenting complaint,[19] and hemoabdomen,[20,21] arrhythmias, tachycardia,[12,17] severe hyperglycemia, and hyperlactemia are commonly reported in horses with pheochromocytomas.[19] Hyperglycemia previously has been described in humans with pheochromocytomas because of increased glycogenolysis and inhibition of insulin secretion caused by increased plasma concentrations of catecholamines.[22] Hyperglycemia could have been secondary to pituitary pars intermedia dysfunction (PPID) in the pony we report here. Nevertheless, the pony responded to insulin therapy and hyperglycemia did not recur. Hyperlactemia has been associated with vasoconstrictive ischemia or hemorrhagic shock in cases of pheochromocytoma.[19]

Pheochromocytomas have been described in large animals as single lesions or as part of a multiple endocrine-like syndrome.[23,24] Other endocrine tissues affected by hyperplasia or neoplasia in multiple endocrine-like syndrome include the thyroid gland, parathyroidal C cells, and the pituitary pars intermedia. Concomitant adrenal hyperplasia and bilateral pheochromocytomas have been described,[19] and 14/32 and 2/32 of horses diagnosed with PPID reportedly had diffuse adrenocortical hyperplasia and pheochromocytoma, respectively, in a retrospective study.[25]

Adrenergic crisis has been described in humans with pheochromocytomas during induction of anesthesia and intubation.[26] Phenoxybenzamine, an adrenergic α-blocker, is the drug of choice to prevent this complication,[27] and the protocol used here was adapted from recommendations for humans[28] and pharmacological and anecdotal reports in horses.[29,30] Administration of β-blockers to individuals with pheochromocytomas without prior administration of adrenergic α-blockers has been discouraged because of the risk of unopposed α-adrenergic receptor stimulation causing a hypertensive crisis.[31,32] Administration of phenoxybenzamine before propranolol would have been indicated in this case.

Surgical removal of the tumor is indicated for humans and small animals with functional and symptomatic pheochromocytomas. Laparoscopic removal is the preferred technique, but laparotomy also is described.[32] To the best of our knowledge, surgical removal of a pheochromocytoma in a horse has not been reported, although the surgical technique for adrenalectomy is described in normal horses.[33,34] Because of the size and location of the mass, an open approach via the left flank with the pony in right lateral recumbency and under general anesthesia was planned.

Dopamine receptors are expressed in human adrenal tumors including pheochromocytomas and D2 receptors have inhibitory effects on norepinephrine secretion.[35] The hypothesis of a possible effect of dopamine agonists in the control of hormonal hypersecretion associated with adrenal tumors has been formulated but not proven.[36] Pergolide, a dopamine agonist, was administered to the pony described here for the treatment of PPID. The effects of pergolide on pheochromocytomas in horses are speculative, but interestingly, there was remission of clinical signs during treatment.

In conclusion, measurement of catecholamines and their metabolites in plasma and urine can be used in the diagnosis of suspected pheochromocytoma. Further information regarding the concentrations of catecholamines and their metabolites in healthy and ill horses and in horses with pheochromocytomas would help clinicians in managing horses in which this tumor is suspected.

Footnotes

[a] Cardell Veterinary Monitor 9402, CAS Medical Systems, Brandford, CT, USA
[b] Ringer-Lactat "Bichsel" ohne/sans Glucose, Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
[c] Vetalgin®, MSD Animal Health GmbH, Luzern, Switzerland
[d] Fluniximin, Dr. E. Graeub AG, Bern, Switzerland
[e] Cobactan® IV 4.5%, MSD Animal Health GmbH, Luzern, Switzerland
[f] Magnesiumsulfat "Bichsel" 10%, Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
[g] Natrium chloratum "Bichsel," Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
[h] Lidocain 2% Streuli, Streuli Pharma AG, Uznach, Switzerland
[i] Propranolol retard, Helvepharm AG, Frauenfeld, Switzerland
[j] Cyclocapron®-Injektionslösung, Pharmacia GmbH/ Pfizer GmbH, Berlin, Germany
[k] Caninsulin®, MSD Animal Health GmbH, Luzern, Switzerland
[l] Novorapid®, Novo Nordisk Pharma AG, Küsnacht, Switzerland
[m] Prascend®, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland
[n] Phenoxybenzamin HCl BP, Christoffel-Apotheke, Bern, Switzerland
[o] Dexdomitor®, Provet AG, Lyssach, Switzerland
[p] L-Polamivet®, MSD Animal Health GmbH, Luzern, Switzerland
[q] Valium®, Roche Pharma (Schweiz) AG, Reinach, Switzerland
[r] Propofol 1% MCT, Fresenius Kabi, Oberdorf, Switzerland
[s] Pentothal, Ospedalia AG, Hünenberg, Switzerland
[t] Attane™, Provet AG, Lyssach, Switzerland
[u] Lidocain 2% Streuli, Streuli Pharma AG, Uznach, Switzerland
[v] Dobutrex®, Teva Pharma AG, Basel, Switzerland
[w] Noradrenalin Sintetica, Sintetica S.A., Mendrisio, Switzerland

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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