

Diagnosis and treatment of equine Cushings syndrome



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Equine Cushings syndrome is a common problem of aged horses and ponies.

It presents with a variable combination of clinical signs hallmarked by hirsutism. Laminitis is frequently the most devastating consequence. Many affected horses are euthanased during a severe bout of laminitis, or due to other complications associated with the syndrome. Trends in horse ownership and horses presented for veterinary care are changing and aged horses are presented more frequently for veterinary care. They are often highly experienced and valued by their owners as companion or teacher, and their value should not be underestimated.

Recently drug therapy for affected horses has become affordable to many clients and despite limited research evidence, clinical results have had a significant impact on the course of the syndrome for many horses. This article will review some clinical aspects and focus on diagnosis and treatment of the syndrome

Pathophysiology

Equine Cushings syndrome, by definition, refers to a syndrome of hyperadrenocorticism, like in man and dogs, but the pathophysiology and resultant clinical syndrome in the horse are quite distinct.

The equine syndrome is caused by hyperplasia or adenoma of the pars intermedia of the pituitary gland with virtually all cases pituitary in origin. Cushings syndrome in man and dogs, in comparison, may be adrenal or pituitary in origin and if pituitary, usually involves the pars distalis, the major site of ACTH production from the pituitary.

The pars intermedia is poorly vascularised and relies on neurotransmitters released from axons from the hypothalamus to control secretion. That is, not releasing factors from the hypothalamus like the pars distalis. The main neurotransmitter is dopamine which has an inhibitory role. The loss of tonic inhibition by dopamine is responsible for excess pars intermedia activity and ECS.

Aged horses and ponies are susceptible to a loss of dopamine leading to excessive hormone production from the pars intermedia and recent research suggests that this may be due to oxidative damage (McFarlane et al 2003). Excessive hormone production leads to hyperplasia of that part of the pituitary gland which may then lead to adenoma formation. Spontaneous adenoma formation may also occur and may be how the syndrome develops in younger horses.

Resultant excess hormones secreted by the pars intermedia melanotrope cells in ECS horses include large amounts of beta-endorphin, corticotrophin-like intermediate peptide (CLIP) and melanocyte stimulating hormone (MSH), and smaller amounts of adrenocorticotrophic hormone (ACTH).

While the proportion of ACTH produced from the pars intermedia is small, the marked over activity of the ECS pars intermedia results in excess ACTH production. Therefore, we can still use the term Cushings syndrome, although some authors prefer to use the term pituitary pars intermedia dysfunction (PPID). Due to the fact that adenoma formation does not occur in every case, the terms pituitary adenoma and pituitary tumour have largely been dropped.

Epidemiology

ECS is a common syndrome which affects more than 10 per cent of horses over 15 years of age (McGowan 2003). It affects horses, ponies and donkeys with no sex predilection. However, ponies have been reported to be more likely to develop ECS (McGowan 2003). Although the average age of diagnosis is 19, the frequency of diagnosis of ECS increases with advancing age (Brosnahan and Paradis 2003) and ECS is rarely seen in horses less than 10 years old.

CLINICAL SYNDROME

Clinical signs

The precise relationship between the clinical syndrome and pathophysiology of ECS is still under investigation; however the clinical signs have been well documented. Signs are predominantly attributed to hyperadrenocorticism and studies showing clinical improvement using cortisol inhibitors have demonstrated this (McGowan and Neiger 2003). However, the effects of other hormones secreted from the pars intermedia are not well known, neither are the effects of compression of the pars nervosa or pars distalis in some horses.

Effects from extension of the tumour to the brainstem are rare, although blindness from pituitary

neoplasia has been reported in a horse. While seizures have been occasionally reported in horses with ECS, the cause of the seizures has not been demonstrated to be due to the pituitary disease.

Common signs include hirsutism, lethargy, weight redistribution, recurrent or chronic laminitis, susceptibility to infections and polyuria/polydipsia.

Laminitis is frequently the most devastating clinical sign with severely affected horses having to be euthanased, although interestingly, some horses with ECS do not develop laminitis at all.

Clinical presentation can vary enormously (Table 1) and while obvious hirsutism combined with two or more other clinical signs is quite specific for ECS, problems can occur when relying on clinical signs alone for diagnosis particularly if the diagnosis occurs in winter or when horses have been clipped.

Clinical pathology

Routine haematology and biochemistry is not useful in the diagnosis of ECS. It may provide information about concurrent problems in an aged horse, but is normal in many cases of ECS. While some authors have suggested an increase in liver enzymes associated with ECS, this is not specific for ECS, and the majority of horses with ECS do not have such elevations. A stress leucogram, as seen in dogs, is rarely present, and if inflammatory changes are seen they frequently represent concurrent illness rather than the effects of hypercortisolaemia. Despite it fitting with the pathophysiology of hyperlipaemia, ECS is not a well recognised cause of hyperlipaemia in the horse.

Routine haematology and biochemistry is useful in the assessment and monitoring of a horse with ECS as it helps identify concurrent problems that exist which may affect prognosis and response to therapy.



Fig 1 - An aged mare with ECS displaying hirsutism and apparent weight loss due to muscle wasting

Table 1 - Clinical signs and their frequency of occurrence in horses with ECS

Clinical sign	Hillyer and others 1992	Van der Kolk and others 1993	Donaldson and others 2002	McGowan and Neiger 2003
Total number studied	17	21	27	20
Mean age (years)	20	21	19 (median)	19
Hirsutism	94%	100%	59%	100%
Laminitis	82%	24%	74%	80%
Weight loss or redistribution	88%	38%	33%	65%
Lethargy	82%	-	19%	95%
Polyuria/polydipsia	76%	-	7%	55%
Hyperhidrosis	60%	5%	29%	30%
Bulging supraorbital fat	12%	19%	26%	50%
Concurrent infections	65%	19%	30%	35%

From: McGowan C.M. (2003) *Diagnostic and Management Protocols for Equine Cushing's Syndrome In Practice* 25(10), 586-592.

DIAGNOSIS

It is important to consider your reasons for diagnosis before deciding on a diagnostic protocol. If the reason for diagnosis is to initiate and potentially monitor therapy, then the method of diagnosis needs to be most accurate as treatment is expensive and life-long. There are many tests used for the diagnosis of ECS, but limited information is available assessing the sensitivity and specificity of many of them. The gold standard test is the post mortem examination of the pituitary, so clearly, the ability to assess tests based on the gold standard is limited. In the author's opinion, the dexamethasone suppression test is the best choice currently available (Table 2).

Basically there are two types of endocrine tests, basal and dynamic. Basal tests are those that can be obtained with a single sample and therefore have been popular with veterinarians and clients due to simplicity and reduced cost, especially if the client is a long way from the practice. However, the benefits from this are generally offset by the reduction in sensitivity and specificity of diagnosis.

Dynamic endocrine testing can provide much greater diagnostic sensitivity and specificity over simple measurement of basal hormone levels because they evaluate the integrity of endocrine regulatory feedback loops.

Basal Tests

Basal ACTH is the best option for a basal diagnostic test. However, the author recommends monitoring serum insulin concentration during the course of treatment (see monitoring section below). New research is being undertaken in the US to validate using beta-endorphin and alpha-MSH as a basal test, though this is not commercially available.

Basal plasma ACTH concentration

Plasma ACTH concentration has been shown to be quite sensitive (>90 per cent), although data on its specificity is limited. Horses with ACTH values greater than 50 pg/ml are very likely to have ECS. The drawback of ACTH is that it is labile and requires separation and chilling within three hours of collection, and must not be kept in glass tubes (Vacutainer tubes) as the ACTH is adsorbed onto glass. However, this can be achieved in practice provided you take a pipette, plastic storage container

and esky with ice packs with you. Blood can be collected in an EDTA vacutainer, allowed to separate by gravity, and separated and chilled on ice within an hour. It is advisable to check with your laboratory for any additional requirements they may require before collecting the sample.

Blood glucose concentration

Elevations in blood glucose as a diagnostic test was developed on the premise that horses with ECS have a high risk of developing secondary insulin resistance and hyperglycaemia. However, this does not occur in all cases of ECS, reducing the sensitivity of the test.

Urinary corticoid:creatinine ratio

Is generally higher in horses with ECS, but has a low sensitivity and specificity so is not recommended for diagnosis.

Insulin

Basal serum insulin concentration has also shown to be a sensitive (>90 per cent) test for the diagnosis of Cushings disease, but has been shown to have a low specificity so is not recommended as a diagnostic test. False positives in ponies with insulin resistance can occur, particularly if they are overweight.

Cortisol

Basal serum cortisol concentration has no value as a diagnostic test for ECS. It can be low, normal or elevated in horses with ECS. Some laboratories have suggested measurement of serum cortisol concentration twice in 24 hours to determine if there is a loss of diurnal variation in horses with ECS. However, despite a loss of diurnal rhythm generally occurring in horses with ECS, serum cortisol concentration varies too much over 24 hours for the difference between two samples to be of diagnostic value (McGowan and Neiger 2003).

DYNAMIC ENDOCRINE TESTS

The dexamethasone suppression test has the highest sensitivity and specificity for the diagnosis of ECS (Dybdal et al 1994) and so is regarded as the diagnostic test of choice.

Low dose dexamethasone suppression test (DST)

The aim of the DST is to detect a failure of suppression of cortisol following the administration of dexamethasone in horses with ECS. The rationale is that the ACTH and resultant adrenal cortisol production from affected horses are not affected by negative feedback. The pars intermedia is not affected by negative feedback, so affected horses fail to show a suppression of cortisol following administration of the exogenous glucocorticoid, dexamethasone. When samples are collected 20 hours apart the test approaches 100 per cent sensitivity and specificity. The DST is not affected by the time of day; however, frequently it is convenient to perform an overnight test starting the afternoon before.

Protocol for the DST

- Collect a baseline serum blood sample followed by injection of 40 µg/kg dexamethasone intramuscularly.
- Collect a second serum sample between 18 and 24 hours later and both samples submitted to a laboratory for cortisol analysis. (Heparinised plasma samples can also be taken).
- Cortisol is reasonably stable so both samples can be submitted as whole blood together, although it is pertinent to chill the samples in a refrigerator in hot areas.
- Normal horses show suppression of cortisol concentration of around 70- 80 percent from baseline.
- Following administration of dexamethasone, affected horses have serum cortisol greater than 40 nmol/l from a baseline of around 100 nmol/l while normal horses have suppression to less than 20 nmol/l.
- The "gray zone" in horses that suppress between 20 and 40 nmol/l is difficult to interpret. Horses with high baseline values (>150 nmol/l) usually have slightly less suppression and values less than 40 nmol/l are considered a normal suppression in this case. However, if in doubt, the test should be repeated or an ACTH test taken to help confirm the result.



Fig 2 - A recently clipped gelding with ECS. Note the apparent weight loss, particularly over the epaxial muscles

ACTH stimulation test.

The ACTH stimulation test assesses abnormal adrenal function so is therefore not relevant for the investigation of ECS. While some horses with ECS have adrenal hyperplasia and an exaggerated response to ACTH, it does not reliably distinguish between normal and affected horses.

Thyrotropin releasing hormone (TRH) stimulation test

The TRH stimulation test has been used extensively in the UK due to popular opinion that this test was "safer" than the DST. However, in the experience of the author, the test has a low sensitivity and specificity, with false positives, especially in horses with initially elevated plasma cortisol concentrations. False positives have also been demonstrated in horses that are unwell for other reasons (Thompson et al 1995). Pharmaceutical grade TRH is expensive to obtain in Australia and the test has poor diagnostic value, therefore, there is little rationale for its use.

Combined Dexamethasone Suppression/TRH stimulation test

The combined DST and TRH stimulation test was developed in an attempt to increase the sensitivity of the TRH stimulation test by suppressing serum cortisol using dexamethasone prior to the administration of TRH. While only one study has been published on its use, the author has used the test extensively for research purposes. Interestingly, despite the poor diagnostic value of the TRH stimulation

test, this combination does appear to be able to clearly distinguish between normal horses and those with ECS. Horses with ECS consistently show an increase in cortisol concentration in response to TRH and also a failure of suppression of cortisol following dexamethasone.

The test is easier to interpret with 2 points of difference between normal and ECS horses rather than one with the DST alone, although the increase in sensitivity and specificity is probably small. The disadvantage, however, is the added cost and time in performing this test.

The test involves collection of a baseline serum or heparinised plasma blood sample followed by injection of 40 µg/kg of dexamethasone intramuscularly. Three hours after the dexamethasone injection, a second blood sample is collected and 1 mg of TRH is injected intravenously. Further blood samples are collected 30 minutes after TRH injection and 22 to 24 hours after dexamethasone injection. Samples are submitted to a laboratory for cortisol analysis.

Horses with ECS have an initial suppression of cortisol three hours post dexamethasone followed by an increase post TRH such that they have serum cortisol concentrations 30 minutes post TRH that are not different from baseline (un-suppressed) or elevated, and 22 to 24 hours post dexamethasone that are un-suppressed.

Risks of dynamic endocrine tests

Some veterinarians and horse owners have raised concern about



Fig 3 - Bulging of the supraorbital fat pads in a pony with ECS

the possibility of exacerbating laminitis or inducing an attack of laminitis due to dynamic endocrine tests increasing the exposure of horses to corticosteroids. In the author's opinion, there is little doubt that excessive prolonged doses of corticosteroids can cause laminitis, particularly in a predisposed horse.

However, the risk of the dexamethasone suppression test is minimal, and the benefits far outweigh the risks. The dose given is low, less than half a single therapeutic dose, and given only once. Further, despite the concerns, no adverse effects of the dynamic endocrine testing have been reported and studies involving administration of dexamethasone to over 121 horses (66 of them with ECS) on numerous occasions have concluded that the administration of dexamethasone is safe (Dybdal et al 1994).

Part of the problem is the unclear and probably multifactorial pathogenesis of laminitis in horses with ECS. One theory is that corticosteroids potentiate the vasoconstrictive effects of catecholamines.

Increasing the exposure of corticosteroids, in theory could increase the vasoconstrictive effects. However, pergolide, an ergot alkaloid with peripheral vasoconstrictive properties has been used for the

treatment of ECS without concerns or reports of exacerbating laminitis.

A more recent theory is that corticosteroids act indirectly (via inducing insulin resistance) rendering glucose unavailable to the lamellar cells with subsequent failure of the hoof lamellar dermo-epidermal junction (French and Pollitt 2004).

If this were the case, these effects would take time and the small dose of dexamethasone or endogenous cortisol fluctuations would not affect the overall insulin resistance in a horse with hyperadrenocorticism. Another problem is that horses with ECS will undoubtedly have bouts of laminitis recurring and occurring at any time, so there is a high risk of a false association of dynamic endocrine testing and laminitis.

TREATMENT/MANAGEMENT

The key to successful management of a horse with ECS is good client communication. While not all owners will elect to treat ECS medically, many will, and the veterinary surgeon should not presume a value an aged horse when discussing the decision with the owner.

If medical treatment is not elected, veterinary attention should be focused on ensuring the animal is

Table 2 - Summary of tests used in the diagnosis of ECS

TEST	Sensitivity	Specificity	Cost	Simple?
DST	++++	++++	Low	Yes - but need 2 visits
Basal ACTH	+++	+++	Low	No - specific handling requirements
Combined DST/TRH	++++	++++	High	No - need 2 visits and 4 samples
Clinical signs	++	++	Low	Yes
UCCR	+++	++	Low	Yes - but requires urine collection
Basal insulin	+++	++	Low	Yes
Glucose	++	+++	Low	Yes
TRH stimulation	++	++	High	Medium - need 3 samples collected over an hour
ACTH stimulation	++	++	Medium	Yes - 2 samples collected over 2 hours

++++ close to 100%, +++ 80-90%, ++ 50-80%

From: McGowan C.M. (2003) *Diagnostic and Management Protocols for Equine Cushings Syndrome In Practice 25(10), 586-592.*

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Clinical Review



Figure 4 - Abnormal coat shedding in a horse with ECS. Note also pot belly and lethargic appearance



Figure 5 - Excessive sweating in a hirsute pony mare with ECS despite cool ambient temperature (photo taken in the UK)

well managed. Management of laminitis, secondary infections, including parasitism, clipping hair and careful attention to teeth and diet may be adequate to keep the horse comfortable in its final years.

In aged horses with ECS, there is a high possibility of serious dental problems as well as periodontitis, so dental work should be carried out with due veterinary care including sedation, pain relief and anti-inflammatory or other medication as necessary.

Medical therapy has become more affordable and more commonly used in Australia, despite there being no veterinary drugs specifically licensed for the treatment of horses with ECS. There is limited research evidence for the use of any drug in the management of the syndrome. However, the author has had success with both trilostane and pergolide. Trilostane (Vetoryl, Arnolds Veterinary Products Ltd., UK) is not marketed in Australia, so pergolide is the first option for treatment.

There are two types of drugs used to treat ECS:

1. Dopamine agonists (pergolide and bromocriptine) and
2. Cortisol inhibitors (Trilostane)

Cyproheptidine, a serotonin antagonist has also been used, but has had limited efficacy and the rationale for use is not clear. Historically, it was used as a less expensive option than pergolide, but now this is not the case so there is little reason for its use at all.

Dopamine agonists

Pergolide (pergolide mesylate) (Permax, Eli Lilly, 0.05 mg, 0.25 mg and 1 mg tablets) is the most commonly used dopamine agonist in Australia. At about \$3 to \$4 a day for a 500 kg horse it is affordable for many horse owners.

Some veterinarians find it easier to write a script for the medication as some human pharmacies can provide the drug at a reasonable cost for the owner. Bromocriptine (Bromocriptinemesylate) (Parlodel) is also available, but limited data have reported it to be poorly absorbed orally. Both drugs are licensed for people with Parkinsons disease and no formal clinical trials in animals have been performed. Retrospective clinical trial data have shown pergolide treatment to decrease plasma ACTH concentration and improve clinical signs based on owner perceptions in as many as 85 per cent of cases over

approximately two months' therapy (Donaldson and others 2002).

The dose rate that is most cost effective is the low dose: 0.002 mg/kg/day, which works out at 1 mg per 500kg horse. I recommend starting at that dose rate and assessing after several weeks the clinical improvement. Should the improvement be less than anticipated, the dose can be increased weekly by 250 microgram increments until a satisfactory clinical response is seen.

Dose rates of up to 0.01 mg/kg have been used, however at the higher dose rates, adverse effects of anorexia and depression may be frequently seen. If these side effects are seen the dose should be reduced gradually until an optimal dose is found. Remember that the dose rate of 0.002 mg/kg/day is the low-dose and attempts to reduce the dose further to save money can result in treatment failure. Long-term, some horses have been managed on less than this dose, but reduction should be monitored carefully.

Cortisol inhibitors

Trilostane (Vetoryl, Arnolds Veterinary Products Ltd, UK) is a competitive inhibitor of steroid synthesis. This is the only treatment

which has been assessed prospectively and over a long period.

Improvements in the combined DST and TRH stimulation test as well as measured clinical variables in a group of 20 horses were observed (McGowan and Neiger 2003). There was a reduction in lethargy in all horses post treatment. Polyuria and/or polydipsia, present in 11 horses, was reduced in all after treatment. Recurrent or chronic laminitis improved in 81 per cent of cases and no side effects were reported (Figure 6).

The dose rate is 1 mg/kg/day and the drug comes as 60 or 120 mg capsules. The dose should be given once a day in the afternoon or evening.

MONITORING THERAPY AND PROGNOSIS

While dynamic endocrine tests are most accurate in diagnosis of ECS, basal tests are probably the most useful for monitoring therapy. Therefore a reversal in the dexamethasone suppression test should not be expected. This is probably because no treatment for ECS can actually reverse the pathology that is occurring. Even pergolide



Figure 6a & 6b - Horse with ECS before and after 12 months of therapy using Trilostane

which should increase endogenous dopamine, and restore pars intermedia inhibition, is probably given at too low a dose to really inhibit pars intermedia overproduction. This is even more the case in more advanced cases and those with adenoma formation.

To monitor clinical signs is crucial. Body condition score, demeanour, Obel grade of lameness, frequency of bouts of laminitis and water intake can be monitored. Pergolide at the low-dose may not restore normal coat shedding, and trilostane rarely does, although both treatments appear to improve coat quality, as this a frequently reported by owners.

Glucose has been suggested as a simple monitoring test for ECS, but can vary considerably throughout 24 hours so results should be interpreted with caution. Insulin can be useful as a prognostic indicator and for monitoring the response to treatment, but as with glucose, may vary considerably over 24 hours.

Insulin and glucose are affected by exercise and feeding, so if using either to monitor the progress of a case, time of sampling also needs to be standardised as well as ensuring samples are not collected within at least four hours of exercise or feeding.

Insulin, collected at midday, has been shown to have at least 90 per cent sensitivity and specificity for prediction of survival to two years with horses with serum insulin < 62µU/ml more likely to survive than those with insulin > 188µU/ml (McGowan et al 2004).

While the corollary has not been tested, an extrapolation from this data, and the authors experience is that horses that maintain insulin < 100 µU/ml have a better prognosis long term than those where serum insulin continues to increase.

In all cases treatment of ECS is life long so embarking on treatment means a large financial commitment for the owner. Medical therapy does not completely stop the progression of the disease, but can alleviate clinical signs and improve the quality of life of animals on treatment. Not all horses will respond to therapy, but many horses can continue in comfort for many years.

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