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. 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.

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,
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 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 remained normal to mildly low. Mean NIBP noncorrected to heart level was 62–79 mmHg (reference, 88 ± 14 mmHg). 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 (100 mL/kg/d), metamizole (45 mg/kg IV once), flunixin meglumine (1.1 mg/kg IV q12 h), and cefquinome (1 mg/kg

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.

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.
The ventricular tachycardia was treated with magnesium sulfate (12.5 g IV over 25 minutes) diluted in 1L of 0.9% NaCl and lidocaine (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 (0.78 mg/kg PO once) was given because of concern about the catecholamine effect on cardiac receptors and, tranexamic acid (5 mg/kg IV once) was administered because of its antifibrinolytic effects. Protamine zinc insulin (0.1 IU/kg SQ once) was administered because of its antifibrinolytic effects. Protamine zinc insulin was given IV once) followed by an IV CRI of regular insulin (0.01–0.02 IU/kg/h) was given and blood glucose concentration returned to normal within 12 hours. The mare remained hypoglicemic 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), and therapy with pergolide (2.5 μg/kg PO q24h) was initiated.

Plasma norepinephrine and epinephrine, plasma free and total normetanephrine and metanephrines as previously described in dogs. 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 collected 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 remaining horse was recovering from their diseases, and not severely ill at the time of sampling. Creatinine concentration was increased (104 pg/mL; RI, <28 pg/mL in April), and therapy with pergolide (2.5 μg/kg PO q24h) was initiated.

Plasma samples were collected simultaneously for the measurement of catecholamines and metanephrines as previously described in dogs. 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 collected 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 concentration was increased (104 pg/mL; RI, <28 pg/mL in April), and therapy with pergolide (2.5 μg/kg PO q24h) was initiated.

Plasma norepinephrine and epinephrine, plasma free and total normetanephrine and metanephrine were determined by high-performance liquid chromatography (HPLC) and tandem mass spectrometry. Plasma norepinephrine, epinephrine, total normetanephrine, and total metanephrine were quantified by HPLC with a cavitary chromophore containing 280 μL of 20% HCL. Urinary pH was measured using pH indicator strips (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.

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The results were 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.
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 latero-caudal part of the lesion was slightly heterogeneous 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 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. 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. 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. 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.

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. 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. 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.

### 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     | 0.16     | 0.10     | 0.06     |
| U-dopamine: creatinine (nmol/mmol)              | 20.9     | 11.6     | 2.1      |          |
| 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     |          |          |

**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.
nonadrenal diseases, and healthy controls. Pheochromocytoma is considered highly probable in humans with plasma concentrations of normetanephrines and metanephrines >4 times the reference concentration.

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 animals.

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. Methoxytyramine, a catecholamine metabolite, is also glucuroconjugated in horses. 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 study 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. Nevertheless, the large differences between the case and controls support the diagnosis of pheochromocytoma.

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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. 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.

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. 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. 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 noradrenaline secretion. 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. 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

- Cardell Veterinary Monitor 9402, CAS Medical Systems, Brandford, CT, USA
- Ringer-Lactat “Bichsel” ohne/sans Glucose, Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
- Vetaglin®, MSD Animal Health GmbH, Luzern, Switzerland
- Fluixinim, Dr. E. Graeub AG, Bern, Switzerland
- Cobacan® IV 4.5%, MSD Animal Health GmbH, Luzern, Switzerland
- Magnesiumsulfat “Bichsel” 10%, Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
- Natrum chloratum “Bichsel,” Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
- Lidocain 2% Streuli, Streuli Pharma AG, Uznach, Switzerland
- Propanolol retard, Helvepharm AG, Frauenfeld, Switzerland
- Cyclokapron®, Injektionslösung, Pharmacia GmbH/ Pfizer GmbH, Berlin, Germany
- Caninsulin®, MSD Animal Health GmbH, Luzern, Switzerland
- Novorapid®, Novo Nordisk Pharma AG, Kopenhagen, Switzerland
- Prascend®, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland
- Phenoxybenzamin HCl BP, Christoffel-Apotheke, Bern, Switzerland
- Dexdomitor®, Provet AG, Lyssach, Switzerland
- L-Polamivex®, MSD Animal Health GmbH, Luzern, Switzerland
- Valium®, Roche Pharma (Schweiz) AG, Reinach, Switzerland
- Propofol 1% MCT, Fresenius Kabi, Oberdorf, Switzerland
- Pentothal, Ospedalia AG, Hünenberg, Switzerland
- Attane®, Provet AG, Lyssach, Switzerland
- Lidocain 2% Streuli, Streuli Pharma AG, Uznach, Switzerland
- Dobutrex®, Teva Pharma AG, Basel, Switzerland
- Noradrenalin Sintetica, Sintetica S.A., Mendrisio, Switzerland
- Propofol 1% MCT, Fresenius Kabi, Oberdorf, Switzerland
- Caninsulin®, MSD Animal Health GmbH, Luzern, Switzerland
- Vetalgin, Dr. E. Graeub AG, Bern, Switzerland
- Phenoxybenzamin HCl BP, Christoffel-Apotheke, Bern, Switzerland
- Ringer-Lactat “Bichsel” ohne/sans Glucose, Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland
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- Lidocain 2% Streuli, Streuli Pharma AG, Uznach, Switzerland
- Dobutrex®, Teva Pharma AG, Basel, Switzerland
- 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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