DEALING WITH EQUINE PITUITARY PARS INTERMEDIA DYSFUNCTION (EQUINE CUSHING'S DISEASE) IN EQUINE PRACTICE

Recommendation formulated as a consensus view by:

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Description

Equine pituitary *pars intermedia* dysfunction (PPID, Equine Cushing's disease) is a common neurodegenerative endocrine disease associated with ageing. About 20% of horses aged 15 years or older may be affected although the disease is also seen in younger horses [1].

Clinical signs

PPID often initially presents with laminitis, especially in mature to elderly horses, although the disease is likely to have been present for some time prior to development of laminitis. Further clinical signs include hypertrichosis and abnormal hair-shedding patterns, muscle atrophy leading to a "pot-belly" and/or "wasted topline" appearance, abnormal fat distribution (especially periorbital), lethargy, polydipsia and polyuria, excessive sweating, susceptibility to secondary infections, infertility and rarely, seizures.

Diagnosis

Field diagnosis is often made on the basis of specific signs like hypertrichosis or failure to shed. However, laboratory testing is also of major importance for several reasons including diagnosis of equivocal cases, for differentiating from Equine Metabolic Syndrome, for owners reluctant to start life-long treatment without strong evidence as well as for monitoring of treatment efficacy.

Recommended diagnostic tests for PPID

Currently available diagnostic tests which are recommended by the panel comprise:

1. Basal plasma ACTH concentration
2. Overnight dexamethasone suppression test (ODST)
3. TRH stimulation test (measuring ACTH)

(See appendix for full description of tests)

Variation in results from different analysers, at different times of year and in different geographic locations makes it important that individual laboratories establish and validate reference intervals.

Additional valuable tests

Measuring serum insulin and glucose (fasting and/or after glucose challenge) are also recommended as indicators of laminitis risk, diabetes mellitus and prognosis, which is worse in PPID cases with marked hyperinsulinaemia [2]. Routine haematology and biochemistry is not useful in establishing a diagnosis of PPID although a general health screen and faecal worm egg count may form a useful adjunctive part of PPID investigation by identification of concurrent disease.

Treatment and Monitoring of PPID

Treatment efficacy can be evaluated empirically after one month on the basis of clinical response: improvement of the general attitude, increasing activity, start of hair shedding and a decrease in water consumption (if previously polydipsic).

Response of laboratory test results to pergolide treatment is expected within a month of initiating treatment or increasing the dosage. Approximately 75% of horses initially treated with pergolide will show significant improvement or normalisation of test results although after 6 months this may fall to below 60% suggesting that ongoing monitoring every 3-6 months is warranted.

For best practice the panel recommends the following general protocol for management of PPID cases:

1. Obtain baseline clinical and endocrine values e.g. basal plasma ACTH, basal insulin and glucose, and document clinical findings.
2. Owners should be encouraged to monitor appetite, hair coat, water intake and bed wetting when housed, body condition score including estimation of muscle loss as well as fat score, laminitis/lameness and general demeanor monthly.
3. Calculate the starting dose of pergolide based on approximately 0.002 mg/kg PO q24h (to the nearest 0.5 mg total dose).

Body Weight	Starting Daily Dose
200-350 kg	0.5 mg
350-600 kg	1.0 mg
601-850 kg	1.5 mg

4. After one month of treatment, re-evaluate baseline clinical and endocrine values as well as owner-reported improvements. One or more clinical signs is expected to improve and/or the basal ACTH to have returned to normal or close to normal range for that time of year.
5. If clinical and/or endocrine improvements are not noted, increase the dose of pergolide by 0.001 mg/kg BW.
6. Re-evaluate monthly with increases in the pergolide dose by 0.001 mg/kg BW until clinical signs and endocrine variables have improved or a maximal dose of 0.010 mg/kg BW has been reached.
7. If signs of inappetance or depression are observed, reduce the dose by increments of 0.001 mg/kg BW and investigate for concurrent disease.
8. Once the signs have been successfully controlled, clinical and endocrine monitoring can be reduced to 2-4 times per year, with at least one of these scheduled for between August and October.
9. Owners should continue to monitor at least monthly and alert their veterinarian if there is deterioration or development of any new clinical signs.
10. If clinical signs and endocrine test results are well controlled for > 3 months, a slow reduction in the dose by 0.001 mg/kg BW per month can be attempted, with a minimal dose not less than 0.002 mg/kg BW. Doses less than 0.002 mg/kg BW may result in treatment failure and reductions below this dose rate should be monitored carefully.

Possible dilemmas arising during PPID management

A. Results from the selected endocrine test are in the "grey-zone"

Suggested solutions

- Re-test using the same test in 3 – 6 months (except ODST between August and October)
- Re-test using a different test (consider TRH stimulation)
- Re-test between August and October using seasonally adjusted reference ranges (when test sensitivity is greatest)
- Limit potential confounding factors (e.g. stress, pain, sedation)

B. Serum insulin concentration remains elevated despite normalisation of ACTH or ODST

Suggested solutions

- Consider careful dietary control by restricting non-structural carbohydrate access (e.g. cereals, grass). Do not severely calorie restrict PPID horses due to risk of exacerbating catabolism. Ensure adequate protein intake.
- Increase exercise (if laminitis is well controlled)
- Metformin therapy (Safety and efficacy of metformin in diabetes mellitus cases has not been established to date [3]).

C. Continued laminitis

Suggested solutions

- As for B. above
- Use appropriate farriery and shoeing support

D. Inappetance

Suggested solutions

- Reduce pergolide dose, followed by gradual increase again
- Dental examination – in every case
- Further clinical investigation as warranted
- Blood test to look for alternative causes such as liver disease, inflammatory disease, etc…

E. Marked weight loss

Suggested solutions

- As for D. above
- Check plasma and urine glucose for signs of marked hyperglycaemia and diabetes mellitus

APPENDIX – TESTING FOR PPID

1. BASAL PLASMA ACTH CONCENTRATION

Pros

- *A single blood sample is adequate in the majority of cases*
- *Seasonal reference ranges published to allow testing at any time of year* [4]

Cons

- *Sample requires prolonged chilling*
- *Seasonally adjusted reference intervals must be used*
- *Severe stress or pain may affect result*

Procedure

1. Collect EDTA plasma sample at any time of day
2. Chill sample within 3 hours of collection
3. Centrifuge prior to shipping to laboratory (timing of centrifugation unimportant as long as sample is chilled within 3 hours)
4. Ship to laboratory in chilled packaging (freeze centrifuged plasma if delivery is delayed)

Interpretation

High plasma ACTH concentrations are indicative of PPID. Precise cut-off values may vary between laboratories and at different times of year.

A combination of 3 published studies (n=95), including *post mortem* confirmation of diagnosis and cut-offs of 35 pg/mL (7.7 pmol/L) and 55 pg/mL (12 pmol/L), indicated an overall test sensitivity of 84% and specificity of 97% [5,6,7].

"Borderline" test results (upper limit of reference interval ± 10 pg/mL) may warrant re-testing in 3-6 months (aim for August-October if possible), TRH stimulation or overnight dexamethasone suppression test.

[Conversion factor for ACTH: pg/mL → pmol/L (x 0.2202); pmol/L → pg/mL (x 4.541)]

Further comments

- Plasma ACTH increases in August, September and October in both normal and PPID cases (figure 1). Seasonal reference intervals are available at some laboratories and increases the sensitivity of testing (Liphook Equine Hospital, UK: plasma ACTH cut-offs 29 pg/mL (November to July) and 47 pg/mL (August to October) [4]).
- Isolation distress and mild to moderate illness and pain do not appear to affect plasma ACTH. General anaesthesia, strenuous exercise, sedation, severe illness and severe pain may all increase plasma ACTH.

- Collecting paired plasma ACTH samples 10 minutes apart has been recommended by one study [5] to take account of possible short-term variation in basal ACTH in PPID cases. However, this only appears to be clinically significant in a small minority of cases.
- ACTH concentrations may vary slightly through the day and therefore standardisation of sampling times is preferable when further samples are taken for comparison during monitoring.

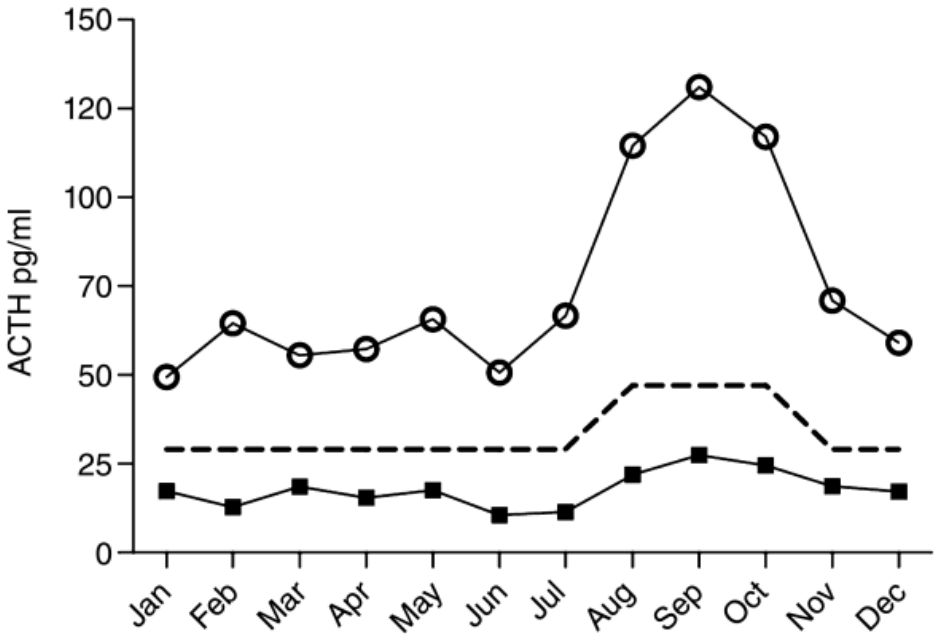

Figure 1. Illustration of seasonal variability of plasma ACTH in normal (n=156, black squares) and PPID horses (n=962, white circles). Dashed line represents upper limit of reference range (reproduced with kind permission of Equine Veterinary Journal from Copas and Durham 2012, 4)

2. OVERNIGHT DEXAMETHASONE SUPPRESSION TEST (ODST)

Pros

- Cortisol assays may be more widely available than ACTH
- Cortisol more stable *in vitro* than ACTH

Cons

- Requires veterinary involvement on 2 consecutive days
- Perceived risk of laminitis in association with dexamethasone administration
- False positive results common in autumn (no seasonal reference intervals established)

Procedure

1. Collect baseline serum or plasma (consult receiving laboratory) sample for cortisol (this sample can be omitted)
2. Inject 0.04 mg/kg BW dexamethasone iv or im
3. Collect further sample for cortisol between 19 - 24 hours later
4. Centrifuge prior to shipping to laboratory

Interpretation

High serum or plasma cortisol concentrations 19-24 hours following dexamethasone are indicative of PPID. The generally accepted cut-off is 27 nmol/L (1 μg/dL, 10 ng/mL).

Combination of 3 published studies (n=111), including post mortem confirmation of diagnosis and a cut-off of 27 nmol/L, indicated an overall test sensitivity of 89% and specificity of 88% [5,8,9].

[Conversion factor for cortisol: ng/mL → nmol/L (x 2.759); nmol/L → ng/mL (x 0.362)]

Further comments

- Although it is common practice to collect samples for cortisol both before and after dexamethasone, the test is interpreted on the basis of the second sample and therefore it is possible to omit the first sample.

3. TRH STIMULATION TEST *(measuring ACTH rather than cortisol)*

Pros

- Possible increased sensitivity compared to other tests

Cons

- Availability and cost of exogenous TRH
- Possible mild adverse reactions to TRH (trembling, yawning, lip-smacking, flehmen) described in 12.5% of horses in one study [5]
- No seasonal reference intervals established and therefore cannot be interpreted between August and October.

Procedure

1. Collect baseline EDTA plasma sample for ACTH analysis
2. Inject 1 mg TRH iv
3. Collect a further EDTA plasma sample between 10 and 30 minutes following TRH. Greater sensitivity and specificity may be obtained with earlier sampling times (see below).
4. Process plasma samples as per measurement of basal plasma ACTH procedure above

Interpretation

PPID cases have significantly greater increase in plasma ACTH than normal horses following TRH (figure 2).

One small study (n=16), including post mortem confirmation of diagnosis and a cut-off of ***100 pg/mL (22 pmol/L) at 10 minutes*** post-TRH, indicated a test sensitivity and specificity of 100% [5].

A combination of 2 published studies (n=64), including post mortem confirmation of diagnosis and a cut-off of ***35 pg/mL (7.7 pmol/L) at 30 minutes*** post-TRH, indicated an overall test sensitivity of 97% and specificity of 91% [5,7].

[Conversion factor for ACTH: pg/mL → pmol/L (x 0.2202); pmol/L → pg/mL (x 4.541)]

Further Comments

- Measurement of *cortisol* before and after TRH injection does not differentiate PPID from normal horses.
- This test can be especially useful in cases which produce "borderline" results in plasma ACTH or ODST or cases where laboratory results differ significantly from clinical suspicions.

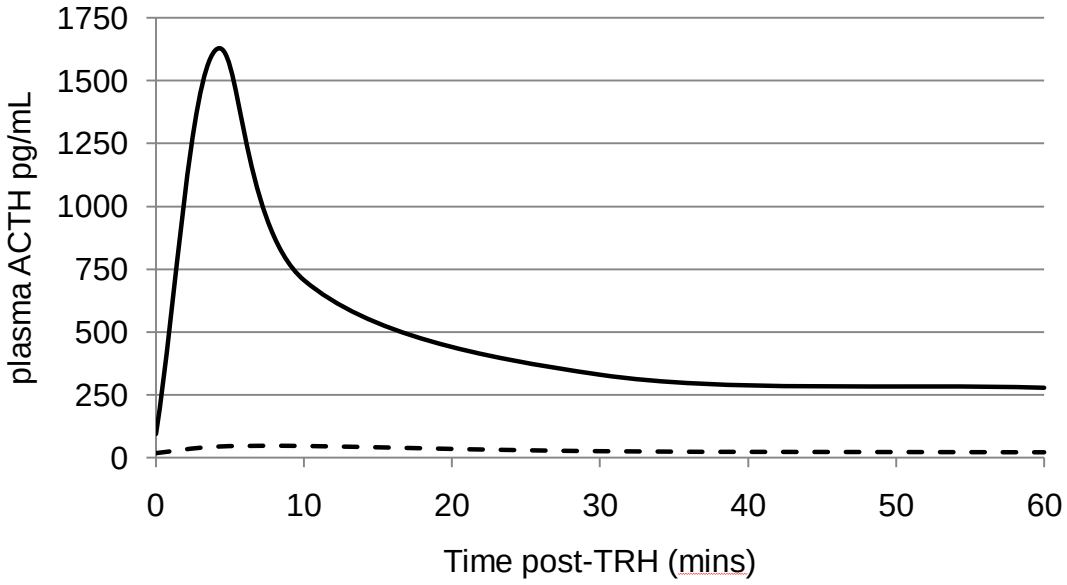

Figure 2. Illustration of mean ACTH response in normal (dashed line) and PPID horses (solid line) following 1 mg TRH given iv at time 0 [data from refs 5,7,10].

References

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