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Diagnostic Frequency, Response to Therapy, and Long-Term Prognosis among Horses and Ponies with Pituitary Par Intermedia Dysfunction, 1993–2004

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Background: Pituitary pars intermedia dysfunction (PPID) is common in older horses.

Objectives:: To determine diagnosis frequency, prognostic factors, long-term survival, and owner satisfaction with treatment.

Animals: Medical records from horses diagnosed with PPID, 1993–2004.

Methods: A retrospective cohort design with data collected from the Veterinary Medical Data Base (VMDB) and a cohort of 3 VTHs. Proportional accessions, annual incidence, and demographics were compared for all accessions. During the same period, a subset of medical records (n = 44) was extracted and owners (n = 34) contacted to obtain long-term follow-up information.

Results: Diagnoses of PPID were reported for 217 horses that presented to VTHs and were reported to the VMDB. Proportional diagnosis increased from 0.25/1,000 in 1993 to 3.72/1,000 in 2002. For 44 horses included in the follow-up study, the most commons signs were hirsutism (84%) and laminitis (50%). Of 34 horse owners contacted, the average time from onset of signs to diagnosis was 180 days. Improvement in $\geq$ 1 signs, 2 months after diagnosis, was reported by 9/22 (41%) of horse owners. Clinical signs and clinicopathologic data were not associated with survival, and 50% of horses were alive 4.6 years after diagnosis. Cause of death among horses (15/20; 85%) was euthanasia, and 11/15 (73%) were euthanized because of conditions associated with PPID. Most horse owners (28/29; 97%) said they would treat a second horse for PPID.

Conclusion and Clinical Importance: PPID was diagnosed with increasing frequency, and 50% of horses survived 4.5 years after diagnosis. Owners were satisfied with their horses' quality of life and would treat a second horse if diagnosed.

Key words: Epidemiology; Equine; Metabolic disease; Pituitary par intermedia dysfunction.

Equine pituitary pars intermedia dysfunction (PPID) is one of the most commonly diagnosed equine endocrinopathies.[1] It is a chronic progressive disease of older horses, and diagnosis is based on clinical signs and laboratory test results.[2] Clinical signs of PPID include hirsutism, laminitis, bulging supraorbital fat, abnormal fat distribution, lethargy, polyuria, and polydipsia, susceptibility to infections, hyperhidrosis, and inappropriate lactation.[3] The disease often is characterized by increases in plasma and serum ACTH, glucose, and insulin concentrations, but these analytes also may be within normal reference ranges. Plasma cortisol concentration is variable and may be decreased.[4–6] Laboratory diagnosis of PPID can be problematic because of seasonal variation in plasma ACTH concentration and in the cortisol response to the dexamethasone suppression test (DST). In a previous report in 29 ponies and 10 mares, plasma cortisol concentrations at the end of the DST were significantly higher in September when compared with January.[7]

Laboratory studies to diagnose PPID are common, but to the authors' knowledge no studies to date have examined prognostic factors associated with long-term survival of horses after diagnosis of PPID. At least 2 studies, however, have evaluated short-term survival in horses with PPID. In 1 study in 20 horses with PPID,

Abbreviations:

ACTH	adrenocorticotropic hormone
AST	aspartate aminotransferase
CK	creatine kinase
DST	dexamethasone suppression test
GGT	gamma-glutamyl transpeptidase
MSU	Michigan State University
OSU	Ohio State University
PPID	pituitary pars intermedia dysfunction
TRH	thyroid releasing hormone
UT	University of Tennessee
VMDB	Veterinary Medical Data Base
VTH	Veterinary Teaching Hospital

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low serum insulin concentration before treatment was significantly associated with improved short-term survival up to 1–2 years.[8] In a second study, comparison of plasma ACTH concentrations at baseline with those median of 2 months (range: 1–15 months) after treatment were found to be helpful when monitoring treatment of PPID in 42 horses, but improvement in clinical signs was considered the most important indicator of prognosis.[9]

Previous studies of horses with PPID have been limited because of small sample size, lack of information from horse owners, and lack of long-term follow-up of cases. The purpose of the present study was to identify trends in the diagnosis of PPID in horses presented to VTH's. In addition, clinical and laboratory factors associated with long-term prognosis, client perception of treatment, and quality of life were assessed in a subsample of horses with PPID.

Material and Methods

The study was conducted using a retrospective cohort design. Medical records of horses entered into the VMDB during a 12-year period, from 1993 to 2004, were searched with the following diagnoses: Cushing's disease, pituitary adenoma, pars intermedia pituitary adenoma, and pituitary adenocarcinoma. A sample of convenience was chosen from the sampling frame of horses accessed by VTHs participating in the VMDB. In addition, horses with PPID that were accessed by the Ohio State University, a VTH that did not contribute to the VMDB, during the same time period were identified. The time period selected (1993–2004) coincided with the period before the voluntary recall of FDA-approved pergolide mesylate.[a] This time period (compared with the period after 2007) might represent a more accurate estimate of the treatment response of horses with PPID. After the voluntary recall, only compounded pergolide mesylate formulations were available for treatment of PPID. The efficacy and potency of these compounded products recently has come into question and likely affects how horses respond to treatment and may affect long-term survival.[10]

Choice of the subsample was based on the number of cases reported by institutions reporting to the VMDB and a search of medical records from OSU together with logistic limitations regarding travel and access to medical records from these institutions. This group was used to create all owner reported data. Inpatient medical records from 3 VTHs, MSU, OSU, and UT, were selected to be reviewed. Clinicians were identified at MSU and OSU, and data from patient medical records were extracted by one of the authors (JRS). Historical and demographic information, clinical signs, laboratory test results, and treatments administered were extracted from the medical records. Client contact information was recorded.

Criteria for inclusion in the follow-up study required that one or more of the following be recorded in the medical record: (1) hirsutism, (2) a plasma cortisol concentration > 1.0 μg/mL, 17–19 hours after the start of the standardized overnight DST, (3) a plasma cortisol concentration that increased ≥ 2× baseline, 30 minutes after administration of TRH, or (4) a plasma cortisol concentration that increased > 66% above baseline, 30 minutes after administration of TRH or a cortisol concentration ≥ 1.0 μg/mL, 19–21 hours after administration of dexamethasone by the combined DST/TRH stimulation test.

Telephone interviews of horse owners included in the follow-up study were conducted over a 6-month period (from July 15, 2004 to December 15, 2004) by an author (JRS) with a questionnaire designed, according to previously published guidelines.[11] Information requested from horse owners included date of onset of clinical signs, current status of the horse, compliance with treatment prescribed, response to treatment, date of death or euthanasia where applicable, cause of death or reason for euthanasia, and owner satisfaction with treatment. Information that owners could not recall was listed as missing. The time when clinical signs were first observed was given as a date, or months, or years, before date of diagnosis. Time from onset of clinical signs to date of diagnosis was obtained by subtracting the date- or midpoint of month from the date of diagnosis. A positive response to treatment was defined as improvement in 1 or more clinical signs at 2 months post-treatment without an increase in severity for any other signs exhibited at presentation. A 2-month follow-up period was chosen because it is the period of time when horse owners were likely to see improvement in clinical signs of PPID.[12] An increase in severity of 1 or more of the signs recorded at presentation, or no change in all signs, was considered a negative response to treatment. The denominators for data from medical records and specific questions on the follow-up telephone survey varied because of missing information or inability of horse owners to recall information. All data were transferred from questionnaires to a commercial software database program[b], and subsequently exported to a statistical software program[c] for analysis.

Data analysis

The number of PPID diagnoses among horses each year in the VMDB was divided by the total accessions for the year to estimate the annual proportional diagnoses of PPID. Continuous variables were summarized by the mean and standard deviation or median and range, depending on the distribution of data. Median values for continuous clinicopathologic data obtained from medical records of the 44 horses identified for the follow-up survey were used to stratify cases into those at, below, or above the median value. A second series of comparisons were conducted by stratifying clinicopathologic data based on whether values were within or outside of the standard reference interval.[13] Categorical variables and strata created from continuous variables were tested for association with survival days by the method of Kaplan-Meier.[c] Animals alive at the end of the study period were right censored.

Results

A total of 15 VTHs participated in the VMDB from January 1, 1993 to June 30, 2004. From the 270 case records identified, there were 217 records of 134,632 accessions (1.6 cases per 1,000 accessions) that matched the search criteria, after exclusion of horses seen by ambulatory or field service units. Proportional diagnoses of PPID increased during the study period from a low of 0.25 cases per 1,000 accessions in 1993 to a high of 3.7 cases per 1,000 accessions in 2002 (Fig 1). Horses with a diagnosis of PPID were older; 7 (3%) <10 years, 35 (16%) between 10 and 15 years of age, and 175 (81%) ≥ 15 years. When compared with all accessions ≥10 years, horses with PPID were significantly more likely to be geldings (OR 1.3; 95% CI: 1.02–1.74).

An additional 14 cases were identified from patient records at OSU. From the 3 institutions included in the follow-up sample, MSU contributed 48 cases, OSU 14 cases, and UT 58 cases. A total of 44/120 (37%) of these cases met the case definition for inclusion in the

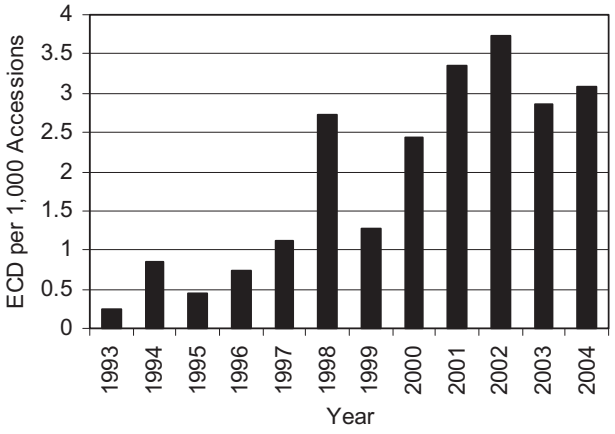

Fig 1. Proportional diagnosis of pituitary pars intermedia dysfunction among horses and ponies accessed by veterinary teaching hospitals reporting to the Veterinary Medical Data Base, 1993–2004.

follow-up study and included 13/48 (27%) cases from MSU, 13/14 (93%) cases from OSU, and 18/58 (31%) cases from UT. Follow-up telephone information was obtained for 34/44 (77%) of these cases. Owners could not be reached in 10/44 (23%) of the cases.

Among horses in the follow-up study sample (n = 34), owners reported the median time interval between the onset of clinical signs reported by the owner and date of diagnosis (n = 20) as 180 days (range: 1–1,824 days). The mean age of PPID patients at diagnosis (n = 36) was 21.6 ± 6.6 years. The mean age for horses (n = 29) was 20.1 ± 6.2 years and for ponies (n = 7) was 24.1 ± 8.0 years (P = .27). The mean age for horses with hirsutism (n = 30) was 19.5 ± 6.5 years and for those without hirsutism (n = 6) mean age was 19.9 ± 7.5 years (P = .52). Sex distribution included 28 (64%) geldings and 16 (36%) mares; 35 (80%) of study patients were horses and 9 (20%) were ponies.

Table 1. Clinical signs in a group of horses and ponies (n = 34) with equine Cushing's disease.

Sign	No. (%)
Hirsutism	37 (84)
Laminitis	22 (50)
Muscle atrophy	10 (23)
Hyperhydrosis	9 (20)
Weight Loss	9 (20)
Polydipsia	9 (20)
Polyuria	7 (16)
Lethargy	6 (14)
Pendulous abdomen	5 (11)
Supraorbital fat	3 (7)
Other signs	<2%

Clinical signs exhibited by patients at presentation are shown in Table 1. The most frequent signs recorded were hirsutism (84%) and laminitis (50%). The most frequent method of diagnosis was by hirsutism only in 15 (34%), and by hirsutism and DST test results in 10 (23%) of the study horses (Table 1). No cases were diagnosed solely by use of TRH test results. In the final analysis, 34 horses had all or some laboratory test results; 50% of these horses had laboratory test results outside of the normal reference interval including: creatine kinase 27/34 (79%), aspartate aminotransferase 22/34 (65%), glucose 19/34(56%), and gamma glutamyl transferase 17/34 (50%) (Table 2).

Resting cortisol concentrations were available for 32/44 (73%) of study horses. The median value was 116 nmol/L (range: 34–330), and 12/32 (38%) were above the upper end of the reference interval (165.6 nmol/L). Mean resting cortisol concentration ranged from a low of 41.6 nmol/L in the fall (September to November) to a high of 106.2 nmol/L in the summer (June to August), but these differences were not statistically significant (Fig 2). Glucose (median, 121.5 mg/dL; IQR: 108.5–167 mg/dL) and resting cortisol (median, 30.35 nmol/L; IQR: 5.5–72.5 nmol/L)

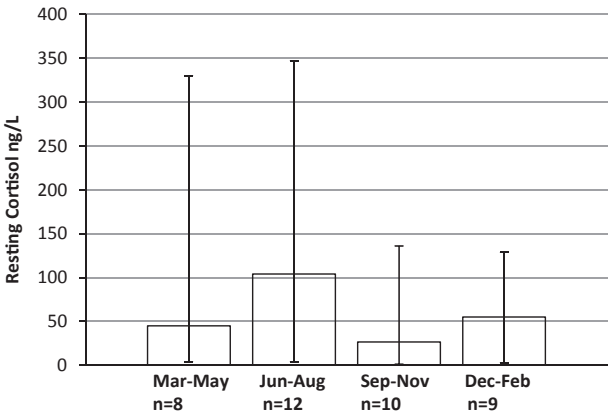

Fig 2. Seasonal median and range for plasma resting cortisol concentration among horses and ponies (n = 39) with pituitary pars intermedia dysfunction. Differences among seasons were not statistically significant. [Correction made after online publication April 24, 2012: the legend for Figure 2 has been changed.]

Table 2. Laboratory values in horses and ponies with a diagnosis of pituitary pars intermedia dysfunction (n = 34) in which > 50% of the horses were outside reference intervals.

Test	No.	Mean ± SD	Median/Range Interval	Reference
Gamma-glutamyl transpeptidase (IU/L)	34	36 ± 53	22 (10–319)	2.7–22
Glucose (mg/dL)	34	134.7 ± 42.8	118.5 (91–285)	62–114
Aspartate aminotransferase (IU/L)	34	313.1 ± 99.4	301.5 (134–661)	116–287
Creatine kinase (IU/L)	34	333.1 ± 218.2	281 (103–1,133)	34–166

results were not statistically different in horses with laminitis, when compared with glucose (median: 116.5 mg/dL; IQR: 107–135 mg/dL; $P = .68$) and resting cortisol (median, 30.6 nmol/L; IQR: 5.05–67.5 nmol/L; $P = .91$) results in horses without laminitis.

Treatments administered after diagnosis were available for 34/44 (77%) of study horses. Pergolide was given to 16/34 (47%), cyproheptadine to 12/34 (35%), and both pergolide and cyproheptadine to 6/34 (18%). Follow-up information from horse owners indicated that 6/34 (22%) discontinued treatment, and both pergolide and cyproheptadine were represented. The most frequent reason for discontinuing treatment was lack of response. Three of 5 horse owners (60%) who discontinued treatment reported that they restarted treatment at a later date. Twenty-eight of 29 horse owners (97%) stated that they would initiate treatment for a second horse if diagnosed with PPID.

The effects of treatment on clinical signs recorded at diagnosis, when re-evaluated 2 months post-treatment, were based on responses of 34/44 (77%) owners contacted (Table 3). For the majority of horses, clinical signs did not change over the first 2 months post-treatment. Hirsutism decreased in 7/25 (30%) and increased in 2/25 (9%). Laminitis improved in 5/14 (38%) of study horses. Owners providing information on type of treatment and response to treatment at 2 months (n = 22) reported that those treated with pergolide (n = 10) and cyproheptadine (n = 7) had positive response rates of 40 and 29%, respectively, whereas 3/5 (60%) of horses treated with both drugs had a positive response.

Long-term survival is shown in Figure 3. Of 34 horse owners contacted, 29 (85%) were able to provide information on survival time after diagnosis. The number of horses alive at the end of the study period was 14/29 (48%). Fifty percent of the study patients were alive 4.6 years after diagnosis and 25% were alive at 5.3 years. The horse with the longest survival time was alive at the termination of the study and had survived 6.3 years after initial diagnosis. Nine of 34 (26%)owners were able to evaluate performance level 1 year after diagnosis of PPID. Performance level was assessed by those owners to be a median of 90% (range: 13–100%) of that before the onset of clinical signs of PPID. Death by euthanasia was reported by owners in 15/20 (85%) of 237 study patients, and 11/15 (73%) were euthanized for clinical signs associated with PPID. Four of 15 (27%) of those horses were euthanized for conditions unrelated to PPID. Three of 20 (15%) horses died a natural death and the reason for euthanasia was not given in the remaining 2/20 (10%) horses. None of the demographic, clinical, or laboratory characteristics were significantly associated with long-term survival (data not shown).

Table 3. Owner's (n = 34) perception of response to treatment with pergolide, cyproheptadine, or both among horses and ponies with equine Cushing's disease, 1993–2004.

		Change in Clinical Sign		
Sign	N	Decreased	Increased	No Change
Hirsutism	25	7 (30)*	2 (9)	14 (61)
Laminitis	14	5 (38)		8 (62)
Muscle atrophy	4	1 (25)		3 (75)
Hyperhydrosis	5	1 (20)	1 (20)	3 (60)
Weight Loss	3			2 (100)
Polydipsia	7	1 (14)	2 (29)	4 (57)
Polyuria	5		1 (20)	4 (80)
Lethargy	3			2 (100)
Pendulous abdomen	4		1 (25)	3 (75)
Supraorbital fat	1			1 (100)
Other (ataxia, seizures)	2			

*Number (percent).

Table 4. Owner's (n = 34) perception of response to treatment with pergolide, cyproheptadine, or both among horses and ponies with pituitary par intermedia dysfunction (PPID), 1993–2004.

		Change in Clinical Sign		
Sign	N	Decreased	Increased	No Change
Hirsutism	25	7 (30)*	2 (9)	14 (61)
Laminitis	14	5 (38)		8 (62)
Muscle atrophy	4	1 (25)		3 (75)
Hyperhydrosis	5	1 (20)	1 (20)	3 (60)
Weight Loss	3			2 (100)
Polydipsia	7	1 (14)	2 (29)	4 (57)
Polyuria	5	1 (20)		4 (80)
Lethargy	3			2 (100)
Pendulous abdomen	4	1 (25)		3 (75)
Supraorbital fat	1			1 (100)
Other (ataxia, seizures)	2			

*Number (percent).

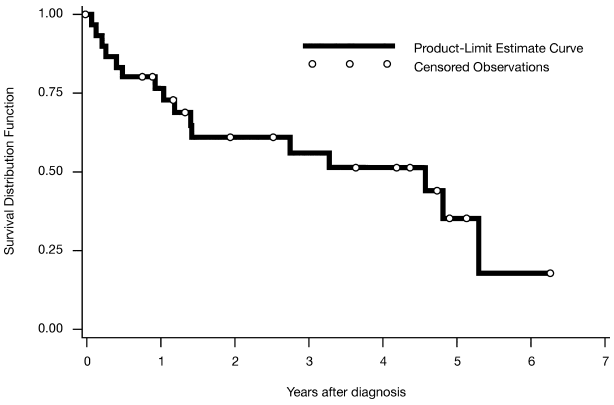

Fig 3. Survival after diagnosis among horses and ponies (n = 29) with pituitary pars intermedia dysfunction.

Discussion

There was an increase in proportional diagnosis of PPID among VTHs reporting to the VMDB during

the study period. We were, however, unable to determine whether this trend was caused by increased awareness and use of existing diagnostic tests by clinicians, or a true increase in incidence of PPID. During the period of this study, several reports evaluating the validity of diagnostic tests for PPID and reviews of the subject matter were published. Thus, the increase in diagnosis of horses with PPID is likely because of increased awareness rather than an actual increase in incidence.[14–17]

There were 28 (64%) geldings and 16 (36%) mares in this study sample. Although publications suggest that there is no sex predilection for PPID in horses, there is at least 1 earlier report suggesting males may be predisposed to PPID.[14–16] Perhaps the strongest evidence to date is from the 217 horses reported here that showed a weak, but significant, association with geldings. Other reports suggested that female horses might be predisposed (as is the case for human beings with pituitary tumors), but those observations may have been attributable to the tendency to allow broodmares to live longer.[18,19] The reason for the sex predilection identified in the present study is not known, but awareness of increased risk in geldings may prompt earlier recognition and testing when subtle clinical signs consistent with PPID are observed.

In this study, there was a prolonged period of time (range: 1 day–5 years) between the onset of clinical signs noticed by horse owners and the diagnosis of PPID, suggesting in most cases that onset of disease is insidious and initial signs are not considered serious enough to alarm horse owners. The mean age at diagnosis among horses included in the follow-up study (21.6 ± 6.6 years) was similar to that of horses with PPID in 4 previously published studies. Median ages of horses in these studies were 19.5, 23, 21, and 21 years.[8,15,20,21] In the present study, ages of ponies and horses were similar as were the ages of study patients with and without hirsutism. PPID may be under-recognized in younger horses.[22] A diagnosis may be missed because of the commonly held belief that PPID is associated with older age and hirsutism, and owners may delay in bringing the condition to the attention of veterinarians because of the lack of acute or life-threatening early clinical manifestations of disease.

Hirsutism and laminitis were the most frequent clinical signs reported at the time of diagnosis among study horses. Although there is no scientific evidence to support the hypothesis, hirsutism is thought to develop years after the onset of pathologic changes in the pars intermedia. In previous studies, hirsutism was exhibited by a variable proportion of study patients.[16,23] The proportion of horses with hirsutism ranged from 28 to 100% in 4 studies.[2,7,9,24] Hirsutism was present in 37/44 (84%) of horses in the present study. The differences in proportion of horses exhibiting hirsutism among studies may be dependent on the frequency with which clinicians pursue a laboratory diagnosis of PPID in horses without hirsutism.

Laminitis was reported in 24–84% of horses with PPID in 3 previous studies.[14,16,25] In the current follow-up study, 22/44 (50%) horses presented with acute laminitis or had a history of chronic laminitis. The exact pathogenesis of laminitis in horses with PPID remains unknown, but endogenous cortisol (in the presence of epinephrine, norepinephrine, and serotonin) potentiates constriction of the digital vein and artery.[26] Furthermore, increased cortisol activity leads to insulin resistance which may contribute to delayed glucose uptake. In the current study, there was no significant difference in median resting cortisol concentrations when horses with a history of laminitis (or laminitis on presentation) were compared with those without laminitis. However, other proopiomelanocortin-derived hormones, including cortitropin-like intermediate peptide (CLIP), ACTH, MSH, and ß-endorphins, as well as 11-ß-hydroxysteroid dehydrogenase activity, a metabolite of ACTH, secreted by the pars intermedia during PPID, could have glucocorticoid-like activity, which might explain the discrepancy between horses with laminitis (50%) and those with high plasma cortisol concentrations (38%).

Diagnosis of PPID can be difficult in early cases. Typically, the diagnosis of PPID is based on the presence of clinical signs, laboratory test results, or both. A commonly recognized clinical sign of PPID is hirsutism or an abnormal shedding pattern. Hirsutism was reported in 28/34 (84%) and used by itself or with diagnostic tests to diagnose PPID in 80% of horses in this study. Pituitary pars intermedia dysfunction is the only known cause of hirsutism in horses and therefore was considered to be as accurate as laboratory diagnosis, when present.[1,15,27] Therefore, laboratory diagnosis usually is reserved for horses that are suspected of having PPID, but have not developed overt clinical signs.

The DST is commonly used for diagnosis of PPID and has been considered the "gold standard" by many equine clinicians.[28] The DST is convenient and easy to perform, and requires 2 blood samples taken 18–20 hours apart.[17] However, the DST requires administration of dexamethasone, which may exacerbate laminitis in affected horses.[29] The DST test was used alone or with hirsutism to diagnose PPID in nearly half 20/44 (48%) of the horses in this study (Table 1). These results indicate that because the DST was frequently used to diagnose PPID in this study, clinicians have confidence in the use of it to diagnose PPID. Also, it appears to be safe to administer and there were no reports of laminitis caused by administration of dexamethasone in horses in this study.

The combined DST/TRH test was recently validated for the diagnosis of PPID.[15] In that study, the DST/TRH test had a sensitivity, specificity, positive predictive, and negative predictive value of 88, 76, 71, and 90%, respectively. However, the test was not as specific as the TRH component alone (92%). The DST/TRH test was used in 11/44 (25%) of horses in the study reported here. Although the DST/TRH is more accurate than DST alone, it requires dexamethasone and TRH administration and the collection of a minimum of 4 blood samples (0, 3, 3.5, and 18 hours).

Also, commercial or reagent grade TRH is an off-label product and carries some risk, although no adverse responses were noted in the medical records of horses given TRH in this study.

In addition to the use of specific diagnostic testing for PPID, CBC, and serum biochemistry, results can be abnormal. Mean and median values for most hematologic test results were within normal reference intervals, but hematologic data (CBC) may indicate mild anemia, absolute or relative neutrophilia, and absolute or relative lymphopenia. One or more of these abnormalities is reported to occur in approximately one-third of horses with PPID.[3,16,17,30] In the current study, 11/28 (39%) of study patients had lymphopenia, 3/33 (9%) had anemia, and 10/27 (37%) had neutrophilia, and of those horses with data for all 3 variables 16/26 (62%) exhibited 1 or more of these abnormalities. Neutrophilia and lymphopenia in horses with PPID have been associated with increased cortisol activity (ie, "stress" leukogram) or the presence of chronic inflammation, whereas anemia has been associated with chronic disease. Approximately 38% of horses in the follow-up study had high cortisol concentrations and evidence of neutrophilia with lymphopenia. Clinicians should consider PPID in older horses with abnormal hematologic test results because these results may indicate secondary infection such as pneumonia, dental abscesses, and sinusitis, which commonly occur in horses with PPID.[28]

Along with hematologic abnormalities, changes in serum biochemistry results can be present or indicate PPID. Mean and median values for most serum chemistry results in the follow-up study were within established reference intervals. However, 50% or more of horses in this study had results that exceeded the upper limit of the reference interval for glucose, CK, AST, or GGT. Increased blood glucose concentration (hyperglycemia) is the most consistent biochemical abnormality in horses with PPID.[3] The increase in plasma glucose concentration is likely because of an increase in blood cortisol concentration or cortisol-like activity. Hyperglycemia was observed in 17/44 (39%) of horses in the follow-up study and 14/37 (38%) of horses with hirsutism were hyperglycemic. In a previous study, hyperglycemia was found in 7/22 (32%) of all horses with PPID and all of these horses exhibited hirsutism, but the differences in findings between the previous and the current studies were not statistically significant (P = .59 and .21, respectively).[6]

An increase in serum AST activity is likely because of muscle injury, hemolysis, or liver disease, and an increase in serum CK indicates striated muscle injury. In a study of 15 horses with PPID, the authors reported that muscle wasting was the result of atrophy of types 2A and 2B oxidative muscle fibers and loss of type 2B myofibers.[31] In that study, mild nonspecific noninflammatory myopathic alterations were observed, but CK activities were in the normal reference range for all horses. However, in that same study, horses with PPID had ultrastructural changes consistent with altered carbohydrate metabolism and oxidative damage, which in time could lead to muscle cell damage and increased CK and AST activities in horses with advanced PPID. The observation of hirsutism in 84% of horses in the study reported here indicated that horses were suffering from advanced PPID and may explain the increased muscle enzyme activities.

In addition to muscle injury, the increase in AST activity found in the current study is consistent with a previous report and may be because of hemolysis or liver disease.[28] Also, increased AST and GGT activities could be because of hepatocellular damage arising from fat infiltration and altered glucose metabolism within hepatocytes or because of steroid hepatopathy.[32] Horses seem relatively refractory to steroid hepatopathy in comparison with dogs.[28,33]Typically in dogs, increased liver enzyme activity and hepatomegaly caused by increased hepatic glycogen storage are common adverse effects of both exogenous and endogenous glucocorticoids or, in advanced cases, to hepatopathy caused by a persistent increase in plasma cortisol concentration.[34] Among study horses with increased resting cortisol concentrations (n = 10) a positive, but nonsignificant degree of correlation (r = 0.32; P = .37) was found between GGT and resting plasma cortisol concentration. Because most of the horses had normal plasma cortisol concentrations, altered liver enzyme activity may have been the result of other cortisol-like products (eg, CLIP, MSH, endorphin) produced by the pars intermedia in horses with PPID.

Most horses (62%) had resting cortisol concentrations lower than or within the normal reference range, but 38% of horses had resting plasma cortisol concentrations > 165.6 nmol/L, the upper limit of the reference interval. Two previous studies cited plasma cortisol concentrations in horses with PPID to be lower than in normal control horses in the same study,[4,5] and other studies have cited higher than normal plasma cortisol concentrations in horses with PPID compared with control horses.[17] Therefore, the variability in cortisol concentration among individual horses precludes the use of a single measurement for diagnostic purposes. Although there were no statistical differences in cortisol concentrations among seasons, this may be caused by the small sample size and variability in cortisol concentrations among horses.

Horse owners reported that response to treatment (when measured after 2 months) was higher in horses treated with a combination of pergolide and cyproheptadine (60%), followed by pergolide (40%) or cyproheptadine (29%) alone. Although the differences in response rates were not statistically significant, this may be caused by small sample size. These results agree with the trend found in 2 previously published reports citing higher response rates (85 and 86%) with pergolide and lower response rates (28 and 33%) with cyproheptadine.[21,35] Differences among the 3 studies may be because of the conservative criteria used to define response in the current study and the methods used to obtain subjective information. The data presented here (compared with the period after 2007) may more accurately reflect the true effect of treatment as

perceived by owners because the inclusive dates (1993–2004) of the medical record search reported here coincided with the period, before the voluntary recall of the FDA-approved pergolide mesylate[a] (recall date, March 20, 2007). After that date, only compounded pergolide formulations were available and recently the stability and efficacy of these products has come into question.[10] Thus, treatment with compounded pergolide mesylate because of its unreliable drug concentrations and efficacy may affect how horses respond and long-term survival.

To the authors' knowledge there are no prior studies on long-term survival of horses with PPID. Among horses in the follow-up study, there was no association between clinical signs or laboratory test results and long-term survival. In an earlier study of 4 horses with hirsutism, the mean survival time was 192 ± 59 days with a range of 120–368 days.[25] In a study of 21 horses treated with trilostane, 14/21 (70%) survived 12 months, and 11/21 (55%) were alive 2 years post-treatment.[21] Among study horses, the median survival time was 4.6 years and the longest nonsurvivor lived for 6.4 years after diagnosis. Differences in survival time among studies may be because of different inclusion criteria and duration of disease, before diagnosis. In previous studies, all horses exhibited hirsutism before testing for PPID.[21,25] These study patients were selected based on diagnostic codes from the VMDB consistent with diagnoses of PPID and not specific clinical signs of disease (eg, hirsutism or treatment). Therefore, the population of horses with PPID reported here may be more representative of the general population of PPID patients that represent all stages of the disease. However, because horses in this study were from VTHs (many of them referral centers), these horses may be in the later stages of the disease, as compared with horses presented to private practice. Therefore, the long-term survival rate may be an underestimate of the survival among horses in the general population. The cause of death for most study horses was euthanasia owing to one or more of the clinical signs that usually are associated with PPID.

The possibility of recall bias exists with all retrospective studies. Horse owners were questioned about events that occurred from 6 months to 12 years in the past; therefore information may not be remembered or may be biased. If the owner was unsure, information was recorded as missing. To test the potential of recall bias, the time from onset of clinical signs to diagnosis was evaluated for individual years from 1993 to 2004. These values then were averaged for the period 1993–1998 and compared with the average for the period from 1999 to 2004. The results indicated no significant difference among years or time periods in time from onset of signs to diagnosis of PPID, as reported by owners.

Unfortunately, information on dosage and source of drug (ie, compounded versus commercial preparations) was not available in this study, and the type of preparation and formulation may have affected the response rates seen in study horses. However, FDA-approved pergolide mesylate was readily available and widely used at VTHs during the study period. The evaluations of response to treatment and level of performance after diagnosis were based on the owner's perception rather than objective criteria. Although information based on owner recollection of events in the distant past may not be precise, it currently is the best information available. A prospective study would provide more precise information, but because of the limited number of cases at any 1 hospital that would be available for study and the duration of follow-up necessary, it would be impractical to conduct.

These data suggest that the frequency of diagnosis of PPID is increasing and there is a weak, but statistically significant association with geldings. Survival time among horses with PPID could not be predicted based on clinical signs at presentation, initial clinical findings, or routine laboratory test results. Although most horses eventually were euthanized as a result of clinical conditions related to PPID, survival time after diagnosis was considerably longer than has been reported in previously published studies. The owner's preference to treat a 2nd horse, if diagnosed with PPID, and the level of performance at 1 year after diagnosis were used as surrogate measures for quality of life. Although the owner's perception of treatment response was low, 9/34 (26%) horse owners contacted were able to estimate the level of performance at a median of 90% of that before diagnosis, 1 year after diagnosis. Most horse owners 28/29 (97%) indicated that they would treat a 2nd horse with PPID. This evidence suggests that the majority of horse owners are satisfied with the quality of life experienced by horses after diagnosis with PPID.

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Footnotes

[a] Permax, Eli Lilly & Co, Indianapolis, IN
[b] Microsoft Excel 2003, Microsoft Corp Redmond, WA
[c] SAS, version 9.1.3, SAS Institute, Cary, NC

References

1. Toribio RE. Diagnosing equine pars intermedia dysfunction: Are we there yet? J Vet Intern Med 2005;19:145–146.

2. McCue PM. Equine Cushing's disease. Vet Clin North Am Equine Pract 2002;18:533–543.

3. Love S. Equine Cushing's disease. Br Vet J 1993;149:139–153.

4. Beech J, Garcia M. Hormonal response to thyrotropin-releasing hormone in healthy horses and in horses with pituitary adenoma. Am J Vet Res 1985;46:1941–1943.

5. Eiler H, Oliver JW, Andrews FM, et al. Results of a combined dexamethasone suppression/thyrotropin-releasing hormone stimulation test in healthy horses and horses suspected to have a pars intermedia pituitary adenoma. J Am Vet Med Assoc 1997;211:79–81.

6. Keen JA, McLaren M, Chandler KJ, McGorum BC. Biochemical indices of vascular function, glucose metabolism and oxidative stress in horses with equine Cushing's disease. Equine Vet J 2004;36:226–229.

7. Donaldson MT, McDonnell SM, Schanbacher BJ, et al. Variation in plasma adrenocorticotropic hormone concentration and dexamethasone suppression test results with season, age, and sex in healthy ponies and horses. J Vet Intern Med 2005;19:217–222.

8. McGowan CM, Frost R, Pfeiffer DU, Neiger R. Serum insulin concentrations in horses with equine Cushing's syndrome: Response to a cortisol inhibitor and prognostic value. Equine Vet J 2004;36:295–298.

9. Perkins GA, Lamb S, Erb HN, et al. Plasma adrenocorticotropin (ACTH) concentrations and clinical response in horses treated for equine Cushing's disease with cyproheptadine or pergolide. Equine Vet J 2002;34:679–685.

10. Davis JL, Kirk LM, Davidson GS, Papich MG. Effects of compounded and storage conditions on stability of pergolide mesylate. J Am Vet Med Assoc 2009;234:385–389.

11. Dillman DA. Mail and Internet Surveys; The Tailored Design Method. 2nd ed. Hoboken NJ: Wiley; 2007.

12. Schott HC, Coursen CL, Eberhart SW, et al. The Michigan Cushing's project. In: Proceedings of the 47th Annual Convention of the American Association of Equine Practitioners; 2001:22–4.

13. Duncan JR, Prasse KW. Veterinary Laboratory Medicine, Clinical Pathology, 2nd ed. Ames, IA: Iowa State University Press; 1986:229–234.

14. Couetil L, Paradis MR, Knoll J. Plasma adrenocorticotropin concentration in healthy horses and in horses with clinical signs of hyperadrenocorticism. J Vet Intern Med 1996;10:1–6.

15. Frank N, Andrews FM, Sommardahl CS, et al. Evaluation of the combined dexamethasone suppression/thyrotropin-releasing hormone stimulation test for detection of pars intermedia pituitary adenomas in horses. J Vet Intern Med 2006;20:987–993.

16. Hillyer M, Taylor FGR, Mair TS, et al. Diagnosis of hyperadrenocorticism in the horse. Equine Vet Educ 1992;4:131–134.

17. Dybdal NO, Hargreaves KM, Madigan JE, et al. Diagnostic testing for pituitary pars intermedia dysfunction in horses. J Am Vet Med Assoc 1994;204:627–632.

18. Gribble DH. The endocrine system. In: Catcott EJ, Smithcors JF, eds. Equine Medicine and Surgery, 2nd ed. Wheaton, IL: American Veterinary Publications; 1972: 433–57.

19. Heinrichs M, Baumgartner W, Capen CC. Immunocytochemical demonstration of proopiomelanocortin-derived peptides in pituitary adenomas of the pars intermedia in horses. Vet Pathol 1990;27:419–25.

20. Donaldson MT, LaMonte BH, Morresey P, et al. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). J Vet Intern Med 2002;16:742–746.

21. McGowan CM, Neiger R. Efficacy of trilostane for the treatment of equine Cushing's syndrome. Equine Vet J 2003;35:414–418.

22. Donaldson MT, Jorgensen AJ, Beech J. Evaluation of suspected pituitary pars intermedia dysfunction in horses with laminitis. J Am Vet Med Assoc 2004;224:1123–1127.

23. Dybdal N. Pituitary pars intermedia dysfunction (equine Cushing's-like disease) In: Robinson N, ed. Current Therapy in Equine Medicine, 4th ed. Philadelphia, PA: WB Saunders; 1997:449–501.

24. Loeb WF, Capen CC, Johnson LE. Adenomas of the pars intermedia associated with hyperglycemia and glycosuria in two horses. Cornell Vet 1966;56:623–639.

25. van der Kolk JH, Kalsbeek HC, van Garderen E, et al. Equine pituitary neoplasia: A clinical report of 21 cases (1990-1992). Vet Rec 1993;133:594–597.

26. Eyre P, Elmes PJ, Strickland S. Corticosteroid-potentiated vascular responses of the equine digit: A possible pharmacologic basis for laminitis. Am J Vet Res 1979;40:135–138.

27. van der Kolk JH WT, Kalsbeek HC, Breukink HJ. Laboratory diagnosis of equine pituitary pars intermedia adenoma. Domest Anim Endocrinol 1995;12:35–39.

28. Schott HC. Pituitary pars intermedia dysfunction: Equine Cushing's disease. Vet Clin North Am 2002;18:237–270.

29. Green EM, Hunt EL. Hypophyseal neoplasia in a pony. Compend Contin Educ Pract Vet 1985;7:S249–57.

30. van der Kolk J. Equine Cushing's disease. Equine Vet Educ 1997;9:209–214.

31. Aleman M, Watson JL, Williams DC, et al. Myopathy in horses with pituitary pars intermedia dysfunction (Cushing's disease). Neuromuscul Disord 2006;16:737–744.

32. Field JR, Wolf C. Cushing's syndrome in a horse. Equine Vet J 1988;20:301–4.

33. Cohen ND, Carter GK. Steroid hepatopathy in a horse with glucocorticoid-induced hyperadrenocorticism. J Am Vet Med Assoc 1992;200:1682–4.

34. Johnson SE, Scherding RG. Diseases of the liver and biliary tract. In: Birchard SJ, Scherding RG, eds. Saunders Manual of Small Animal Practice, 2nd ed. Philadelphia, PA: WB Saunders; 2000:824–73.

35. Schott HC, Graves EA, Refsal KR, et al. Diagnosis and treatment of pituitary pars intermedia dysfunction (classical Cushing's disease) and metabolic syndrome (peripheral Cushing's syndrome) in horses. Proceedings of the 5th World World Cong Vet Derm 2005;5:159–169.