What is PPID?
The pituitary gland lies below the hypothalamus at the bottom of the horse’s brain. It consists of three major hormone-releasing lobes: the pars distalis, the pars nervosa and the pars intermedia.

All horses, whether they have PPID or not, react to stress by releasing ACTH from the pars distalis into the blood. This tells the adrenal glands to release cortisol, which plays a role in the ‘fight or flight’ response. The high levels of cortisol in the blood feed back on the pars distalis, reducing ACTH production.

In a normal horse, the pars intermedia plays a role in seasonal changes, metabolism, and inflammation, producing a peptide called POMC, which is initially changed to ACTH. Then around 98% of ACTH is changed to alpha-MSH, beta-endorphin, and CLIP. The remainder changes, metabolism, and inflammation, producing a peptide called POMC, which is initially changed to ACTH. Then around 98% of ACTH is changed to alpha-MSH, beta-endorphin, and CLIP. The remainder

What causes PPID?
The cause of PPID is still unknown, but research suggests that localised oxidative stress may contribute to dopaminergic neuron damage and cell death. Dr Dianne McFarlane found decreased activity of the antioxidant manganese superoxide dismutase in the pars intermedia in older horses, that could contribute to the risk of PPID developing with age. She also found evidence of protein misfolding in the pars intermedia of horses with PPID, similar to that found in Parkinson’s disease.

In her presentation on the pathophysiology of PPID at the 2011 Equine Endocrinology Summit, Dr McFarlane suggested that there may be several syndromes that lead to PPID, such as metabolic disorders like EMS, toxins in the environment, stress, or genetic predisposition. This might explain why individual horses with PPID can have differing symptoms and hormone levels.

Diagnosis of PPID
Diagnosis of PPID is based on clinical signs and history, backed up by above normal ACTH blood test results. Although incidence increases with age, horses as young as six or seven have been diagnosed with PPID.

Clinical signs
Clinical signs vary between horses and with the stage of the disease, and are often mistaken for normal ageing. Experts often group clinical signs into early or advanced stage, but there is likely to be overlap. Symptoms are often worse during the autumn ‘seasonal rise’.

Early signs may include:
- Long hair on legs, neck and face.
- Delayed or patchy shedding of haircoat.
- Muscle loss along topline.
- Lethargy / depression / docility.
- Decreased athletic performance.
- Laminitis, usually with abnormal fat deposits and insulin dysregulation.

As the condition becomes more advanced, additional signs may include:
- Puffy eyelids and mucky eyes.
- Infertility / loss of seasons.
- Recurrent infections such as sinuses, abscesses, skin infections, and increased parasite burdens.
- Potbelly due to loss of muscle tone.
- Abnormal sweating / thermoregulation – hyperhydrosis (increased sweating) or anhydrosis (lack of normal sweating). Sweating may be patchy and in unusual places.
- Significant weight loss.
- Polyuria / polydipsia (increased drinking and urination).
- Abnormal coat – from a thicker than normal summer coat, long coarse hairs in the coat or patches of long hair to a long shaggy coat (hypertrichosis) that doesn’t shed at all.
- Hyperglycaemia (above normal blood glucose concentrations).
- Neurological symptoms such as ataxia, seizures and blindness.

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Laminitis

Equine Pituitary Pars Intermedia Dysfunction

Words by Andrea Jones

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When resting ACTH results are borderline or negative despite a suspicion of PPID, the TRH stimulation of ACTH may be recommended. A resting ACTH blood sample is collected; then 1mg of TRH is injected, and a further ACTH blood sample collected 10 minutes later. Horses with PPID appear to produce more ACTH in response to an injection of TRH than normal horses. Currently this test cannot be used in the autumn, and more research is required to define normal reference ranges. All horses suspected of having PPID should be tested for insulin dysregulation using either a resting insulin test, or if no clinical signs of insulin dysregulation are seen, or if resting insulin test results are normal, an oral sugar test to assess laminitis risk.

The dexamethasone suppression test, once considered the gold standard for PPID testing, is no longer recommended as it may cause laminitis, requires two vet visits, cannot be used in the autumn, and may only detect advanced cases. Tests measuring cortisol are not diagnostic for PPID.

All horses have a ‘seasonal rise’ in pars intermedia hormone production in the autumn, probably to help them prepare for the winter, starting as days begin to get shorter and is considered significant from August to October. The increase is greater in horses with PPID, making this the best time to test ACTH, as long as seasonally adjusted reference ranges are used. A diagnosis of PPID should only be made if there are clinical signs of PPID. There is no way of knowing whether the ACTH in a blood sample is from the pars intermedia, and suggests PPID if abnormally high, or has been produced by the pars distalis as part of a normal stress response. Stress can be due to pain, such as laminitis, illness, excitement, exercise, travelling, use of a twitch, veterinary procedures such as dental work, or ‘white coat phobia’. Some medicines increase ACTH, including clenbuterol (Ventipulmin). Note also that freezing a blood sample before it has been separated by centrifuge can lead to falsely high ACTH results. In the future, testing of other PPID hormones may be commercially available, which may make blood testing more accurate.

Although it isn't yet known whether having EMS causes PPID, it seems that horses with EMS may be at greater risk of developing PPID as they get older, and therefore horses with EMS should be monitored and tested for PPID, and their diet, weight, and exercise addressed with the aim of reversing EMS. Vet's are also noticing that there appear to be a transitional period as horses with EMS develop PPID during which their insulin concentrations, and therefore risk of laminitis, increase.

Blood tests

As PPID is a progressive disease, blood tests are often negative in the early stages, but false positives are also seen when ACTH is released as part of the normal stress response. Hormone levels are affected by seasons and geographical location, are released in pulses so concentrations can change within minutes, and vary considerably between affected horses.

The Equine Endocrinology Group (EEG) has published recommendations for the diagnosis of PPID (http://sites.tufts.edu/equineendogroup/) and suggests initially testing. Resting ACTH concentration requires a single blood draw and can be done at any time of the day or year, as long as seasonally adjusted reference ranges are used, and the horse is not stressed before or during the blood collection. Note that ACTH can be measured using different assays, with different reference ranges. Therefore, results from laboratories may not be comparable. Horses in the UK that have not been diagnosed with PPID may be eligible for a free ACTH test until 31 October 2015 – see www.talkaboutlaminitis.co.uk.

Blood levels of ACTH may be used to define normal reference ranges for the diagnosis of PPID (http://sites.tufts.edu/equineendogroup/) and suggests initially testing. Resting ACTH results are usually elevated in the early stages, but false positives are also seen when ACTH is released as part of the normal stress response. Hormone levels are affected by seasons and geographical location, are released in pulses so concentrations can change within minutes, and vary considerably between affected horses.

It is suggested that horses with PPID have blood tests every six months, with one test during the seasonal rise, to monitor the progression of the disease and their response to treatment. Currently there is no research that supports the use of herbal, homoeopathic, or other non-medical treatments for PPID. Some owners report improvements in depression and coat shedding with Vitex agnus castus, but research by Jill Beech et al (2002) found no improvement in hormone levels, and that clinical signs sometimes worsened when PPID horses were treated with Vitex agnus castus.

Management is also very important and should be optimised. Excess hair should be clipped and rugs used to help regulate the horse's body temperature. The diet should contain above minimum levels of quality protein, minerals, vitamins, and essential fatty acids, with energy levels appropriate for the horse's lifestyle, and sugar and starch amounts kept low if the horse has insulin dysregulation. In theory, feeds high in antioxidants could help to slow the hyperplasia, and hypertrophy associated with the excess production, and thereby reducing the clinical signs of PPID. It isn't currently known whether treatment with pergolide will prevent or slow the hyperplasia, and hypertrophy associated with the excess hormone production of the pars intermedia, but in theory this seems possible.

In addition, research by Gille et al (2002) found that pergolide protects dopamine-producing neurons under conditions of elevated oxidative stress, and Dr McFarlane has theorised that any antioxidant and neuroprotective properties of pergolide could be beneficial in slowing the progression of PPID, suggesting that early treatment with pergolide may be advisable.

The initial dose of Prascend recommended is 0.002mg/kg bodyweight once a day, so 1mg for a 500kg horse. However, the dose may depend on the stage of the PPID, the season and other factors, and it should be titrated to the lowest effective dose for each individual horse based on response to therapy, whether that is improvement in clinical signs and blood results, or signs of intolerance. Many horses require an increased dose during the seasonal rise, with a subsequent reduction in dose around Christmas.

Some horses go off their food or become depressed when starting treatment with pergolide, but when introduced gradually, ideally starting with 0.5mg and slowly increasing to the recommended dose, side effects are minimised. Giving pergolide at different times to bucket feeds has helped some horses overcome inappetence.

Response to treatment is individual, but the EEG suggests that within 30 days of starting treatment, an improvement in lethargy and depression, PU/PD, and blood glucose concentrations should be seen, with improvements in haircoat abnormalities, improved topline and reduced incidences of laminitis, and infections within a year. In The Laminitis Site's experience, improvements are often noticed sooner than this, particularly when the PPID has not yet reached the advanced stage.

Blood should be tested one month after starting pergolide to assess response to treatment. PPID horses treated with pergolide and retested every four weeks showed significant reductions in resting ACTH levels, but TRH stimulation of ACTH results rose initially, suggesting resting ACTH may be more suitable for monitoring response to treatment.

Conclusion

While there is still a lot to learn about PPID, recent advances in our knowledge have enabled horses to be diagnosed and started treatment much earlier in the disease process, with the result that many horses with PPID are living quality lives well into old age.

Abbreviations

Alpha-MSH – alpha-melanocyte-stimulating hormone
ACTH – adrenocorticotropic hormone
CLIP – corticotrophin-like intermediate peptide
EEG – Equine Endocrinology Group
EMS – Equine Metabolic Syndrome
PPID – Pituitary Pars Intermedia Dysfunction
POMC – pro-opiomelanocortin
TRH – thyrotropin-releasing hormone

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About the authors: Researcher Andrea Jones founded The Laminitis Site after nursing her Irish cob through laminitis with severe rotation in all four feet. The work of The Laminitis Site is funded entirely by donations from every foot. The Laminitis Site was founded entirely by donations and in 2013 The Laminitis Site was registered as a company with charitable purposes to provide information and education, to carry out research and to care for equids with laminitis. The Laminitis Site’s philosophy of “identify and remove/treat the cause and support and realign the feet” has helped hundreds of horses around the world recover from laminitis. Andrea lives in France with her husband, Dr Martin Lolley, three horses, dogs and cats and enjoys dawdling and walking her dogs.