Pituitary Pars Intermedia Dysfunction (Equine Cushing’s Disease)

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Pituitary Pars Intermedia Dysfunction (PPID) is the correct term for the disease commonly known as Equine Cushing’s Disease. The latter term is technically incorrect because it is now known that the disease is different from human Cushing’s disease. It is a condition of older horses and typically develops in horses over 15 years of age although it can develop in younger animals. Up to 30% of aged horses have the condition and the risk of developing the disease increases directly with age such that most horses in their late 20’s and even 30’s will have the condition. The disease tends to be seen more commonly in ponies but this may be because ponies tend to live longer rather than because ponies are at greater risk of the disease.

Aetiology
The condition is due to over-activity of one part (the intermediate lobe) of the pituitary gland the excessive release of certain metabolically active proteins and hormones. The pituitary gland is located beneath the brain and releases its products in response to signals from nerves that originate in another area of the brain called the hypothalamus. Damage to these nerves causes the pituitary to enlarge and produce excessive quantities of hormones. The hormones known to be of importance are adrenocorticropic hormone (ACTH), endorphins and melanocortins but there are many others produced. The disease progresses gradually as the nerves to the pituitary slowly degenerate. It is unknown how the increases in pituitary hormones result in many of the clinical signs that are seen.

Clinical Signs
Hirsutism is the term for excessive hair growth or abnormal retention of the hair coat in the summer and PPID is the only condition that causes this abnormality. The presence of an abnormally long hair coat in an older horse is very strong evidence of PPID (Figures 1 and 2).

Abnormal fat deposition and insulin resistance may develop in up to 60% of horses with PPID. The implications of insulin resistance are discussed under Equine Metabolic Syndrome (EMS). Pituitary Pars Intermedia Dysfunction and EMS are often confused as both conditions result in insulin resistance; however, the reasons for the insulin resistance are different. Furthermore, a number of additional signs are seen with PPID. The differences between the two conditions are discussed under EMS. A common site of increased fat deposition is around the eyes.

Laminitis is the most serious complication of PPID and is associated with considerable suffering and potentially euthanasia. In the UK the majority of cases of laminitis are caused by either EMS or PPID and
PPID should therefore be investigated in older horses that develop laminitis. PPID should also be suspected if laminitis occurs in the autumn and winter.

Muscle wasting may be seen in some cases and is usually most obvious over the hindquarters.

Increased drinking (polydipsia) and urination (polyuria) may occur in up to a third of horses with PPID; the reasons for this are unknown. There are many other causes of increased drinking and urination but in an older horse observation of these signs should prompt investigation of Cushing's disease.

Increased sweating (hyperhidrosis) may be seen even in horses that don't have an excessively long haircoat.

Lethargy or a more docile temperament may be observed and usually resolves with treatment.

Seizures, weakness, blindness and collapse are seen rarely in advanced cases and are thought to be the result of the enlarged pituitary putting pressure on other areas of the brain.

Infertility may occur in mares as a result of altered hormone production.

Infectious disease occurs more commonly in horses with PPID compared to normal horses of the same age because some of the hormones released with the condition suppress the immune system. Common infections include ringworm, sinus infection, pneumonia, and foot abscesses. Horses with PPID are also more likely to have infections without showing clinical signs and have been shown to be more susceptible to parasites.

**Diagnosis**

Definitive diagnosis of PPID can be difficult as the changes in the pituitary and the resultant blood and external changes can be variable between animals. In addition there is a gradual progression from normal to increased pituitary function making it difficult to draw an arbitrary cut-off in classifying an animal as diseased. Furthermore, pituitary function varies with season in all horses and this has to be accounted for when testing is performed. In advanced cases with marked hirsutism and other suggestive signs the diagnosis may be made on clinical signs alone. Clinical signs other than hirsutism are not a reliable means of making a diagnosis but should prompt further testing.

Changes on routine blood samples are not specific for the diagnosis of PPID but, as with clinical signs, they may give an indication that the condition is present. Changes that may be seen include high white cell counts and evidence of secondary infection, high glucose and high liver enzymes. All
of these changes have many other potential explanations.

Specific diagnosis of PPID requires measurement of hormones in the blood. This may be done on a single blood sample or the pituitary gland’s response to specific tests may be assessed.

**Cortisol** levels have traditionally been used as an indicator of PPID. Cortisol is released from the adrenal glands in response to increased hormone production from the pituitary. Unfortunately horses with PPID often have normal levels of cortisol and conversely normal horses may have high levels if they are affected by pain, stress and other factors. Levels of cortisol in urine and saliva have also been measured but are unreliable.

**Insulin** levels are increased in 60% of horses with PPID and may be an indicator of the severity of disease. However, insulin levels are also high in horses with EMS and horses that are painful, stressed or have recently been fed. Therefore, further tests are required to distinguish PPID from other potential causes of high insulin.

**Adrenocorticotropic hormone (ACTH)** is released in increased quantities from the pituitary gland and provides a reliable test for the diagnosis of PPID. The value of the test has increased now that the normal seasonal changes in ACTH levels are understood and differentiation of normal and abnormal is more reliable. ACTH levels decrease rapidly in stored blood and it is therefore important that samples are transported for analysis rapidly and are kept frozen or chilled.

The **Dexamethasone Suppression Test** has traditionally been regarded as the gold-standard test. More recently however concerns have been expressed that this test is unable to detect early cases of the disease and other tests may be more sensitive. The test involves taking a blood sample to measure natural cortisol, giving artificial cortisone (dexamathasone) and then taking another blood sample the following day to see whether natural cortisol levels have decreased. In horses with PPID there is no reduction. Because more than one sample is required the test is more expensive than testing ACTH. In addition, the test is unreliable in late summer and the autumn when the pituitary gland is naturally hyperactive.

The **Thyrotropin Releasing Hormone (TRH) Stimulation Test** assesses the pituitary gland’s response to administration of TRH. In horses with PPID the pituitary gland has an exaggerated response to TRH and increased levels of ACTH and subsequently cortisol (released from the adrenal gland in response to ACTH) can be identified in blood. Measurement of ACTH following TRH stimulation is the most reliable. Unfortunately, TRH is very expensive and hard to obtain limiting the availability of this test.

Other tests are potentially available but are not used widely because they fail to offer clear advantages over the ones already described. These include the measurement of melanocyte stimulating hormones, assessing the response to domperidone stimulation and examining the pituitary gland using magnetic resonance imaging (MRI) or computed tomography (CT).

**Treatment**

Fortunately effective treatment for PPID is available in the form of **pergolide** and this drug has been licensed specifically for horses recently. Pergolide stimulates dopamine receptors in the brain and thereby replaces the activity of the damaged nerve supply to the pituitary gland. This results in reduction of hormone production to normal levels. The dose range is wide and the improvement in clinical signs and ACTH levels is often used to determine the best dose rate for each horse.

Cyprohepatidine is an anti-histamine that has a range of other effects in the brain and has been suggested to be of use for PPID. On its own it is not very effective but in some cases it may be beneficial in association with pergolide. Trilostane is used for the treatment of Cushing’s disease in dogs but is not effective in horses because of fundamental differences in the disease between the two species.

A number of natural remedies have been suggested as treatments for PPID but none have been proven to be effective. Only one, a chasteberry (Vitex agnus castus) extract, has been tested in a controlled manner and it failed to resolve clinical signs or improve diagnostic test results in 14 horses. Subsequent treatment of the same horses with pergolide was effective in all but one case.

Horses with PPID require extra attention to be paid to dental care, hoof care and parasite control. Those with dental disease may benefit from cubed diets that are designed for older animals and are easy to chew. Horses with excessive hair coat
benefit from regular clipping. Many horses with PPID develop insulin resistance and this may need to be managed in much the same way as it is for EMS (see the specific recommendations under EMS). With good management there is no reason why horses with PPID cannot live a long and normal life and continue in normal work.

**Welfare Implications**

The major welfare implication of this condition is the increased risk of laminitis. Failure to provide adequate dental, hoof and other routine care can also have a significant impact on the welfare of affected animals.

**Disease Control and Prevention**

The disease is a natural degenerative condition and therefore there is nothing that can be done to prevent it. Horses that are kept in good health and have high levels of anti-oxidants may be less likely to develop the nerve damage that is responsible for the condition but this is unconfirmed. It has been suggested that horses with EMS are more likely to develop the condition however this is unproven. Similarly it has been suggested that feeding anti-oxidants may be beneficial but there is some doubt whether feeding anti-oxidants actually results in increased levels of anti-oxidants in the brain. Early treatment with pergolide may slow the progression of the disease but again this is unproven.

**Summary of Key Learning Points**

- Pituitary Pars Intermedia Dysfunction is the correct term for Equine Cushing’s disease. This is a distinct condition from Equine Metabolic Syndrome but the two diseases have some common features.
- PPID is a natural degenerative disease that affects older horses
- Normal nerve supply and therefore inhibition of the pituitary is lost resulting in increased hormone production
- A range of clinical signs may be seen. Hirsutism is the most reliable indicator of the disease
- Laminitis is the most serious clinical sign that develops
- A number of diagnostic tests are available, the most commonly used being measurement of ACTH and the Dexamethasone Suppression Test
- Pergolide is the most effective treatment
- Prognosis is good with good management

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