UK-VET Equine

A guide to PPID

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Pituitary pars intermedia dysfunction (PPID) is a common endocrine disorder of older equids. With a disease prevalence of over 20% in horses and ponies aged 15 years and older (Ireland and McGowan, 2018), it is of considerable importance in equine practice. This guide focuses on three broad challenges faced by veterinary surgeons regarding this disorder:

- **Owner recognition of the disorder:** many clinical signs of PPID are mistakenly considered normal signs of ageing by owners (Ireland et al, 2011) including a long hair coat (hypertrichosis) and/or delayed shedding and muscle atrophy (presenting as a wasted topline and/or a pot belly). This can delay presentation until the development of concurrent disease or laminitis, making treatment more difficult.
- **Interpretation of borderline test results:** although there have been many tests used to diagnose PPID in the past, testing practices are becoming more standardised with a better understanding of which test to use and when. However, borderline results and how to explain these to clients remains a potential challenge.
- **Monitoring cases beyond initial treatment:** medical treatment of PPID is now the accepted 'norm' and owners should be fully informed about the treatment options. However, medical treatment is just the first step and the challenge for veterinary surgeons, and key to success in management of PPID is monitoring and follow-up in the context of geriatric horse health and welfare.

This guide aims to provide veterinary surgeons with practical advice on the diagnosis and treatment of PPID, based on the best available evidence from published research.

PPID quick guide

Pathophysiology

PPID is an age-related neurodegenerative disorder of dopaminergic neurones in the pars intermedia of the pituitary gland, with loss of dopaminergic inhibition of pars intermedia melanotropes leading to overproduction and elevated circulating concentration of pro-opiomelanocortin (POMC)-derived peptides including α-melanocyte stimulating hormone (α-MSH), β-endorphin, corticotrophin-like intermediate peptide (CLIP), and adrenocorticotrophic hormone (ACTH). Although a useful marker for diagnosis of PPID, much of the ACTH is biologically inactive so hyperadrenocorticism does not occur. The overactive pars intermedia becomes hyperplastic on histological examination initially, and in later stages can become adenomatous, although it is not a primary tumour as many owners may assume (McFarlane, 2011).

Although we still know relatively little about many of the peptides released by the abnormal pituitary pars intermedia and their clinical consequences, it is important to convey an appropriate understanding of the pathophysiology of PPID to horse owners so that they can understand the potential for medical treatment and monitoring of the disease. A comparison with Parkinson's disease in humans is often the best way to explain PPID, rather than talking about tumours in the pituitary.

Clinical presentation

There is increasing recognition of the spectrum of clinical signs exhibited by affected animals, and awareness that early cases may present with few or subtle signs of disease. The most frequently reported clinical signs of PPID include hypertrichosis and/or other hair coat abnormalities; laminitis; epaxial muscle wastage or muscle atrophy; weight loss and lethargy (Ireland and McGowan, 2018). However, apart from hypertrichosis, these signs are non-specific for PPID and other causes must always be considered.

Most published information pertaining to the clinical presentation of PPID comes from small case series, often including a significant proportion of animals with advanced disease or complicated by concurrent diseases of old age. This is particularly where owners have missed early signs, mistakenly considering them normal signs of ageing.

Age: this is the most important risk factor for the development of PPID with an 18% increase in the odds of having PPID per year from 15 years of age (McGowan et al, 2013a). PPID has also been recognised in younger horses, however reports in horses <10 years old are very rare.

Hypertrichosis and/or delayed shedding: this is most specific clinical sign, although in the early stages and in light breed horses it can be relatively subtle and missed by horse owners, or erroneously assumed to be a normal part of ageing. Despite this, owners recognise hair coat changes more reliably than veterinary surgeons during a one-off examination, presumably due to their longer-term perspective (McGowan et al, 2013a).

Muscle atrophy: normally presenting as a wasted topline and/or a pot belly, this is a common early sign occurring in 48% of horses with PPID (McGowan et al, 2013a), again recognised by horse owners but not necessarily as a potential sign of PPID (Ireland et al, 2011).

Laboratory testing

While clinical signs in advanced cases may be convincing, laboratory testing will be required in the majority of suspected PPID cases for diagnostic confirmation, and also as a useful aid in monitoring response to treatment. Routine haematology and biochemistry are not useful diagnostic tests for PPID; however they may be beneficial for the identification of concurrent disease (see management later).

Newer concepts

- **Earlier diagnosis:** detection of earlier cases of PPID can present difficulties as the clinical signs are more subtle, and laboratory abnormalities less pronounced, but basal ACTH is still the standard.
- **Concurrent investigation of insulin dysregulation:** vital for determining the risk of laminitis and prognosis as well as directing management (Durham et al, 2014). This can be achieved by using basal or dynamic (post prandial) analysis of insulin to detect hyperinsulinaemia (Frank and Tadros, 2014).
- **Learning how to deal with borderline results:** basal ACTH and insulin may return borderline or 'grey zone' results, indicating the need for repeat or dynamic testing. Communication of such possibilities with clients prior to initial testing will ensure clients are on board.

Despite concerns of missing early cases, a review of all post-mortem examinations in equids aged 15 years and older reported pituitary pars intermedia adenomatous hyperplasia or adenoma in 27% (Miller et al, 2016), only marginally higher than that reported using basal ACTH and seasonally adjusted reference ranges in the same age group (McGowan et al, 2013a).

Diagnostic testing

Initial visit: basal plasma ACTH and basal serum insulin (for protocols see *Table 1*). It is important not to solely rely on laboratory testing and results must be interpreted in the light of clinical findings.

- If basal ACTH is above laboratory reference range and compatible clinical signs are present start treatment
- If basal ACTH is negative and there is a high clinical suspicion of PPID or if basal ACTH is in the 'grey zone' consider:
  - Restest in the autumn (August–October) when sensitivity is greater
  - Use the TRH stimulation (of ACTH) test (*Table 1*)
  - In some cases trial medical treatment can be considered

Rather than previous recommendations to avoid laboratory testing during the autumn, the more marked seasonal increase in PPID cases compared with unaffected horses is now considered to improve diagnostic accuracy. Using a single cut off derived from a clinical gold standard of hirsutism and three clinical signs for PPID compared with age-matched controls with no clinical signs, the sensitivity and specificity for basal ACTH were 80 and 83% respectively in the non-autumn months, but this rose to 100% and 95% during the autumn months (McGowan et al, 2013b).

Table 1. Diagnostic test protocols

Diagnostic test	Protocol	Interpretation	Additional considerations
For diagnosis of PPID: basal ACTH	1. Collect blood into EDTA tube 2. Chill the sample as soon as possible (within 3 hours of collection) 3. Separate the plasma prior to shipping to laboratory experienced in measuring equine ACTH 4. Chill (do not freeze unless centrifuged) during shipping to laboratory	• Values vary between laboratories and assays. Refer to individual laboratory reference intervals for more details • Generally clear negative considered to be <29 pg/ml* in non-autumn months and <49 pg/ml during August–October • 'Grey zone'/equivocal results (variably reported as 30–50 pg/ml for non-autumn and 50–100 pg/ml in the autumn) (EEG, 2017)	• Avoid collecting within 2 hours of feeding or after a prolonged fast • Collect sample at any time of day (but be consistent if re-testing for comparison later) • ACTH is likely affected by many biologic events especially stress and pain, but also exercise and feeding • Higher concentrations (and sensitivity) seen in autumn therefore use seasonally adjusted reference ranges
For diagnosis of PPID: TRH stimulation	1. Collect baseline EDTA plasma sample for ACTH assay (sample handling as above) 2. Administer 1 mg TRH**, *** IV 3. Collect 2nd EDTA plasma sample at 10 minutes following TRH 4. Process both plasma samples as basal ACTH procedure above	• For 10 minute post-TRH sample normal generally considered to be <110 pg/ml in non-autumn months • Values vary between laboratories and assays. Refer to individual laboratory reference intervals for more details	• TRH not licensed for use in horses • Side effects are not uncommon and include transient muscle fasciculations, yawning, lip-smacking, flehmen and coughing • Seasons have profound effect, with response to TRH greater during autumn and a much higher cut off (EEG, 2017) • Ideally avoid concentrate feeding for 3–4 hours prior to testing
For diagnosis of insulin dysregulation: basal insulin	1. Feed only hay (ideally low non-structural carbohydrate; soak if necessary) overnight or have short fast (< 4 hours) before the test. If grazing cannot be avoided it should be restricted/poor quality 2. Collect blood into serum (plain) tube for shipping to laboratory experienced in measuring equine insulin 3. Can send chilled with ACTH sample but does not require chilling within 3 hours or separation	• Generally <15 μIU/ml* = low risk/normal • 15–20 μIU/ml = weak positive • > 20 μIU/ml increasing severity of ID	• The previously-recommended prolonged fast prior to sampling and cut-off of 20 μIU/ml for diagnosis of EMS results in a very low sensitivity and is no longer recommended by the authors • Horses and ponies already being fed a diet of soaked hay (e.g. as part of laminitis management) before initial sampling are more likely to return a negative basal insulin but may still show ID in dynamic tests

- If basal hyperinsulinaemia is detected, manage insulin dysregulation (as well as PPID if ACTH is also positive).
- If PPID positive: if basal hyperinsulinaemia is not present or insulin is mildly elevated, perform dynamic insulin testing (*Table 1*).

For diagnosis of insulin dysregulation: dynamic insulin – the oral glucose test	1. Stable the horse and feed only 1 slice of hay the evening before (or fast for 6 hours before the test) 2. The following morning the owner feeds 1 g/kg bodyweight (BWT) powdered glucose/dextrose, mixed with 1g/kg BWT unmolassed low NSC chaff (e.g. Happy Hoof) and 1g/kg water 3. Owner records how long the horse takes to consume the feed. If the feed is not completely consumed, weigh the residual feed to allow an estimate of how much glucose has been consumed 4. Collect a blood sample for insulin and glucose 2 hours after the feed was given	• Insulin < 85 µIU/ml = normal • 85–125 µIU/ml = borderline insulin dysregulation • >125 µIU/ml = positive insulin dysregulation • If the feed was incompletely consumed, inform the laboratory how much was consumed and, in combination with the glucose concentration, they can adjust their interpretation accordingly	• Recent work from Australia looking at the development of laminitis following a high NSC feed challenge compared with the OGT has shown that increasing laminitis risk was associated with higher post glucose insulin concentration. This work has supported a lower cut off of <65 µIU/ml based on 2 hour insulin concentration only (Meier et al, 2017)

* Immunlite 1000 or 2000 (Siemens). ** The dosage of TRH is the same regardless of the size of the horse although a 0.5 mg TRH dose is usually given to small ponies (<250 kg). Administering 50–200% of the dose has no effect on diagnostic outcome. *** TRH is not licensed for use in horses in the UK

PPID treatment

While some owners will elect to only manage individual clinical signs, there is evidence supporting significant clinical and endocrinological improvements in more than three quarters of affected horses (NADA, 2011) with improvements maintained over many years. Although horses diagnosed with PPID have an increased risk of mortality (hazard ratio 9.3), the median life expectancy following diagnosis is 9.8 years (interquartile range 9.0–10.7 years) (Welsh et al, 2016).

Medication

Medical treatment of PPID involves pergolide mesylate (Prascend®, Boehringer Ingelheim), a dopamine agonist, which is licensed for use at a dose from 1.3–2.4 µg/kg PO q24h. Treatment should be initiated at the low end of the dose range (to the nearest 0.5 mg) and gradually increased, if required, based on clinical and endocrinological response (Prascend SPC, Durham et al, 2014) (*Table 2*). Owners should be made aware that treatment is life long and that regular monitoring of their horse along with treatment will allow for the best outcome. (See *Table 3* for suggested protocol).

As with all medication, treatment with pergolide is associated with some potential adverse events. Although these are typically regarded as rare to very rare (see SPC†), in the authors' experience decreased appetite occurs more commonly in up to a third of horses, particularly when first initiating treatment (NADA, 2011). It is generally transient; however stopping treatment and re-introducing it at a lower dose before gradually increasing may be beneficial (Durham et al, 2014).

Management and monitoring PPID horses

General health management (for geriatric horses): aged and geriatric horses have an increased susceptibility to a range of conditions and diseases even without PPID. These are particularly dental disease (including severe conditions such as diastema and periodontitis), lameness, eye condi-

Table 2. Treatment protocol (Prascend SPC)

Horse bodyweight	Number of tablets	Starting dose	Dosage range
200–400 kg	1/2	0.5 mg	1.3–2.5 µg/kg
401–600 kg	1	1.0 mg	1.7–2.5 µg/kg
601–850 kg	1 1/2	1.5 mg	1.8–2.5 µg/kg
851–1000kg	2	2.0 mg	2.0–2.4 µg/kg

Table 3. Suggested monitoring protocol

Step	Action
1	Obtain baseline data: clinical signs of PPID, any concurrent disease, take samples for basal ACTH and basal insulin* (*Table 1*)
2	Start treatment with pergolide at 2 µg/kg (dose range 1.3–2.4 µg/kg) PO q24h (see *Table 2*)
3	Initial monitoring visit: 4–6 weeks after initiating treatment repeat endocrine testing – take sample for basal ACTH and document improvement in clinical signs** Expect basal ACTH to have decreased substantially (by at least 50%) or be within the normal reference range, bearing in mind the seasonal increase in ACTH from late summer. One or more clinical signs should have also improved, with the earliest reported improvements often in the horse's demeanour (EEG, 2017)
4	Adjust dose if necessary: if clinical signs and/or diagnostic test results show that PPID is not adequately controlled, it is recommended to increase the total daily dose by 0.5 mg increments every 4 to 6 weeks until stabilisation occurs and if the drug is tolerated at that dose (Prascend SPC). Careful reduction of the total daily dose using the same increments can also be attempted in well-controlled horses on high doses or in horses undergoing trial treatment
5	Long-term monitoring***: once a suitable improvement has been noted, follow-up monitoring can decrease to one or two times a year. This should include: ● Annual general health monitoring ● Annual or biannual monitoring of clinical signs of PPID ● Annual or biannual**** endocrine monitoring of both ACTH and insulin dysregulation

* If negative consider dynamic test for insulin dysregulation such as the oral glucose test (Durham et al, 2014). ** Owners can be encouraged to monitor and record these, e.g. monthly. *** Owners can be directed to useful owner information advice resources such as www.careaboutcushings.co.uk. ****If owners will commit to biannual monitoring, at least one follow-up test a year should be during the autumn when there is peak ACTH and maximal ACTH activity

It is important to note that licensed VMPs have strict pharmacovigilance requirements and undergo periodic safety update reports, which can lead to changes to the product's SPCsand its labelling. All suspected adverse events should therefore be reported to the marketing authorisation holder or the VMD.

tions, heart or lung conditions and skin conditions (including tumours such as sarcoids and melanomas) (Ireland, 2016). Therefore, management of the PPID horse involves monitoring and management of diseases of older horses, as treatment failure may occur if concurrent diseases are ignored or assumed to be directly associated with PPID. An example is alterations in blood tests which have been reported as associated with PPID (EEG, 2017), yet these have only been found in case series and not in appropriately controlled field-based epidemiological research (Ireland and McGowan 2018). PPID may increase the risk of intestinal parasitism, but does

Figure 1. Geriatric horse showing muscle wasting/ weight loss and incomplete haircoat shedding that would prompt a clinical suspicion of PPID, but could also be associated with other diseases.

not alter a routine haematological or biochemical profile (McGowan et al, 2013a).

Maintaining the PPID patient requires careful attention to preventive healthcare, in particular hoof care, dental prophylaxis, vaccination, anthelmintic administration and nutrition. Animals with hypertrichosis benefit from being clipped, particularly during the summer months, and regular clipping of excessive hair coat may be required throughout the year. PPID cases are often considered to be more susceptible to infections, therefore early identification and aggressive treatment of any secondary infections is warranted, as even minor infections can become difficult to manage in PPID patients. Attention to dietary requirements is also important, with PPID horses at risk for muscle loss and also laminitis. Ideally the diet should be balanced with a high quality protein source provided (as well as vitamins and minerals) to allow muscle gain, but low glycaemic to minimise hyperinsulinaemia.

A combination of monitoring for general geriatric health, for clinical signs of PPID and endocrinological monitoring including basal ACTH concentration and insulin dysregulation will provide the information. If owners are fully informed of the high prevalence of conditions in their horses' age bracket, and engage in regular health checks with appropriate blood testing, then the best outcomes can be achieved. EQ

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†The Prascend SPC states: in rare cases inappetance, transient anorexia and lethargy, mild central nervous system signs (e.g. mild depression and mild ataxia), and colic have been observed in horses. In very rare cases sweating has been reported. If signs of dose intolerance develop, treatment should be stopped for 2 to 3 days and reinstated at one half of the previous dose. The total daily dose may then be titrated back up to the desired clinical effect by 0.5 mg increments every 2 to 4 weeks.


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