

Pituitary Pars Intermedia Dysfunction in Aging Horses

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Pituitary pars intermedia dysfunction (PPID), also known as Pituitary adenoma and Equine Cushing's Disease (ECD), is the most common endocrinologic problem in horses. In a retrospective study of older horses that were presented to TCSVM between the years 1989-1999, 10% of the horses over 20 years of age were affected by this problem. The percentage increased as the population aged from 20 to 35+. In the survey study at Tufts, PPID was diagnosed by a veterinarian in 8% of the horses but 30% of the old horse owners who did not have a veterinarian diagnosis of PPID, reported changes in their horses haircoat that was compatible with the disease (longer haircoat than in the past, incomplete shedding, required body-clipping in summer). In another study, the average age of affected animals was 21 years with the youngest case reported to be 7 years of age.

The most common clinical sign of PPID is hirsutism, an excessively long, curly haircoat. It may be present over the entire body, found in patches or represented by long guard hairs in the jugular furrow. Affected horses may have delayed shedding or may not shed their haircoats in the summer. The haircoat changes may be very subtle in the beginning. PPID horses are more likely to experience laminitis than other horses. Other clinical signs include hyperhidrosis, polydipsia/polyuria, muscle wasting, blindness (rare), seizures (rare) and increased susceptibility to infections. The most common clinicopathologic abnormality found in affected horses is hyperglycemia. Less commonly, a neutrophilia with lymphopenia have been seen.

The pathology associated with this disease is hypertrophy, hyperplasia and adenoma formation of the pars intermedia of the pituitary gland. At post mortem, the pituitaries are enlarged sometimes up to 5 times the normal weight. The increased size can lead to compression of surrounding tissues in the pituitary gland and the hypothalamus. These hyperplastic changes lead to excess production of various proopiomelanocortin (POMC) peptides, such as, α MSH, β MSH, β -endorphin, corticotropin-like intermediate lobe peptide (CLIP) and ACTH.

It has been suggested that the processing of POMC peptides in the pars intermedia of the horse is normally inhibited by dopaminergic innervation. In pars intermedia tumors, the level of dopamine is markedly decreased in the hypothalamus of affected horses. This decrease releases the dopaminergic inhibition of the pars intermedia, which results in increased production of end-hormones.⁵ Adrenal hyperplasia is a secondary consequence of this disease and results in a loss of the diurnal variation in the secretion of cortisol.

The question becomes why is there a decrease in dopamine in the pars intermedia in some horses as they age and not others. There is immunohistochemical evidence of loss of dopaminergic neurons. McFarlane's work suggests dopaminergic neurodegeneration in PPID may occur secondary to oxidative stress. Apparently dopaminergic neurons are more sensitive to oxidative damage. This may be due a byproduct of dopamine metabolism, free radicals.

What is the best diagnostic test for confirmation of PPID? This is a question that we thought that we knew the answer to 5 years ago but in the past few years our tests have become less definitive. Endogenous levels of ACTH are generally elevated. In one of the first studies at Tufts, normal ACTH

levels for horses and ponies were determined to be 18.67 ± 6.79 pg/ml and 8.35 ± 2.92 pg/ml. Values in affected animals were elevated to a mean of 199.18 ± 182.8 pg/ml and 206.21 ± 319.56 pg/ml. The range in both groups was wide; therefore, endogenous ACTH levels >27 pg/ml in ponies and >50 pg/ml in horses was considered diagnostic of PPID. Another clinical test that was helpful in the diagnosis of pituitary disease in the horse is the overnight dexamethasone suppression test. The expected response in the normal horse is the suppression of cortisol levels below $1 \mu\text{g/ml}$. The horse with a pituitary adenoma will not suppress. What we know now is that there is a seasonal variation to hormone production. It was shown that ACTH levels and the dexamethasone suppression test can lead to false positives if sample were taken from August to December. The reliability of the combined dexamethasone suppression/ thyrotropin releasing hormone test has also been questioned. Even at post mortem there are inconsistencies between pathologists.

Plasma insulin levels are often higher in horses with PPID. The normal levels in hay- and grain- fed animals are $11.9 \pm 2.0 \mu\text{U/ml}$ and $16.4 \pm 3.2 \mu\text{U/ml}$. In another study, horses with PPID had average insulin levels of $105.1 \pm 20.2 \mu\text{U/ml}$. This may be helpful in your diagnosis but not all PPID have elevated insulin. There may also be confusion as to whether you have a horse with PPID or metabolic syndrome or both. Anecdotal reports have hypothesized that fatter horses are more prone to develop PPID as they age. Perhaps insulin resistance plays a role in the development of the disease.

So how do we make a positive diagnosis? Certainly if you have an older horse with a shaggy haircoat in the summer, you can be fairly sure that the cause is PPID. The problem comes with the horse that has minimal haircoat changes. Testing these animals for ACTH levels or a dexamethasone suppression test from January through August will give you the highest likelihood on not having a false positive.

In the past, the treatment of ECD has been relegated to management. This still has important therapeutic value. Whole body clipping may be necessary in animals with severe hirsutism. The immune system of the affected horse is thought to be somewhat suppressed because of the constant levels of cortisol. Consequently the horses are more prone to infection and heal more slowly. Any injuries or infections should be treated aggressively.

Two medical protocols have developed. The drugs that have been used are cyproheptadine and pergolide. Their use has produced anecdotal evidence of a varied clinical response. A few small clinical trials have been reported but no blinded studies have been performed. A wide range of dosages exist for each drug. Horses are generally started on a low dose which is increased if no effect is seen.

Cyproheptadine is an antiserotonergic drug that was reported to have induced remission of pituitary-associated Cushing's disease in humans. Its use in horses has produced varying reports of efficacy. Couetil found that clinical signs improved in 69% of affected horses and ponies with cyproheptadine, while ACTH decreased in 45% of the cases and increased in 40%. This study and other anecdotal reports of clinical improvement, the absence of side effects and the low cost of the drug have contributed to its continued use to treat PPID. Its future use may be limited by market availability. This work was done before we knew about the seasonal variation of ACTH so any increase or decrease may be due to that.

Pergolide is a dopaminergic agonist used in the treatment of PPID. In PPID, the levels of dopamine are decreased. This decrease is consistent with the release of dopaminergic inhibition, which results in increased production of the end-hormones. Pergolide appears to be safe and active when used as replacement therapy.

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