New Member Primer – How to Get a Correct Diagnosis

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The Equine Cushings and Insulin Resistance Group was formed for dissemination of information and sharing of experiences among owners and professionals dealing with Equine Cushing's Disease. We also routinely deal with other conditions that have similarities to Cushing disease and with laminitis in general since it is frequently associated with these conditions. The amount of information in the files and the archived discussions is huge, and easily overwhelming. This file was put together in an effort to supply basic information and definitions.

Equine Cushing's disease, also known as pituitary pars intermedia dysfunction (PPID), and Insulin Resistance (IR) are ***distinctly separate conditions***. The often overlapping signs and symptoms can make diagnosis difficult.

Equine Cushing's Disease - Pituitary Pars Intermedia Dysfunction (PPID)

Cushing's/PPID is a disorder of the pituitary gland and results in hormonal disturbances. The pituitary gland secretes high levels of the hormone ACTH which stimulates the production of cortisol, a stress hormone. This is generally considered a disease of middle-aged or geriatric equines.

Although the most distinctive clinical sign of Cushing's/PPID is a long hair coat which does not shed out, the first symptom is often unexplained laminitis in the autumn.

Other symptoms include:

- Muscle wasting
- Difficulty with temperature regulation; both excessive sweating and anhydrosis may be seen
- Mammary enlargement and/or milk production in some mares
- Fatty sheath and/or heavy sheath secretions in some geldings
- Lethargy, poor performance and frequent infections
- Oral ulcers
- Skin changes may be seen such as thickening, darkening, flaking or unpleasant odor.

Diagnostic Tests

Endogenous ACTH – a single blood draw to measure the level of endogenous ACTH (adrenocorticotrophic hormone) is diagnostic for Cushing's in equines. (1) The sample requires special handling for accuracy.

Dexamethasone Suppression – measures cortisol response to a dexamethasone challenge. While considered the "gold standard" by some, it may pose a risk of precipitating or exacerbating laminitis. (1, 2)

Both of these tests are subject to "seasonal" elevation in late summer/early fall (August through December and sometimes longer).

Treatment Options

Equine Cushing's/PPID is controlled with the medication Pergolide, available only by veterinary prescription through compounding pharmacies. Follow up testing of ACTH levels is recommended to

determine if the dose is adequate or excessive. Some equines may need a higher dose during the autumn and winter but are able to return to their normal maintenance dose in spring.

The herb Chaste Tree Berry (available in several forms) may control symptoms for some horses, especially if there is an element of excessive prolactin production. Most equines with a definitive diagnosis of Cushing's will eventually need to be maintained on pergolide. (3)

Effective treatment also involves other measures to directly address insulin resistance, hypothyroidism and laminitis if these are present.

Equine Insulin Resistance

Insulin Resistance (IR) is a condition where cells do not respond to insulin, the hormone primarily responsible for transporting glucose into the cells. It is sometimes also referred to as "Equine Metabolic Syndrome" or by the terms "Pre-Cushings" or "Cushingoid" which further complicates obtaining a correct diagnosis. While IR often occurs in the horse with PPID***, it is a distinctly separate condition from Cushing's disease and it can occur without Cushing's.***

Symptoms of Insulin Resistance:

- Easy weight gain, which may begin as early as age 4 or 5.
- Cresty neck, lumpy fat deposits at the base of the neck, behind the shoulder, at the base of the tail, fatty sheath or udder and thick throatlatch. These fat deposits will usually persist even if the horse loses weight elsewhere on the body
- Puffiness (fat) in the hollows above the eyes
- History of laminitis, commonly induced by grass
- Advanced symptoms include increased thirst and urination, loss of body condition, especially muscle, weakness, low energy levels
- Ravenous appetite as a response to poor glucose transport into cells

Diagnostic Tests

The blood tests for insulin resistance are ***Insulin*** and ***Glucose***. Most university and commercial labs offer these tests. Testing should be done in the morning. Horses should ***not*** be fasted before this testing but should not be fed anything but hay or pasture for at least 4 hours prior to the test. Free access to hay before testing is ideal. The horse also should not be exercised within 4 hours of the test and avoid shipping before testing if at all possible. Stress and exercise influence glucose and insulin dynamics. As we are evaluating the relation of Insulin and Glucose to each other, they need to be from the same blood draw.

Glucose to Insulin Ratio (G:I ratio) - a ratio <4.5 is diagnostic for Insulin Resistance, while a ratio between 4.5 and 10 represents compensated IR.

RISQI – is a proxy developed by researchers at Virginia Polytechnic Institute. RISQI stands for "reciprocal of the square root of insulin" and is calculated by the equation 1/square root of insulin. A RISQI value of 0.2 to 0.32 represents compensated insulin resistance while a value of less than 0.2 indicates failed compensation (high risk of laminitis). RISQI correlates well with G:I ratio. [4]

For more detail see the article *"Diagnosing Insulin Resistance"* in the Education files.

While not all obese horses have IR, the risk of laminitis is significantly increased when obesity is associated with a low G:I ratio or RISQI.

Treatment of Insulin Resistance

The primary treatment for Insulin Resistance is a low sugar/starch diet and exercise with the objectives of

- lowering circulating insulin levels by lessening the dietary glucose challenge and
- improving cellular sensitivity to insulin.

Exercise, while an excellent means of improving insulin sensitivity is often not an option initially because of laminitis.

The Emergency Diet – "Starvation" diets to address obesity by providing small amounts of "poor" quality hay have been universally unsuccessful for the IR horse. The ***temporary "Emergency Diet"*** was developed to address the IR horse's immediate needs for adequate gut fill, appropriate energy levels to support requirements, and to improve insulin sensitivity. The diet includes:

- Soaked/drained grass hay at 1.5-2.0% of body weight. Studies have shown that soaking/draining can remove up to 30% of the soluble carbohydrates.
- Beet pulp as a carrier for minerals and vitamins (and can add hay cubes for flavor)
- Soak and rinse 0.5-1.0 pounds BP and top dress with:
- 1/2 teaspoon Magnesium Oxide 56% per 500lbs body weight (each ½ teaspoon provides approximately 1.5 grams of magnesium)
- Vitamin E – 1000 IU per 500lbs body weight (5 - 400 IU human gel capsules from drug store for 1000lb horse)
- 2 oz flax (fresh ground or buy ground stabilized flax)
- 1 to 2 oz iodized salt (regular iodized table salt, approximately 1 to 3 heaping Tablespoons)
- Cinnamon is no longer routinely recommended

For details of the diet, see the article *"Emergency Diet"* in the Start Here folder in the group's files.

Long Term Diet – The goal is to keep ESC (simple sugars) plus starch below 10%. As soon as possible, hay analysis should be done to determine sugar/starch levels and to correct mineral balance. If the hay analysis shows ESC + starch at 10% or less the owner may be able to stop soaking hay. Minerals that need to be added can be mixed with a flax base. This diet should be maintained until the ideal weight is obtained AND neck crest and fat pads have diminished.

There are usually rapid body changes in the first few weeks and at 4 months these horses look dramatically better. Owners may be tempted to allow them to graze again. Limited grazing, early in the morning, *with a muzzle* might be tolerated but the owner should be aware of their horse's triggers and watch for inflammation along the crest (bumps, hives, lumpiness) and heat in the feet. By 6 months, the horse should be markedly improved and by 1 year some horses may be able to tolerate grazing again with careful management but many will remain sensitive to any grazing. The objective is to keep the horse at an ideal weight permanently and avoid any future episodes of laminitis.

The Importance of Exercise – Exercise vastly improves insulin sensitivity but, obviously, the acutely laminitic horse cannot tolerate exercise. However, with recovery, exercise is to be encouraged as long as the horse tolerates it. Even hand walking, 30 minutes per day (straight lines, no tight turns) is beneficial. As the horse's condition improves, the level of exercise should increase. The importance of

exercise in the IR prone horse cannot be understated. IR can be avoided completely with adequate exercise and diet management.

Laminitis

Symptoms of Laminitis and Founder

Laminitis is inflammation and loosening of the connection between the hoof capsule and the coffin bone. Founder is when the coffin bone has changed position relative to the hoof capsule – rotation or sinking. The signs and symptoms vary greatly depending on the severity of the laminitis. From least to most severe they include:

- Less spontaneous activity
- Less spontaneous trotting/cantering
- "Depression"
- Reluctance to turn (puts more weight on one foot or refuses to cross legs over)
- Reluctance to move forward when led
- Lying down more than normal (when pain severe, stays down most of the time)
- Standing with the front feet further in front of the body than normal and the hind feet further under the body than normal
- Stiffness in the shoulder muscles
- Buckling at the knee
- Refusal to move
- Hind end muscles tightly bunched up (shifting most of their weight to the hindquarters)

Examination of the feet may show (usually worst in front feet):

- Feet feel warmer/hotter than usual
- Pulses in the arteries running over the sesamoid bones at the back of the ankle are very strong and pounding
- Puffiness or redness at the coronary band
- Pain on sole pressure about ¼ to ½ inch in front of the point of the frog
- A bruised appearance to the sole
- Red or black discoloration of the white line
- Widening of the white line
- Appearance of rings on the feet that are close together at the toe but get progressively wider over the quarters and heels
- Penetration of the coffin bone through the sole

Diagnosis

Diagnosis of laminitis is based primarily on symptoms. X-rays will determine the degree of severity (rotation or sinking).

Treatment Options

- Treat the primary condition- Cushing's Disease and/or Insulin Resistance - as above to eliminate the laminitis trigger.

- Provide support to the internal structures of the hoof by supporting the sole with Styrofoam taped on with duct tape or hoof boots and pads.
- Expert hoof care is CRITICAL and involves trimming to realign any malposition of the coffin bone as a result of damage to the laminae, and trimming at frequent enough intervals to maintain this correction (this may mean every one to two weeks initially).
- Obtain X-rays to determine the position of the coffin bone

Hypothyroidism – Secondary to IR or Cushing's (PPID)

Primary hypothyroidism in horses is rare and is most often secondary to primary IR or Cushing's. Symptoms are VERY nonspecific and many overlap considerably with those of insulin resistance and or Cushing's:

- slow shedding/longer than normal coat
- poor energy levels and exercise tolerance
- horse may be irritable and sensitive to touch.

Hypothyroidism cannot be diagnosed with any certainty by symptoms alone – blood tests are required.

Treatment Options

- Provision of adequate correctly balanced minerals in the diet to support thyroid function
- Provision of a thyroid supplement such as Thyro-L (levothyroxine sodium), at least initially.

Despite the fact that the weight of the evidence points to hypothyroidism as being secondary to IR/ PPID rather than related to any primary pathology of the thyroid gland, the use of Thyro-L remains popular among practitioners, often because of favorable clinical responses in terms of energy level and attitude. If thyroid supplementation is used, it should be done only with frequent monitoring to avoid over supplementation, keeping T4 and T3 within normal limits and with the realization that endogenous production of thyroid hormone may well normalize as the metabolic syndrome comes under control. Tapering of supplementation is advisable as clinical status and insulin results improve.

Other Diagnostic Tests

Domperidone Response Test - Still experimental but may be the PPID test of the future. This involves oral (or possibly intravenous) dosing with the drug domperidone, which causes an approximately 300% rise in ACTH in a horse with PPID but not in a normal horse. [5]

TRH Stimulation Test - An older test for Cushing's, does not give consistent results.

Combined Dexamethasone Suppression/TRH Stimulation - Test for Cushing's disease – involves both tests as above.

Urinary Cortisol:Creatinine Ratio - Test done on urine as a screen for Cushing's disease. Not 100% diagnostic but highly suggestive. More accurate than blood cortisol levels in detecting increased production of cortisol.

Cortisol Rhythm – this test is not diagnostic for Cushing's.

T4 And T3 - Thyroid function tests.

Chemistry Screen - Checks for organ function, dehydration, blood sugar, electrolyte abnormalities. With Cushing's/insulin resistance, should also request testing for blood cholesterol and triglyceride levels.

Glossary of Terms

ACTH: A hormone produced by the pituitary gland that triggers production of cortisol from the adrenal gland.

CUSHINGS DISEASE or pituitary pars intermedia dysfunction (PPID): PPID begins when neurons in the intermediate lobe of the pituitary gland degenerate and produce less dopamine. Without dopamine, the pituitary cells secrete uncontrolled levels of hormones, including ACTH. In other species, pituitary tumors may also produce other hormones, such as Prolactin. Studies are currently underway to determine if this is the case in horses as well.

CORTISOL: A hormone produced by the adrenal gland which is released naturally during times of stress (e.g. excitement, transport, exercise, infections, trauma, pain, fear). When production is abnormally high and sustained, it can result in impaired immune function, resistance to insulin, electrolyte abnormalities and impaired ability to utilize protein in the diet.

GLUCOSE: D-Glucose is the primary carbohydrate metabolite and is utilized by the tissues in greater amounts than any other monosaccharide. Glucose is stored as glycogen in muscle cells and in the liver.

I**NSULIN**: A hormone produced by the pancreas which is needed for cells to be able to take in glucose derived from dietary carbohydrates, and to take in amino acids (proteins) to use in manufacture of enzymes, cell structures and muscle. High insulin levels are commonly seen in insulin resistance. IR may be seen as a result of the high cortisol production in classical Cushing's/PPID. Ponies and "easy keeper" breeds of horses appear to be genetically predisposed to insulin resistance.

INSULIN RESISTANCE (IR): A condition where the cells of the body do not respond to insulin signaling. As a result, the pancreas produces more insulin than normal in an attempt to move glucose and protein into the cells. This is similar to Type II diabetes in humans. Unlike humans, horses rarely have high glucose, except in very severe cases. Also termed Equine Metabolic Syndrome, Syndrome X.

> **Compensated IR**: Pancreatic insulin production that maintains insulin mediated glucose uptake (RISQI 0.02 to o.32 or G:I ratio 4.5 to 10). A predictor for pre-laminitic syndrome.
> **Failed Compensation**: RISQI <0.02 or G:I ratio <4.5, very high laminitis risk.

LEPTIN: A protein secreted by adipose (fat) tissue that acts on the brain to regulate food intake; leptin resistance may contribute to voracious appetite seen with IR.

LAMINITIS: Inflammation of the laminae – tissues that connect the coffin bone to the hoof wall inside the foot.

Founder: Often used synonymously with laminitis. Some people use the term founder to indicate horses whose coffin bone has come loose from its hoof wall attachments and is displaced.

PRE-CUSHINGS: A term sometimes used to describe horses that may have some symptoms of Cushing's disease but cannot be confirmed to have it on laboratory testing. Some of these horses only have insulin resistance. Others may be in the early stages of Cushing's and only show exaggerated ACTH seasonal rises in the fall.

PROLACTIN: A hormone produced by the pituitary gland that causes mammary development and production of milk. In people and experimental animals, some pituitary tumors produce high levels of Prolactin.

ROTATION (of the coffin bone): Movement of the coffin bone away from a parallel position with the hoof wall, so that it's tip is pointed down toward the sole.

SINKER: A form of laminitis where the attachments of the coffin bone are weakened/lost around most of its circumference so that the whole bone sinks down inside the hoof and is putting pressure on the sole.

T4 – The largely inactive form of thyroid hormone – the most common thyroid function test.

T3 – The metabolically active form of thyroid hormone.

References:

[1] Cornell University Animal Health Diagnostic Laboratory, 2006. http://www.diaglab.vet.cornell.edu/endo/vetserv.asp*, Equine Cushings test.*

[2] Johnson PJ, Messer NT, Slight SH, Wiedmeyer C, Buff P, Ganjam, VK (2004) Endocrinopathic Laminitis in the Horse. Clinical Techniques in Equine Practice. 3:1; pp 45-56.

[3] Laminitis Trust Clinical Trial. http://www.laminitis.org/Vitex%20trial.html.

[4] Treiber, et al. Evaluation of genetic and metabolic predispositions and nutritional risk factors for pasture-associated laminitis in ponies. (J Am Vet Med Assoc 2006;228:1538–1545)

[5] Sojka, J.E., Paige Jackson, L., Moore, G. and Miller, M. Domperidone Causes an Increase in Endogenous ACTH Concentration in Horses With Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease). In: (Ed.), 52 Annual Convention of the American Association of Equine Practitioners - AAEP, 2006 - San Antonio, TX, USA. Ithaca: International Veterinary Information Service (www.ivis.org), 2006; Document No. P5356.1206. http://www.ivis.org/proceedings/aaep/2006/sojka/chapter.asp?LA=1 .