Evaluation of suspected pituitary pars intermedia dysfunction in horses with laminitis

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Objective—To determine prevalence and clinical features of pituitary pars intermedia dysfunction (PPID) in horses with laminitis.

Design—Case series.

Animals—40 horses with laminitis.

Procedures—Horses with laminitis that survived an initial episode of pain and were not receiving medications known to alter the hypothalamic-pituitary-adrenal axis were tested for PPID by evaluation of endogenous plasma ACTH concentration. Signalment, suspected cause, month of onset and duration of laminitis, Obel grade of lameness, pedal bone rotation, physical examination findings, results of endocrine function tests, treatment, outcome, and postmortem examination findings were recorded.

Results—Prevalence of PPID as defined by a single high plasma ACTH concentration was 70%. Median age of horses suspected of having PPID (n = 28) was 15.5 years, and median age of horses without PPID (12) was 14.5 years. Laminitis occurred most frequently in horses with and without suspected PPID during September and May, respectively. Chronic laminitis was significantly more common in horses suspected of having PPID. In horses suspected of having PPID, the most common physical examination findings included abnormal body fat distribution, bulging supraorbital fossae, and hirsutism. Five horses suspected of having PPID had no clinical abnormalities other than laminitis. Seventeen horses suspected of having PPID that were treated with pergolide survived, and 3 horses that were not treated survived.

Conclusions and Clinical Relevance—Evidence of PPID is common among horses with laminitis in a primary-care ambulatory setting. Horses with laminitis may have PPID without other clinical signs commonly associated with the disease. (J Am Vet Med Assoc 2004;224:1123–1127)

Laminitis is a common, painful, and life-threatening condition with numerous causes. In 1998, 13% of farms in the United States reported a horse with laminitis and 4.7% of horses with laminitis died or were euthanatized.1 A thorough understanding of the etiology of laminitis is necessary for effective treatment and prevention. Most retrospective studies2-5 of horses with laminitis are of horses treated in a hospital setting, and the onset of laminitis is frequently associated with gastrointestinal tract disease. However, this may not be an accurate reflection of laminitis in horses because many are managed by primary-care veterinarians. Results of studies6-8 on naturally occurring laminitis reveal the etiology to be unknown in 23% to 48% of cases. Although laminitis is a common sequel to pituitary pars intermedia dysfunction (PPID [also known as equine Cushing's disease]), PPID is infrequently mentioned as a cause of laminitis. However, in 3 retrospective studies9-11 of horses with PPID, laminitis occurred in 24% to 82% of horses. It is possible that studies on laminitis have not reported PPID as an etiology because affected horses lacked other classical clinical signs of PPID; therefore, endocrine function testing was not performed.

Pituitary pars intermedia dysfunction is the most common equine endocrinopathy. Van der Kolk et al12 reported that 0.5% of horses admitted to a veterinary teaching hospital had PPID. This disease is being more commonly diagnosed because of increases in the awareness of the disease, availability of convenient diagnostic tests, and size of the population of geriatric horses. Evaluation of resting (baseline) endogenous plasma ACTH concentration is a convenient, readily available test with good sensitivity and specificity.13-15

The association between PPID and laminitis is intriguing. Because laminitis is a frequent sequela to PPID, which commonly affects older horses, it is reasonable to suspect that PPID would be prevalent among older horses with laminitis. A multicenter case-control study of the risk factors for laminitis identified an increased risk of chronic laminitis in older horses; however, the cause of laminitis was not investigated.16 Pituitary pars intermedia dysfunction could be the cause of increased risk of laminitis in older horses because PPID is more common in older horses. The purpose of the study reported here was to determine prevalence of PPID in horses with laminitis in a primary-care ambulatory setting. We also sought to describe the clinical features of horses with laminitis and PPID because we hypothesized that many affected horses do not have the physical examination abnormalities commonly associated with PPID.

Materials and Methods

All horses examined by the first author, in the ambulatory service of the Department of Clinical Studies, New Bolton Center from July 1996 to September 2002, that received a diagnosis of laminitis were tested for PPID. The diagnosis of laminitis was made on the basis of physical examination findings, including a palpable increase in hoof temperature, bounding digital pulses, sensitivity to hoof testers, or characteristic gait and stance. Radiography of the distal portion of the affected limbs was performed in all horses. The diagnosis of PPID was made by evaluation of endoge-
Enogenous plasma ACTH concentration by use of a chemiluminescent immunoassay (reference range, 2.0 to 7.7 pmol/L [9 to 35 pg/mL]).

Endogenous plasma insulin concentration was measured by use of a radioimmunoassay (reference range, 57.4 to 215.3 pmol/L [8 to 30 µU/mL]).

All endocrine assays were performed at the Diagnostic Laboratory of the College of Veterinary Medicine, Cornell University. Because of the possibility that severe pain could cause an increase in ACTH concentration, samples for endocrine testing were taken after the acute phase of pain had resolved. Horses were excluded from evaluation by use of ACTH concentration if they received medications known to alter the hypothalamic-pituitary-adrenal axis or if they were euthanatized during the test.

Horses were treated with medications known to alter the hypothalamic-pituitary-adrenal axis or if they were euthanatized during the test. Horses that had ACTH concentrations above the reference range (n = 9) or were not tested (3), the cause of laminitis was unknown (9), associated with dexamethasone administration for recurrent airway obstruction (2), or associated with inadvertent consumption of a large amount of grain (1). In the latter 3 horses, plasma ACTH concentrations were not determined because of the effects of dexamethasone on the hypothalamic-pituitary-adrenal axis or intractable pain; for the purposes of the study, these horses were not considered to have PPID. Excessive consumption of lush pasture was considered a possible cause of laminitis because of the time of year at the onset of lameness and access to lush pasture was reported in 7 of 28 horses suspected of having PPID and 7 of 12 horses without PPID.

The median age of horses suspected of having PPID was 15.3 years (range, 3 to 28 years). There were 7 Quarter Horses, 6 Welsh ponies, 4 ponies of mixed breeding, 3 Morgans, 2 Arabians, 2 Thoroughbreds, 1 Connemara pony, 1 Standardbred, 1 Tennessee Walking Horse, and 1 Warmblood. There were 17 geldings and 11 mares. Median age of horses without PPID was 14.5 years (range, 5 to 19 years). There were 3 Welsh ponies, 2 Tennessee Walking Horses, 2 ponies of mixed breeding, 1 horse of mixed breeding, 1 Appaloosa, 1 Arabian, 1 Quarter Horse, and 1 Warmblood; 9 horses were geldings and 3 were mares.

The most frequent months of onset of laminitis among horses with or without suspected PPID were September (n = 6) and May (5), respectively. There was no significant difference (P = 0.16) in month of onset of laminitis between groups. Statistical evaluation after collapsing groups into 3-month quarters did not reveal a significant seasonal difference between groups.

Chronic laminitis was significantly more common in horses suspected of having PPID (n = 22), compared with horses with ACTH concentrations within reference range (5). Median clinical severity of laminitis (Obel grade) among both groups of horses was 2 (range, 1 to 4). Median degree of rotation of the distal phalanx from the hoof wall among horses with or without evidence of PPID was 6° (range, 0° to 34°) and 8° (range, 0° to 12°), respectively (P = 0.54).

Clinical signs in horses suspected of having PPID included abnormal fat distribution (n = 16), bulging supraorbital fossa (13), hirsutism (10), hyperhidrosis (4), polyuria-polydipsia (4), dermatophilosis (1), and lethargy (1). Five horses did not have any clinical signs of PPID other than laminitis. Median number of clinical signs of PPID was 2 (range, 0 to 6 signs).

For the purposes of this study, horses with ACTH concentrations within reference range were classified as not having PPID; however, many had clinical signs of PPID, including bulging supraorbital fossae (n = 5), abnormal fat distribution (3), hirsutism (2), hyperhidrosis (2), dermatophilosis (1), and lethargy (1). Four horses did not have any clinical signs of PPID other than laminitis. Median number of clinical signs of PPID was 1 (range, 0 to 3 signs).

Median ACTH and insulin concentrations in horses suspected of having PPID were 20.9 pmol/L (95.1 pg/mL; range, 7.9 to 163.2 pmol/L [36.1 to 741.0 pg/mL]) and 774.9 pmol/L (108 µU/mL; range, 53.1 to 3,954.9 pmol/L [7.4 to 551.2 µU/mL]), respectively. Median ACTH and insulin concentrations of horses classified as not having PPID were 5.0 pmol/L (22.8 pg/mL; range, 1.7 to 7.5 pmol/L [7.5 to 34.1 pg/mL]) and 976.9 pmol/L (136.1 µU/mL; range, 92.6 to 1,543.3 pmol/L [12.9 to 215.1 µU/mL]), respectively. There was no significant (P = 0.15) correlation between ACTH concentration and Obel grade among horses suspected of having PPID, nor was there a significant (P = 0.36) difference in insulin concentrations between horses with and without suspected PPID.

Additional diagnostic tests performed in horses with endogenous ACTH concentrations within reference range included the thyrotropin releasing hormone (TRH) stimulation test for cortisol response (n = 3 horses), TRH stimulation test for thyroid function (2), and dexamethasone suppression test (DST) (1).
Evaluation of the cortisol response to TRH revealed baseline cortisol concentrations in the 3 horses within reference range and increases of 81%, 98%, and 120%, respectively, to 15 to 30 minutes after administration of TRH, suggesting the possibility of PPID. Evaluation of the thyroid hormone response to TRH revealed low baseline thyroxine concentration and baseline triiodothyronine concentration within reference range in both horses that were receiving phenylbutazone at the time of the test. After administration of TRH, serum thyroxine concentrations reached maximum values of 440% and 260%, compared with baseline values, whereas triiodothyronine concentrations reached maximum values of 401% and 171%. A dexamethasone suppression test in 1 horse revealed typical suppression of the hypothalamic-pituitary-adrenal axis.

Median duration of treatment with pergolide in horses suspected of having PPID (n = 21) was 11 months (range, 1 to 72 months). The condition of 2 horses deteriorated rapidly before treatment was initiated, and those horses were euthanatized within 1 week of the diagnosis of PPID; the owners of 3 horses declined treatment. Seventeen horses suspected of having PPID that were treated with pergolide survived, whereas 3 horses that were not treated survived (P = 0.14).

Eight horses suspected of having PPID were euthanatized, and postmortem examinations were performed in 6 horses; an adena of the pars intermedia was confirmed in all 6 horses. Horses were euthanatized because of intractable laminitis (n = 3), recurrent airway obstruction (1), septic tenosynovitis secondary to a foot abscess (1), and ataxia associated with vertebral hemangiosarcoma (1). Additional postmortem examination abnormalities included adenocortical hyperplasia (n = 4), gastric ulceration (3), cestodiasis (2), pulmonary abscess, jugular vein thrombophlebitis, and transitional cell carcinoma of the bladder (1 each). Median time from onset of laminitis to euthanasia was 2 months (range, 1 to 46 months).

Two horses with plasma ACTH concentrations within reference range were euthanatized because of laminitis 1 week and 38 months after the onset of laminitis. Postmortem examination was not performed on either horse.

**Discussion**

The diagnosis of PPID was made in this study on the basis of high baseline plasma ACTH concentration. Although the DST has excellent sensitivity and specificity,9 we felt that administration of dexamethasone was not justified in horses with laminitis because of the reported association between laminitis and corticosteroid administration. The sensitivity and specificity of the chemiluminescent immunoassay for ACTH in the diagnosis of PPID are 84% and 78%, respectively.9 Healthy aged and young horses have similar ACTH concentrations.10,11 Although the effects of pain and illness on ACTH concentration in horses have not been systematically evaluated, experimentally induced, short-term, moderate foot pain does not significantly alter plasma ACTH concentration in horses,12 and Couetil et al10 reported ACTH concentrations within reference ranges in 4 horses hospitalized for various illnesses that did not have PPID. Furthermore, in our study, 30% of horses with laminitis had ACTH concentrations within reference range. We obtained samples for determination of ACTH concentration after the initial episode of pain had resolved. Horses without high ACTH concentrations were not included in the PPID group, although many of them had clinical signs of PPID. The authors recognize that not all horses with PPID have high ACTH concentrations and that evaluation of a single sample may lead to a false-negative diagnosis. Although false-positive results might occur because of the stress associated with laminitis and subsequent ACTH release, we think this is unlikely to explain our results.

Mean age of horses with PPID in previous studies4,6,10 was 19 to 21 years, which would appear to represent an older population than the median age of 15.5 years in our study. Previous reports of horses with PPID were retrospective studies from a referral hospital population and therefore might have represented more severely affected horses in the later stages of the disease. Results of the study reported here are consistent with 3 previous descriptive and epidemiologic studies12-14 of laminitis, which revealed that increasing age is a risk factor for laminitis. Age was a risk factor for chronic but not acute laminitis in a population of horses at a veterinary teaching hospital.14 In a combined referral hospital and primary-care practice population, age was again a risk factor for chronic but not acute laminitis.15 The risk of chronic laminitis was clearly increased for older horses in a population of horses at 6 collaborating teaching hospitals.15 In 1 of these studies, colic and grain overload were the most common causes of laminitis; however, in 20% of horses, the cause was unknown.6 Although PPID is associated with both acute and chronic laminitis, it is likely that the chronic nature of PPID would result in chronic laminitis.

Ponies comprised 11 of the 28 equids suspected of having PPID, and 6 of these were Welsh ponies. Furthermore, all ponies had hyperinsulinemia. In an investigation of a treatment for grass-induced laminitis, Welsh ponies were also most common.44 Ponies may be predisposed to PPID; although nearly 40% of the equids suspected of having PPID were ponies, only 7.5% of the general population of equids seen during the study were ponies. Most horses suspected of having PPID in our study were geldings, which is similar to the composition of the practice population. In previous reports, it has been suggested that PPID is more common in females6,10 or males.7,22 A case-control study would be necessary to determine the importance of sex and breed as risk factors for PPID.
Among horses suspected of having PPID, the onset of laminitis occurred most frequently during September, although there was no significant difference between groups. Time of year has been reported as a risk factor for chronic but not acute laminitis. Forty-three percent of 183 cases of chronic laminitis occurred in the third quarter of the year in a study performed at the Texas Veterinary Medical Center. The reason for the seasonal increase in laminitis is unclear. It is possible that seasonal variation in the nutrient quality of grass is associated with the onset of laminitis because many of the horses in our study were maintained on pasture. Excessive carbohydrate consumption has been associated with naturally occurring and experimentally induced laminitis. In 1 investigation, the greatest increases in hydrolyzable carbohydrates in pasture occurred in the mid-Atlantic region in autumn and early spring. Because consumption of hydrolyzable carbohydrate causes laminitis, this may explain the high frequency of laminitis in September in our study. In an evaluation of the exposure of endophyte-infected fescue as a risk factor for laminitis, the greatest number of cases of laminitis occurred during August and September. A seasonal increase in the content of ergot alkaloids in endophyte-infected tall fescue also occurs in some regions in autumn. Finally, seasonal changes in photoperiod may also affect the occurrence of laminitis through alterations in pituitary function. Although PPID may be an important direct cause of laminitis, breed, dietary, and seasonal factors may have a potentiating effect.

Most of the horses suspected of having PPID in our study did not have hirsutism, which is 1 of the most conspicuous and common clinical signs of PPID. Previous retrospective studies of PPID have revealed that hirsutism occurs in as many as 94% of cases; however, retrospective studies may have a selection bias for horses with hirsutism because it is a pathognomonic clinical sign.

The most common clinical sign among the horses suspected of having PPID in the study reported here was an abnormal distribution of fat, including fat deposition in the crest of the neck or the dorsal aspect of the back and tail head. This clinical sign is in contrast to simple obesity in horses in which fat is deposited around the neck, back, tail head, ribs, and flank and caudal to the triceps. The frequency of abnormal distribution of fat in our study was consistent with previous epidemiologic studies of laminitis. In a multicenter case-control study of the risk factors for laminitis, a crested neck was significantly associated with both acute and chronic laminitis. A crested neck was observed in 12% and 15% of horses with acute and chronic laminitis, respectively. Hyperadrenocorticism causes redistribution of fat to the trunk and upper portion of the back in humans and a potbellied appearance in dogs. Abnormal distribution of fat has been reported in 12% to 66% of horses suspected of having PPID but has not been previously reported as the most common clinical finding.

Because some horses with ACTH concentrations within reference range had clinical signs of PPID, we pursued additional diagnostic tests for PPID, including the TRH stimulation test. Although some clinically normal horses may have a small increase in serum cortisol concentration in response to TRH administration, this increase is not as great as that observed in horses suspected of having PPID. However, the sensitivity and specificity of the TRH stimulation test have not been determined. In our study, there was a large increase in cortisol concentration (81% to 120% greater than baseline) in response to TRH administration in 3 horses with ACTH concentrations within reference range; therefore, these horses may have had PPID, and the prevalence of PPID among horses with laminitis is likely to be higher than reported. One horse had a TRH response test result consistent with PPID and a pituitary pars intermedia tumor confirmed post-mortem, but had plasma ACTH concentration within reference range and unremarkable results of the DST.

The hypothalamic-pituitary-thyroid axis was also evaluated in 2 horses with laminitis and ACTH concentrations within reference range. Baseline thyroid hormone concentrations were low. This may have been attributable to administration of phenylbutazone for laminitis. Stimulation tests revealed a large increase in triiodothyronine and thyroxine concentrations, which is also consistent with that seen when thyroid-stimulating hormone is given to horses receiving phenylbutazone.

There are several potential reasons for the hyperinsulinemia seen in 8 of 9 horses in the non-PPID group. Because 3 of these horses had abnormal results of the TRH stimulation test, it is possible that they were incorrectly classified and did have PPID, which is frequently accompanied by hyperinsulinemia. Because most of these horses were overweight, it is possible that hyperinsulinemia was associated with obesity. For example, 1 horse with high insulin concentration, hyperglycemia, a crested neck, and a body score of 8/9 was treated with phenylbutazone, corrective trimming, and dietary restriction. After 4 months of treatment, body weight decreased by 14%, glucose and insulin concentrations were within reference range. Baseline thyroid hormone concentrations were low. This may have been attributable to administration of phenylbutazone for laminitis. The detection of hyperinsulinemia in our study was notable because alterations in glucose metabolism have been implicated in the pathogenesis of laminitis.

In humans, insulin resistance and obesity are associated with abnormal activity of the isofrom of 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1), which converts inactive cortisone to active cortisol. In the hoof lamellae of horses with laminitis, 11β-HSD1 activity may also be abnormal. Although laminitis was most frequently associated with PPID in the study reported here, it is possible that some horses were affected by abnormal 11β-HSD1 activity, which warrants further investigation.

Numerous mechanisms for corticosteroid or PPID-induced laminitis have been proposed. Corticosteroids sensitize the digital arterial and venous endothelium of horses to the effects of catecholamines. Hypertension has been reported in horses with laminitis and hyperadrenocorticism, but it has not been critically evaluated. Hypertension is common in dogs with hyperadrenocorticism. The catalytic effects of corticosteroids may also affect the integrity of the laminae.
Our findings suggest that PPID is common among horses with laminitis in a primary-care setting. Furthermore, horses with PPID and laminitis may not have hirsutism but frequently have abnormal distribution of fat. Identification of PPID in horses with laminitis and subsequent treatment with pergolide may improve outcome.

References