

Pheochromocytoma in the Horse and Measurement of Norepinephrine Levels in Horses

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SUMMARY

Ten cases of pheochromocytoma in horses were obtained from the literature and a computer search of medical records. The clinical, laboratory and pathological features of pheochromocytoma in horses were reviewed. Pheochromocytoma is a catecholamine secreting tumor which tends to occur in older horses without breed or sex predisposition. It is usually unilateral adrenal medullary in location and benign. Malignancy was present in one horse. The most common clinical signs were sweating, tachycardia, tachypnea, muscle tremor and anxiety; however the tumor may be asymptomatic. Clinical signs were nonspecific and could be confused with other diseases, especially abdominal pain. Hyperglycemia is a consistent finding. Venous norepinephrine levels were measured in normal horses. Norepinephrine measurements may prove to be a diagnostic aid in horses with pheochromocytoma.

RÉSUMÉ

Phéochromocytome équin et détermination de la teneur du sang de chevaux en norépinéphrine

Cet article présente une analyse de dix phéochromocytomes équins dont les informations pertinentes proviennent de publications et de dossiers médicaux, ceux-ci consultés à l'aide d'un ordinateur. Il contient aussi une revue des signes cliniques, des résultats d'exams de laboratoire et des lésions relatifs à ce néoplasme. Le phéochromocytome est une tumeur qui sécrète des catécholamines et qui tend à se développer chez des chevaux âgés, indépendamment de leur race ou de

leur sexe. Il est ordinairement unilatéral, se situe dans la zone médullaire des surrénales et affiche un caractère bénin; il se révéla toutefois malin, chez un des dix chevaux impliqués dans cette étude. Les signes cliniques les plus communs se traduisent par de la transpiration, de la tachycardie, de la tachypnée, des tremblements musculaires et de l'anxiété; la tumeur peut cependant être asymptomatique. N'étant pas spécifiques, les signes cliniques peuvent se confondre avec ceux d'autres affections, en particulier les douleurs abdominales. L'hyperglycémie accompagne toujours le phéochromocytome. On a recherché la teneur sanguine en norépinéphrine, chez des chevaux sains, parce que ce paramètre peut aider à diagnostiquer un phéochromocytome équin.

INTRODUCTION

Pheochromocytomas are tumors of chromaffin cells derived from neuroectodermal tissue (1). They may be asymptomatic or produce clinical signs related to the synthesis and secretion of catecholamines (1,2,3). Pheochromocytomas have been reported in horses (4,5,6,7,8), cattle (9,10,11,12), sheep (9), dogs (13,14), and people (15,16,17). Definitive antemortem diagnosis of functional pheochromocytoma has been made in the dog (14) and people (16,17) but not in the horse.

The purpose of this study is to review the literature and present data obtained from a medical records search and, one case report on pheochromocytoma in the horse. Venous norepinephrine levels were measured to obtain data on normal catechola-

mine levels in horses without pheochromocytoma.

LITERATURE REVIEW

Five cases of pheochromocytoma in the horse have been reported in the literature (4,5,6,7,8). Some clinical and pathological features of pheochromocytoma in these horses are presented in Table I (Cases 1-5). A pheochromocytoma was an incidental finding in a 21 year old Thoroughbred gelding (Case 3). Only one horse had a malignant pheochromocytoma (Case 4). This was a six month old Standardbred filly which presented with neurological signs referable to spinal cord disease. At necropsy there was multiple pheochromocytoma's in both adrenal glands with metastasis to the liver, lungs, vertebral canal, azygous vein and left scapula (7). Clinical signs and laboratory findings consistent with a hormonally active pheochromocytoma have been reported in three horses (Cases 1,2,5, Table II). In two cases there was an acute onset of signs with a rapid clinical progression. In case 1, a 25 year old Thoroughbred mare suffered an acute onset of muscle tremors and sweating and died nine days before she was due to foal (4). In case 5, the mare presented with an acute onset of abdominal pain and sweating and died one and one-half hours after exploratory celiotomy (8). In a 15 year old cob mare (Case 2) the signs of sweating, polydipsia, polyuria, apprehension and rapid respiration were paroxysmal with a protracted clinical course.

Evidence for catecholamine release from a pheochromocytoma as the cause of the clinical signs and labora-

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tory findings in horses with suspected functional pheochromocytoma is shown by interpretation of the findings in terms of excessive adrenergic receptor stimulation. In the horse sweating and muscle tremor are caused by beta-2-adrenergic receptor stimulation (18,19,20,21). Tachycardia, gastrointestinal ileus and mydriasis are adrenergic mediated (22,23). Hyperglycemia is produced by catecholamine infusion (19,21). Neutrophilia and hemoconcentration occur with increased systemic catecholamines and elevations in plasma creatine kinase occur after adrenaline administration in the horse (19,23). Increased blood urea nitrogen may occur secondary to hemoconcentration and splanchnic vasoconstriction.

All of the reported cases of pheochromocytoma were diagnosed by necropsy and histopathological examination of the tumor. Of the four horses with benign pheochromocytoma the tumor was nodular and encapsulated in three horses (Cases 1-3) and in one horse (Case 5) the tumor was cystic and had ruptured.

The histology of pheochromocytoma in these horses varied and was similar to that described in people and domestic

animals (2,3,24,25). Chromaffin-positive cells were demonstrated in pheochromocytoma from two horses (Cases 2,3). Ultrastructurally cytoplasmic secretory granules typical of pheochromocytoma and normal adrenal medullary cells were shown in three horses (Cases 3,4,5.) (26).

Other histological findings in horses with benign pheochromocytoma included cystic endometrial glands, hydropic degeneration of beta cells of the pancreatic islets, cystic ovarian degeneration (Case 2), extensive replacement of myocardium by fibrous and areolar tissue (Case 3), peracute hepatocellular necrosis and multiple foci of acute myocardial infarction (Case 5).

MATERIALS AND METHODS

Medical Records Search for Pheochromocytoma in Horses

A computer search of medical records from 22 North American universities was performed to obtain records on horses which had a pheochromocytoma.¹ Once the medical records were identified requests were sent to the appropriate veterinary universities to obtain the records.

Measurement of Venous Norepinephrine Levels in Horses

Using high performance liquid chromatography equine venous norepinephrine levels were determined as previously described (27). Blood samples for analysis were collected by jugular venipuncture into EDTA tubes containing 100 uL of 0.25 M sodium bisulfate. The sodium bisulfate is an antioxidant added to prevent norepinephrine degradation.

Venous norepinephrine levels were measured in 20 randomly selected horses. To determine the effect of excitement on venous norepinephrine levels, venous samples were taken from ten ponies on three occasions. At sampling the ponies were classified as being calm (did not avoid restraint or jugular venipuncture) or excited (avoided restraint, apprehensive appearance, avoided jugular venipuncture).

RESULTS

Medical Records Search

Five cases of pheochromocytoma in horses were obtained by the computer search of medical records. Upon request the respective veterinary universities provided the full medical record on each horse. The clinical and

TABLE 1
SOME CLINICAL AND PATHOLOGICAL FEATURES OF PHEOCHROMOCYTOMA IN TEN HORSES^a

Case	Age (years)	Breed	Sex	Presenting Complaint	Outcome	Pheochromocytoma ^b	
						Adrenal Involved	Tumor Diameter (cm)
1	25	Thoroughbred	Mare	Muscular tremors, profuse sweating	Died	R	10 x 12
2	15	Cob	Mare	Excessive sweating, polydipsia, apprehensive tachypnea, weight loss	Euthanized	R	2 x 1
3	21	Thoroughbred	Gelding	Diarrhea	Euthanized	L	10 x 12
4	6 mos	Standardbred	Filly	Spinal cord disease	Euthanized	L and R	Malignant with metastases
5	17	Quarterhorse	Mare	Abdominal Pain	Died after celiotomy	R	6
6	15	Grade	Gelding	Swelling of left maxillary area	Euthanized, adenocarcinoma of nasal mucosa diagnosed	—	—
7	15	Shetland Welsh	Gelding	Esophageal obstruction	Died	L	2½
8	20	American Saddlebred	Gelding	Abdominal Pain	Euthanized at surgery due to inoperable intestinal strangulation	R	2
9	12	Quarterhorse	Mare	Laminitis, mastitis	Euthanized due to severe laminitis	L	2½ x 1½
10	13	Thoroughbred	Stallion	Exercise intolerance and tachypnea, abdominal pain	Euthanized	R	10

^aCases 1-5 previously reported (4,5,6,7,8); cases 6-10 obtained via computer search of medical records of 22 North American veterinary colleges.

^bAll pheochromocytomas were benign except in case 4. Functional tumor suspected in cases 1, 2, 5 and 10.

R = Right.

L = Left.

¹Veterinary Medical data processing, Cornell University, Ithaca, New York.

pathological features of pheochromocytoma in these horses is summarized in Table I, cases 6-10. Pheochromocytoma was diagnosed in each horse by necropsy and histopathological examination of the tumor. Grossly, all pheochromocytomas were described as well encapsulated circumscribed nodules in the adrenal gland. Histological features of each pheochromocytoma was consistent with previous description (see literature review). Of the equine pheochromocytoma cases obtained only case 10 showed substantial evidence of a functional pheochromocytoma (Table II).

Case 10 was a 13 year old Thoroughbred stallion presented for mild abdominal pain. The owner commented that the horse had developed poor exercise tolerance in the past few months and that rapid respiration persisted for half an hour after exercise.

When examined, the horse was sweating and had muscle tremors. The pulse was 80 beats per minute, respiratory rate 90 per minute and temperature 38.5°C. Gastrointestinal ileus was present. The venous hematocrit was

55%. A pelvic flexure impaction was diagnosed and therapy instituted. The colic resolved in two days, however the rapid pulse and respiratory rates persisted. Thoracic radiographs at this time were negative for signs of cardiac abnormality or inflammatory lung disease. Laboratory work revealed a neutrophilia and lymphopenia. Serum biochemistry determinations two days after the colic resolved revealed an elevated lactate dehydrogenase 1312 I.U./L (normal 41-104 I.U./L) and elevated creatinine kinase 230 I.U./L (normal 2.4-23.4 I.U./L). Hyperglycemia was present, (glucose 137 mg/dL, normal 75-115 mg/dL) when blood glucose was determined five days after the colic resolved.

The pulse rate remained above 70 beats per minute for seven days after the colic episode by which time variable atrial and ventricular arrhythmias were noted and ventral edema developed. The respiratory rate varied between 50 and 100 per minute. The horse's attitude, pulse rate and respiratory rate would change rapidly. The horse's condition remained unchanged

and euthanasia was elected 15 days after presentation. Postmortem and histological examination revealed extensive areas of myocardial degeneration which were more severe on the right side as represented by several white foci 2-3 mm in diameter. There was a well encapsulated 10 cm diameter pheochromocytoma of the right adrenal gland.

Of the ten horses listed in Table I the average age of the horses with benign pheochromocytoma was 17 years and the average age of those with a suspected functional pheochromocytoma was 17.5 years. No breed or sex predisposition to pheochromocytoma was apparent. All benign pheochromocytomas were adrenal in origin and unilateral. Only one horse (Case 4) had a malignant tumor and this filly was much younger than the other horses. The tumor occurred in the right adrenal in five horses and the left adrenal in three horses. The adrenal gland involved and the tumor size in one horse (Case 6) was not clearly recorded. Tumor size varied (2-12 cm diameter) and did not show a correlation with the presence or absence of signs attributable to a hormonally active pheochromocytoma.

TABLE II
CLINICAL SIGNS AND LABORATORY FINDINGS IN FOUR HORSES
SUSPECTED OF HAVING A HORMONALLY ACTIVE PHEOCHROMOCYTOMA

Horse	Clinical Signs	Laboratory Findings
Case 1	Profuse sweating Tachycardia Muscle tremors Anxiety Tachypnea Mydriasis Pyrexia	Hyperglycemia Elevated blood urea nitrogen Elevated serum aspartate amino transaminase
Case 2	Excessive sweating Tachycardia correlated with episodes of sweating and apprehensiveness Constant tachypnea Variable appetite Weight loss Polydipsia Polyuria Laminitis	Constant hyperglycemia Glucosuria Negative insulin tolerance test Abnormal glucose tolerance test
Case 5	Sweating Tachycardia Muscle tremors Anxiety Gastrointestinal ileus Myositis (postoperative)	Hyperglycemia Neutrophilia Lymphopenia Hemoconcentration Metabolic acidosis Elevated creatine kinase Elevated blood urea nitrogen
Case 10	Sweating Tachycardia Muscle tremor Tachypnea Gastrointestinal ileus Cardiac arrhythmias Exercise intolerance	Hyperglycemia Neutrophilia Lymphopenia Hemoconcentration Elevated creatine kinase Elevated lactate dehydrogenase

Venous Norepinephrine Measurements

Circulating venous norepinephrine levels in 20 randomly selected horses had a mean value of 250 pg/mL (range 120 to 300 pg/mL). At sampling ponies were judged to be calm on 18 occasions and excited on 12 occasions. Venous norepinephrine levels had a mean value of 325 pg/mL (range 140 to 450 pg/mL) in calm subjects and a mean of 700 pg/mL (range 400 to 1200 pg/mL) in the excited subjects.

DISCUSSION

Many features of pheochromocytoma in the horse are similar to those in people and other domestic animals. These include the absence of breed or sex predilection, the predominance of unilateral adrenal medullary location, the low incidence of malignancy, similar tumor size range and similar clinical signs caused by excessive systemic catecholamines (1,2,9,10-14,16,17,24). There are no reports on the incidence of pheochromocytoma in the horse. The signs are variable and may be con-

fused with those of other diseases, particularly abdominal pain. Definitive antemortem diagnosis of a functional pheochromocytoma in a horse has not been made, and it is possible that many cases are not recognized, similar to the situation in people (28). Signs may be paroxysmal. Suspicion of pheochromocytoma should be aroused when a mature horse has episodes of, or a sudden onset of sweating, tachycardia, tachypnea, muscle tremors and anxiety. The onset of acute signs in horses with suspected functional pheochromocytomas may be related to the fact that mass release of catecholamines from pheochromocytomas is precipitated by procedures which exert mechanical influences on the tumor (17,29). Pressure may cause expulsion of catecholamine enriched blood from sinusoidal spaces in the tumor (29). This could have occurred in association with expressions of abdominal pain in two horses (Cases 5 and 10) and due to uterine size in late pregnancy in a mare (Case 1).

Laboratory findings may support a diagnosis of pheochromocytoma but are not specific. Hyperglycemia was a consistent finding in horses with suspected functional pheochromocytoma as is the situation in human pheochromocytoma (17). Neutrophilia, lymphopenia hemoconcentration, elevated creatine kinase and blood urea nitrogen were each present in more than one horse although not all horses had a comprehensive laboratory investigation. In these horses there was no correlation between tumor size and the production of signs caused by catecholamine release. This may be because catecholamine release from pheochromocytomas may be greater than the rate of that from the normal adrenal medullary tissue and that pheochromocytomas have the same ultrastructural appearance despite the tumor catecholamine content and a six-fold difference in the rate of catecholamine turnover (3,24).

Myocardial lesions (acute myocardial infarction, case 5 and myocardial degeneration, case 10) in horses with hormonally active pheochromocytoma could have been caused by mass catecholamine release from the tumor. Myocardial ischemia and necrosis is reported in animals subject to large catecholamine doses, people treated

with catecholamines for shock, and is common in people with pheochromocytoma (15,23,30). Cardiac arrhythmias probably developed secondary to myocardial damage due to high systemic catecholamines in one horse (Case 10).

Now that venous norepinephrine levels have been measured in normal horses it will be of great interest to obtain measurements from equine pheochromocytoma patients, especially while the horse is exhibiting clinical signs. In people venous norepinephrine levels in pheochromocytoma patients are ten to fifty times higher than those in other hypertensive patients (31). Should the same trend be present in equine pheochromocytoma then venous norepinephrine measurement could become a diagnostic test for catecholamine producing tumors. This would be invaluable due to the nonspecificity of clinical signs and laboratory findings in horses with hormonally active pheochromocytoma.

Pheochromocytoma in the horse presents a challenging diagnostic problem. Evaluation of therapy in this condition will not be possible until the tumor is identified in the live horse.

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