Proceedings of the 12th International Congress of the World Equine Veterinary Association
WEVA

November 2 - 5, 2011
Hyderabad, India

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Clinical and laboratory diagnosis of endocrine disorders in horses

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The most common endocrine disorders of horses are pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome (EMS). Although hypothyroidism is also suspected and treated in many equids, clear documentation this syndrome has rarely been described in horses and it is often confused with EMS.

Pituitary pars intermedia dysfunction (PPID): PPID, also known as Equine Cushing’s disease, is the most common endocrinopathy of equids. PPID increases in prevalence with age and may affect 15-20% of equids over 15 years of age and hair coat changes, consistent with PPID were recently reported in nearly 40% of equids (mostly ponies) over 30 years of age. There is no apparent sex or breed predilection; however, PPID is more common in ponies than horses. Cushing’s disease in horses develops consequent to hyperplasia or adenoma formation in the pars intermedia that appears to be due to loss of dopaminergic hypothalamic innervation. Abnormal pars intermedia cells, melanotropes, produce excessive amounts of pro-opiomelanocortin (POMC) and a number of POMC-derived peptides including immunoreactive adrenocorticotropic (ACTH) peptides, although the ACTH peptides may not all be bioactive.

A variety of clinical signs can be observed in PPID-affected equids: lethargy, muscle wasting, localized fat deposition, polyuria and polydipsia, chronic laminitis, recurrent infections, and neurological deficits. However, an essentially pathognomonic sign of PPID is a long and often curly hair coat that fails to shed, reported in more than 80% of cases. Hair coat changes with PPID appear to progress over several years from delayed shedding and persistence of long hairs under the jaw, ventral neck, and palmar and plantar aspects of the distal limbs to a generalized long, shaggy hair coat that fails to shed. Although the term hirsutism has become firmly ingrained in the equine veterinary literature to describe this characteristic hair coat, a more appropriate descriptor is hypertrichosis as the hairs of PPID-affected equids are characterized by persistence in the anagen (growth) phase. Chronic, insidious-onset laminitis is perhaps the major clinical complication of PPID with nearly 50% of horses affected. Although the condition is more amenable to management in ponies due to their lower body weight, chronic or recurrent pain with exacerbation of laminitis or associated foot abscesses is often the reason for euthanasia.

Diagnosis of PPID: Practically, the diagnosis of PPID is most commonly made by observation of hypertrichosis and other clinical signs in older equids. Abnormal laboratory data in horses with PPID may include mild anemia, an absolute or relative neutrophilia, and an absolute or relative lymphopenia. The most common abnormality detected on serum biochemical evaluation is mild to moderate hyperglycemia, reported in 25-75% of cases, depending on the upper end of the reference range used. Additional abnormal biochemical findings may include elevations in liver enzyme activities, hypercholesterolemia, and hypertriglyceridemia. Although establishing a diagnosis of PPID in equids with obvious hypertrichosis is straightforward, making the diagnosis in less severely affected horses, that may have laminitis as the only sign, can be challenging. As a result, a number of endocrine
tests have been used to evaluate horses with suspected PPID but the two most widely accepted tests are measurement of plasma ACTH concentration and the overnight dexamethasone suppression test.

**Plasma ACTH concentration.** Measurement of plasma ACTH concentration is a useful screening test to support a diagnosis of PPID and plasma concentrations exceeding 35 pg/ml are commonly found in ponies and horses with PPID and equids with advanced PPID often have values >100 pg/ml. Unfortunately, ACTH secretion is pulsatile in nature and plasma concentrations can vary by 50-100% in blood samples collected within a few minutes of each other. Thus, monitoring horses for decreases in ACTH concentration to assess response to treatment can be problematic. Another limitation of using plasma ACTH concentration to support a diagnosis of PPID is that commercial laboratories may use different assays to measure ACTH and results from one lab may be as much as 3-fold greater as compared to results from another lab. Thus, when using this test, samples should be consistently sent to the same lab for testing. A final limitation of plasma ACTH concentration is seasonal variation in test results. In normal ponies and horses without signs of PPID, plasma ACTH concentrations measured from late July through November (in the northern hemisphere) can be above the cut-off for diagnosis of PPID. Normal results at this time of year remain useful to exclude a diagnosis of PPID; however, elevations are difficult to interpret. Recently, seasonally adjusted reference ranges, with an increased cut-off value in the fall, have been suggested. However, adjusted reference ranges remain to be validated and, again, would likely be affected by the assay used.

**Dexamethasone suppression test:** The overnight dexamethasone suppression test (ODST) is considered by many equine clinicians to be the “gold standard” endocrinologic test to support a diagnosis of PPID. However, there is concern, although poorly documented, that administration of dexamethasone may induce or exacerbate laminitis in PPID-affected equids. The overnight DST consists of measuring cortisol in the late afternoon (typically 17:00) followed by administration of dexamethasone (40 µg/kg, IM = 20 mg to a 500 kg horse) and subsequently measuring plasma cortisol concentration 15 and 19 hours later (08:00 am and 12:00 the following day). The major limitation of the ODST is that it requires two or three visits to the horse. However, considering the fact that the most important value is the cortisol concentration 19 hours following dexamethasone administration, the ODST can be simplified by dispensing dexamethasone to the client for IM administration and limiting the test to one visit the following morning.

**Equine metabolic syndrome (EMS):** Middle-aged obesity (body condition score 7-9 on a scale of 1 to 9) accompanied by insidious-onset laminitis is a syndrome that has been recognized by equine practitioners for decades. Equine metabolic syndrome (EMS) is a recently coined name that has gained acceptance to describe this condition. Clinical signs of laminitis commonly develop while horses are grazing spring pasture but can also occur at other times of the year and in horses without pasture access. Affected horses tend to be aged between 10 to 20 years of age and there does not appear to be a sex predilection. Occasionally, the syndrome can occur in younger animals that have been overfed. Pony breeds, domesticated Spanish mustangs, Peruvian Pasos, Paso Finos, Andalusians, European Warmbloods, American Saddlebreds, Arabians, and Morgan horses are more commonly affected than Thoroughbreds, Standardbreds, or Quarter Horses. This breed disparity is supportive of a genetic predisposition. Insulin resistance (IR) is the primary endocrinopathy induced by obesity in EMS-affected horses.
**Diagnosis of EMS:** Diagnosis of EMS is based on physical characteristics, specifically obesity and/or regional fat deposition with or without laminitis. Further support for EMS can be provided by detection of fasting hyperinsulinemia (>42 uU/mL or >300 pmol/L). To screen suspect equids for hyperinsulinemia, blood samples should be collected in the morning after an overnight fast or, at a minimum, 6 hours after meal feeding (even hay feeding can cause a mild increase in insulin in horses). It is important to remember that medications can sometimes alter blood glucose and insulin concentrations (i.e., α2-agonists such as xylazine or detomidine). Thus, blood samples should be collected before sedation that may be needed for farrier work or other diagnostic procedures. Of interest, some clinicians consider current upper limits for fasting insulin concentration to be too liberal and have recently suggested that the upper limit of the reference range for insulin in healthy horses should be reduced to ≈30 uU/mL or 200 pmol/L.

Unfortunately, EMS-affected horses do not consistently manifest hyperinsulinemia. In cases in which further evidence to support EMS is needed (e.g., for clients that refuse to believe that their overweight horse may be at risk for laminitis), an intravenous glucose tolerance test (IVGTT) can be performed. In the IVGTT, blood glucose concentration is measured before and for 3-4 hours after administration of an intravenous bolus of glucose (0.1-0.3 g/kg). In the normal state, blood glucose and insulin concentrations should return to baseline within 1 to 2 hours. Glucose intolerance (another name for IR) is present when insulin concentrations remain elevated for more than 3 hours after glucose administration. Recently, an even more simple oral sugar challenge test was validated in normal horses and horses with documented IR. The test consists of administering an oral dose of Karo syrup (15 mL/100 kg body weight = 50 mg/kg sugar) and measuring serum insulin concentration every 30 minutes for 2 hours. A greater insulin response was found in horses with IR and it was suggested that the test could be further simplified by collected a single blood sample 60 or 90 minutes after administration of Karo syrup.

**Hypothyroidism:** In the past, the syndrome of obesity and insidious onset laminitis now recognized as EMS was commonly attributed to hypothyroidism and detailed descriptions of hypothyroidism can still be found in equine medicine textbooks. However, experimental hypothyroidism in equids, induced either by thyroidectomy or administration of propylthiouracil, has never resulted in development of laminitis. Syndromes of thyroid gland dysfunction that are recognized in equids include goiter, commonly due to excess iodine in feed supplements, and a congenital hypothyroidism-dysmaturity syndrome.

Unfortunately, random measurement of circulating thyroid hormone concentrations in patients with a wide array of presenting complaints can return low values in as many as 25% of tested animals. This can likely be attributed to the influence of many factors (e.g., age, ambient temperature, level of exercise, concurrent disease, medication use, etc.) on resting thyroid hormone concentrations. Unfortunately, this type of testing has resulted in frequent diagnosis of “hypothyroidism” as the cause of many problems including poor performance, myopathy, infertility, agalactia, anhidrosis, and laminitis.

There are few well documented reports of hypothyroidism in horses in which thyroid gland dysfunction has been further supported by documenting blunted responses to administration of thyrotropin (TSH) or thyrotropin-releasing hormone (TRH). Unfortunately, lack of an assay for endogenous TSH, the routine screening test in humans and dogs, further complicates evaluation of possible hypothyroidism in horses.