# UPDATE ON PITUITARY PARS INTERMEDIA DYSFUNCTION (PPID)

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Objectives of the presentation:

1. Know how to recognize a horse affected with PPID
2. Know the pros and cons of the available diagnostic tests for PPID
3. Understand how comorbidities (insulin resistance) affect the prognosis of PPID
4. Understand treatment options for PPID

## Clinical definition and signs

Pituitary pars intermedia dysfunction (PPID) is a neurodegenerative disorder of aged horses. Up to 30% of aged horses may be affected[1]. Affected horses are typically greater than 15 years old, but PPID has occasionally been reported in horses as young as 8 years old. Any breed can be affected including ponies and donkeys. Macro or micro adenomas of the pars intermedia of the anterior pituitary gland lead to the clinical signs. The clinical signs vary as to the severity of disease.

Early (less severe) PPID

1. Delayed shedding of haircoat, regional hypertrichosis
2. Changes in attitude, lethargy, performance
3. Loss of musculature
4. Hyperhidrosis or anhidrosis
5. Infertility
6. Laminitis, white line disease, sole abscesses
7. Regional adiposity
8. Tendonitis/desmitis

Advanced (severe) PPID

1. All signs listed above, increased severity
2. PU/PD
3. Weight loss/Severe muscle atrophy
4. Generalized hypertrichosis, non-shedding
5. Recurrent infections (including parasitism)
6. Pendulous abdomen
7. Blindness/neurological disease
8. Mammary gland secretions

Pathophysiology

The anterior pituitary gland consists of 3 lobes: pars distalis, pars intermedia, and pars tuberalis. The pars intermedia lies between the pars distalis and the pars tuberalis. The pars intermedia contains melanotropes which produce pro-opiomelanocortin (POMC) peptides. The POMCs include precursors for adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone (MSH), beta-endorphins, and corticotropin-like intermediate peptide (CLIP)[1]. The pars intermedia is innervated by dopaminergic neurons from the hypothalamus. Formation of adenomas is thought to be due to oxidative damage to dopaminergic neurons. The lack of dopaminergic input leads to abnormal hormone release from the pituitary adenoma and is the basis for the mainstay of treatment, the dopamine agonist pergolide[1].

The clinical signs are produced due to excessive amounts of POMC peptides produced by the pars intermedia produces and loss of negative feedback[1]. Hormones such as ACTH act on the adrenal glands to increase release of cortisol. The cortisol normally feeds back on the pituitary to stop release of ACTH, but the diseased pars intermedia does not respond to the negative feedback.

Diagnostic testing and laboratory findings

Laboratory findings: In some affected horses, complete blood count results may show persistent leukocytosis with mature neutrophilia and lymphopenia (stress leukogram). Hyperglycemia is a common biochemistry finding, especially in advanced cases. Some horses

will have elevated liver enzyme activities, increased triglycerides, and hyperinsulinemia (see below).

Diagnostic testing: There are 3 tests that are currently recommended for diagnosis of PPID: endogenous ACTH measurement, thyrotropin releasing hormone (TRH)/ACTH response test, and low dose dexamethasone response test. The test to use depends on the laminitis status of the horse and preferences of the owner and examining veterinarian. The first two tests, endogenous ACTH and TRH/ACTH response test, are recommended by the Equine Endocrinology working group http://sites.tufts.edu/equineendogroup/. The dexamethasone suppression test was originally considered to be the gold standard test for PPID. Concerns about links between laminitis and exogenous steroid administration have led to less recommended use of this test, but many practitioners still use it. The links between steroid administration and laminitis do not have strong scientific evidence at this time[2], but good client communication is recommended. If results are going to be compared year to year or before and after treatment, be sure that the same laboratories are used to run the samples.

1. Endogenous ACTH. This test measures basal concentrations of ACTH. No fasting is required, but the horse should be as unstressed as possible. Transport can cause mild changes so ideally the horse is tested at his/her home farm or after an overnight stay in another facility[3]. An EDTA sample is collected in a glass or plastic tube and the plasma needs to be removed after centrifugation within 30 minutes of collection, preferably sooner. The plasma is typically frozen in plastic tubes before shipment overnight. Interpretation of results will also depend on the reference ranges of the lab for the assay used, but for many labs, a value <35 pg/ml is expected mid-November-mid-July in the USA. The fall months are often higher due to seasonal changes, and a value of less than 50 pg/ml is normal for many laboratories from mid-July-mid-November. Greater than 100 pg/ml is considered positive. It is essential to check with the laboratory that you are working with because the assays are different. For example, the Auburn University Endocrinology Laboratory has much lower normal ranges and most horses are less than 20 pg/ml during spring, summer, and winter, and less than 35 pg/ml in the fall[4, 5].

2. TRH/ACTH Stimulation test. This test measures the release of ACTH in response to TRH. Normal horses should have a small increase in ACTH when TRH is administered (ACTH < 110 pg/ml). Horses with PPID have a larger increase (>200 pg/ml). To perform the test, allow hay but no grain within 12 hours and the same comments about sample handling and stress apply as written for endogenous ACTH above. Collect a baseline EDTA plasma sample, administer 1 mg TRH (if >250 kg, use 0.5 mg if <250 kg) IV and collect another EDTA sample 10 minutes after the TRH administration. Baseline ACTH and ACTH post TRH are measured in the plasma samples. There are no seasonal reference ranges for this test, so the current recommendation

is to not perform the test mid-July-mid-November, although this may change in the future as more research is performed. For non-fall months, ACTH concentrations 10 minutes after TRH should be less than 110 pg/ml, and greater than 200 pg/ml is considered positive. Reference ranges may be different between laboratories so be sure to check.

3. Low dose dexamethasone suppression test. To perform this test, no fasting is required and should be performed on a horse with minimal stress. A baseline serum sample (plain red top tube) is collected at about 5pm for cortisol measurement and then 40 micrograms/kg dexamethasone is administered intramuscularly. A second serum sample is collected 19-20 hours later for cortisol measurement. The endogenous cortisol will be suppressed through negative feedback in normal horses, so the second cortisol sample should be less than 1 microgram/dl (units may vary between labs so read the interpretation)[1].

**Baseline cortisol concentrations fluctuate widely in affected horses, so baseline cortisol and diurnal cortisol are useless tests for evaluating PPID status.**

Testing for insulin resistance: Horses with both PPID and insulin resistance are more likely to have laminitis[6], so testing for insulin resistance is an essential part of the diagnosis of PPID. Insulin resistance is typically evaluated by measurement of baseline insulin or by a dynamic test such as an oral glucose test (OGT) or combined insulin glucose tolerance test (CGIT) or insulin tolerance test (ITT). If a dynamic test will be used, insulin resistance testing should be performed on a different day than TRH/ACTH testing or the overnight dexamethasone suppression test[7]. A baseline insulin could be collected at the same time as the baseline sample for the TRH/ACTH testing.

Treatment

Management of nutrition and comorbidities: Treatment of PPID is not just through pharmacological management. Dental care, parasite control, hoof trimming, body clipping, and nutritional management all need to be part of the therapy to ensure maximum longevity and quality of life. Horses with laminitis will require dedicated hoof care with a good working relationship between the veterinarian, the owner, and the farrier. Horses that are insulin resistant will require very strict management of carbohydrate intake. Nonstructural carbohydrate (NSC) intake should be less than 10-15%. Grass or alfalfa hay, commercial low starch feeds and limited intake of fresh pasture grass are recommendations to keep NSC content low in the diet. Medications to manage insulin resistance such as metformin (30 mg/kg given 1 hour before feeding) may be considered if diet and PPID treatment with pergolide are not sufficient to lower insulin concentrations and manage laminitis.

Treatment: Pergolide mesylate (FDA approved Prascend®) is the drug of choice for horses with PPID. Pergolide is a dopamine agonist which downregulates POMC peptide production. Endogenous ACTH concentrations and clinical signs should improve with Prascend treatment in PPID affected horses. The label recommendation is to start a 400-500 kg horse at 1mg (2 mcg/kg) PO once a day and reevaluate in 30 days. Anorexia is the most common adverse effect and often resolves if the dose is reduced and then very slowly increased again. Anorexia typically resolves within 30 days of starting treatment. Treatment is lifelong and may require dose adjustment if the clinical signs progress.

Horses that are refractory to treatment may be managed by increasing the pergolide dose by 0.5-1 mg/day for 500 kg horse every 30-60 days until clinical signs are better managed. A maximum of 3-5 mg/day is typically reached. Cyproheptadine (0.25 mg/kg orally twice a day or 0.5 mg/kg orally once daily) can also be added or used instead of pergolide in refractory cases, but be aware of side effects such as colic.

| **Drug** | **Drug Class** | **Dose Range** | **Frequency** | **Route** | **Indications** |
|---|---|---|---|---|---|
| **Prascend** | **Dopamine agonist** | **2 mcg/kg** | **Q24** | **PO** | **PPID** |

REFERENCES

Excellent resource for information:
https://sites.tufts.edu/equineendogroup/files/2017/11/2017-EEG-Recommendations-PPID.pdf

1. McFarlane, D., Equine pituitary pars intermedia dysfunction. Vet Clin North Am Equine Pract, 2011. 27(1): p. 93-113.

2. Cornelisse, C.J. and N.E. Robinson, Glucocorticoid therapy and the risk of equine laminitis. Equine Veterinary Education, 2013. 25(1): p. 39-46.

3. Fazio, E., et al., Circulating beta-endorphin, adrenocorticotrophic hormone and cortisol levels of stallions before and after short road transport: stress effect of different distances. Acta Vet Scand, 2008. 50: p. 6.

4. Schreiber, C.M., et al., Seasonal variation in results of diagnostic tests for pituitary pars intermedia dysfunction in older, clinically normal geldings. J Am Vet Med Assoc, 2012. 241(2): p. 241-8.

5. Funk, R.A., et al., Seasonal changes in plasma adrenocorticotropic hormone and alpha-melanocyte-stimulating hormone in response to thyrotropin-releasing hormone in normal, aged horses. J Vet Intern Med, 2011. 25(3): p. 579-85.

6. Karikoski, N.P., et al., Lamellar pathology in horses with pituitary pars intermedia dysfunction. Equine Vet J, 2016. 48(4): p. 472-8.

7. Restifo, M., et al., Effects of fasting and the oral sugar test on thyrotropin-releasing hormone stimulation test results in horses. Journal of Veterinary Internal Medicine, 2015. 29: p. 1231.