Pituitary Pars Intermedia Dysfunction: Challenges of Diagnosis and Treatment

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Despite increased recognition of pituitary pars intermedia dysfunction (PPID) in horses, diagnosis and treatment of this disorder remains challenging. Hirsutism is the best clinical indicator of PPID, and currently, the overnight dexamethasone-suppression test is the most accepted and practical supportive endocrinologic laboratory test. Treatment success is best accomplished with a dopamine agonist (pergolide) coupled with careful management and reassessment twice a year, including repeat endocrinological testing. Author's address: Department of Large Animal Clinical Sciences, D-202 Veterinary Medical Center, Michigan State University, East Lansing, MI 48824; e-mail: schott@cvm.msu.edu.

1. Introduction

Diagnosis and treatment of pituitary pars intermedia dysfunction (PPID) in horses, commonly referred to as equine Cushing's disease, has increased dramatically over the past decade. Increased recognition of the disease is likely a result of clients maintaining their equine companions to more advanced ages as well as increasing provision of health care (i.e., nutrition and dentistry) to these older horses. All breeds and types of equids can be affected with PPID, but Morgan horses and ponies seem to be at greater risk.[1,2] There is no gender predilection; age of onset of clinical signs is generally 18–23 yr, but horses as young as 7 yr have been reported to have PPID (Table 1).[3–9]

In humans and dogs, Cushing's disease is most commonly attributed to a corticotroph adenoma in the pars distalis (anterior lobe) of the pituitary gland. In contrast, Cushing's disease in horses is almost exclusively attributed to hyperplasia or adenoma formation in the pars intermedia; consequently, PPID is the preferred term for the disorder. Recent evidence suggests that PPID is more likely a primary hypothalamic disease caused by oxidant-induced injury and degeneration of dopaminergic neurons that regulate the pars intermedia.[10] Hypothalamic dopaminergic neurons normally exert an inhibitory effect on production of pro-opiomelanocortin (POMC) by pituitary pars intermedia melanotropes. Thus, loss of inhibitory control leads to proliferation of pars intermedia melanotropes and excess production of POMC-derived peptides, including adrenocorticotropin (ACTH).

2. Clinical Findings

Clinical signs in 176 horses with PPID are detailed in Table 2.[3–9] The classic clinical sign of PPID in horses is hirsutism, which is a long and curly hair coat that fails to shed. In some affected horses, coat-color changes can also occur. The pathogenesis of hirsutism, characterized by arrest of hair follicles in telogen, remains poorly understood. Hyperhidrosis (excessive sweating) is also observed in up to two-thirds of horses with

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Table 1. Characteristics of 176 Horses and Ponies With Clinical Signs of Pituitary Pars Intermedia Dysfunction

	Heinrichs et al. (1990)*	Hillyer et al. (1992)	Boujon et al. (1993)*	van der Kolk et al. (1993)*	Couëtil et al. (1996)	Schott et al. (2001)	Frank et al. (2006)*
number of equids	19	17	5	21	22	77	17
number of ponies	NR**	11 (65%)	NR	12 (63%)	11 (50%)	15 (19%)	0 (0%)
age: mean (range)	19.1 (7–31)	20.2 (12–34)	18.2 (13–24)	21 (12–30)	21.5 (8–31)	22.8 (12–34)	23 (9–33)
sex	11♀/6♂/2NR	6♀/11♂	4♀/1♂	8♀/13♂	11♀/11♂	37♀/40♂	8♀/9♂

*Reports in which pituitary gland pathology was confirmed by post-mortem examination.
**NR, not reported.

PPID, most commonly over the neck and shoulders, and it has been attributed to a thermoregulatory response to the long-hair coat. Lethargy, or decreased performance, has also been reported in horses with PPID. Loss of epaxial and rump muscle mass because of protein catabolism with increased cortisol activity can be notable in more advanced cases. Dental abnormalities that can lead to painful mastication and quidding may also compromise feed intake and contribute to weight loss in some horses. Combined with, or often preceding, loss of muscle mass can be deposition of fat along the crest of the neck, over the tail head, and in the sheath of male horses. Another area where abnormal fat deposition may occur is above and behind the eyes (supraorbital fossa).

Chronic, insidious-onset laminitis is perhaps the major clinical complication of PPID with >50% of horses affected in most reports.[4,6–9] Although this condition is more amenable to management in ponies because of their lower body weight, chronic or recurrent pain with exacerbation of laminitis and associated foot abscesses is often the reason euthanasia is pursued. Polyuria (PU) and polydipsia (PD) develops in about one-third of horses with PPID.[2] Equids with PPID may have delayed wound healing and can have secondary infections including skin infections, recurrent subsolar abscesses, alveolar periostitis and sinusitis, conjunctivitis, gingivitis, and bronchopneumonia. Other clinical signs that have been reported in horses with PPID are persistent lactation and infertility, which are probably a consequence of altered release of prolactin and gonadotrophic hormones. Signs of central nervous system (CNS) dysfunction, including ataxia, blindness, and seizure-like activity, are also occasionally observed in equids with PPID, but the cause of these neurological deficits is poorly understood. A final, and sometimes disastrous, musculoskeletal complication that may develop in an occasional horse with PIPD is suspensory ligament desmitis and breakdown.

Abnormal laboratory data in horses with PPID may include mild anemia, an absolute or relative neutrophilia, and an absolute or relative lymphopenia.[1,2] The most common abnormality detected on serum biochemical evaluation is mild to moderate hyperglycemia, which is reported in 25–75% of cases depending on the upper limit of the reference range used. Additional abnormal biochemical findings may include elevations in hepatic enzyme activities, hypercholesterolemia, and hypertriglyceridemia. Urine specific gravity ranged from 1.022 to 1.047 in a series of 18 PPID horses, but glucosuria was not detected unless hyperglycemia (>175–200 mg/dl) was also present.[11] In addition, silent urinary-

Table 2. Clinical Signs in 176 Horses and Ponies With Pituitary Pars Intermedia Dysfunction

	Heinrichs et al. (1990)*	Hillyer et al. (1992)	Boujon et al. (1993)*	van der Kolk et al. (1993)*	Couëtil et al. (1996)	Schott et al. (2001)	Frank et al. (2006)*
hirsutism	47%**	94%	100%	100%	95%	83%	77%
hyperhidrosis	NR***	59%	67%	NR	14%	33%	NR
weight loss/muscle wasting	NR	88%	NR	38%	50%	47%	35%
abnormal fat distribution	NR	12%****	67%	19%****	9%****	29%	NR
lethargy	NR	82%	NR	NR	43%	NR	NR
chronic laminitis	NR	82%	NR	24%	59%	52%	29%
polyuria and polydipsia	26%	76%	17%	NR	32%	34%	NR
chronic infections	32%	48%	33%	NR	27%	NR	NR
neurological signs, including seizures	21%	6%	50%	10%	NR	NR	NR

*Reports in which pituitary gland pathology was confirmed by post-mortem examination.
**The low frequency of hirsutism in this report may be due to the fact that it was a pathological study in which clinical signs were not comprehensively described.
***NR, not reported.
****Reports describing only supraorbital fat deposition.

tract infection (urine bacterial colony forming unit counts >10,000/ml) can be found in an occasional horse (unpublished observation).

3. Diagnosis

Clinical Signs

Practically, the diagnosis of PPID is most commonly made by observation of hirsutism and other supportive clinical signs in older equids.[1,2] In fact, in a recent study that compared the sensitivity, specificity, and positive and negative predicative values of hirsutism with results of a combined dexamethasone suppression/thyrotropin-releasing hormone stimulation test, presence of hirsutism had greater diagnostic accuracy than endocrinologic test results.[9] Because hirsutism seems to be a pathognomonic clinical feature of PPID, an "over the fence" diagnosis by this finding alone is often made. However, to provide the best service to the horse and its owner, a complete physical exam, including a good oral exam and determination of body condition score (BCS) and weight, should be performed when patients are initially evaluated for suspected PPID. In addition, collection of blood samples for a complete blood count, serum chemistry profile, and baseline endocrinologic testing are also recommended if the clients desire to provide the highest level of care for their horses. Endocrinologic tests that are available include both dynamic tests assessing the responsiveness of the hypothalamic pituitary adrenal (HPA) axis as well as single-sample "screening" tests.

Dynamic Endocrinologic Tests

Loss of Diurnal Cortisol Rhythm

Because endogenous cortisol concentration can be low, within the reference range, or elevated in horses with PPID, measurement of plasma-cortisol concentration alone is not a valid diagnostic test.[1,2] Endogenous cortisol concentration has also been well documented to have a diurnal rhythm in horses; there is an increase in the morning hours and a nadir around midnight. Dybdal et al.[12] originally reported loss of this diurnal pattern in horses with PPID but stated that "diurnal variations in plasma cortisol concentration were not statistically different between control horses and those with PPID." Although the number of horses tested was rather small (12 control and 12 PPID horses), these authors[12] concluded that large variations in cortisol concentrations at all times of the day precluded use of loss of diurnal rhythm as an accurate diagnostic test for PPID. Nevertheless, based on this study, one private laboratory[a] continues to recommend this test as a screening tool for evaluation of horses with suspected PPID. Loss of diurnal rhythm is arbitrarily defined as <30% variance between cortisol concentrations measured in plasma samples collected in the morning and evening. This protocol is reportedly based on testing ~1000 horses with suspected PPID; however, the population evaluated with the test was skewed to breeding animals with infertility. Further, the investigator advocating loss of cortisol rhythm as a diagnostic test for PPID has suggested that this test is more sensitive than the dexamethasone-suppression test, "because equine Cushing's disease must be present for five or more years" for the latter test to become useful.[13] Unfortunately, the claims made by this investigator are difficult to substantiate because the data on which the claims are based have not been published.[13] Finally, a number of external stressors including fasting, changes in stabling, anesthesia and surgery, and disease (e.g., laminitis) may all increase plasma cortisol concentration as well as alter diurnal rhythm. Thus, loss of diurnal cortisol rhythm cannot be recommended as an accurate diagnostic test for PPID.

Dexamethasone Suppression Test

The overnight dexamethasone suppression test (ODST) is considered by many equine clinicians to be the "gold standard" endocrinologic test to support a diagnosis of PPID. The major limitation of the ODST is the concern, albeit poorly documented, that administration of the test dose of dexamethasone may exacerbate laminitis. As originally published by Dybdal et al.,[12] the ODST consists of measuring cortisol in the late afternoon, administering dexamethasone (40 μg/kg, IM or 20 mg to a 500 kg horse), and subsequently, measuring plasma cortisol concentration the following morning, 15 and 19 h after dexamethasone administration. A normal result is suppression of endogenous cortisol concentration to a value <1 μg/dl (~30 pmol/l) after dexamethasone administration, whereas a cortisol concentration exceeding this value at either 15 or 19 h supports a diagnosis of PPID. It is important to emphasize that this test is one of the few that was validated in horses in which pars intermedia pathology was confirmed at necropsy examination. However, it also warrants emphasis that most of the horses in this study also had rather advanced clinical disease.

The obvious limitation of this ODST test protocol for ambulatory practitioners is that it requires three visits to the horse. As a consequence, the test has been modified to collection of only one follow-up sample, usually between 17 and 19 h after dexamethasone administration. Furthermore, the cortisol value of greatest interest is that in the post-dexamethasone administration sample because cortisol concentration in the pre-dexamethasone administration sample can be below, within, or above the limits of the reference range. At present, no diagnostic or prognostic information is really gleaned from this pre-dexamethasone administration sample cortisol concentration. Thus, a further modification of the ODST can be to dispense the dose of dexamethasone to the client and have them administer it intramuscularly to their horse; the vet-

erinarian can make a single farm visit the next morning for examination of the horse and collection of the post-dexamethasone administration blood sample. However, a disadvantage of this modification is that the dose of dexamethasone could affect other blood measurements, specifically glucose. Nevertheless, this one-visit test can be useful for veterinarians with a large practice area, and it can be a useful protocol for follow-up endocrinologic testing for patients that are already receiving treatment.

When using the ODST for diagnostic evaluation of suspected PPID, this author likes to think of the dose of dexamethasone as a "sledgehammer" in terms of providing feedback to the HPA. In other words, failure of dexamethasone to induce suppression of endogenous cortisol concentration is strongly supportive of PPID. Thus, another limitation of the ODST is that it may not be accurate for diagnosis of PPID in earlier stages of the disease process when some feedback to the HPA remains. For most horses with "early PPID" and normal ODST results, this may not be an important limitation; in the early stages of PPID, medical treatment of PPID may be difficult to justify, because clipping the hair coat and improving management (e.g., nutrition, dentistry, deworming, etc.) may be all the additional care that is needed. The exceptions, of course, are horses suffering from laminitis and competitive horses that are showing a decline in performance. In such horses, repeat testing in 2–4 wk can be useful, because one small study found that ODST results were not always consistent over time.[14] Next, the difference between test results revealing partial suppression and complete suppression (to <1 μg/dl) remains unclear. It would seem logical that horses with partial suppression would have less severe disease than horses with essentially no suppression, but such an assumption cannot currently be supported by either clinical or post-mortem data.

Thyrotropin Releasing Hormone Stimulation Test

Thyrotropin releasing hormone (TRH), produced in the hypothalamus, stimulates release of thyrotropin (TSH) from the pituitary gland. However, in both humans with Cushing's disease and horses with PPID, exogenous TRH administration also increases plasma concentrations of ACTH, α-melanocyte stimulating hormone (α-MSH), and cortisol.[15,16] This response has been attributed to upregulation and expression of TRH receptors in hyperplastic/adenomatous corticotropes in the pars distalis as well as in hyperplastic/adenomatous melanotropes in the pars intermedia. As originally described by Beech and Garcia,[15] the TRH stimulation test involves administration of 1 mg of TRH (0.5 mg to a pony) IV and measurement of plasma cortisol concentration before and from 15 to 60 min after TRH administration. In 11 equids (7 horses and 4 ponies) with PPID, plasma cortisol concentration increased by 120% 30 min after TRH administration, whereas the increase was only ~20% in 12 healthy mature horses.[15] Although these authors did not specify either a percentage or absolute increase in cortisol concentration that they considered diagnostic for PPID, subsequent authors have suggested that plasma cortisol concentration should increase by 30–50% 30 min after TRH administration.[2,16] The advantage of the TRH stimulation test over the ODST is that it is considered safer to perform in laminitic horses, because dexamethasone administration is avoided. Unfortunately, because the test measures a percentage increase in cortisol concentration, interpretation of the results can be complicated by variation in baseline cortisol concentration. Further, McFarlane et al.[16] recently found a $>30\%$ and a $>50\%$ increase in cortisol concentration in 10 of 16 and 7 of 16 normal horses, respectively, which indicates that the TRH stimulation test may not be the most appropriate diagnostic test for PPID.

Combined DST/TRH Stimulation Test

In an attempt to overcome the problem of variability of baseline cortisol concentration and to improve test sensitivity and specificity, a combined DST/TRH stimulation test was developed by investigators at the University of Tennessee.[9,17,18] In theory, administration of dexamethasone before TRH leads to suppression of ACTH release from pars distalis corticotropes such that any increase in cortisol after TRH administration can be attributed to pars intermedia melanotropes. With the most recent modification (simplification) of this test, dexamethasone (40 μg/kg) is administered 3 h before TRH administration to suppress endogenous cortisol concentration to similar baseline values in both PPID-affected and normal horses. Cortisol concentration is subsequently measured 30 min after TRH administration and again 24 h after dexamethasone administration (two cortisol measurements after the post-dexamethasone baseline sample). Either a $\geq 66\%$ increase in plasma cortisol concentration 30 min after TRH administration or a plasma cortisol concentration >1 μg/dl 24 h after dexamethasone administration is considered diagnostic for PPID.[18] In a recent report in which the combined DST/TRH stimulation test results were compared with histological findings in the pituitary glands of 42 horses (age, 2–33 yr), the combined test was more accurate (81%) than either the DST (71%) or TRH (71%) component of the test alone.[9] Unfortunately, all endocrinologic test results were less accurate than hirsutism alone (86%). Furthermore, the combined test is both more expensive for the client as well as less practical for the ambulatory clinician than the ODST. As a consequence, use of this combined test has not gained wide acceptance.

Single-Sample Endocrinologic Tests

Although dynamic endocrinologic tests generally provide greater information about the status of the

HPA axis, they are cumbersome for ambulatory practitioners and more expensive for their clients. Thus, the ideal endocrinologic test would consist of measuring one or more hormones or other markers of PPID in a single blood sample collected without administration of any exogenous agent.

POMC-Derived Peptides

Because horses with PPID produce excessive amounts of POMC and POMC-derived peptides, including ACTH, α-MSH, and β-endorphin (β-END), circulating concentrations of these hormones were logical choices to measure. In fact, increased plasma ACTH, α-MSH, and β-END concentrations have been documented in horses with PPID.[7,19,20] However, sample handling can be problematic; for example, ACTH can be adsorbed onto glass and degraded by proteolytic enzymes in both whole blood and plasma. Although reference range values exceeding 50 pg/ml (~11 pmol/l) are generally considered elevated, various laboratories may use different assays for measuring ACTH and report varying values. Finally, measurement of α-MSH and β-END are not commercially available.

Recent reports have also documented substantial seasonal variation in both plasma ACTH and α-MSH concentrations; >90% of normal ponies and horses had ACTH concentrations above the threshold value for diagnosis of PPID in September compared with <5% in January or May.[19,21] The higher values in the fall seem to be a consequence of changes in pituitary gland function with decreasing day length (hormonal changes associated with preparation for winter). Of interest, although less affected by season than ACTH concentration, ODST results were also abnormal (supportive of PPID) in 10 of 39 (26%) equids in September.[21] These recent findings seem to have led to a decline in the popularity of using plasma ACTH concentration as the sole endocrinologic test for diagnosis of PPID. Furthermore, regardless of the endocrinologic test employed, test results obtained from August to September (in the northern hemisphere) should be interpreted with caution, and it is perhaps better to avoid performing these tests during this time of year altogether.

Insulin

It has long been recognized that equids, especially ponies, with PPID are less able to utilize orally or intravenously administered glucose because of insulin insensitivity.[4,11,22] Additionally, the frequency of hyperinsulinemia seems to be greater than that of hyperglycemia.[4,11,23,24] Because cortisol and insulin have antagonistic metabolic effects, hyperinsulinemia has often been attributed to excess circulating cortisol in PPID-affected animals. As a consequence, measurement of serum insulin concentration has also been investigated as a potential single-sample endocrinologic test for a diagnosis of PPID. In a report of 12 horses and ponies with clinical signs of PPID and histologically confirmed lesions in the pars intermedia, measurement of fasting insulin concentration had a sensitivity of 92% using a cutoff point of 57 μU/ml (~400 pmol/l; there was a range of 35–260 μU/ml in PPID-affected animals compared with a range of 27–53 μU/ml in normal horses).[23] Unfortunately, hyperinsulinemia can accompany other disorders such as the recently described equine metabolic syndrome.[25] Thus, use of serum insulin concentration alone as a supportive test for diagnosis of PPID can be misleading, because hyperinsulinemia is not specific for PPID. Nevertheless, measurement of fasting insulin concentration at the initial evaluation of horses suspected to have PPID is worthy of consideration. McGowan et al.[26] recently reported that the long-term survival for horses with PPID was poorer when concurrent hyperinsulinemia was detected before treatment. This is logical, because an elevated fasting insulin concentration, supportive of a risk for development of type II diabetes, would suggest dysregulation of glucose homeostasis, a major metabolic complication of PPID.

Radiography, Computed Tomography, and Magnetic Resonance Imaging

Ventrodorsal radiography and computed tomography have been used to document enlargement of the pituitary gland in equids with PPID[27]; however, the sensitivity and specificity of imaging modalities has not been evaluated. They would not be expected to approach 100%, because the diseased pituitary was grossly increased in size in only 68% of horses with PPID in one report.[3] Thus, at present, these procedures constitute both an unnecessary risk (general anesthesia) and expense to provide limited diagnostic information. These imaging modalities, or magnetic resonance imaging, may become more important tools if surgical treatment of PPID becomes an option in the future.

What Constitutes a Gold Standard?

Whenever a diagnostic test is developed to test for a disease, a "gold standard" for comparison is required to establish the sensitivity, specificity, and overall accuracy of the test. So what constitutes a gold standard for diagnosis of PPID? Many investigators have used presence of one or more clinical signs, specifically hirsutism, as their gold standard, whereas others have argued that histopathological evidence of abnormal pituitary pars intermedia tissue is essential for confirmation of the disease. So who is right? This is actually not such an easy question to answer, and to address it, we should reconsider the currently accepted term for the disease: pituitary pars intermedia dysfunction. The word dysfunction clearly suggests that a gold standard should include some clinical or laboratory abnormality of the disease in addition to histopathological evidence of pars intermedia pathology. As mentioned previously, hirsutism seems to be

pathognomic for PPID in older equids. Thus, presence of this clinical sign could be considered the gold standard, at least for more advanced cases of PPID. Histopathological evidence of disease would also seem to be an excellent gold standard. However, hypothalamic neuronal degeneration leading to hyperplasia and/or development of micro- or macroadenomas in the pars intermedia likely progresses over a long time such that pathologic changes may be present for years before clinical signs of PPID become apparent. Thus, in actuality, histopathological evidence of disease may not be the most appropriate gold standard. To evaluate this supposition, McFarlane et al.[28] recently evaluated the degree of agreement between seven veterinary pathologists asked to examine histological sections of pars intermedia tissue collected from 10 horses with mild signs of PPID. They found that post-mortem assessment was in agreement with ante-mortem endocrinologic test results 79% of the time, but they also reported that there was minimal agreement between pathologists for 5 of 10 tissues samples examined histologically.[28] Another recent study documented that the size and histological anatomy of the pituitary gland varies with age and gestation status in mares and also found histological lesions in the pars intermedia of nearly 50% of horses without clinical signs of PPID.[29] These data further call into question the validity of histopathological evidence of pars intermedia disease as a gold standard, at least until uniform diagnostic criteria are established by veterinary pathologists.

Challenges of Diagnosis—Does a "Pre-Cushingoid" Disease Exist?

It is clear that most equine practitioners have little difficulty making a diagnosis of PPID in horses with obvious hirsutism. Unfortunately, hirsutism is not always present with PPID, and we remain challenged when asked to examine mature horses with acute or chronic laminitis that have minimal haircoat changes. There is also a lot of current interest in the potential detrimental effects of "early PPID" on competitive performance of middle-aged and older horses that may have intermittent foot soreness or other vague clinical complaints. Establishing a diagnosis of PPID in these less severely affected horses that are possibly earlier in the course of the syndrome is currently one of the greatest challenges facing equine veterinarians caring for these middle-aged to older equine athletes. Unfortunately, there has been little investigation of endocrinologic testing in this population of horses. As a result, approach to these patients is currently based on subjective information and experience. This author still recommends a complete diagnostic evaluation, including physical examination, a complete blood count and serum biochemistry, and lateral hoof radiographs. In addition, I currently recommend endocrinologic testing including an ODST and measurement of ACTH and insulin concentrations as a baseline hormonal profile. Interpretation of these test results is not often straightforward, and testing may need to be repeated 30–60 days later. As will be discussed in the following section, these patients may be treated with various medications in a "trial and error" approach in an attempt to limit the damage that may accompany laminitis or to enhance performance.

4. Treatment

Management

Treatment of equids with PPID initially involves attention to general health care along with a variety of management changes to improve the condition of older animals. In the earlier stages of PPID, body clipping, correction of dental abnormalities, and improved nutrition may be the only actions needed. Affected horses or ponies may also have to be separated from herd mates if they are not getting adequate access to feed. Because the major musculoskeletal complication of PPID is chronic laminitis, regular hoof care is essential to lessen the risk of flare-ups. Because many PPID-affected patients may also have secondary infections, long-term or intermittent administration of antibiotics, typically a potentiated sulfonamide, may be necessary.

Medical Treatment

Medications used to treat equids with PPID include serotonin antagonists (cyproheptadine) and dopamine agonists (pergolide mesylate).[1,2] Cyproheptadine, a drug with anti-serotonin actions, was one of the initial drugs used for treatment of PPID, because serotonin had been shown to be a secretagogue of ACTH in isolated rat pars intermedia tissue. Furthermore, the drug was effectively used to treat human patients with Cushing's disease.[30] Although early reports that treatment with cyproheptadine (0.25 mg/kg, q 12–24 h, PO) resulted in clinical improvement have been disputed because of the similar clinical improvement seen with improved management alone, it is likely that this drug may be of some benefit to horses with PPID. Adverse effects of cyproheptadine seem to be minimal. Because the drug also has anti-histamine actions, mild sedation may be noticed when higher dosages are used.[31]

Because loss of hypothalamic dopaminergic innervations seems to be a critical pathophysiologic mechanism for PPID, treatment with dopaminergic agonists represents a logical approach to therapy. Unfortunately, early dosage recommendations of pergolide (6–10 μg/kg, q 24 h, PO [3–5 mg/day for a 500-kg horse]) were prohibitively expensive for many clients, especially before the era of compounding pharmacies.[31] However, at the 1995 Annual American Association of Equine Practitioners Convention, Peters et al.[32] presented a series of equids that were reported to respond favorably to a much lower dose of pergolide (2 μg/kg, q 24 h, PO [1 mg/day for a 500 kg horse]). This report prompted increased use of pergolide, and treatment of PPID

with this drug has subsequently been shown to be more effective than treatment with cyproheptadine in three independent studies.[8,33,34] The most common adverse effect of pergolide, recognized in 5–10% of horses, is a mild decrease in appetite during the first few days after treatment has been initiated.[8] When this problem develops, treatment is stopped for a couple of days and reinstituted at one-half the previous dose; most horses seem to tolerate this approach. Exacerbation of laminitis with pergolide therapy was also an anecdotal concern when use of the drug became popular several years ago. However, no evidence has been forthcoming to support that pergolide treatment may increase the risk of development or exacerbation of laminitis in horses with PPID.

Recently, studies by McGowan et al.[35] in the United Kingdom have examined the use of trilostane for treatment of equids with PPID.[26,35] Trilostane (currently not available in the United States) is a competitive inhibitor of 3-β-hydroxysteroid dehydrogenase, an adrenocortical enzyme necessary for production of cortisol. Because adrenocortical hyperplasia is recognized in, at most, 20% of horses with PPID,[3,5] drugs targeting adrenal steroidogenesis would intuitively seem less likely to be effective than drugs acting to decrease production and secretion of POMC peptides by the pars intermedia. Nevertheless, treatment with trilostane (0.4–1.0 mg/kg, q 24 h in feed) was shown to be effective in reversing clinical signs in a series of equine PPID cases, yet correction of abnormal endocrinologic test results was less convincing.[35]

Challenges of Treatment

Despite fairly common acceptance that pergolide is the drug of choice for treatment of PPID, equine practitioners are faced with numerous challenges with medical treatment of this disorder. First, none of the drugs used for treatment of PPID are approved for use in horses. Second, neither safety studies nor pharmacological studies to document bioavailability of these orally administered medications and variability in drug absorption, metabolism, and elimination have been performed in horses or ponies. Third, veterinarians are occasionally faced with pregnant mares that seem to have an acute onset of PPID signs during gestation. Although no published data exist, mares with this problem have been treated with pergolide without apparent adverse effects, which leads this author to conclude that the current "standard of practice" does not find use of pergolide in pregnant mares contraindicated.

On a more practical note, deciding when treatment should be initiated can also be challenging. Because hirsutism can be effectively managed for $\geq$1 yr by body clipping alone, should all horses with hirsutism receive drug treatment? The answer to this question is dependent on both the owner's concerns and finances. A clear argument can be made in support of medical treatment when clinical signs are initially recognized, because this can minimize progression of PPID and prolong the life of the older horse. At present, however, no data exist to document that early medical intervention affects long-term outcome. Next, it is unclear whether drug treatment needs to be continuous or if it can be intermittent; only long-term longitudinal studies comparing various treatment regimens would answer this question, and such studies are unlikely to be performed. Finally, it is unknown whether or not multiple drug treatment (e.g., concurrent use of pergolide and cyproheptadine or pergolide and trilostane) could produce a greater clinical response than use of pergolide alone. Again, long-term prospective studies would be necessary to determine the potential synergistic effects of a multiple-drug approach compared with treatment of PPID with pergolide alone.

At present, it is the author's recommendation that initial medical treatment for equids with PPID should be pergolide at a dose of 2 μg/kg, q 24 h, PO. If no improvement is noted within 4–8 wk, the daily dose can be increased by 2 μg/kg monthly up to a total daily dose of 6 μg/kg. Assessment of clinical improvement can be challenging, depending on the time of year that treatment is started. For example, improved shedding of hair coat is better recognized if treatment is initiated in March compared with October. Nevertheless, owners frequently report other responses to medication including improved attitude and energy level, decreased water consumption, and decreased sweating. If only a limited response is observed with 6 μg/kg of pergolide daily and endocrinologic test results remain abnormal, cyproheptadine (0.25 mg/kg, q 12 h, PO) is added to pergolide therapy. However, it should be emphasized that these recommendations are based on the author's clinical experience alone.

Pergolide mesylate is available as pharmaceutical-grade tablets (Permax) or through a number of compounding pharmacies as either a liquid suspension or a dry granule form (as a top dressing for feed or formulated into a horse treat). The major advantage of the compounded products is lower cost, and this author prefers a liquid suspension because of the concern that use of horse treats could lead to accidental consumption of a large dose of pergolide. Recently, concerns have also been raised that pergolide may not remain stable in an aqueous solution (suspension) for $>$7 days, and most compounding pharmacies now only dispense a 30-day supply of the suspension. One pharmacy that the author routinely uses recently tested stability of its pergolide suspension and found no degradation after 30 days (under ideal storage conditions).

As with many chronic diseases in the horse, specific nutrient supplementation and complementary or alternative therapies, including acupuncture, homeopathy, and herbal remedies, have been recommended and used in equids with PPID. Both magnesium and chromium supplementation have

been advocated for supportive treatment of this condition. Magnesium supplementation (to achieve a dietary calcium to magnesium ratio of 2:1) has been recommended, because magnesium deficiency seems to be a risk factor for insulin insensitivity and type 2 diabetes in humans; additionally, anecdotal reports suggest that supplementation may help horses with obesity-associated laminitis. Similarly, chromium supplementation is recommended to improve carbohydrate metabolism (specifically glucose uptake) and improve insulin sensitivity in type-2 diabetes, and supplementation with chromium tripicolinate has been shown to increase glucose uptake during a glucose tolerance test in normal yearlings.[36] Over the past few years, an herbal product made from chasteberry (Evitex, formerly Hormonize) has also been advocated for treatment of PPID. However, the claim was supported with a series of case testimonials in which the diagnosis of PPID was poorly documented, and a field study presented at the 2002 Annual American Association of Equine Practitioners Convention by Beech et al.[37] showed that this herbal product was ineffective for treatment of PPID.

As mentioned above, a final challenge is how to approach treatment of mature, non-hirsuit horses with insidious-onset laminitis or horses suffering from chronic laminitis for which an inciting cause cannot be identified and endocrinologic test results are non-supportive of PPID. In these instances, pergolide is sometimes tried for 3–6 mo as a "trial and error" treatment in these individuals. Unfortunately, because clinical improvement is the only endpoint assessed with this approach, efficacy of the medication is impossible to establish. Nevertheless, because adverse effects of pergolide and cyproheptadine seem to be minimal, such "trial and error" treatment is not unreasonable to pursue as long as clients are informed of the limitations to this approach.

Monitoring Disease Progression

It is important to recognize that the rate of clinical improvement is higher than that for normalization of hyperglycemia and endocrinologic test results. Thus, it is prudent to measure blood glucose concentration and perform follow-up endocrinologic testing (ODST or plasma ACTH concentration) regularly. When managing an equid with PPID, these tests should be repeated about 1 mo after a change in medication dose or twice yearly in horses that seem to be stable.

Prognosis

Once present, PPID is a lifelong condition, and the prognosis for correction of the disorder is poor. However, PPID can be effectively treated with a combination of management factors and medications. Thus, the prognosis for life is guarded to fair. There has been limited longitudinal studies of equids with PPID, but in one report, survival time from initial diagnosis to development of complications necessitating euthanasia ranged from 120 to 368 days in four untreated horses.[11] Furthermore, there are numerous anecdotal reports of horses being maintained for several years as long as response to medical treatment was favorable and close patient monitoring and follow-up was performed. Because a recent case series found that concurrent presence of hyperinsulinemia with PPID was a negative prognostic factor,[26] measurement of fasting insulin concentration in the initial evaluation and ongoing management of horses with PPID is also recommended.

5. Case Examples

Case 1

Case 1 is a 28-yr-old Dutch Warmblood mare. The mare had had a successful career as a dressage horse and was acquired by the current owner 7 yr previously for occasional light dressage work and trail riding. Over the past 5 yr, the mare had received thyroid hormone supplementation for mild lethargy and delayed shedding of the winter hair coat (dynamic testing of the hypothalamic-pituitary-thyroid axis had not been pursued). Additional problems included loss of muscle mass over the topline during the previous winter and intermittent painful swellings along the abdomen that resolved without specific treatment. There was no history of laminitis. The mare received regular dental care, and she was on a diet of Equine Senior (4 lbs twice a day) and ad libitum hay or pasture depending on the time of year.

The mare was presented to the referring veterinarian for a general health exam in July of 2005 and was found to be in good body condition (BCS = 5 of 9), but long hairs were apparent under the chin and along the back of the forelimbs and hindlimbs. No major health problems were detected, but an ODST was pursued for evaluation of possible PPID. The pre-dexamethasone cortisol concentration was 121 nmol/l (reference range = 85–180 nmol/l), and an 18-h post-dexamethasone cortisol concentration was 124 nmol/l (reference range = <30 nmol/l). Based on these results, treatment with pergolide was recommended.

The mare was subsequently presented to Michigan State University's Veterinary Teaching Hospital 1 mo later for a second opinion (Fig. 1). Examination findings were similar to those reported previously with the additional finding of several crusted skin lesions along the abdomen and rump. No significant dental abnormalities were found. BCS was 5 of 9, and weight was 510 kg (Fig. 2).

Case 1 Questions

1. Should the Dexamethasone Suppression Test Be Repeated?

It certainly could be repeated to provide further supportive evidence for PPID, but there is no reason to discount the results provided by the referring veterinarian. We elected not to repeat the test, because it would have required overnight hospitalization.

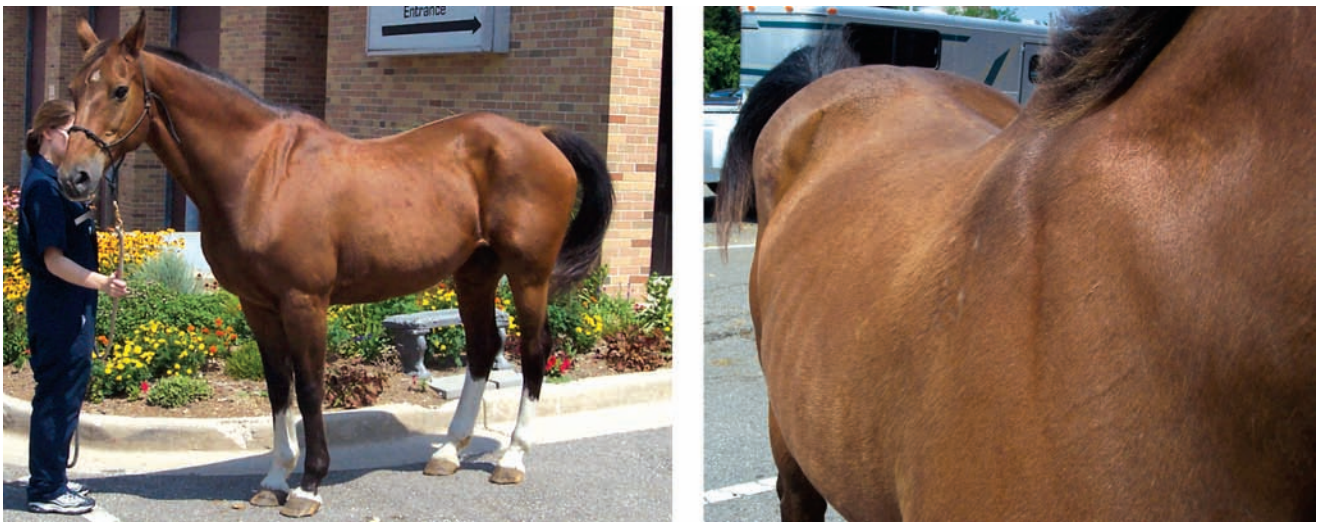

Fig. 1. 28-yr-old Dutch Warmblood mare at initial presentation to Michigan State University in August of 2005. Note general good body condition (left, BCS = 5 of 9) with ribs apparent on closer inspection from the shoulder area (right).

2. What Other Diagnostic Tests Should Be Considered?

A complete blood count and serum chemistry profile were recommended as a minimum data base for this geriatric horse, and no significant abnormal results were detected. Serum glucose concentration was 107 mg/dl. Urine was passed in the holding stall; a sample collected from the stall floor revealed a specific gravity of 1.027, and reagent-strip analysis did not reveal any abnormalities. In addition, serum insulin and plasma ACTH concentrations were measured, and results were 136 pmol/l (19 μU/ml; reference range = $<$300 pmol/l or $<$42 μU/ml) and 24.9 pmol/l (113 pg/ml; reference range = 2–10 pmol/l or $<$45 pg/ml), respectively. Lateral front foot radiographs could also have been taken as a baseline for future comparison, but these were not pursued at the time.

3. What Treatment(s) Are Recommended?

The mare was already in a good management program and was receiving regular farrier and veterinary care, including dentistry. Diet was considered appropriate, and the mare was at the appropriate body condition. Although probably of limited efficacy, thyroid hormone supplementation (1 scoop) was continued on the recommendation of the referring veterinarian. Although clinical signs of PPID were limited to long hairs under the chin and behind the legs and a mild decrease in musculature along the topline, both the ODST results and the mildly elevated ACTH concentration supported PPID. Treatment with pergolide

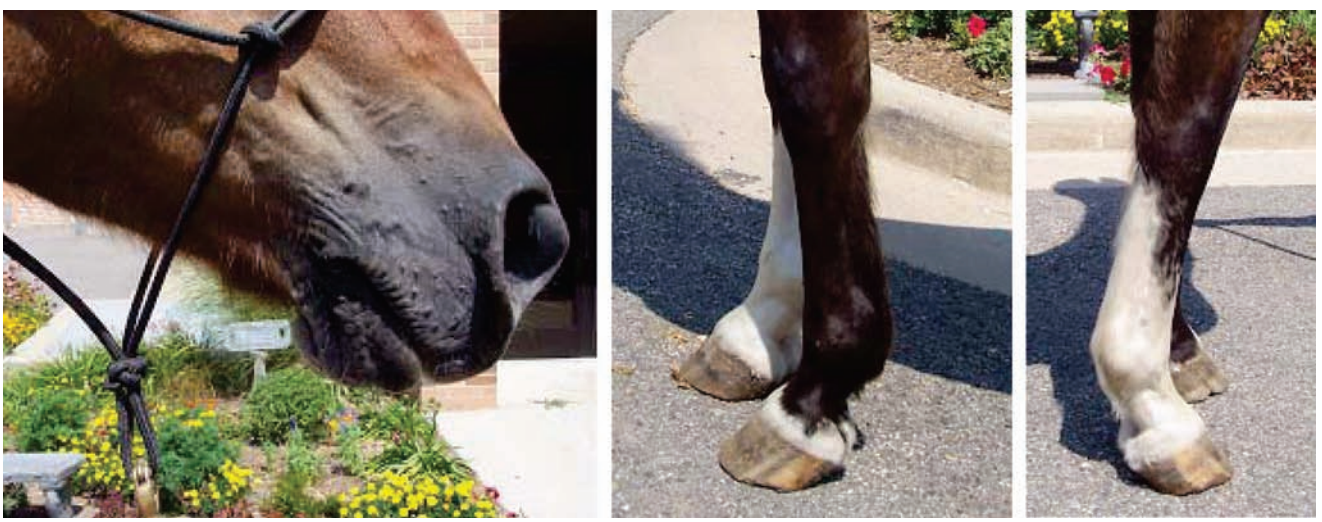

Fig. 2. 28-yr-old Dutch Warmblood mare with long hairs apparent under chin and on the palmar aspect of the forelimbs.

was not considered absolutely necessary in light of the mare's general good health and few clinical signs, but the owners wanted to provide the best possible care to prolong the mare's life. Thus, a prescription for a compounded pergolide suspension (1 mg, q 24 h, PO) was provided. The owner was also encouraged to provide the mare with a more regular exercise program of 3 times/wk for 30–45 min.

4. What Follow-up Evaluation Is Necessary?

Clinical assessment of the efficacy of pergolide treatment would be difficult until the following spring when shedding could be observed. However, repeating the OSDT was recommended in 4–6 mo to determine if a normal response to dexamethasone had returned.

Case 1 Progression

The ODST was repeated in November of 2005 and yielded a pre-dexamethasone cortisol concentration of 105 nmol/l and a 17-h post-dexamethasone cortisol concentration of 27 nmol/l. Based on these normal results, continued treatment with pergolide (1 mg/day, q 24 h, PO) was recommended. In the fall, the mare had also been moved from Michigan to Illinois, and she was reported to have lost nearly 50 kg during the early fall (BCS = 3 of 9). Because no other disease problem was apparent, weight loss was attributed to a lack of pasture access and decreased hay feeding at the initial stable where the mare was boarded. The mare was moved to a new facility, and the amount of Equine Senior fed was increased to a total of 10–12 lbs/day, and a fat supplement was added to the diet. By late March of 2006, the mare had regained nearly 60 kg and was reported to be starting to shed the winter hair coat earlier than in the last few years. The Equine Senior was cut back to 4 lbs twice a day. Again, continued treatment with pergolide (1 mg/day, q 24 h, PO) was recommended, pending the repeat of the ODST later in the summer.

Case 1 Comments

This mare is an example of a fairly mild case of PPID in which treatment with pergolide was not entirely necessary but could certainly be justified in an attempt to prolong the healthy life of the mare. In cases with similar mild clinical signs that have no evidence of laminitis, the author discusses the pros and cons (largely financial) of pergolide treatment and lets the owner decide whether or not to treat. If a horse with similar mild clinical signs has had a prior or current episode of laminitis that was unassociated with any other medical disorder, treatment with pergolide is more strongly recommended.

Case 2

Case 2 is a Morgan gelding born in 1979. The owner had acquired the gelding for occasional use as a show horse and for pleasure riding in 1988 (at 9 yr of age). About 1 mo after purchase, the gelding was evaluated for mild soreness in both front feet. The problem was attributed to an increase in workload and responded to treatment with a course of phenylbutazone. No further diagnostics were pursued at that time. The horse subsequently performed well for several years during which time it had a BCS of 6–7 of 9. Diet was either hay or pasture with a handful of concentrate once a day. The gelding was retired in 1996 and remained "in good flesh" with a cresty neck, and it never had any episodes of clinical laminitis. During retirement, diet was primarily forage (pasture or hay) and a small amount of Equine Senior (a handful twice a day). The horse was initially presented to Michigan State University's Veterinary Teaching Hospital in September of 1998 for evaluation of bilateral forelimb lameness. Physical-exam findings were within normal ranges, although the horse did have a mildly cresty neck; BCS was 6 of 9 (weight was not recorded). The winter hair coat was starting to grow, but the gelding was reported to have had a normal summer hair coat, although shedding the last spring was considered a bit delayed (there was no obvious hirsutism or excessively long hairs apparent). Front foot radiographs revealed laminar thickening bilaterally, mild rotation of both coffin bones, and lucent lines in the distal aspect of the hoof walls in both front feet, consistent with laminitis (Fig. 3).

The horse received therapeutic trimming and shoeing (front feet only) and was discharged with a recommendation for restricted exercise and administration of 1 g phenylbutazone, q 12 h, PO. Reexamination 45 days later revealed limited improvement, and because there were no recent medical problems that would have predisposed the horse to development of laminitis, a consultation for possible endocrinopathic laminitis was pursued. At the time, the surgeon managing the laminitis had concerns that the ODST could exacerbate laminitis. Thus, a TRH stimulation test (1 mg TRH, IV) was pursued, and an exaggerated (>50% from baseline) increase in cortisol concentration at 15 and 30 min after TRH administration supported a diagnosis of PPID (Table 3). Both ACTH (22.6 pmol/l, 102 pg/ml) and insulin (1081 pmol/l, 151 IU/ml) concentrations were also elevated. A CBC had all results within reference ranges as did a serum chemistry profile, although glucose concentration was 118 mg/dl. BCS was 7 of 9, and body weight was 490 kg.

Case 2 Questions

1. What Disorder(s) Does This Horse Have?

In addition to laminitis, endocrinologic test results provide support for both PPID (exaggerated cortisol response to TRH and mildly elevated ACTH concentration) and insulin resistance (overweight, cresty neck, and elevated fasting glucose and insulin concentrations). Based on further data published since the time of this horse's initial evaluation, the author no longer recommends use of the TRH stim-

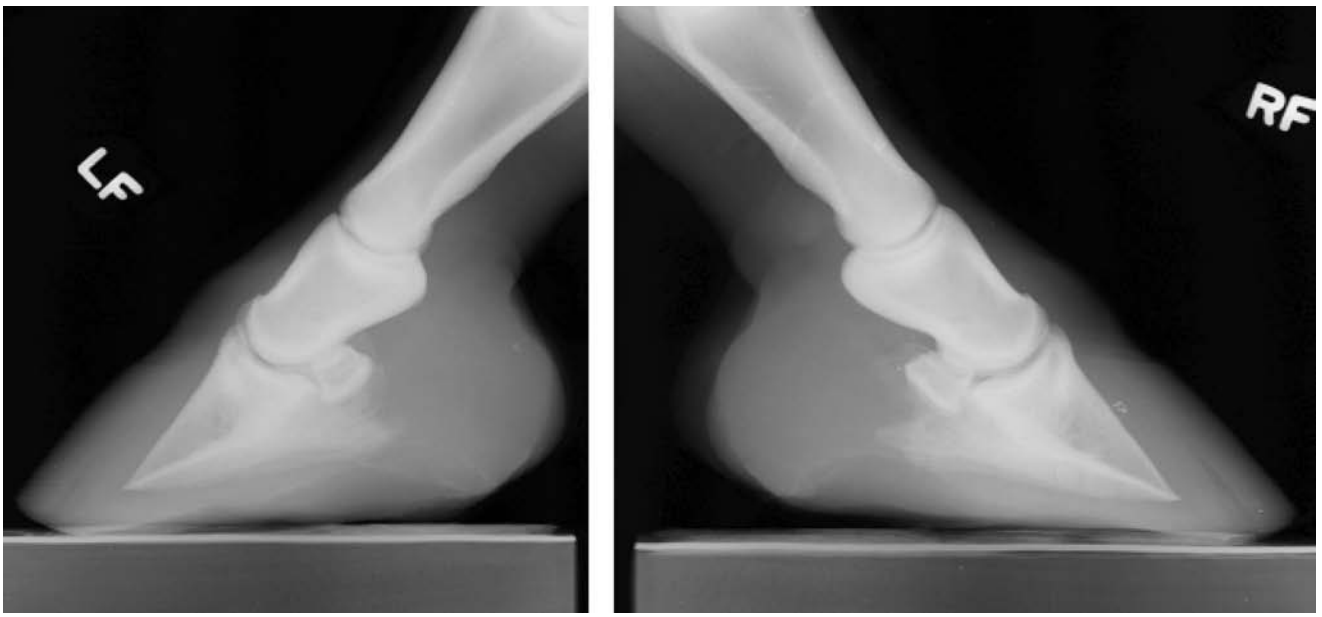

Fig. 3. Lateral radiographs of a 19-yr-old Morgan gelding with recent onset of bilateral forelimb lameness; laminar thickening, mild rotation of the third phalanx, and lucent lines in the distal aspect of the hoof walls in both front feet were consistent with laminitis.

ulation test as a screening tool for PPID and prefers the ODST despite active laminitis. As an alternative, plasma ACTH concentration can also be used as a screening test (except for in August and September in the northern hemisphere). Insulin resistance can be a component of both PPID and the recently coined equine metabolic syndrome, and thus, the elevated insulin concentration has low specificity for PPID. At present, it remains unclear whether or not equine metabolic syndrome may be a precursor syndrome of PPID in equids, although this author tends to consider them as separate syndromes.

2. What Treatment(s) Are Recommended?

In addition to ongoing management of laminitis with hoof care and continued use of phenylbutazone, treatment with pergolide (1 mg/day, q 24 h, PO) was recommended. Because of the BCS of 7 of 9, the owner was also encouraged to decrease feed intake (1–2 flakes of grass hay twice a day) and start to exercise the horse lightly when the laminitis became more stable.

Case 2 Progression

Re-examination in March of 1999 revealed that the horse was essentially sound, and BCS had decreased to 6 of 9, although a cresty neck remained. Phenylbutazone had been discontinued 30 days previously, and a return to a mild exercise program was recommended (on soft ground). Treatment with pergolide (1 mg/day, q 24 h, PO) was continued with dosage adjustment based on follow-up endocrinologic testing. The horse shed the winter hair coat normally in the spring of 1999 and remained sound for the next 2 yr.

In February of 2001, the horse was presented for evaluation of a flare-up of laminitis. It had been moved to a retirement farm during the previous year. The horse had been turned out to better pasture (summer and fall) and had also been receiving ~4 lbs of Equine Senior once a day. BCS had again increased to 7 of 9, and weight was 485 kg. Vital parameters were within normal ranges, but the gelding was lame at a walk in both front feet, despite starting treatment with phenylbutazone 10 days previously. In addition, areas of the hair coat were noted to be long and curly with patchy sweating observed. Lateral foot radiographs revealed changes similar to the original examination with slightly more remodeling of the distal third phalanx. A CBC and serum chemistry profile had results

Table 3. TRH Stimulation Test Results in a 19-yr-old Morgan Gelding Resulted in a >50% Increase in Cortisol Concentration 15 and 30 mins After Administration of 1 mg of TRH, IV

TRH stimulation test (1 mg TRH IV)	Pre-TRH	15 mins	30 mins	60 mins	90 mins
Cortisol concentration (nmol/l)	55	111	105	56	89

These results were supportive of, but not definitive for, PPID.

within the reference ranges with the exception of mild hypoalbuminemia (2.8 g/dl; reference range = 3.5–4.7 g/dl); glucose concentration was 108 mg/dl. Urine was passed, and a free-catch sample revealed a specific gravity of 1.028. Reagent-strip analysis did not reveal any abnormalities.

Treatment of laminitis involved further corrective trimming and shoeing. In addition, endocrinologic testing was repeated. An ODST yielded a pre-dexamethasone cortisol concentration of 212 nmol/l and a 17-h post-dexamethasone cortisol concentration of 178 nmol/l. Serum insulin was 372 pmol/l (52 μU/ml).

Additional Case 2 Questions

1. What Further Treatment(s) Are Recommended?

Clinical signs of PPID were no longer being controlled with 1 mg pergolide, q 24 h, PO, and there was minimal suppression of endogenous cortisol concentration in response to dexamethasone administration. Thus, more aggressive medical treatment of PPID was warranted. For this gelding, the dose of pergolide was increased to 2 mg, q 24 h, PO, but other options were available (e.g., addition of cyproheptadine or trilostane) with a repeat ODST to be performed in 2–3 mo. Next, although fasting-insulin concentration was considerably lower than in 1998, the elevated value still supported insulin resistance, and coupled with excessive body condition, diet was changed to grass hay only. Access to pasture was to be limited in the spring, and exercise was to be started as foot pain resolved.

Case 2 Progression After Re-Evaluation

Re-examination in March of 2001 revealed that the horse was essentially sound. BCS had decreased to 6 of 9, and weight was 470 kg. Phenylbutazone had been discontinued 10 days previously, and a return to a mild exercise program was again recommended. Treatment with pergolide (2 mg/day, q 24 h, PO) was continued. Although the gelding remained sound and shedding of the hair coat again improved in the spring of 2001, follow-up ODST results, detailed in Table 4, revealed abnormal results in May and September of 2001. As a consequence, treatment with pergolide was increased to 3 mg, q 24 h, PO. Over the next 4 yr, regular farrier work continued, and the gelding remained sound.

The gelding was represented in August of 2005 with complaints of weight loss over the past 3 mo (owners were concerned that ribs were now visible) and a mild flare-up of laminitis ~2 wk previously. This episode of lameness occurred 2 days after trimming and shoeing and resolved with treatment with flunixin meglumine for 2 days. The horse had also been dropping quids since the spring, despite regular dentistry over the past few years. Equine Senior (3 lbs twice a day) had been started ~1 mo previously.

Table 4. ODST Results Over a 5-yr Follow-Up Period in a Morgan Gelding With PPID

ODST Results	Cortisol (pre-dex)	Cortisol (17–19 h post-dex)
May 2001	107	59
September 2001	89	71
Pergolide increased to 3 mg, PO, q 24 h		
November 2001	226	17
October 2002	136	39
May 2003	148	14
March 2004	121	10
August 2004	111	12
July 2005	181	20
May 2006	166	29

Physical examination revealed normal vital parameters with a grade 2/6 holodiastolic murmur, consistent with aortic insufficiency. BCS was 5 of 9, and weight was 430 kg (Fig. 4). Although the owner and retirement farm manager were concerned about the weight loss, body condition was now considered nearly ideal for this gelding. The gelding was sound, and the neck crest had largely disappeared, although small fat pads were still apparent adjacent to the tail head. The hair coat appeared normal, and lateral foot radiographs revealed good alignment of the third phalanx with the dorsal hoof wall. A moderate wave mouth was present, but there were no excessively sharp points. A CBC and serum chemistry profile had results within the reference ranges with the exception of mild hypoalbuminemia (3.3 g/dl; reference range = 3.5–4.7 g/dl); glucose concentration was 99 mg/dl. ACTH concentration (19.6 pmol/l, 88 pg/ml) remained elevated, but fasting insulin concentration (145 pmol/l, 20 IU/ml) was within the reference range.

Treatment included mild correction of the wave mouth and continued administration of pergolide at 3 mg, q 24 h, PO. Again, body condition was considered ideal at this time, but feeding soaked hay cubes, along with longer periods of pasture access, was recommended to maintain current weight.

Case 2 Comments

This gelding is an example of a more severe case of PPID in which medical treatment (with pergolide) was necessary along with the management of chronic laminitis, dentition, and diet. In this case, PPID was accompanied by two common complications: laminitis and insulin resistance. The latter problem likely persisted for a number of years, because the owner and manager were reluctant to have the gelding lose as much weight as recommended, despite frequent encouragement. After 6 yr, body condition finally became more ideal, although the owner remained concerned that the horse was too thin.

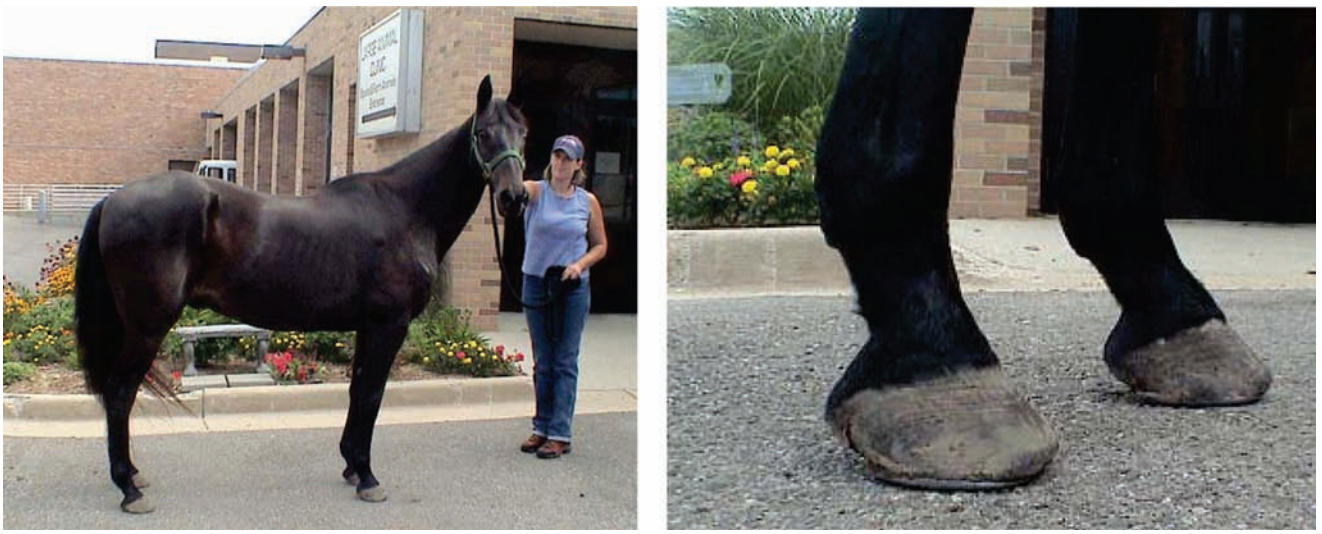

Fig. 4. 26-yr-old Morgan gelding (August 2005) that had been successfully treated for PPID with pergolide for >7 yr.

This case also illustrates the value of repeat endocrinologic testing as part of the monitoring of horses with PPID. Horses with PPID often show clinical improvement with pergolide treatment, yet endocrinologic test results can remain abnormal. Although based on clinical experience alone, this author attempts to achieve both clinical improvement and normalization of endocrinologic test results (specifically ODST results). Ideally, the ODST should be repeated twice a year and routine blood work (CBC and serum chemistry profile) should be performed annually. Combined with this testing, twice yearly detailed physical examinations, including close assessment of hoof conformation and dentition, are recommended. Use of the BCS system and estimation of body weight with a weight tape are also important, with a goal of maintaining a BCS of 5 of 9. The latter measurements are then used to evaluate diet and to make any necessary changes. Although such a comprehensive management program can be costly, it provides the framework for equine practitioners to provide the highest quality of health care for their geriatric patients.

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